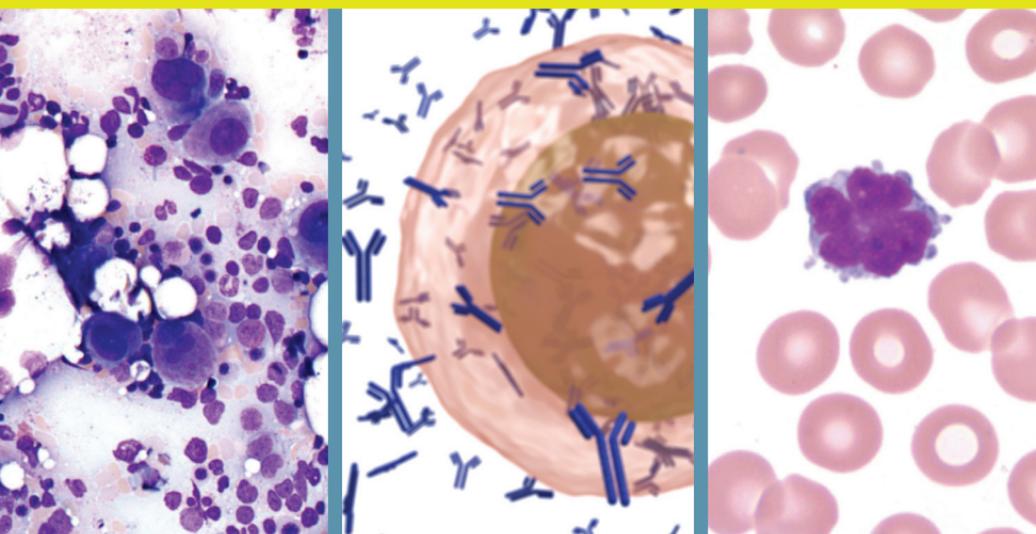


HANDBOOK OF HEMATOLOGIC MALIGNANCIES



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HANDBOOK OF HEMATOLOGIC MALIGNANCIES

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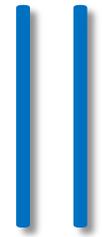
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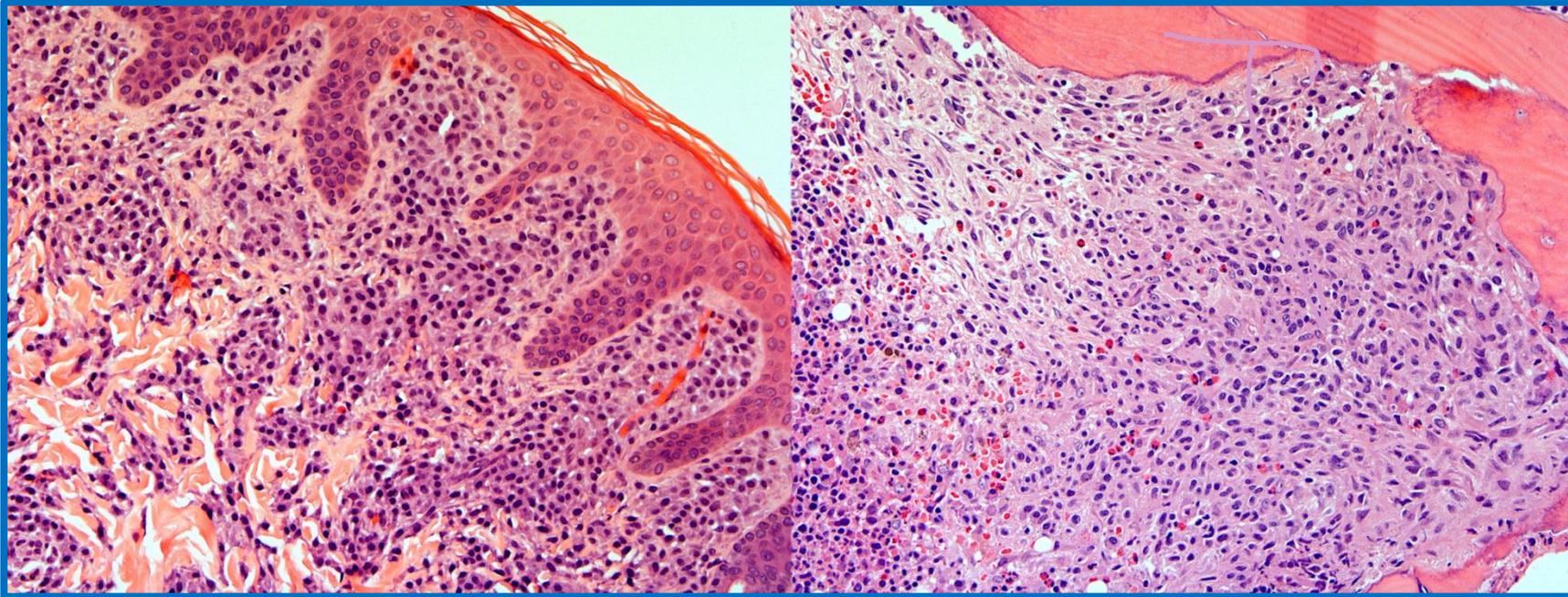
Clinical Case 1



|| Case Presentation

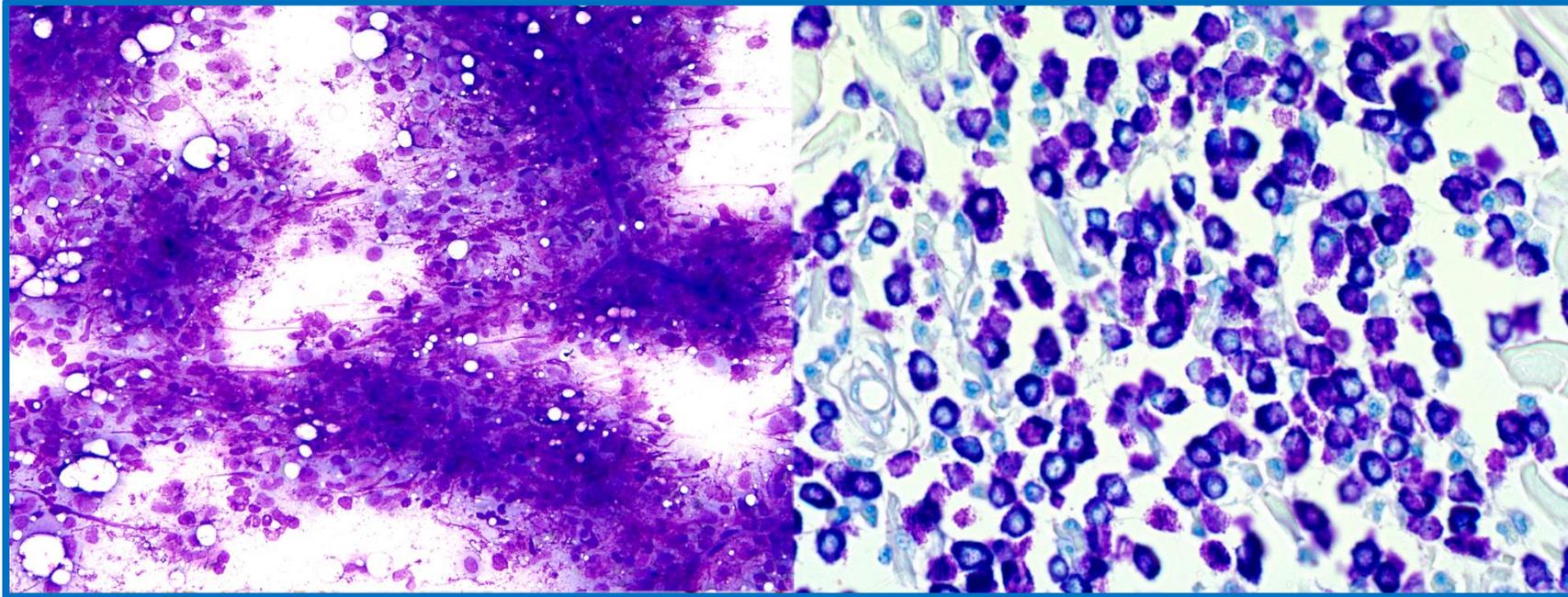
- A 60-year-old female presents with intermittent symptoms of watery diarrhea, skin rash, abdominal cramping, and facial flushing over the past year.
- An infectious workup for the diarrhea has been negative. The patient also reports a 10 lb weight loss over the past year.
- A colonoscopy was performed with biopsies showing areas of dense mast cell aggregates.
- A CBC showed normal WBC count with mild eosinophilia (540 cells/ μ L), mild anemia (10.8 g/dL), and mild thrombocytopenia (138 k/ μ L).
- She undergoes a bone marrow aspiration and biopsy, and the results are as shown in addition to her biopsy of the skin.

|| Case Presentation (Continued) ||



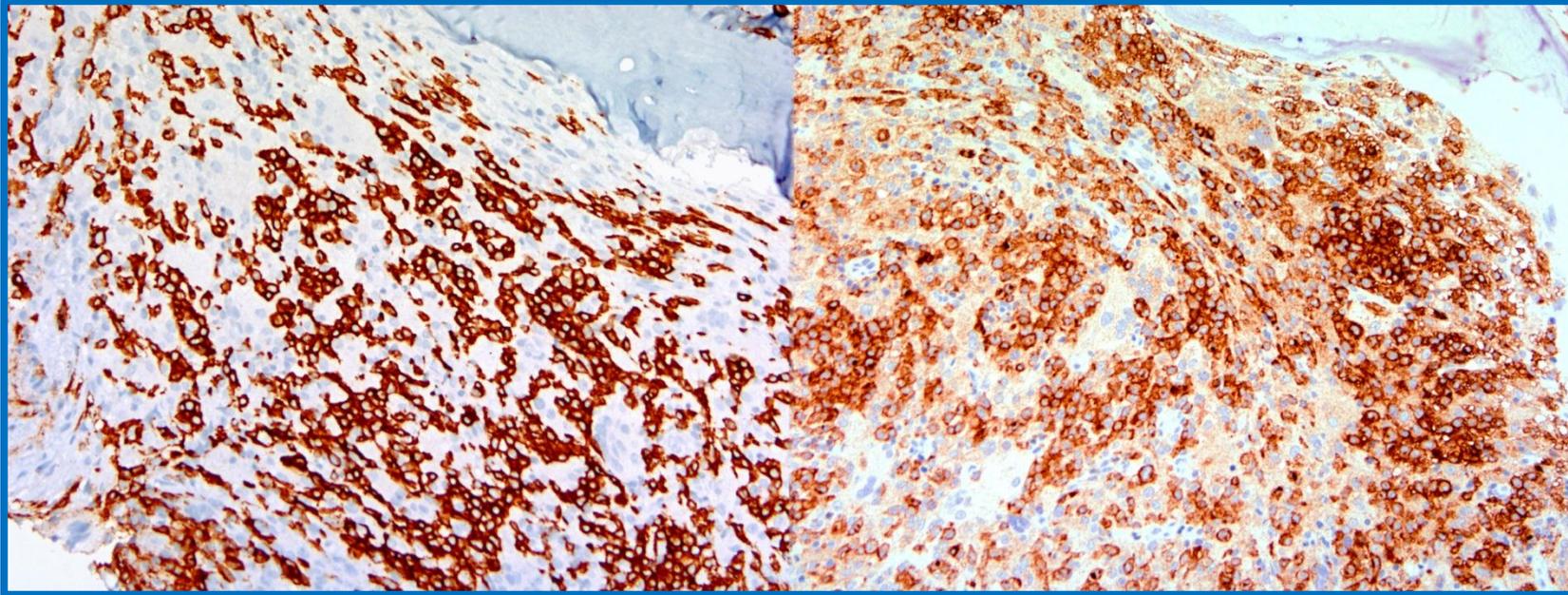
The H&E sections of the skin lesion demonstrated a diffuse cellular infiltrate in the reticular dermis (left, x200 total magnification) as well as bone marrow involvement (right, x200 total magnification). The cells display round to oval, hyperchromatic, spindled nuclei and abundant cytoplasm associated with scattered eosinophils.

|| Case Presentation (Continued) ||



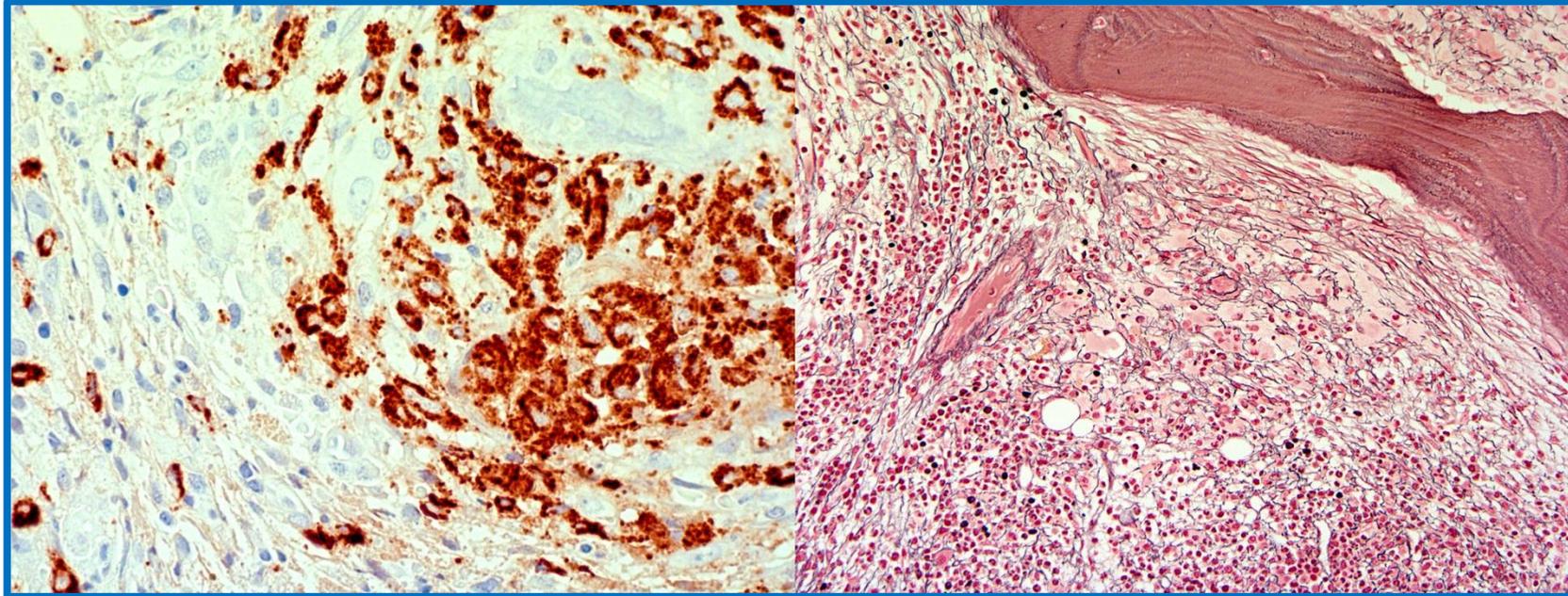
The Wright-Giemsa stained bone marrow aspirate (left, x600 total magnification) and a toluidine blue-stained touch imprint (right, x600 total magnification) highlighted many atypical spindled cells with red-purple cytoplasmic granules (metachromatic staining).

|| Case Presentation (Continued) ||



Immunohistochemical stains showed the neoplastic cells to be positive for CD117 (left, x200 total magnification) and CD25 (right, x200 total magnification).

|| Case Presentation (Continued) ||



Immunohistochemical stains showed the spindled cells are positive for mast cell tryptase (left, x600 total magnification). A reticulin stain highlighted paratrabeular and interstitial moderate-to-severe reticulin fibrosis (right, x200).

|| Case Presentation (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Mast cell activation syndrome
 - B. Serotonin syndrome
 - C. Aggressive systemic mastocytosis
 - D. Mast cell leukemia
 - E. Urticaria Pigmentosa

|| Case Presentation (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Mast cell activation syndrome
 - B. Serotonin syndrome
 - C. Aggressive systemic mastocytosis**
 - D. Mast cell leukemia
 - E. Urticaria Pigmentosa

Explanation: The histologic and clinical findings are most consistent with systemic mastocytosis. CD117 strongly highlights mast cells in tissue and bone marrow, and mast cell tryptase positivity confirms the nature of the atypical spindled cells. CD25 is aberrantly expressed by the mast cells. The *KIT* D816V point mutation should be tested for a possible therapeutic actionable target. Aggressive systemic mastocytosis is a subtype of advanced systemic mastocytosis, characterized by at least one “C finding.” C-findings are evidence of organ dysfunction while “B-findings” refer to evidence of organ involvement. In this case, the patient’s weight loss is due to malabsorption associated with GI-involvement, and not celiac disease. Mast cell leukemia is defined by $\geq 20\%$ BM involvement of atypical mast cells, $\geq 10\%$ circulating mast cells, or in the rare aleukemic variant, circulating mast cells are $< 10\%$ of the total leukocytes, and typically is not associated with skin lesions.

|| Further Testing



- Serum tryptase level is shown to be 727 nanogram/ml. Flow cytometry is performed on the bone marrow aspirate, which confirms mast cell expression of CD117 and CD25. PCR analysis of the bone marrow aspirate shows the presence of *KIT* D816V mutation.

|| Further Testing (Continued) ||

- **Which cell surface marker is aberrantly expressed in mast cells of systemic mastocytosis?**
 - A. CD117
 - B. CD3
 - C. CD34
 - D. CD25
 - E. CD56

|| Further Testing (Continued) ||

- **Which cell surface marker is aberrantly expressed in mast cells of systemic mastocytosis?**
 - A. CD117
 - B. CD3
 - C. CD34
 - D. CD25**
 - E. CD56

Explanation: CD25, as well as CD2, is aberrantly expressed on the mast cells of systemic mastocytosis. Mast cell tryptase can also be demonstrated using immunohistochemistry. CD117 typically strongly highlights mast cells (among other cell types) in tissue or bone marrow, but is a marker of normal mast cell lineage. CD34 is a vascular endothelial and myeloblast marker, and typically used to assess the blast count in bone marrow core biopsies. CD3 is a pan T-cell marker.

|| Case Presentation

- **A patient with recently diagnosed systemic mastocytosis is found to have a leukocytosis of 44,000/liter, with mild eosinophilia (650 cells/ μ L) and monocytosis (4,650 cells/ μ L) and a hemoglobin of 8.2 g/dL. What is the most likely diagnosis?**
 - A. Opportunistic parasitic infection
 - B. Opportunistic bacterial infection
 - C. Additional hematologic malignancy
 - D. Opportunistic viral infection
 - E. Development of concomitant autoimmune disease

|| Case Presentation (Continued) ||

- **A patient with recently diagnosed systemic mastocytosis is found to have a leukocytosis of 44,000/liter, with mild eosinophilia (650 cells/ μ L) and monocytosis (4,650 cells/ μ L) and a hemoglobin of 8.2 g/dL. What is the most likely diagnosis?**
 - A. Opportunistic parasitic infection
 - B. Opportunistic bacterial infection
 - C. Additional hematologic malignancy**
 - D. Opportunistic viral infection
 - E. Development of concomitant autoimmune disease

Explanation: Given the patient's history of SM, worsening peripheral blood counts should raise the suspicion for an underlying hematologic neoplasm, or SM-AHN. The most common clonal associated hematologic malignancies are CMML and MDS.

|| Case Presentation (Continued) ||

- **In what subset of systemic mastocytosis patients can imatinib be a useful treatment?**
 - A. Those without skin manifestations of disease
 - B. Those with evidence of mast cell leukemia
 - C. Those without a *KIT* mutation
 - D. Those with a *KIT* mutation
 - E. Those with prominent GI symptoms

|| Case Presentation (Continued) ||

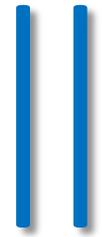
- **In what subset of systemic mastocytosis patients can imatinib be a useful treatment?**
 - A. Those without skin manifestations of disease
 - B. Those with evidence of mast cell leukemia
 - C. Those without a *KIT* mutation**
 - D. Those with a *KIT* mutation
 - E. Those with prominent GI symptoms

Explanation: *KIT D186V* mutation conveys resistance to imatinib.

Companion Case for Chapter 7

Systemic Mastocytosis

*Andrew Kuykendall
and
Kenneth Zuckerman*



Clinical Case 2

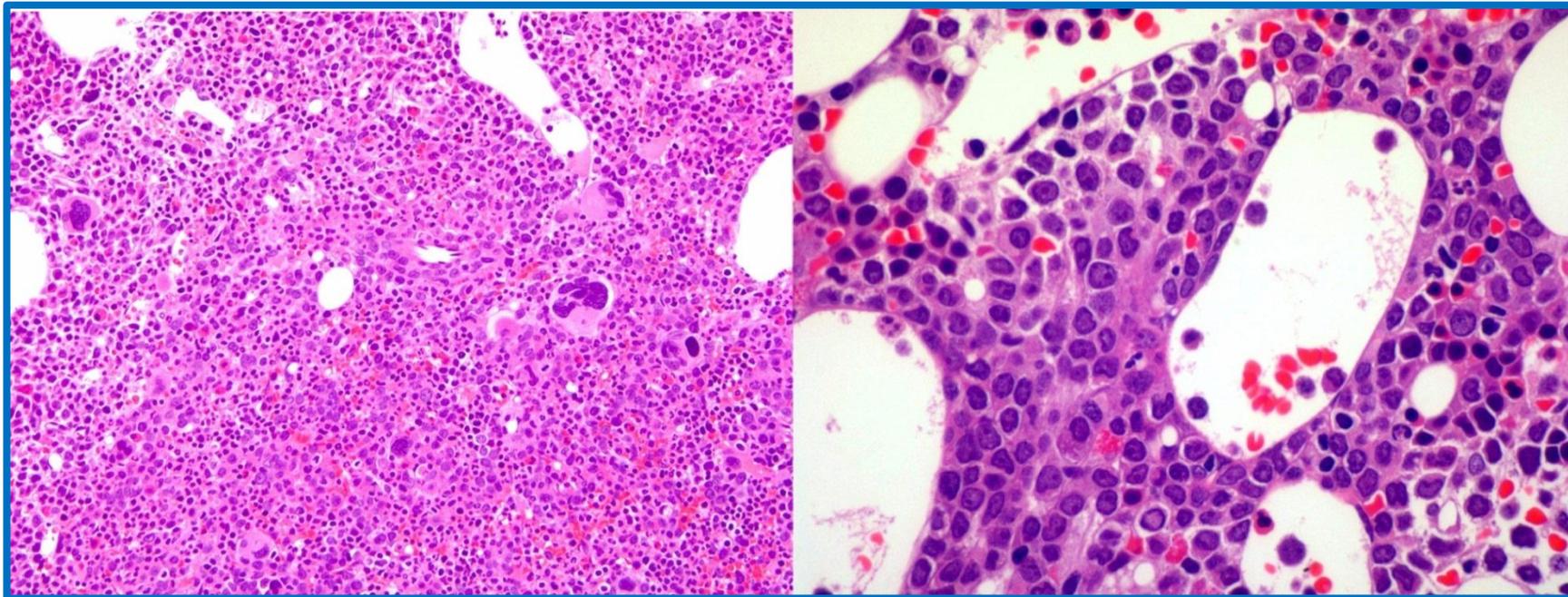


|| Case Presentation

- A 75-year-old male with a PMH of myelodysplastic syndrome presents with severe fatigue and gingival bleeding for the past 4 weeks. A CBC showed WBC count of 23.1 k/ μ L with 31% blasts, hemoglobin of 7.2 g/dL, and platelet count of 47 k/ μ L. He denies lymphadenopathy, fevers, chills, or weight loss. His exam reveals a normal spleen and liver.
- He undergoes a bone marrow aspiration and biopsy.

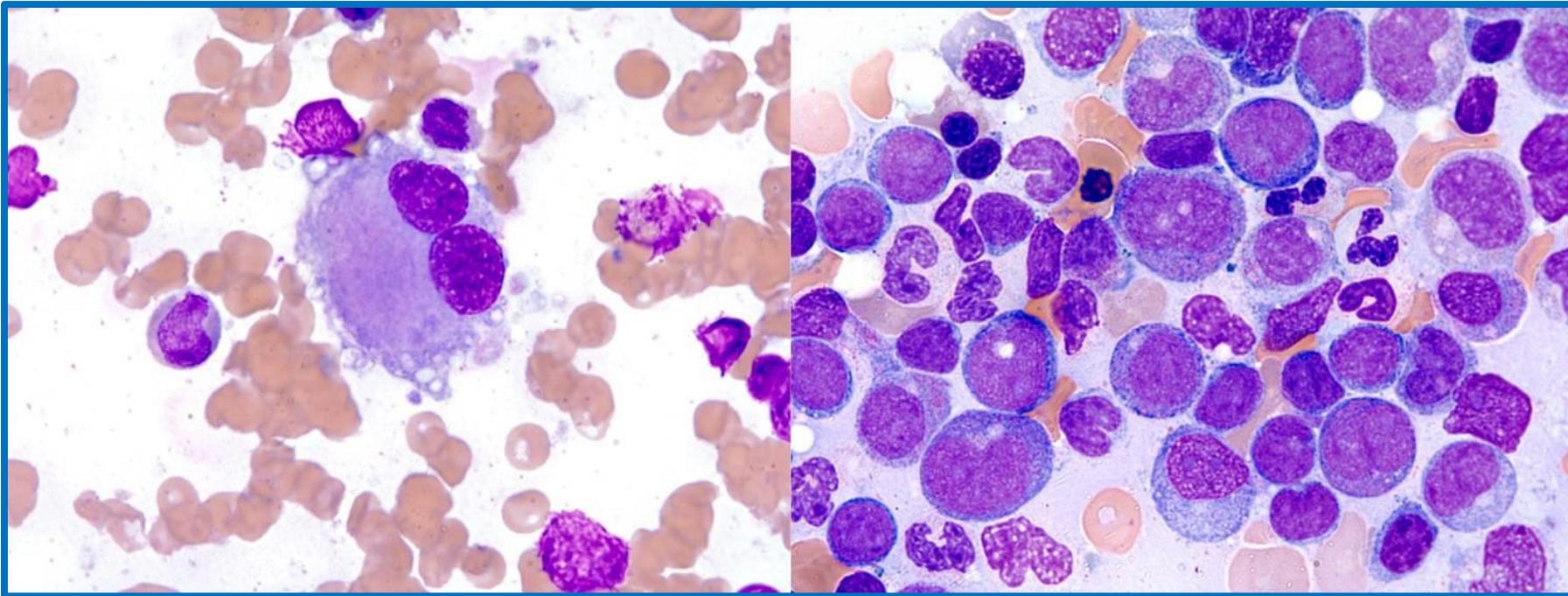
|| Case Presentation (Continued) ||

The bone marrow core biopsy shows dysplastic trilineage hematopoietic elements with abnormal distribution (left panel, H&E, x200). Focally, there was a significant increase of mononuclear precursors/blasts with immature chromatin, high nuclear-to-cytoplasmic ratio, and prominent nucleoli (right panel, H&E, x600).



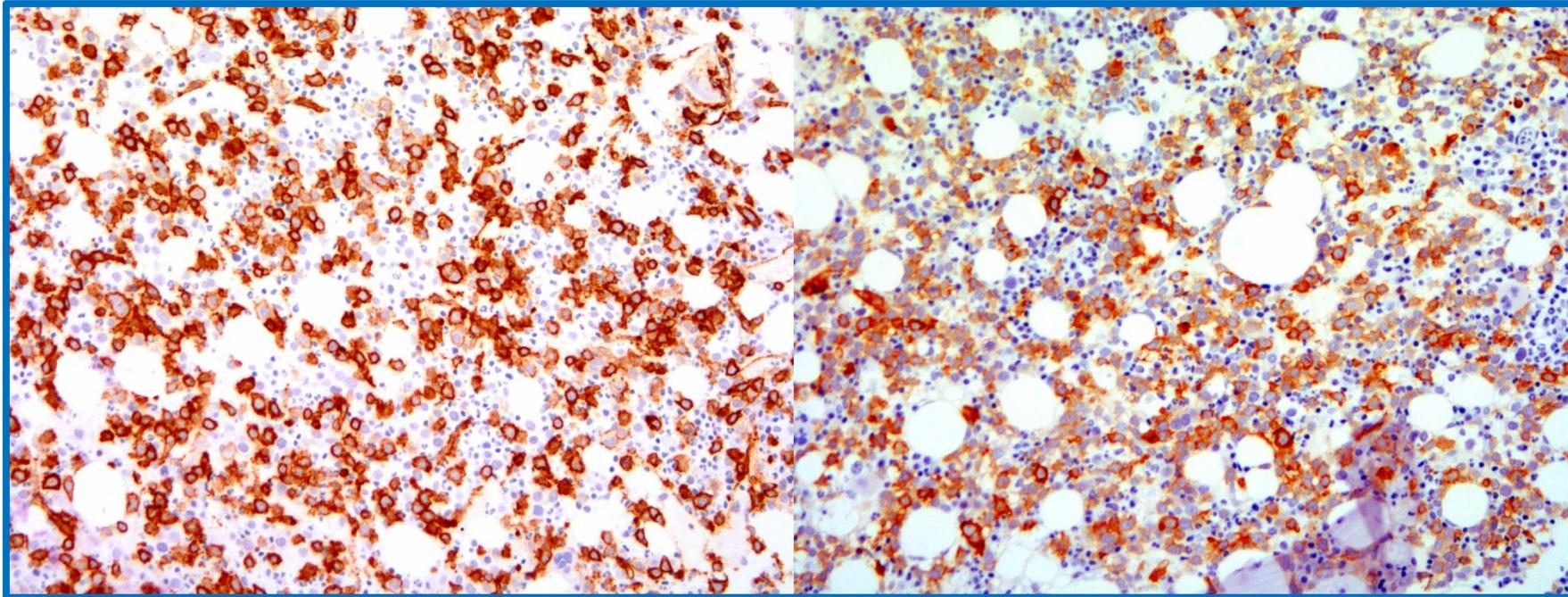
|| Case Presentation (Continued) ||

The aspirate smear shows multilineage dysplasia including a bilobed megakaryocyte with disjointed nuclei as well as neutrophilic hypogranularity and frequent myeloblasts (left and right panels, respectively, Wright-Giemsa, x1000).



|| Case Presentation (Continued) ||

The blasts were immunophenotypically positive for CD34 and CD117 (left and right panels respectively, immunoperoxidase, x200).



|| Flow Cytometry



- The flow cytometry revealed moderate CD34 (+), CD117(+), CD13 (+), CD33 (+), MPO (+), and HLA-DR (+).
- **Which of the following is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia
 - B. Chronic lymphocytic leukemia
 - C. De novo acute myeloid leukemia
 - D. Secondary acute myeloid leukemia
 - E. Diffuse large B-cell lymphoma

|| Diagnosis



- **Which of the following is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia
 - B. Chronic lymphocytic leukemia
 - C. De novo acute myeloid leukemia
 - D. Secondary acute myeloid leukemia**
 - E. Diffuse large B-cell lymphoma
- The patient has a prior history of myelodysplastic syndrome, and peripheral differential cell counts and bone marrow pathology demonstrate blasts more than 20% with multilineage dysplastic changes. IHC studies are consistent with myeloblasts.

|| Prognosis



- **Which karyotype is associated with worse prognosis in secondary AML?**
 - A. t(8;21)
 - B. t(15;17)
 - C. Normal karyotype
 - D. inv(16)
 - E. del(5q)

|| Prognosis (Continued) ||

- **Which karyotype is associated with worse prognosis in secondary AML?**
 - A. t(8;21)
 - B. t(15;17)
 - C. Normal karyotype
 - D. inv(16)
 - E. del(5q)**
- Del 5q, del 7q, t(6;9), 17p abnormality, monosomies 5 or 7, trisomies 8 or 13, and complex karyotypes are associated with worse prognosis in secondary AML

|| Treatment



- **What is the optimal treatment for secondary AML patients who are eligible for intensive chemotherapy?**
 - A. 7+3
 - B. Azacitidine
 - C. Decitabine
 - D. Autologous stem cell transplant
 - E. Ibrutinib

|| Treatment (Continued) ||

- **What is the optimal treatment for secondary AML patients who are eligible for intensive chemotherapy?**
 - A. 7+3**
 - B. Azacitidine
 - C. Decitabine
 - D. Autologous stem cell transplant
 - E. Ibrutinib
- 7+3 induction chemotherapy followed by HiDAC consolidation may be appropriate for secondary AML in younger patients with good performance status.

Companion Case for Chapter 15
Secondary AML and AML With
Myelodysplasia-Related Changes

*Seongseok Yun
and
Jeffrey Lancet*



Clinical Case 3

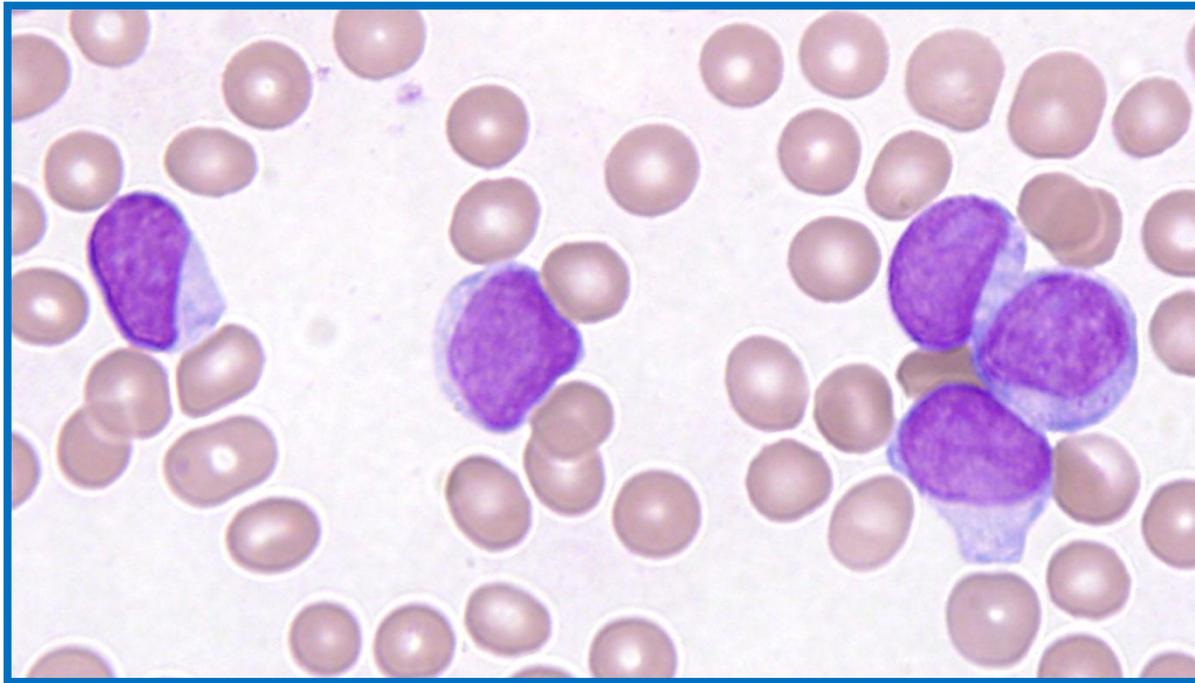


|| Case Presentation

- A 32-year-old male with a history of epilepsy sees his primary care physician for fatigue.
- Review of symptoms revealed headaches and recent blurry vision.
- Subsequent blood work revealed a hemoglobin of 7.2 g/dL, WBC of $112 \times 10^9/L$, and platelets of $65 \times 10^9/L$ with 80% circulating blasts.
- He was urged to go to the hospital where he was admitted for further workup.

|| Case Presentation (Continued) ||

A subsequent CBC showed hemoglobin of 6.2 g/dL, and WBC of $123 \times 10^9/L$, platelet count of $65 \times 10^9/L$ with 85% blasts identified. The peripheral smear is shown below:



- Flow cytometry shows the blasts express myeloid markers (CD34, CD117, CD13, CD33, HLA-DR, and cytoplasmic MPO).

|| Case Presentation (Continued) ||

- **What is the immediate concern for this patient?**
 - A. Acute renal failure
 - B. Infection
 - C. Leukostasis
 - D. Hemorrhage

|| Case Presentation (Continued) ||

- **What is the immediate concern for this patient?**

- A. Acute renal failure

- B. Infection

- C. Leukostasis**

- D. Hemorrhage

- The patient has acute myeloid leukemia (AML) with a hyperleukocytosis as defined as >100 k/ μ L in AML. This places him at risk for thrombosis of microvasculature due to leukostasis by the large and rigid blasts. Leukostasis presents most often with CNS and pulmonary disturbances such as vision changes, somnolence, headaches, respiratory distress, and pulmonary infiltrates.
- Acute renal failure is a consequence of tumor lysis syndrome, which is associated with induction chemotherapy, and can present with oliguria or flank pain and symptoms of electrolyte disturbances such as seizures or tetany with hypocalcemia and/or weakness and paralysis with hyperkalemia.
- Infection, particularly pneumonia or meningitis, could be in the differential diagnosis in patients with pulmonary or CNS symptoms respectively; however, given the white blood cell count in this patient with AML, leukostasis should be empirically treated and not delayed while ruling out infection.
- Hemorrhage risk is more associated with risk of disseminated intravascular coagulation (DIC), which is more associated with acute promyelocytic leukemia (APL). Given the patient's flow cytometry findings and blast morphology, APL is an unlikely diagnosis.

|| Case Presentation (Continued) ||

- **In which condition is leukocytapheresis NOT indicated?**
 - A. Asymptomatic acute myeloid leukemia (AML) with rapidly rising blast count of $125 \times 10^9/L$
 - B. Asymptomatic acute monocytic leukemia with blast count of $70 \times 10^9/L$
 - C. Symptomatic acute promyelocytic leukemia (APL) with blast count $110 \times 10^9/L$
 - D. Symptomatic acute lymphocytic leukemia (ALL) with lymphoblasts of $450 \times 10^9/L$ with symptoms

Note: "Symptomatic" refers to evidence of leukostasis present

|| Case Presentation (Continued) ||

- **In which condition is leukocytapheresis NOT indicated?**
 - A. Asymptomatic acute myeloid leukemia (AML) with rapidly rising blast count of $125 \times 10^9/L$
 - B. Asymptomatic acute monocytic leukemia with blast count of $70 \times 10^9/L$
 - C. Symptomatic acute promyelocytic leukemia (APL) with blast count $110 \times 10^9/L$**
 - D. Symptomatic acute lymphocytic leukemia (ALL) with lymphoblasts of $450 \times 10^9/L$ with symptoms

Leukostasis and hyperleukocytosis of $>100 \times 10^9/L$ in AML, $>400 \times 10^9/L$ in ALL, and $>50 \times 10^9/L$ in monocytic/monoblastic AML subtypes are ASFA Category I indications for emergent leukocytapheresis. However, at these blasts counts with no symptoms of leukostasis, there is no established evidence in the literature to support the use of prophylactic leukocytapheresis in AML or ALL, and thus are Category III indications. Prompt induction chemotherapy and supportive care should be initiated early. The 2013 ASFA Therapeutic Apheresis Guidelines state that AML cases with rapidly rising blasts $>100 \times 10^9/L$ and any monocytic/monoblastic AML subtypes with blasts $>50 \times 10^9/L$ may benefit from prophylactic leukocytapheresis due to the high risk for leukostasis in these groups.

While APL with hyperleukocytosis and leukostasis is not an indication specifically addressed or categorized by ASFA, literature showing any benefit of leukocytareduction in these patients over initiating prompt all trans retinoic acid treatment is lacking. In fact, the limited studies addressing such patients have recommended against this practice due to associated worsening of coagulopathies with the introduction of large bore catheters in those already at increased risk for hemorrhage.

|| Case Presentation (Continued) ||

The patient is started on the cytoreductive agent hydroxyurea while arrangements are made for leukocytapheresis. This includes vascular access, calculating his pheresis volume, and scheduling to have his anticonvulsant medications administered after the procedure.

|| Case Presentation (Continued) ||

- **What kind of vascular access should be established?**
 - A. PICC line
 - B. Double lumen central venous catheter
 - C. Standard intravenous line
 - D. Tunneled central venous catheter

|| Case Presentation (Continued) ||

- **What kind of vascular access should be established?**
 - A. PICC line
 - B. Double lumen central venous catheter**
 - C. Standard intravenous line
 - D. Tunneled venous catheter

Two lines are needed for apheresis, one for withdrawal and one for return. Peripherally inserted central catheters (PICC lines) are long, thin tubes. Apheresis requires rigid catheters that will not collapse from the strong negative pressures during withdrawal; thus PICC lines cannot be used. Peripheral access is an option for a short course of apheresis if the patient has adequate veins and catheters that are a minimum of 17G for withdrawal and 18G for return are used.

If peripheral access is not possible, central venous catheters (CVC) with double lumens are used. Mahurkar, Hickman, and most dialysis-type catheters are appropriate for use. Femoral CVC is ideal for a limited course of apheresis due to relative ease of placement. However, the groin area places the line at increased risk of becoming infected and due to the restriction on patient mobility, this site should not be used if several days to weeks are needed for treatment. A subclavian or internal jugular CVC should be used instead, with the main risk being a possible iatrogenic pneumothorax during placement. While not encountered in hematologic emergencies, one should note that long-term or indefinite need for apheresis would benefit from a tunneled catheter. Also of note, arteriovenous fistulas may be used for the procedure if performed by pheresis personnel experienced in using them.

|| Case Presentation (Continued) ||

- A Mahukar femoral central venous catheter is ordered for the patient and his total blood volume (TBV) was determined as below with patient weight of 75 kg:

$$TBV (mL) = \text{weight (kg)} \times 70 \text{ mL/kg}$$

$$= 75 \text{ kg} \times 70 \text{ mL/kg}$$

$$= 5250 \text{ mL}$$

- An order for removal of 2x TBV (10.5 L) patient blood and replacement by normal saline with calcium gluconate 2 g in 100 mL NS IVPB running at 100mL/hr
 - 6% hydroxyethyl starch (HES) can be added to the anticoagulated blood entering the centrifuge apparatus to help enhance separation of the RBCs from the WBCs and thus provide a higher yield of leukocyte clearance with the procedure; however, due to increased WBC count, it is not necessary.
 - Because HES is also a volume expander, it should be avoided in patients with cardiovascular or renal dysfunction

|| Case Presentation (Continued) ||

- **Should the patient's anemia of hemoglobin 6.2 g/dl be corrected?**
Multiple answers may be correct.
 - A. Yes, give the patient 2 units pRBCs.
 - B. No, transfusion is not indicated for Hgb of 6.2 g/dl.
 - C. Yes, prime the apheresis device with pRBC.
 - D. Yes, slowly infuse pRBC during the apheresis procedure via a peripheral line.

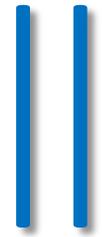
|| Case Presentation (Continued) ||

- **Should the patient's anemia be corrected (hemoglobin 6.2 g/dL)?**
 - A. Yes, give the patient 2 units pRBCs.
 - B. No, transfusion is not indicated for hgb of 6.2 g/dl.
 - C. Yes, prime the apheresis device with pRBC.**
 - D. Yes, slowly infuse pRBC during the apheresis procedure via a peripheral line.**

Normally, a hemoglobin below 7 g/dL is an indication for pRBC transfusion; however, in a patient with leukostasis, transfusion before apheresis should be avoided as it can worsen hyperviscosity. This can be a potential problem during the procedure because of decreased oxygen-carrying capacity resulting from a fraction of the blood being now in the extracorporeal components. To avoid this problem without transfusing the patient, one can prime the apheresis machine with pRBCs. Another alternative is to slowly infuse pRBCs as part of the replacement fluid via a peripheral line. This is especially a concern in pediatric, very small adult, and severely anemic patients.

Companion Case for Chapter 54 Therapeutic Apheresis Indications

*Amanda E. Lo,
Ruchika Goel,
and
Ljiljana V. Vasovic*



Clinical Case 4



|| Case Presentation

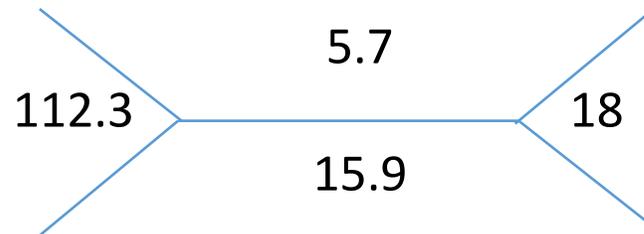
A 15-year-old boy is brought to his primary care physician's office with his mother for a physical exam.

On review of systems, he reports that over the month, he has been experiencing increasing fatigue, bruising with minimal contact, and noticed "lumps in his neck". He denies any recent illness or systemic symptoms. Vitals are WNL and physical exam is notable for two 3–4 cm firm, non-mobile lymph nodes in the anterior cervical chain.

|| Labs

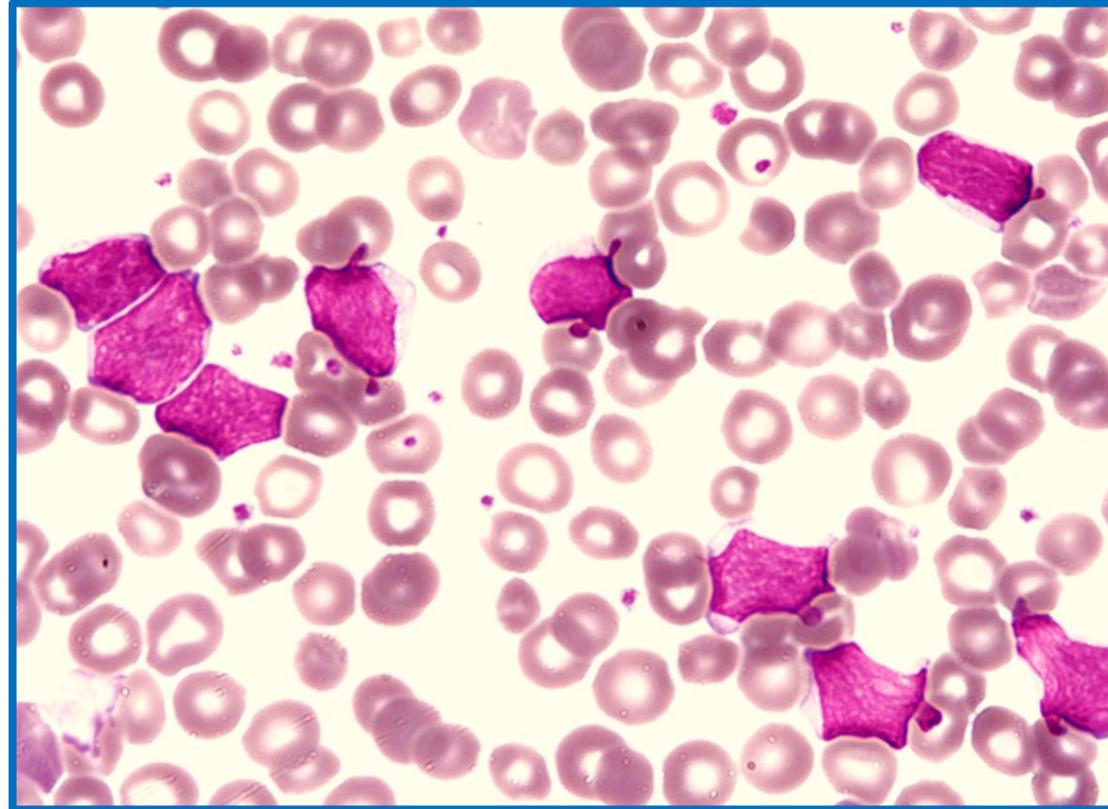


He is directly admitted to the hospital when his CBC returns:



Differential with 62% blasts, 17% lymphocytes, and 19% neutrophils.
Peripheral smear confirms numerous blasts.

Peripheral Blood Smear



Peripheral blood smear shows numerous blasts displaying finely granulated chromatin, irregular nuclei, inconspicuous to small, visible nucleoli and a scanty cytoplasm (Wright stain, x1000).

|| CT Contrast, Anterior to Posterior (C/A/P) ||

- CT scan shows a 6 cm by 8 cm mediastinal mass with diffuse hilar lymphadenopathy, the largest of which measures 4 cm by 3.5 cm.

|| Diagnosis

- **By IHC, blasts are TdT+ and MPO-. What is the most likely diagnosis given the above information?**
 - A. B-cell acute lymphoblastic leukemia
 - B. Acute myeloid leukemia
 - C. Acute lymphoblastic lymphoma
 - D. T-cell acute lymphoblastic leukemia
 - E. Not enough information given

|| Diagnosis (Continued) ||

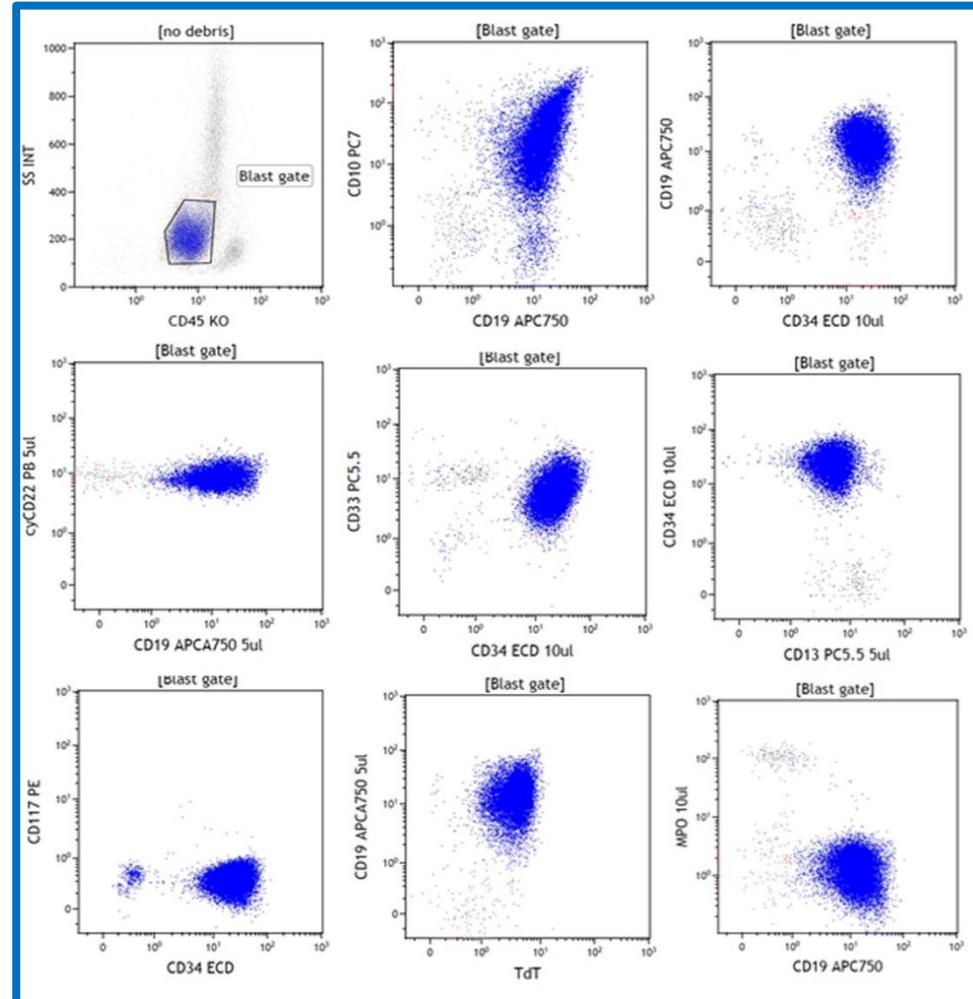
- **What is the most likely diagnosis given the above information?**
 - A. B-cell acute lymphoblastic leukemia
 - B. Acute myeloid leukemia
 - C. Acute lymphoblastic lymphoma
 - D. T-cell acute lymphoblastic leukemia
 - E. Not enough information given**

Answer E is the correct answer. Of all the answer choices given, there is not enough information to differentiate between answer choice A and D. Answer choice B can be ruled out by the negative MPO and positive TdT stain, both consistent with blasts of lymphoid origins. Answer choice C is incorrect as the patient presents with greater than 25% blasts (regardless of mediastinal mass or LAD), consistent with a leukemic process.

|| Bone Marrow Biopsy ||

- A bone marrow biopsy is performed that shows over 55% blasts with morphology similar to the peripheral smear findings.

Flow Cytometry



|| Flow Cytometry Interpretation ||

- **What is the most likely diagnosis given the above information?**
 - A. B-cell acute lymphoblastic leukemia
 - B. T-cell acute lymphoblastic leukemia
 - C. Biphenotypic leukemia
 - D. Not enough information given

|| Flow Cytometry Interpretation (Continued) ||

- **What is the most likely diagnosis given the above information?**
 - A. B-cell acute lymphoblastic leukemia**
 - B. T-cell acute lymphoblastic leukemia
 - C. Biphenotypic leukemia
 - D. Not enough information given

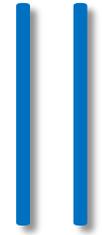
Flow cytometry gating on the blast region detected a distinct population of B-lymphoblasts, phenotypically positive for CD19, cytoplasmic CD22, CD10, TdT, and CD34 with aberrant expression of CD13 and CD33, and negative for cytoplasmic CD3, cytoplasmic MPO, and CD117.

Biphenotypic leukemia refers to a process where blasts resemble that of both lymphoid and myeloid origin. The information given in the case does not support this diagnosis.

Companion Case for Chapter 18

B-Lymphoblastic Leukemia

*Aneesha Hossain
and
Khaled el-Shami*



Clinical Case 5



|| Case Presentation

- A 67-year-old female with no significant past medical history presented to her primary care physician's office for evaluation after several weeks' history of nonspecific complaints such as increasing fatigue, shortness of breath, joint pains, and cough. Routine blood work revealed severe anemia and she was referred to the emergency department for further evaluation. There, CBC revealed hemoglobin 6.5 g/dL, platelets 65 k/ μ L, and a WBC count of 10.5 k/ μ L with 55% circulating blasts.

|| Case Presentation (Continued) ||

- The peripheral smear showed severe normocytic, normochromic anemia without anisocytosis, severe thrombocytopenia, and many circulating blasts. A bone marrow aspirate and core biopsy were obtained. Ancillary studies including evaluation of flow cytometry, FISH, and cytogenetics were performed.

|| Flow Cytometry



- The flow cytometry revealed expression of cytoplasmic MPO, CD13, CD33, as well as CD19, CD10, surface CD22, and cytoplasmic CD79a.
- **Which of the following is the most likely diagnosis?**
 - A. Acute undifferentiated leukemia (AUL)
 - B. Chronic myelogenous leukemia, blastic phase
 - C. Mixed phenotype acute leukemia (MPAL)
 - D. B-lymphoblastic leukemia (B-ALL)
 - E. Acute myelogenous leukemia (AML)

|| Flow Cytometry (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Acute undifferentiated leukemia (AUL)
 - B. Chronic myelogenous leukemia, blastic phase
 - C. Mixed phenotype acute leukemia (MPAL)**
 - D. B-lymphoblastic leukemia (B-ALL)
 - E. Acute myelogenous Leukemia (AML)

The patient has MPAL, based on the presence of MPO positivity for myeloid differentiation as well as 3 B-cell markers (CD19, surface CD22 and cytoplasmic CD79a) for lymphoid lineage.

|| Differential Diagnosis

- Other acute leukemias, including AML, ALL, and AUL must be carefully differentiated from MPAL. This is achieved on the basis of flow cytometry for cellular markers as outlined in the WHO classification.
- Mixed Phenotype Acute Leukemia involves coexpression of markers from different lineages:
 - i. Myeloid Lineage: Myeloperoxidase or monocytic differentiation (nonspecific esterase, CD11c, CD14, CD64, lysozyme)
 - ii. T lineage: Cytoplasmic CD3 (epsilon chain) or surface CD3
 - iii. B lineage: CD19 with CD79a, cytoplasmic CD22, CD10 (note: if CD19 is strongly expressed, only one other B cell marker is needed; if CD19 is weakly expressed, two of the other B cell markers are necessary).

|| Case Presentation



- Further FISH/Cytogenetic analysis revealed translocation (9;22) consistent with MPAL, with t(9;22)(q34;q11.2); *BCR-ABL1*
- Lumbar puncture did not reveal any blasts morphologically nor by flow cytometry.

|| Differential Diagnosis

- **Which of the following are relatively good prognostic factors in this case?**
 - A. $t(9;22)(q34;q11.2)$; *BCR-ABL1*
 - B. Patient age
 - C. Lack of CNS involvement
 - D. Presence of B- and myeloid-markers
 - E. All of the above

|| Differential Diagnosis (Continued) ||

- **Which of the following are relatively good prognostic factors in this case?**
 - A. t(9;22)(q34;q11.2); *BCR-ABL1*
 - B. Patient age
 - C. Lack of CNS involvement**
 - D. Presence of B- and myeloid-markers
 - E. All of the above

Presence of Ph+ chromosome/t(9;22)(q34;q11.2); *BCR-ABL1*, older age, and acute leukemias of ambiguous lineage are all considered poor prognostic factors at this time.

|| Philadelphia Chromosome (*BCR-ABL1*) ||

- **Which of the following is true regarding t(9;22)(q34;q11.2)?**
 - A. Can be associated with several different types of leukemia
 - B. Is associated with a poorer prognosis in B-lymphoblastic leukemia
 - C. May be associated with a very high WBC count at presentation
 - D. Is treated with TKI in addition to chemotherapy when found in conjunction with MPAL or B-ALL
 - E. All of the above

|| Philadelphia Chromosome ||

- **t(9;22)(q34;q11.2); *BCR-ABL1*:**
 - A. Can be associated with several different types of leukemia
 - B. Is associated with a poorer prognosis in B-lymphoblastic leukemia
 - C. May be associated with a very high WBC count at presentation
 - D. Is treated with TKI in addition to chemotherapy when found in conjunction with MPAL or B-ALL
 - E. All of the above**

Ph+ chromosome/t(9;22)(q34;q11.2); *BCR-ABL1* can be found in a number of leukemias, including CML, B-ALL, and MPAL. Presence of t(9;22)(q34;q11.2)/*BCR-ABL1* in adult B-ALL is considered a poor prognostic feature. These patients may have a very high WBC count at presentation. These patients should be treated with induction chemotherapy in conjunction with a tyrosine kinase inhibitor, such as imatinib or dasatinib.

|| Treatment



- **To the best of our current knowledge, what is the optimal treatment for MPAL with t(9;22)(q34;q11.2); *BCR-ABL1* in young, fit individuals?**
 - A. Induction therapy with Cytarabine + Daunorubicin followed by HiDAC consolidation with tyrosine kinase inhibitor
 - B. Induction therapy with ALL-based regimen
 - C. Induction therapy with regimen combining those used for AML and ALL
 - D. Induction therapy with ALL-based regimen with tyrosine kinase inhibitor
 - E. Induction therapy with ALL-based regimen with tyrosine kinase inhibitor followed by allogeneic stem cell transplant in the first complete remission (CR).

|| Treatment (Continued) ||

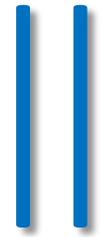
- **To the best of our current knowledge, what is the optimal treatment for MPAL with t(9;22)(q34;q11.2); *BCR-ABL1* in young, fit individuals?**
 - A. Induction therapy with Cytarabine + Daunorubicin followed by high dose cytarabine consolidation
 - B. Induction therapy with ALL-based regimen
 - C. Induction therapy with regimen combining those used for AML and ALL
 - D. Induction therapy with ALL-based regimen with tyrosine kinase inhibitor
 - E. **Induction therapy with ALL-based regimen with tyrosine kinase inhibitor followed by allogeneic stem cell transplant in the first complete remission (CR).**

MPAL with t(9;22)(q34;q11.2); *BCR-ABL1* is considered a high-risk disease, and, similar to Ph+ B-ALL in adults, these patients should be treated with induction chemotherapy along with a tyrosine kinase inhibitor, and, transplant-eligible individuals should receive an allogeneic stem cell transplant in the first remission. Of note, AML regimens have been retrospectively compared to ALL regimens with the latter appearing to have increased benefit.

Companion Case for Chapter 21

Acute Leukemia of Ambiguous Lineage

Keri Maher
and
Ravitharan Krishnadasan



Clinical Case 6



|| Case Presentation

A 55-year-old-male with no significant PMH presented to the emergency department with acute onset of tinnitus, dizziness, and changes in his vision including blurring and double vision. He has been feeling well, other than some moderate headaches that started 1 month prior to this presentation.

Physical exam showed rotary nystagmus and difficulty walking due to ataxia. The patient had normal sensation and strength in all extremities. There were no abnormalities on physical exam including no evidence of lymphadenopathy or hepatosplenomegaly. CBC and CMP were within normal limits. LDH was mildly elevated at 350 U/L. CT of the head without contrast did not show any evidence of intracranial hemorrhage. MRI of the brain with gadolinium demonstrated multiple new areas of enhancement representing at least three separate sites of mostly intraventricular or paraventricular neoplasia. The largest site was very well circumscribed and involved the posterior aspect of the septum pellucida, measuring 2.51 cm x 2.44 cm. There was evidence of mild vasogenic edema without midline shift and no evidence of hydrocephalus. Neurosurgery and oncology were consulted for evaluation.

|| Case Presentation (Continued) ||

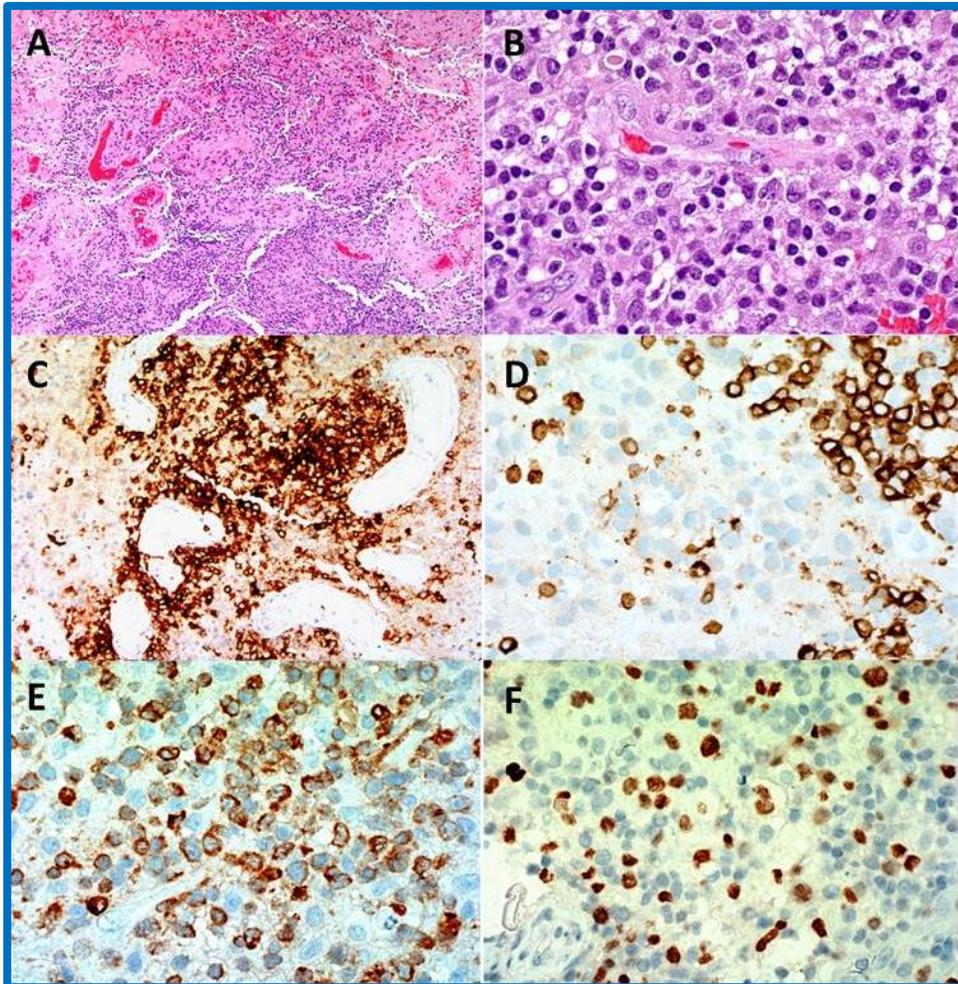
1. **Neurosurgery evaluates the patient and will be able to take him for stereotactic biopsy the next morning. What should be the next step in management of this patient?**
 - A. Start dexamethasone immediately to prevent worsening neurological deficits due to vasogenic edema
 - B. Admit patient to hospital for close neurological monitoring
 - C. Hold steroids until after biopsy to enhance diagnostic yield
 - D. B and C

|| Case Presentation (Continued) ||

1. **Neurosurgery evaluates patients and will be able to take him for stereotactic biopsy the next morning. What should be the next step in management of this patient?**
 - A. Start dexamethasone immediately to prevent worsening neurological deficits due to vasogenic edema
 - B. Admit patient to hospital for close neurological monitoring
 - C. Hold steroids until after biopsy to enhance diagnostic yield
 - D. B and C**

Answer: It is recommended that corticosteroids are not started until a diagnosis is established since they can decrease diagnostic yield. In this case, the patient has mild vasogenic edema without midline shift and biopsy will be obtained the following day; therefore, holding on starting steroids would be appropriate. In situations in which empiric steroids are started due to significant edema or CNS deficits, they should be tapered rapidly prior to biopsy if possible.

Case Presentation (Continued)



Stereotatic biopsy from brain parenchyma shows atypical lymphoid infiltrate associated with vascular proliferation, dilatation, congestion, and focal necrosis (A, H&E, x100). The atypical lymphoid infiltrate consists of predominantly medium- to large-sized cells, with dispersed vesicular chromatin, small but distinct nucleoli, and abundant eosinophilic cytoplasm that were angiocentrically distributed (B, H&E, x600). IHC stain highlights perivascular CD20 positive B-cells (C, x200). The neoplastic cells stained negative for CD3, and positive for BCL-2 and MUM1 (D–F. immunoperoxidase, x200, x600, x600, respectively), suggesting the lymphoma to be nongerminal center B-cell type (non-GCB type).

|| Case Presentation (Continued) ||

The patient was started on dexamethasone following the biopsy and had a dramatic improvement of his symptoms. Staging was performed with ophthalmologic evaluation (i.e., slit lamp), CT scan of the chest/abdomen and pelvis, bone marrow biopsy, and HIV and hepatitis testing. These studies did not find evidence of systemic lymphoma and he was therefore diagnosed with primary CNS lymphoma.

|| Case Presentation (Continued) ||

2. What is this patient's risk category?

- A. Low risk, 2-year survival of 80%
- B. Intermediate risk, 2-year survival of 48%
- C. High risk, 2-year survival of 15%
- D. There is no way to risk-stratify this patient

|| Case Presentation (Continued) ||

2. What is this patient's risk category?

- A. Low risk, 2-year survival of 80%
- B. Intermediate risk, 2-year survival of 48%**
- C. High risk, 2-year survival of 15%
- D. There is no way to risk-stratify this patient

Prognostic Factor	Point
Age >60	1
ECOG performance status >1	1
Elevated serum LDH	1
Elevated CSF protein concentration	1
Involvement of deep brain regions (periventricular, basal ganglia, brainstem and/or cerebellum)	1
Risk Category	2-year survival rate
Low risk (0-1)	80%
Intermediate risk (2-3)	48%
High risk (4-5)	15%

Source: From *J Clin Oncol.* 2005;21(2):266-272.

|| Treatment



3. What would be the appropriate treatment for this patient?

- A. Systemic chemotherapy with R-CHOP
- B. Close observation with MRI with gadolinium every 3 months
- C. Methotrexate based therapy at a dose of at least $1\text{g}/\text{m}^2$
- D. Methotrexate based therapy at a dose of at least $3.5\text{g}/\text{m}^2$

|| Treatment (Continued) ||

3. What would be the appropriate treatment for this patient?

- A. Systemic chemotherapy with R-CHOP
- B. Close observation with MRI with gadolinium every 3 months
- C. Methotrexate based therapy at a dose of at least $1\text{g}/\text{m}^2$
- D. Methotrexate based therapy at a dose of at least $3.5\text{g}/\text{m}^2$**

Answer: High-dose MTX-based chemotherapy is a standard component of initial therapy for PCNSL. In aggregate, the available data suggest that chemotherapy regimens that include high-dose systemic MTX are more effective against PCNSL than either radiation alone or regimens that do not contain MTX.

|| Treatment (Continued) ||

The patient is treated with the DeAngelis protocol, (vincristine, procarbazine, cytarabine, and rituximab). After 2 cycles he had a complete response (CR). He completed a total of 4 cycles with continued CR and received consolidation with two cycles of high dose cytarabine (3g/m²/day on day 1 and 3). He continued on close surveillance and an MRI 1 year later identified recurrent disease.

|| Treatment (Continued) ||

4. What would be the appropriate treatment for this patient?

- A. Whole brain radiation therapy (WBRT) only
- B. Systemic therapy with R-CHOP combined with WBRT
- C. HD-MTX based combination therapy followed by autologous HSCT
- D. No further options given fast relapse. Supportive care is recommended.

|| Treatment (Continued) ||

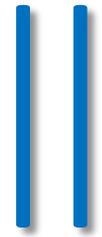
4. What would be the appropriate treatment for this patient?

- A. WBRT only
- B. Systemic therapy with R-CHOP combined with WBRT
- C. **HD-MTX based combination therapy followed by autologous HSCT**
- D. No further options given fast relapse. Supportive care is recommended.

Answer: There is no “right answer” for relapsed PCNSL as practices differ. Of the options presented, “c” would be the best answer. This patient relapsed >6 months from initial induction, which indicates he likely has MTX-sensitive disease. Salvage regimens with dose-intensive HD-MTX-based chemotherapy in combination with other CNS-penetrant agents (ifosfamide, thiotepa, cytarabine, decycyst, etc.), followed by myeloablative therapy and stem cell transplant, have yielded a 2-year PFS rate of 49%.

Companion Case for Chapter 36
Primary Central Nervous System
Lymphoma

*Liliana Bustamante
and
Peter Forsyth*



Clinical Case 7



|| Case Presentation



- A 68-year-old man with a past medical history of hypertension presents with a 2-week history of severe fatigue. He presented to his primary care physician and was found to have an enlarged right inguinal lymph node and splenomegaly on exam.
- Laboratory evaluation revealed a WBC of 3.1 k/ μ L with a normal differential, hemoglobin of 12.7 g/dL, and platelets of 87 k/ μ L.

|| Case Presentation (Continued) ||

- A CT scan of the chest, abdomen, and pelvis showed extensive cervical, abdominal, and inguinal lymphadenopathy.

|| Case Presentation (Continued) ||

- **What other blood tests would you initially order in a patient with extensive lymphadenopathy and pancytopenia?**
 - A. HIV and EBV serology
 - B. Hepatitis panel
 - C. β -2 microglobulin and LDH
 - D. Flow cytometry
 - E. All of the above

|| Case Presentation (Continued) ||

○ **What other blood tests would you initially order in a patient with extensive lymphadenopathy and pancytopenia?**

A. HIV and EBV serology

B. Hepatitis panel

C. β -2 microglobulin and LDH

D. Flow cytometry

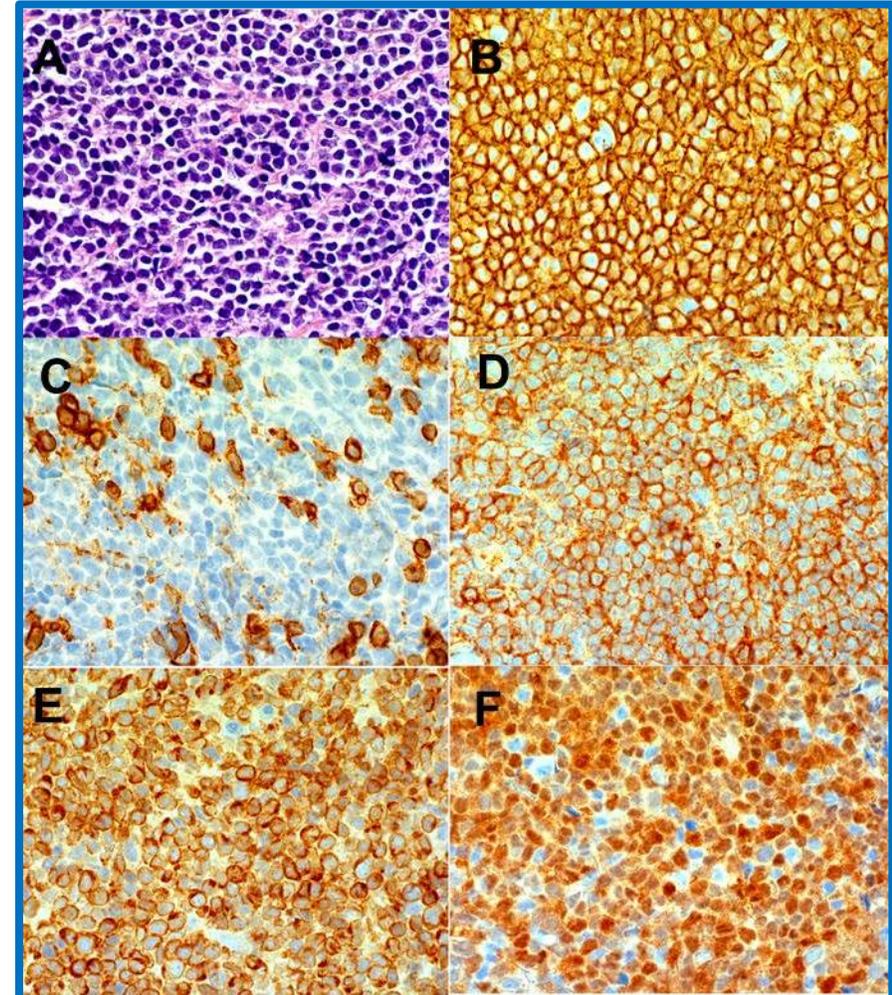
E. All of the above

In evaluating a patient with lymphadenopathy and pancytopenia, it is important to rule out other causes of pancytopenia. In addition, in patients with lymphomas, it is important to order a hepatitis panel (especially prior to the initiation of rituximab), EBV serology, and HIV testing. In addition, elevated β -2 microglobulin and LDH are often seen in some lymphomas and can be prognostic markers.

|| Case Presentation (Continued) ||

The patient underwent an inguinal lymph node biopsy.

- Cross section of a lymph node shows complete effacement of the normal architecture by a monotonous population of atypical small- to medium-sized lymphoid cells with round to oval nuclei, condensed chromatin, some with small visible nucleoli, and scant cytoplasm, in a background of increased vasculature (A, H&E x600). By immunohistochemical staining, the atypical cells were positive for CD20 and negative for CD3 (B and C, immunoperoxidase, x600). The neoplastic B cells also coexpress CD5, BCL1 and BCL-2 (D, E and F, Immunoperoxidase, x600).



|| Case Presentation (Continued) ||

Flow cytometry revealed 60% (of total events) are a lambda-restricted clonal B-cell population with the following phenotype: CD19 (+), CD20 (bright +), CD22 (+), CD5 (+), FMC7 (+), CD23 (-), CD10 (-).

- **Which of the following is the most likely diagnosis?**
 - A. Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - B. Diffuse large B-cell lymphoma
 - C. Marginal zone lymphoma
 - D. Mantle cell lymphoma
 - E. Lymphoplasmacytic lymphoma

|| Case Presentation (Continued) ||

Flow cytometry revealed a 60% lambda-restricted clonal B-cell population with CD19 (+), CD20 (+), CD22 (+), CD5 (+), CD45 (+), FMC7 (+), CD23 (-), CD10 (-).

- **Which of the following is the most likely diagnosis?**
 - A. Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - B. Diffuse large B-cell lymphoma
 - C. Marginal zone lymphoma
 - D. Mantle cell lymphoma**
 - E. Lymphoplasmacytic lymphoma

|| Case Presentation (Continued) ||

- The overall histologic and phenotypic findings are diagnostic of mantle cell lymphoma. Remember that mantle cell lymphoma is a small/medium B-cell malignancy that is typically CD5+, CD10-, and CD23-. CLL/SLL expresses CD5, CD23, and is typically CD20 dim. BCL-1 (cyclin D1) is not seen in CLL/SLL. The cells in the biopsy are predominantly small- to medium-sized, and not large, as would be expected in DLBCL. Cells of marginal zone lymphoma typically are small to medium with abundant pale cytoplasm, and are usually CD5 and CD10 negative. Likewise, neoplastic lymphocytes of lymphoplasmacytic lymphoma are dual CD5 and CD10 negative.

|| Cytogenetics



- **Which cytogenetic abnormality defines mantle cell lymphoma?**
 - A. $t(8;14)(q24;q32)IgH/MYC$
 - B. $t(11;14)(q13;q32)IgH/CCND1$
 - C. $t(9;22)(q34;q11)BCR/ABL1$
 - D. $t(14;18)(q32;q21)IgH/BCL-2$
 - E. $t(15;17)(q24;q21)PML/RAR\alpha$

|| Cytogenetics (Continued) ||

- **Which cytogenetic abnormality defines mantle cell lymphoma?**

A. $t(8;14)(q24;q32)IgH/MYC$

B. $t(11;14)(q13;q32)IgH/CCND1$

C. $t(9;22)(q34;q11)BCR/ABL1$

D. $t(14;18)(q32;q21)IgH/BCL-2$

E. $t(15;17)(q24;q21)PML/RAR\alpha$

Mantle cell lymphoma has a specific cytogenetic abnormality, $t(11;14)(q13;q32)IgH/CCND1$, which is seen in virtually all cases of MCL. This abnormality will not be positive in CLL. The translocation results in overexpression of cyclin D1, which causes abnormal proliferation of malignant cells. The other cytogenetic abnormalities are seen in other malignancies:

$t(8;14)(q24;q32)IgH/MYC$ – Burkitt lymphoma

$t(9;22)(q34;q11)BCR/ABL1$ – Chronic myelogenous leukemia; $BCR-ABL1$ positive B-ALL

$t(14;18)(q32;q21)IgH/BCL-2$ – Follicular lymphoma, DLBCL (rare)

$t(15;17)(q24;q21)PML/RAR\alpha$ – Acute promyelocytic leukemia (APL)

|| Treatment



- **All of the following options would be appropriate in this patient, *EXCEPT***
 - A. R-CHOP
 - B. Watchful waiting
 - C. VR-CAP
 - D. BR (Rituximab + Bendamustine)

|| Treatment (Continued) ||

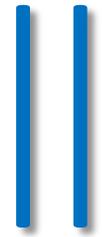
- **All of the following options would be appropriate in this patient, *EXCEPT***
 - A. R-CHOP
 - B. Watchful waiting**
 - C. VR-CAP
 - D. BR (Rituximab + Bendamustine)

This would **not** be an appropriate treatment strategy in this patient, as he has symptomatic disease (fatigue, cytopenias, splenomegaly).

Companion Case for Chapter 34

Mantle Cell Lymphoma

*Samantha Shams
and
Bijal Shah*



Clinical Case 8



|| Case Presentation

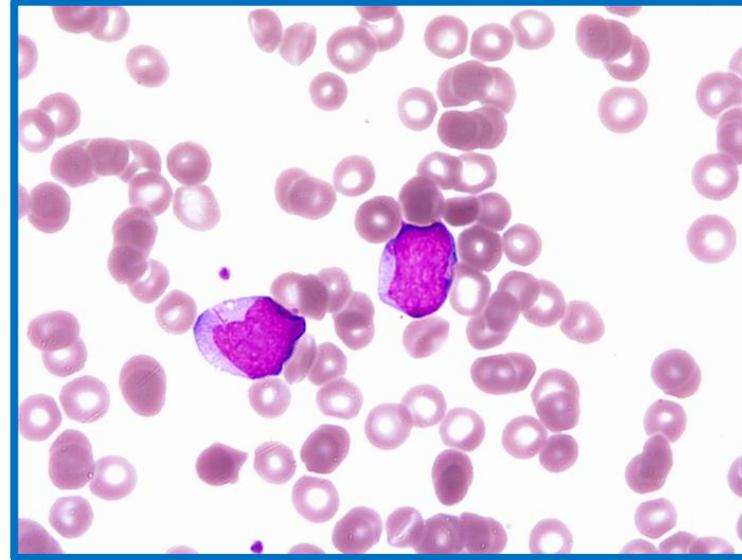
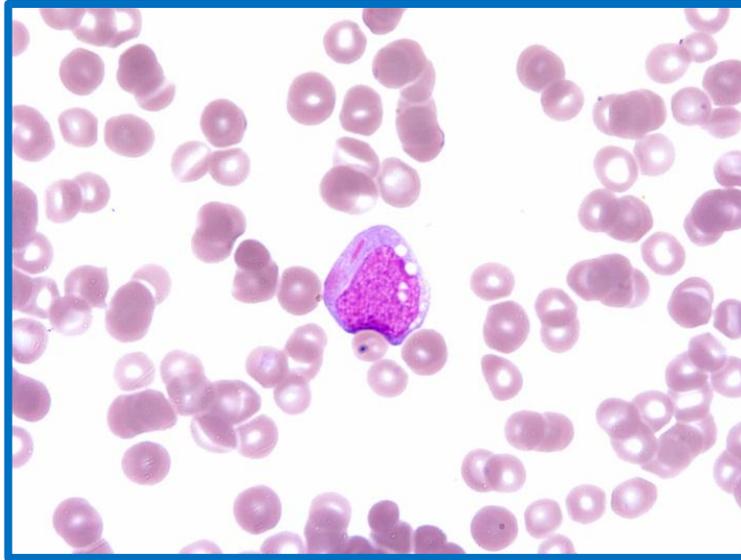


A 57-year-old female with a past medical history of hypothyroidism is referred to your clinic by her primary care physician after her blood work was notable for leukopenia during a routine physical exam.

Laboratory data is notable for a WBC 2.9 L/ μ L (ANC of 493), hemoglobin of 10.1g/dL, and platelets of 116 k/ μ L.

Flow cytometry on peripheral blasts is positive for CD13, CD33, CD34, CD117, HLA-DR. Peripheral smear is as shown.

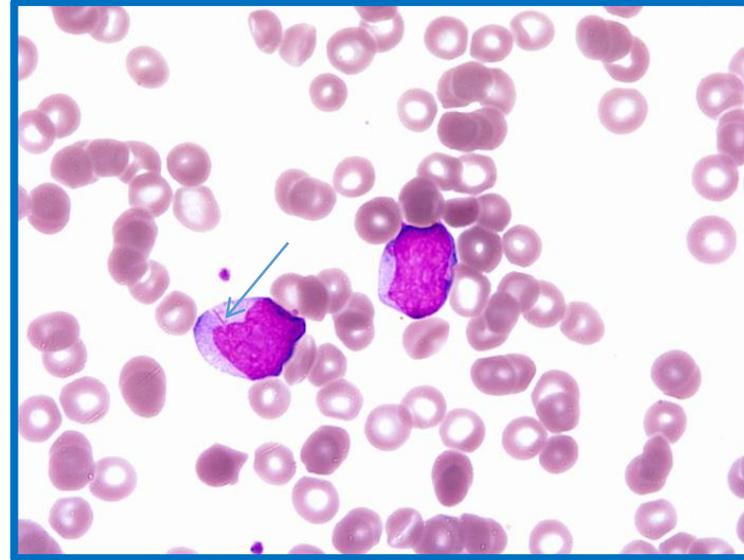
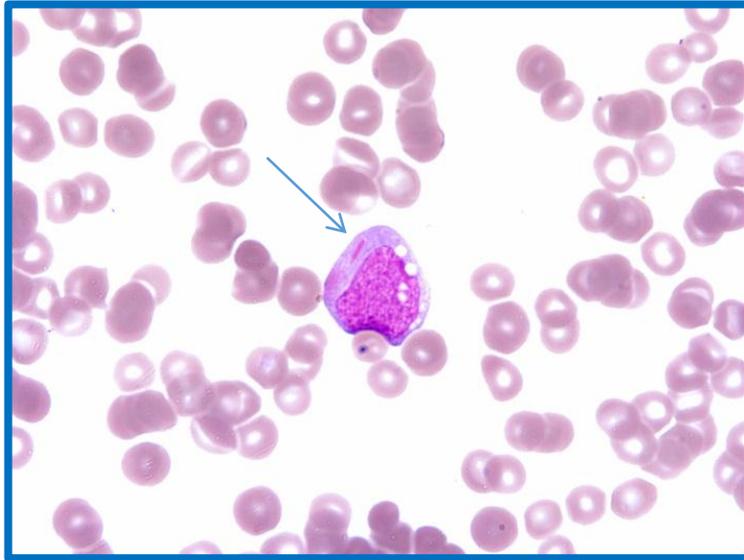
|| Case Presentation (Continued) ||



1. Based on the flow cytometry and above peripheral smear findings, what is the most likely diagnosis?

- A. Acute lymphoblastic leukemia
- B. Chronic myelogenous leukemia
- C. Chronic lymphocytic leukemia with Richter's transformation
- D. Large granular lymphocytic leukemia
- E. Acute myeloid leukemia

|| Case Presentation (Continued) ||

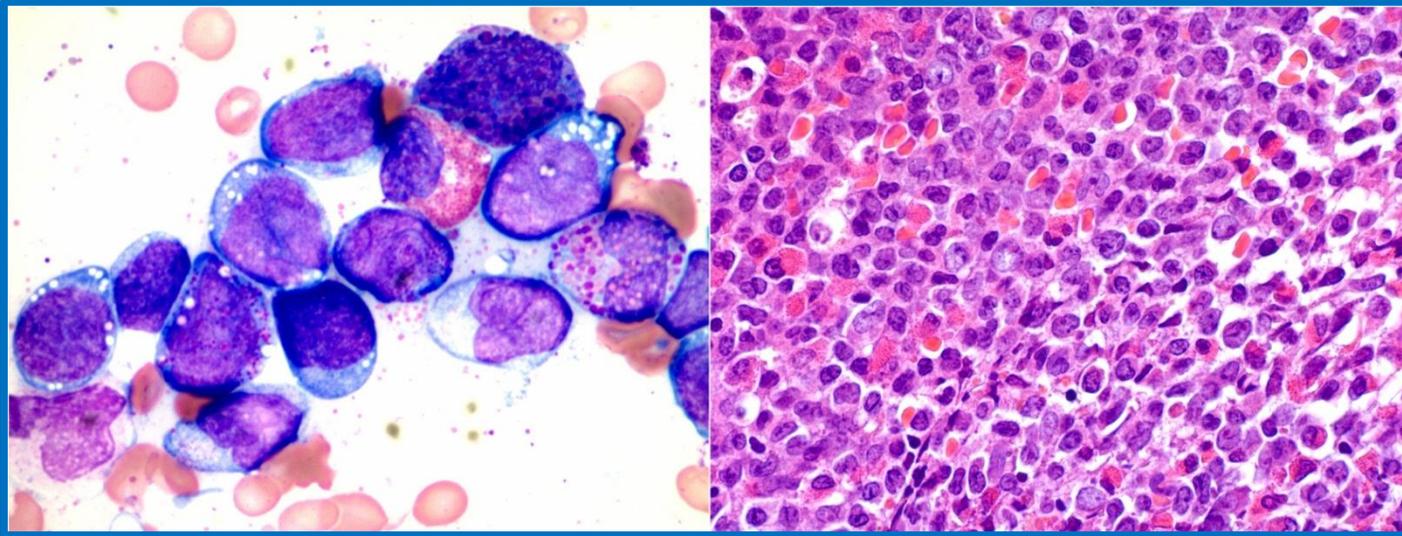


E. Acute myeloid leukemia

Answer:

On flow cytometry, AML blasts most commonly express CD13, CD33, CD34, CD117, and HLA-DR. Review of peripheral blood is notable for auer rods (blue arrows) which are azurophilic granules in the cytoplasm of leukemic blasts. They are commonly seen in acute myeloblastic leukemia with maturation (FAB M2) and acute promyelocytic leukemia (FAB M3).

|| Case Presentation (Continued) ||



Bone Marrow Aspirate:

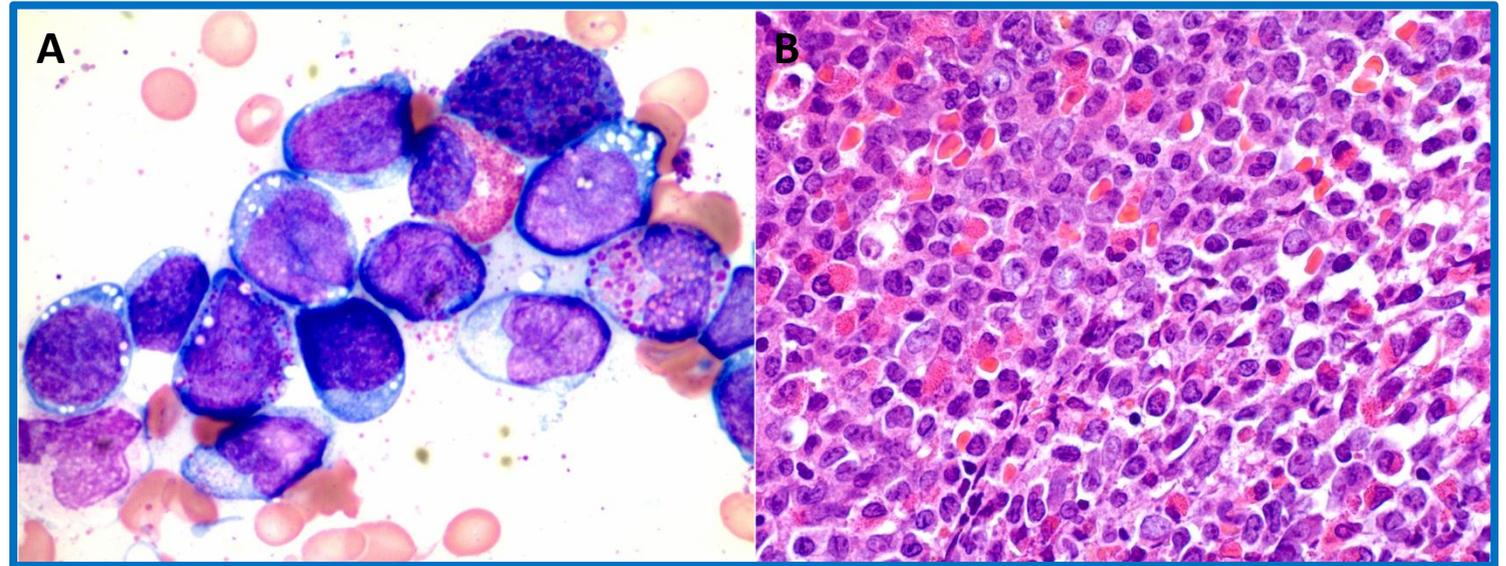
2. Based on the FAB (French-American-British) classification, what subtype of AML is most consistent with the above findings?
- A. M2 (Acute myeloblastic with maturation)
 - B. M3 (Acute promyelocytic leukemia)
 - C. M4eos (Acute myelomonocytic leukemia with eosinophilia)
 - D. M5 (Acute monocytic leukemia)
 - E. M6 (Acute erythroid leukemia)

|| Case Presentation (Continued) ||

C. M4eos (Acute myelomonocytic leukemia with eosinophilia)

Answer:

Bone marrow aspirate and biopsy is notable for numerous myeloblasts admixed with eosinophils consistent with acute myelomonocytic leukemia with eosinophilia (M4eos).



A. Wright Giemsa stained bone marrow aspirate smear consists of many large blasts, some containing azurophilic cytoplasmic granules (myeloblasts) and some displaying convoluted or folded nuclei. Lacy chromatin and cytoplasmic vacuoles (monoblasts and promonocytes), are admixed with eosinophils including dark or basophilic rough granules, or mixed basophilic and eosinophilic granules or red to orange granules in their cytoplasm, respectively. This indicates a different stage of maturation, characteristic of acute myelomonocytic leukemia with eosinophilia (x1000). B. A section of bone marrow biopsy shows sheets of nonocleated immature precursors/blasts with fine chromatin and high N:C ratio as well as many eosinophils and their precursors, rich in orange color cytoplasmic granules (H&E x600).

|| Case Presentation (Continued) ||

3. Based on the WHO classification, presence of which mutation is diagnostic of AML?

- A. $t(9;11)(p22;q23)$; *MLLT3-MLL*
- B. $t(8;21)(q22;q22)$; *RUNX1-RUNX1T1*
- C. $t(1;22)(p13;q13)$; *RBM15-MKL1*
- D. $t(3;3)(q21;q26.2)$; *RPN1-EVI1*
- E. None of the above. A diagnosis of AML requires the $\geq 20\%$ blasts in the bone marrow or peripheral blood.

|| Case Presentation (Continued) ||

3. Based on the WHO classification, presence of which mutation is diagnostic of AML?

- A. t(9;11)(p22;q23); *MLLT3-MLL*
- B. t(8;21)(q22;q22); *RUNX1-RUNX1T1***
- C. t(1;22)(p13;q13); *RBM15-MKL1*
- D. t(3;3)(q21;q26.2); *RPN1-EVI1*
- E. None of the above. A diagnosis of AML requires the $\geq 20\%$ blasts in the bone marrow or peripheral blood.

Answer:

Per WHO guidelines, a diagnosis of AML requires the presence of $\geq 20\%$ blasts in the bone marrow or peripheral blood. However, the presence of certain genetic abnormalities such as t(8;21), inv(16), or t(15;17), and myeloid sarcoma are diagnostic of AML irrespective of bone marrow findings.

|| Case Presentation (Continued) ||

4. What is the most common genetic abnormality associated with this type of leukemia?

- A. t(15;17) (q24.1;q21.1); *PML-RARA*
- B. t(9;11) (p22;q23); *MLLT3-MLL*
- C. t(1;22) (p13;q13); *RBM15-MKL1*
- D. t(9;11) (p22;q23); *MLLT3-MLL*
- E. t(16;16)(p13.1q22); *CBFB-MYH11*

|| Case Presentation (Continued) ||

4. What is the most common genetic abnormality associated with this type of leukemia?

- A. t(15;17) (q24.1;q21.1); *PML-RARA*
- B. t(9;11) (p22;q23); *MLLT3-MLL*
- C. t(1;22) (p13;q13); *RBM15-MKL1*
- D. t(9;11) (p22;q23); *MLLT3-MLL*
- E. **t(16;16)(p13.1q22); *CBFB-MYH11***

Answer:

Abnormalities of inv(16) or t(16;16) are seen in approximately 5% of patients with AML. This genetic abnormality is typically found in patients with acute myelomonocytic leukemia with eosinophilia (AML, FAB M4eo) and confers a good prognosis.

|| Case Presentation (Continued) ||

A patient is noted to have a normal karyotype and cytogenetics is notable for *inv(16)*. Molecular studies are notable for a biallelic CEBPA mutation and *FLT3-ITD* wild-type.

- 5. What is the patient's risk status based on the information above?**
- A. Intermediate risk
 - B. Intermediate-1 risk
 - C. Poor risk
 - D. Favorable risk

|| Case Presentation (Continued) ||

A patient is noted to have a normal karyotype and cytogenetics is notable for inv(16). Molecular studies are notable for a biallelic *CEBPA* mutation and *FLT3-ITD* wild-type.

5. What is the patient's risk status based on the information above?

- A. Intermediate risk
- B. Intermediate-1 risk
- C. Poor risk
- D. Favorable risk**

Answer:

Presence of a core binding factor -inv(16) or t(16;16) on cytogenetics or a biallelic *CEBPA* mutation in the absence of a *FLT3-ITD* mutation confers a good prognosis and those patients are classified as having favorable risk.

|| Case Presentation (Continued) ||

6. Which of the following confers the worst prognosis in AML?

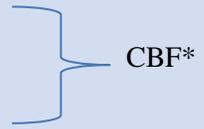
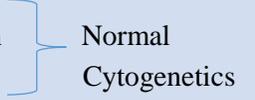
- A. Isolated biallelic *CEBPA* mutation
- B. *NPM1* mutation in absence of *FLT3-ITD* mutation with normal cytogenetics
- C. t(15;17) (q24.1;q21.1); *PML-RARA*
- D. *FLT3-ITD* mutation with normal cytogenetics
- E. Trisomy 8 (+8)

|| Case Presentation (Continued) ||

6. Which of the following confers the worst prognosis in AML?

- A. Isolated biallelic *CEBPA* mutation
- B. *NPM1* mutation in absence of *FLT3-ITD* mutation with normal cytogenetics
- C. t(15;17) (q24.1;q21.1); *PML-RARA*
- D. *FLT3-ITD* mutation with normal cytogenetics**
- E. Trisomy 8 (+8)

Case Presentation (Continued)

Risk Category	Cytogenetics	Molecular Abnormalities
Favorable Risk	inv(16) t(16;16) t(8;21) t(15;17) 	NPM1 positive Isolated biallelic CEBPA mutation FLT3-ITD negative 
Intermediate Risk	Normal Cytogenetics +8 alone t(9;11)	t(8;21) inv(16) t(16;16) 
Poor Risk	Complex Cytogenetics (≥3 clonal abnormalities) Monosomal Karyotypes (-5,-5q,-7,-7q) 11q23 (except t(9;11)) inv(3) t(6;9) t(9;22)	FLT3-ITD Mutation**

Cytogenetic and Molecular Prognostic Factors in AML. * = Core Binding Factor, **Prognostic implication of FLT3-TKD mutations is still controversial and under investigation.

|| Case Presentation (Continued) ||

The patient received induction chemotherapy with 7+3 (Cytarabine 100 mg/m² and Daunorubicin 90 mg/m²). Day 14 bone marrow biopsy revealed <5% blasts. Day 30 bone marrow shows a normocellular marrow with <5% blasts. CBC shows WBC 4.8 L/ μ L (ANC of 2,500), hemoglobin of 12.5 g/dL, and platelets of 130 k/ μ L.

7. What is the next step in managing this patient?

- A. Referral for an autologous stem cell transplant
- B. Consolidation chemotherapy with Cytarabine 3 g/m² x 3–4 cycles
- C. Induction with CLAG (Cladrabine, Cytarabine, G-CSF +/- Mitoxantrone) chemotherapy
- D. Referral for an allogeneic stem cell transplant
- E. Consolidation with Cytarabine 3 g/m² x 3–4 cycles followed by allogeneic stem cell transplant

|| Case Presentation (Continued) ||

A patient receives induction chemotherapy with 7+3 induction chemotherapy (Cytarabine 100 mg/m² and Daunorubicin 90 mg/m²). Day 14 bone marrow biopsy revealed <5% blasts. Day 30 bone marrow shows a normocellular marrow with <5% blasts. CBC shows wbc 4.8 L/μL (absolute neutrophil count of 2,500), hemoglobin of 14.5 g/dL, and platelets of 130 k/μL.

7. What is the next step in managing this patient?

- A. Referral for an autologous stem cell transplant
- B. Consolidation chemotherapy with Cytarabine 3 g/m² x 3–4 cycles**
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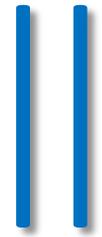
Answer:

Patient had good response to induction chemotherapy and his 30-day marrow is suggestive of complete remission (defined as bone marrow blasts <5%, absolute neutrophil count $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$). Favorable risk patients should receive consolidation with high dose cytarabine chemotherapy and do not need a hematopoietic stem cell transplant in CR1. Allogeneic stem cell transplant is reserved for those who are high-risk disease or those with relapsed disease.

Companion Case for Chapter 14

Acute Myeloid Leukemia

*Varun Dhulipala
and
Kendra Sweet*



Clinical Case 9



|| Case Presentation

- **A 60-year-old otherwise healthy man presents with a painful, progressive neuropathy that significantly limits his mobility. During his workup, an IgG kappa monoclonal protein is found on immunofixation. His M spike is 1.3 g/dL. His kappa free light chain is 10 mg/dL. He has no anemia, hypercalcemia, or renal dysfunction. A CT-based skeletal survey reveals no lytic bone lesions. A bone marrow biopsy reveals 5% to 10% kappa-restricted plasma cells and normal FISH and cytogenetics. What would you do next?**
 - A. Perform a PET CT to look for FDG avid bone lesions.
 - B. Diagnose with MGUS and follow up in 12 months.
 - C. Refer to Neurology to treat for MGUS-associated neuropathy.
 - D. Perform a fat pad biopsy and stain his bone marrow biopsy with Congo red.

|| Case Presentation (Continued) ||

- A. Perform a PET CT to look for FDG avid bone lesions.
- B. Diagnose with MGUS and follow up in 12 months.
- C. Refer to Neurology to treat for MGUS-associated neuropathy.
- D. Perform a fat pad biopsy and stain his bone marrow biopsy with Congo red.**

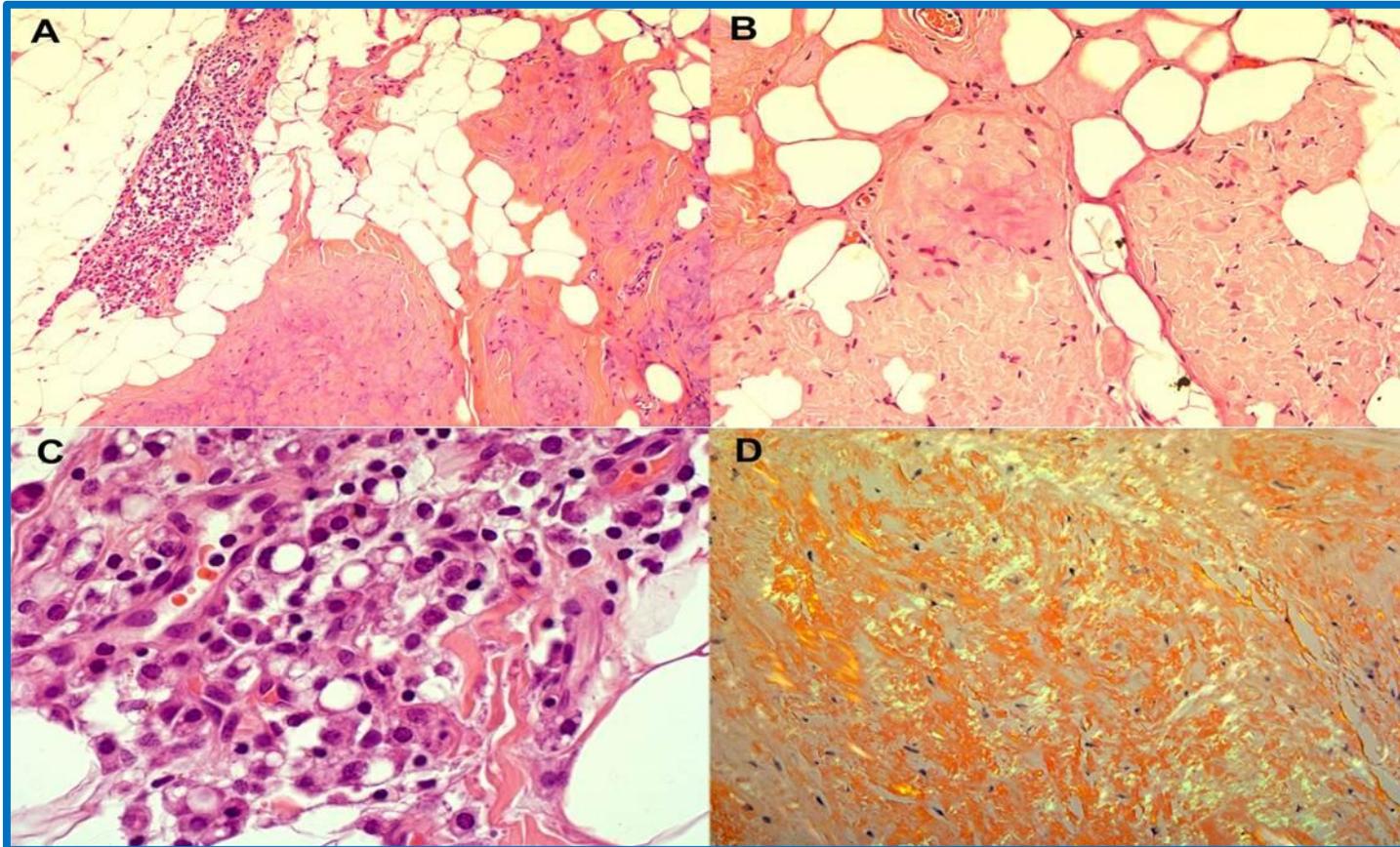
Light chain amyloidosis should be ruled out in this patient by performing a fat pad biopsy and staining his bone marrow with Congo red. A nerve biopsy would be invasive and these tests would establish the diagnosis in ~85% of cases.

CT-based skeletal surveys are very sensitive and a PET CT is not usually required to establish the diagnosis of multiple myeloma.

This patient might still have MGUS but AL amyloidosis needs to be ruled out as a cause of his neuropathy.

Furthermore, MGUS-associated neuropathy is usually associated with an IgM monoclonal protein.

Subcutaneous Mass/Amyloidoma



Subcutaneous mass/amyloidoma shows extracellular depositions of pink, amorphous material in adipose tissue (A,B) and a vessel wall (H&E, x100, x200). Congo red stains amyloid deposition with characteristic apple-green birefringence under polarized light (C, x200).

|| Case Presentation (Continued) ||

- **His subcutaneous mass/amyloidoma stains positive for Congo red. What would you do next?**
 - A. Initiate chemotherapy for his systemic AL amyloidosis.
 - B. Type the amyloid.
 - C. Obtain a nerve biopsy to definitively establish the diagnosis.

|| Case Presentation (Continued) ||

- **His subcutaneous mass/amyloidoma stains positive for Congo red. What would you do next?**
 - A. Initiate chemotherapy for his systemic AL amyloidosis.
 - B. Type the amyloid.**
 - C. Obtain a nerve biopsy to definitively establish the diagnosis.

His amyloid needs to be typed with mass spectrometry (MS) or immunohistochemistry (IHC). MS is the most common method of typing in the United States with specificity and sensitivity exceeding 98% in reference laboratories. In “good hands” IHC can have comparable outcomes but it is more labor intensive and can be operator dependent.

Amyloid typing should always be performed no matter how typical the clinical presentation. Non-AL amyloid can be associated with an MGUS in 5% to 10% of cases (similar to that of the general population).

Chemotherapy should ideally be initiated after the type of amyloid has been determined. Since this can take a long time in institutions where MS or IHC are not readily available, it is reasonable to start treatment while awaiting typing. However, typing results should be always available before an autologous transplant.

Obtaining a confirmatory organ biopsy is usually not necessary if fat and/or marrow stain positive for Congo red.

|| Case Presentation (Continued) ||

- **MS of his fat biopsy reveals kappa light chain amyloidosis. An echocardiogram shows an ejection fraction of 60% and interventricular septum thickness of 14mm (ULN=12mm). NTproBNP and troponin are 900 pg/ml and 0.02 ng/ml, respectively. Creatinine is 1.2 mg/dl and 24-hour urine protein is 1500mg/24 hours. How would you treat him?**
 - A. Refer for autologous stem cell transplant (ASCT).
 - B. Initiate CyBorD.
 - C. Initiate VRD.
 - D. Initiate Rd.

|| Case Presentation (Continued) ||

A. Refer for autologous stem cell transplant (ASCT).

B. Initiate CyBorD.

C. Initiate VRD.

D. Initiate Rd.

The most appropriate next step would be to refer the patient for an ASCT. Although this approach is not supported by phase III data, retrospective series suggest that carefully selected patients can have excellent long-term outcomes.

He appears to be a good transplant candidate despite some cardiac involvement. He did not appear to be very symptomatic from this because his mobility was limited by his neuropathy. This underlines the importance of thorough staging in these patients.

The decision to initiate treatment while waiting for ASCT evaluation and approval is a clinical decision. We usually initiate treatment in patients with symptomatic cardiac involvement, rapidly progressive proteinuria/renal failure, >10% BMPCs, or patients who cannot be evaluated for ASCT in an expedited manner (within a few weeks from diagnosis). Such an approach is experience rather than data driven, since organ function can deteriorate quickly in AL amyloidosis with time. Furthermore, a cycle of chemotherapy in “borderline” transplant candidates can sometimes help identify patients who would not do well with a transplant (i.e., a patient doing very poorly after one cycle of CyBorD is likely to have increased morbidity and mortality and maybe this would factor in the decision to transplant or not).

|| Case Presentation (Continued) ||

- **The patient declines an ASCT. He would like to try upfront chemotherapy. What would you do next?**
 - A. CyBorD (cyclophosphamide, bortezomib, dexamethasone)
 - B. VRD (bortezomib, lenalidomide, dexamethasone)
 - C. Rd (lenalidomide, dexamethasone)
 - D. Melphalan, dexamethasone
 - E. Clinical trial
 - F. A or D or E
 - G. All of the above

|| Case Presentation (Continued) ||

- A. CyBorD
- B. VRD
- C. Rd
- D. Melphalan, dexamethasone
- E. Clinical trial
- F. A or D or E**
- G. All of the above

In this patient with clinically significant neuropathy but also cardiac involvement, CyBorD, melphalan, or a clinical trial are all reasonable options. We usually avoid immunomodulating drugs in patients with cardiac involvement because they are tolerated poorly in this patient population.

The benefit of melphalan is that it will not worsen neuropathy. However, depth of response and time to best response are inferior to a bortezomib-based regimen, which is important to consider in patients with cardiac involvement. If a clinical trial is not available, one can start with melphalan and if he cannot achieve a PR after 2 cycles, switching to CyBorD or CyBorD upfront with close monitoring of his neuropathy are both reasonable options. Second-generation proteasome inhibitors (e.g., ixazomib) are currently in clinical trials in AL and are excellent options for patients with neuropathy.

|| Case Presentation (Continued) ||

- **CyBorD is initiated. After 4 cycles the patient achieves a CR. His neuropathy remains stable. His BNP and troponin remain stable. His proteinuria and creatinine also remain stable. What would you do next?**
 - A. STOP chemotherapy.
 - B. Treat for a total of 6 months.
 - C. Treat for a total of 12 months.
 - D. Switch to maintenance Velcade.

|| Case Presentation (Continued) ||

- A. STOP chemotherapy.
- B. Treat for a total of 6 months.**
- C. Treat for a total of 12 months.
- D. Switch to maintenance Velcade.

There is no good data to support total duration of treatment in AL. We usually treat patients for a total of 6 cycles of chemotherapy and if in VGPR or better offer a trial of observation. If a PR is not achieved after 2 cycles, then a switch in treatment is warranted. There is no data to support a benefit from maintenance treatment in this disease.

Organ response lags behind hematologic response by several months. Of patients who achieve VGPR or better, median time to kidney/heart and nerve response is about 6 and 12 months, respectively. So if the patient has achieved a hematologic VGPR or better, continued chemotherapy will not offer more chances for an organ response, provided there is no hematologic progression.

|| Case Presentation (Continued) ||

- **After 6 cycles of treatment, chemotherapy is stopped and the patient is observed. He remains in CR. After 12 months, his BNP is 400, troponin <0.01, Cr is 1 mg/dL, and proteinuria <500mg/24 hrs. His neuropathy has not improved. At 18 months his immunofixation becomes positive and his free light chains rise to 5mg/dL. His cardiac and renal biomarkers and clinical picture are all stable. What do you do next?**

- A. Continue observation.
- B. Resume treatment.

|| Case Presentation (Continued) ||

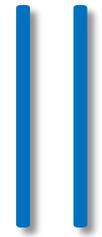
A. Continue observation.

B. Resume treatment.

- The patient has achieved a renal and cardiac organ response but no nerve response. At 18 months, even though he remains clinically stable and has no signs of organ involvement, he has a hematologic relapse. Unlike myeloma, where slow relapses can be observed without treatment in amyloidosis, amyloid deposition is bound to resume when a hematologic relapse occurs. Therefore, treatment should be initiated. At this point in time, the patient should strongly reconsider a transplant, since his cardiac function has improved. Immunomodulatory drugs can also be used or he can be rechallenged with a bortezomib-based regimen.

Companion Case for Chapter 28
Immunoglobulin Light Chain
Amyloidosis

*Taxiarchis Kourelis
and
Morie A. Gertz*



Clinical Case 10



|| Case Presentation

- A 57-year-old female with a history of follicular lymphoma status post multiple lines of chemotherapy (R-CVP, bendamustine, fludarabine, and finally chlorambucil), currently with stable disease, presented with fevers, fatigue, and cough.
- A CT scan of the chest/abdomen/pelvis at the time showed no increase in lymphadenopathy. Hence, there was no change in the care plan.
- A month later she developed multiple skin lesions and her examination was remarkable for a maculopapular rash noted predominantly on face, neck, left shoulder, and scapula.
- Laboratory values at the time revealed a WBC count of 3.6 k/ μ L, hemoglobin 11 g/dL, platelet count of 88 k/ μ L, creatinine 0.91 mg/dL, AST 91 U/L, ALT 37 U/L, and total bilirubin of 1.9 mg/dL.

|| Skin Rash

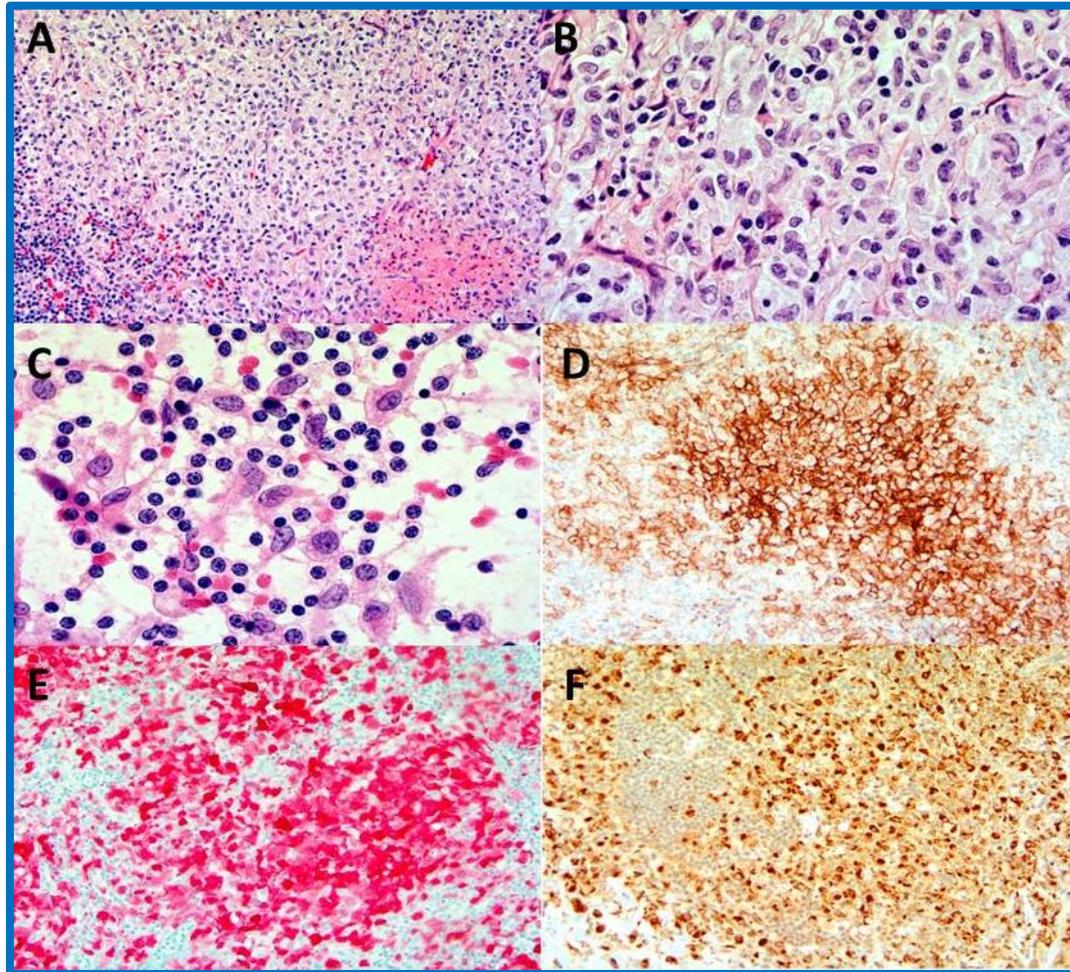


Left to Right: Neck, L upper shoulder, and L scapula



Skin biopsy revealed a diffuse infiltrate of large lymphohistiocytic cells within the dermis and superficial subcutis with an associated mixed inflammatory population of eosinophils, neutrophils, and scattered plasma cells. The cells have oval to reniform nuclei with minimal pleomorphism, occasionally polygonal and multilobated nuclei, vesicular chromatin with delicate grooves, and moderate to abundant amounts of eosinophilic (pink) cytoplasm. The neoplastic cells are positive for CD1a, CD207, S-100, CD4, CD45 (weak), and MUM-1 (focal).

Histology and IHC Staining



The H&E sections demonstrated abnormal histiocytic proliferation associated with an eosinophilic microabscess in a background of small lymphocytes (A, x200) and cytologically the atypical cells showed oval to elongated and convoluted nuclei, vesicular chromatin, and abundant cytoplasm (B, x600). Touch imprint (C, H&E, x600) illustrates characteristic nuclear grooves in the neoplastic cells. IHC stains show these cells to be positive for CD1a (D, immunoperoxidase, x200) and S-100 (E, x200). The cells were also positive for the histiocytic marker CD68 (F, x200).

|| Diagnosis



- **Which of the following is the most likely diagnosis?**
 - A. Histiocytic sarcoma
 - B. Anaplastic large cell lymphoma, *ALK* positive
 - C. Langerhans cell histiocytosis
 - D. Recurrent follicular lymphoma
 - E. Hemophagocytic lymphohistiocytosis

|| Diagnosis (Continued) ||

- **Which of the following is the most likely diagnosis?**

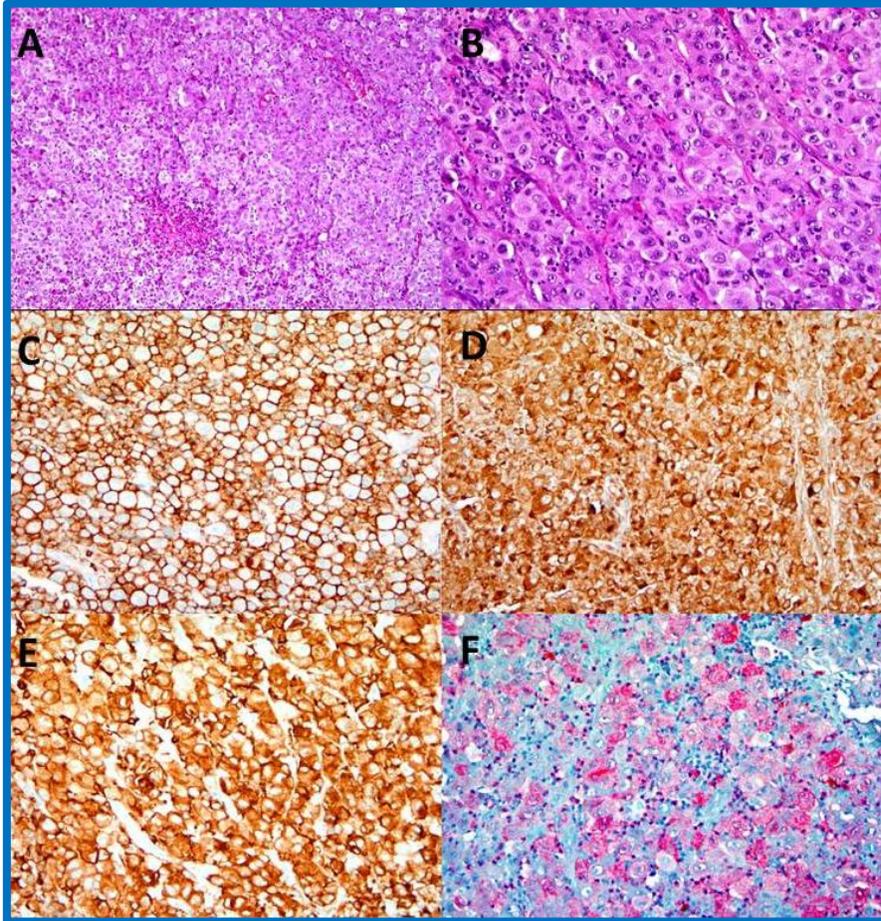
- A. Histiocytic sarcoma
- B. Anaplastic large cell lymphoma, *ALK* positive
- C. Langerhans cell histiocytosis**
- D. Recurrent follicular lymphoma
- E. Hemophagocytic lymphohistiocytosis

The morphologic and phenotypic features (CD1a+, CD207+ [aka Langerin], and S-100+) are most consistent with Langerhans cell histiocytosis (LCH). Although histiocytic sarcoma (HS) may have large cells, pleomorphism and nuclear irregularities are typically present, and HS is a diagnosis of exclusion; hence, the presence of LCH markers would argue against this diagnosis. ALCL, *ALK* positive, will by definition have large cells, but the characteristic nuclear features and LCH phenotype exclude the diagnosis. The phenotypic findings are compatible with LCH, not recurrence of the patient's original follicular lymphoma nor hemophagocytic lymphohistiocytosis. Phagocytosis of hematopoietic elements are not identified in this patient.

|| Differential Diagnosis

- LCH must be distinguished from other histiocytic and dendritic cell disorders, especially histiocytic sarcoma [HS] which is a non-Langerhans cell histiocytic disorder.
- To justify the diagnosis of HS, there is expression of one or more histiocytic markers CD163, CD68 (KP1 and PGM1), and lysozyme, and absence of Langerhans cell markers (CD1a, Langerin/CD207), among other cell types such as follicular dendritic cells (CD21, CD23, CD35) or myeloid markers (CD13, CD33, MPO).

Histology and IHC Staining [Histiocytic Sarcoma (HS)]



As opposed to the LCH case, the images (A and B) showed a diffuse infiltrate of large, histiocytic-appearing cells with round to oval nuclei, distinct nucleoli, and abundant eosinophilic or foamy cytoplasm. The neoplastic cells are positive for leukocyte common antigen, or LCA (A, CD45 (LCA), immunoperoxidase, x600), monocytic/histiocytic markers including CD68 (B, immunoperoxidase x600), CD163 (C, immunoperoxidase, x600) and partially positive for S-100 (D, immunoperoxidase x600).

|| Case Presentation

- A bone marrow biopsy was negative for involvement by both FL and LCH. MRI of the brain was normal. A repeat CT scan of the chest/abdomen/pelvis showed an increased size of lymph nodes and splenomegaly. The patient was diagnosed with multisystem LCH.
- **Which of the following is not a “risk organ” in multisystem LCH?**
 - A. Hematopoietic system
 - B. Liver
 - C. Spleen
 - D. Skin
 - E. CNS

|| Case Presentation (Continued) ||

- **Which of the following is not a “risk organ” in multisystem LCH?**
 - A. Hematopoietic system
 - B. Liver
 - C. Spleen
 - D. Skin**
 - E. CNS

|| Molecular Diagnosis ||

- **Mutation in which gene has been detected in just over 50% of cases of LCH?**
 - A. *JAK2*
 - B. *SRSF2*
 - C. *MYD88 L265P*
 - D. *BRAF V600E*
 - E. *CALR*

|| Molecular Diagnosis (Continued) ||

- **Mutation in which gene has been detected in just over 50% of cases of LCH?**
 - A. *JAK2*
 - B. *SRSF2*
 - C. *MYD88 L265P*
 - D. *BRAF V600E***
 - E. *CALR*

For reasons not entirely clear, over half of LCH patients harbor the *BRAF V600E* mutation.

|| Targeted Therapy

- *BRAF* V600E mutation was tested on the skin biopsy specimen but was negative.
- **Which of the following has shown activity in patients with LCH harboring *BRAF* V600E mutation?**
 - A. Trametinib
 - B. Ipilimumab
 - C. Nivolumab
 - D. Vemurafenib
 - E. Clofarabine

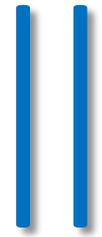
|| Targeted Therapy (Continued) ||

- Which of the following has shown activity in patients with LCH harboring *BRAF* V600E mutation?
 - A. Trametinib
 - B. Ipilimumab
 - C. Nivolumab
 - D. Vemurafenib**
 - E. Clofarabine

Companion Case for Chapter 48

Histiocytic Sarcoma and Langerhans Cell Histiocytosis

*Narendranath Epperla
and
Ehab Atallah*



Clinical Case 11



|| Case Presentation #1



- A 67-year-old female with history of DM presented with anemia and thrombocytosis. Labs showed hgb of 10g/dL, platelet count of 830,000/ μ L. She was initially treated with IV iron for suspected iron deficiency anemia; however, when anemia and thrombocytosis persisted, bone marrow biopsy was performed. She has no prior history of clots, bleeding, or strokes.

|| Bone Marrow Biopsy ||

- She underwent a bone marrow aspiration and biopsy that revealed a hypercellular marrow (60%) with dysmegakaryocytic hyperplasia, increased ring sideroblasts (>15%), and thrombocytosis.
- Megakaryocytes showed dysplastic features with increased small hypolobulated megakaryocytes and few large hyperlobulated forms.

|| Additional Studies

- Cytogenetics: normal female karyotype of 46,XX[20]
- Molecular studies:
 - *SF3B1* mutation positive
 - *JAK2*, *MPL*, *CALR* negative
 - FISH for *BCR-ABL* negative

|| Additional Studies (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Reactive leukocytosis
 - B. MDS/MPN-RS-T
 - C. CML
 - D. Essential thrombocythemia

|| Diagnosis



- **Which of the following is the most likely diagnosis?**
 - A. Reactive leukocytosis
 - B. MDS/MPN-RS-T**
 - C. CML
 - D. Essential thrombocythemia

|| Diagnosis (Continued) ||

- The differential of thrombocytosis includes:
 - Reactive thrombocytosis
 - Essential thrombocythemia
 - Polycythemia Vera
 - CML
 - MDS/MPN-RS-T

|| Diagnosis (Continued) ||

- **Which mutation is highly sensitive/specific for ring sideroblasts?**
 - A. *SF3B1*
 - B. *JAK2*
 - C. *CALR*
 - D. *BCR-ABL*
 - E. MP

|| Diagnosis (Continued) ||

- **Which mutation is highly sensitive/specific for ring sideroblasts?**
 - A. *SF3B1***
 - B. *JAK2*
 - C. *CALR*
 - D. *BCR-ABL*
 - E. MP

|| Treatment and Rationale: ||

- Platelet count at follow up was $>1 \times 10^6/\mu\text{L}$, so treatment with hydroxyurea was recommended.
- Current treatment:
 - ASA 81mg daily
 - Hydrea 500mg daily M-F

Clinical Characteristics of RARS-T (MDS/MPN-RS-T)

- MDS/MPN-RS-T has similar risk of thrombotic events as ET and greater than MDS-RS.
- JAK2 mutation status does not change overall survival in MDS/MPN-RS-T.
- Platelet count $>600,000/\mu\text{L}$ also does not change overall survival.
- *SF3B1* mutation DOES predict better overall, event-free, and leukemia-free survival.

|| Case Presentation #2



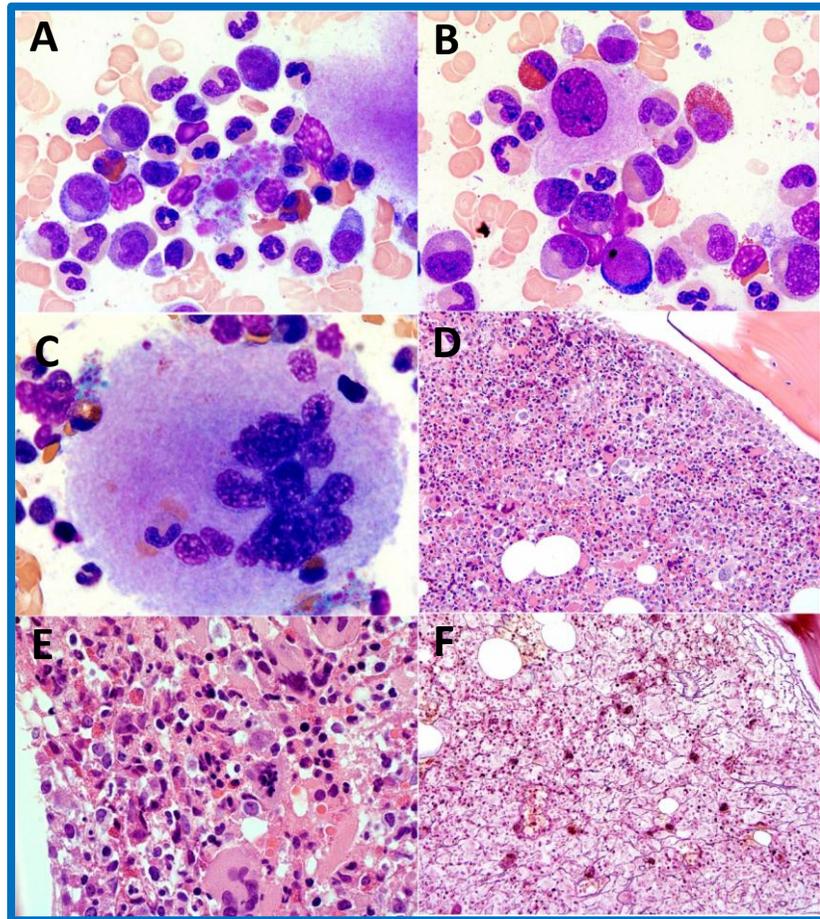
- A 63-year-old male was noted to have leukopenia and anemia on pre-op labs. WBC was 2.8 k/ μ L, HgB 7.9 g/dL, MCV 75 fl, ANC 1,800/ μ L, and platelets 236 k/ μ L. Exam was significant for mildly enlarged spleen (15cm). Hgb electrophoresis was normal; iron studies were normal; B12/folate were normal. SPEP was normal.

|| Peripheral Blood



- Moderate normochromic, normocytic anemia with moderate anisopoikilocytosis; moderate lymphopenia with few reactive lymphocytes, and left shifted myeloid maturation

Bone Marrow Biopsy



The bone marrow aspirate smear shows myeloid predominance with complete maturation and occasional hyposegmented and hypogranulated forms as well as an identifiable dysplastic erythroid precursor with nuclear budding (A, Wright-Giemsa, x1000). The bone marrow aspirate is composed of dysplastic small megakaryocyte with single lobation and a mixture of mainly myeloid and occasionally erythroid precursors/pronormoblasts (B, Wright-Giemsa, x1000). Another field of the bone marrow aspirate contains a giant megakaryocyte with emperipolesis, which is commonly seen in myeloproliferative situation (C, Wright-Giemsa, x1000). The bone marrow core biopsy (x200, and x600) show marked hypercellularity with myeloid and megakaryocytic preponderance (D, H&E, x200) including multiple large-sized megakaryocytes with hyperchromasia or disjointed nuclei (E, H&E, x600). Reticulin stain highlights moderate reticulin fibrosis (reticulin stain, x200).

|| Additional Studies



- Cytogenetics showed normal karyotype.
- *JAK2*, *CALR*, *MPL* mutations were negative.
- NGS panel showed *ASXL1* and *SH2B3* mutations.

|| Diagnosis



- **Which of the following is the most likely diagnosis?**
 - A. MDS/MPN-U
 - B. Myelofibrosis
 - C. CML
 - D. MDS

|| Diagnosis (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. MDS/MPN-U**
 - B. Myelofibrosis
 - C. CML
 - D. MDS

|| Diagnosis (Continued) ||

- **What must be negative to make a diagnosis of MDS/MPN-U?**
 - A. *BCR-ABL* fusion gene
 - B. 9;22 translocation
 - C. *PDGFR alpha*
 - D. *FGFR1*
 - E. All of the above

|| Diagnosis (Continued) ||

- **What must be negative to make a diagnosis of MDS/MPN-U?**
 - A. *BCR-ABL* fusion gene
 - B. 9;22 translocation
 - C. *PDGFR alpha*
 - D. *FGFR1*
 - E. All of the above**

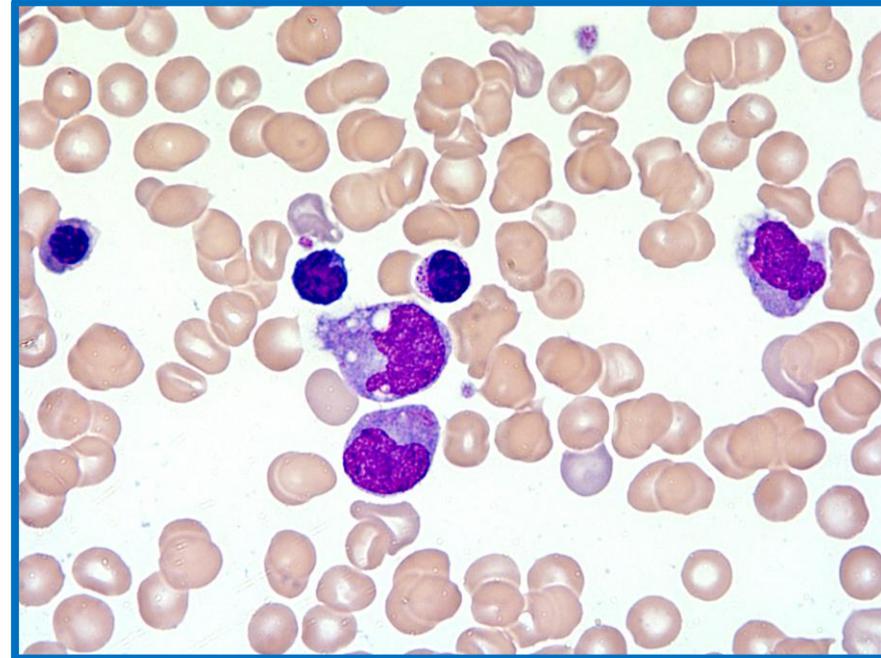
|| Case Presentation #3



- A 2-year-old female presents with fevers and failure to thrive. On exam she is found to have hepatosplenomegaly and lymphadenopathy. Labs are significant for leukocytosis, anemia, thrombocytopenia.

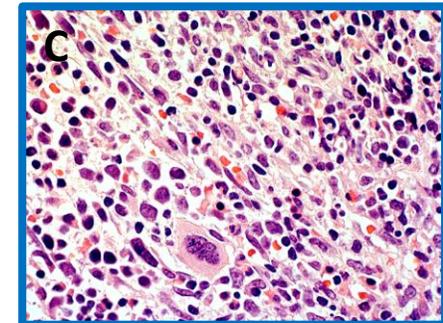
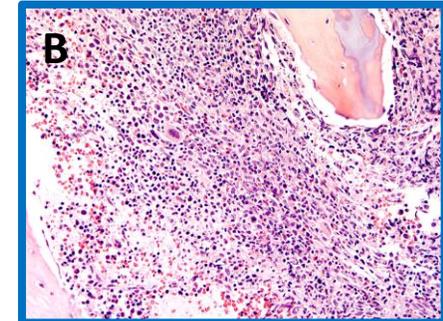
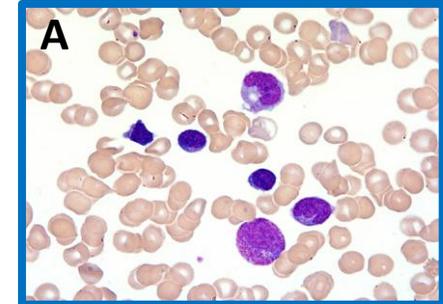
Peripheral Blood

- Leukocytosis with increased atypical monocytes containing abnormal vacuoles, with nucleated “RBCs” and immature granulocytic precursors



|| Bone Marrow Biopsy

- Bone marrow aspirate (A) was hemodilute and composed mainly of peripheral blood components including (2) atypical monocytes, (2) small lymphocytes and (1) promyelocyte. Blasts were not significantly increased in number.
- Bone marrow core biopsy at low and high power (B and C) shows a hypercellular marrow with increased myelomonocytic precursors and decreased megakaryocytes. High power view shows sheets of mononuclear immature or atypical precursors, representative of atypical monocytes with irregular nuclear contours, high N:C ratio and inconspicuous nucleoli, intermingled with a background of erythroid precursors and occasional megakaryocytes.



|| Diagnosis



- **Which of the following is the most likely diagnosis?**
 - A. CNL
 - B. JMML
 - C. Leukemoid reaction
 - D. CMML

|| Diagnosis (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. CNL
 - B. JMML**
 - C. Leukemoid reaction
 - D. CMML

|| Diagnosis (Continued) ||

- **Which congenital syndromes are associated with JMML?**
 - A. Neurofibromatosis
 - B. Noonan syndrome
 - C. Downs syndrome
 - D. A and B

|| Diagnosis (Continued) ||

- **Which congenital syndromes are associated with JMML?**
 - A. Neurofibromatosis
 - B. Noonan syndrome
 - C. Downs syndrome
 - D. A and B**

|| Diagnosis (Continued) ||

- **Which mutations are associated with a self-limited phenotype of JMML?**
 - A. *PTPN-11*
 - B. *K-RAS*
 - C. *N-RAS*
 - D. *CBL*
 - E. *NF1*

|| Diagnosis (Continued) ||

- Which mutations are associated with a self-limited phenotype of JMML?
 - A. *PTPN-11*
 - B. *K-RAS*
 - C. *N-RAS*
 - D. ***CBL***
 - E. *NF1*

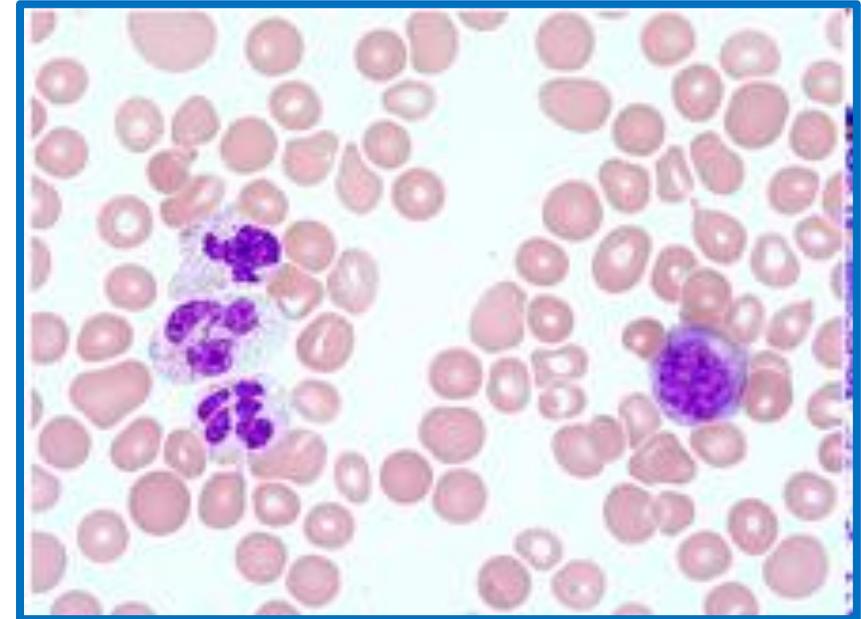
|| Case Presentation #4



- A 70-year-old male presents with anemia and thrombocytopenia. Exam is significant for splenomegaly. On labs, WBC count is $16 \times 10^9/L$ with elevated neutrophil count. FISH/PCR for BCR-ABL is negative.

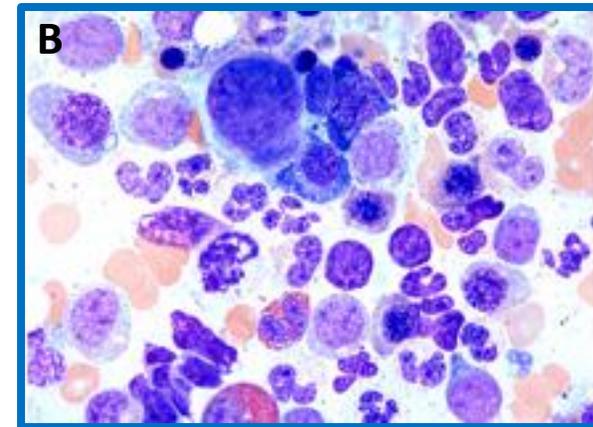
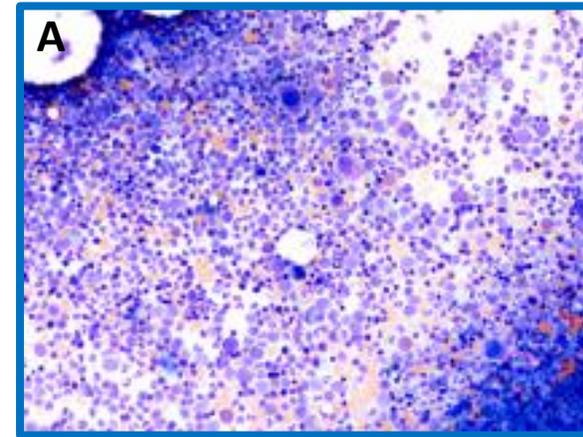
Peripheral Blood

- Peripheral leukocytosis composed of mostly granulocytes with dysplastic features including hypo- or uneven granulation and abnormal segmentation in neutrophils
- Granulocytic maturation with left shift



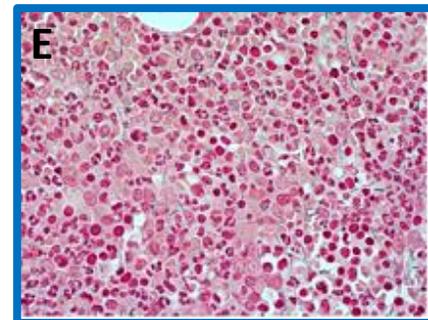
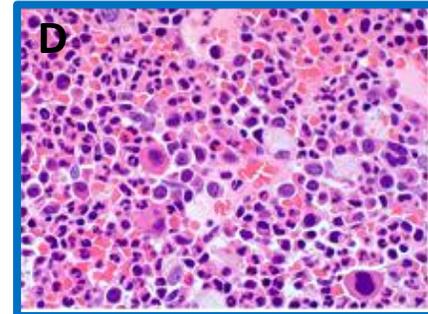
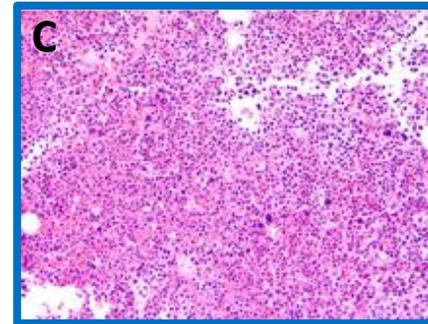
|| Bone Marrow Biopsy

- Bone marrow at low (A) and high (B) power views
- Hypercellular marrow with increased megakaryocytes, myeloid preponderance and dysplasia with micromegakaryocytes and megaloblastoid erythropoiesis



|| Bone Marrow Biopsy (Continued) ||

- Low-power view of bone marrow core biopsy shows hypercellular marrow (>95%) with increased M:E ratio (>15) (C).
- Medium- to high-power view (D) shows hypolobulated and small-sized megakaryocytes intermingled with maturing myeloid precursors.
- Reticulin stain shows normal reticulin fibers (E).



|| Diagnosis



- **Which of the following is the most likely diagnosis?**
 - A. CMML
 - B. Atypical CML
 - C. CNL
 - D. CML

|| Diagnosis (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. CMML
 - B. Atypical CML**
 - C. CNL
 - D. CML

|| Diagnosis (Continued) ||

- **Which mutation is common in atypical CML and is associated with higher WBC count and worse overall survival?**
 - A. *SETBP1*
 - B. *CSF3R*
 - C. *IDH1*
 - D. *SF3B1*

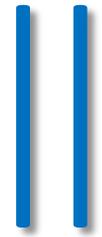
|| Diagnosis (Continued) ||

- **Which mutation is common in atypical CML and is associated with higher WBC count and worse overall survival?**
 - A. *SETBP1***
 - B. *CSF3R*
 - C. *IDH1*
 - D. *SF3B1*

Companion Case for Chapter 12

Myelodysplastic/Myeloproliferative Overlap Syndromes

*Jennifer Eatrides
and
Eric Padron*



Clinical Case 12

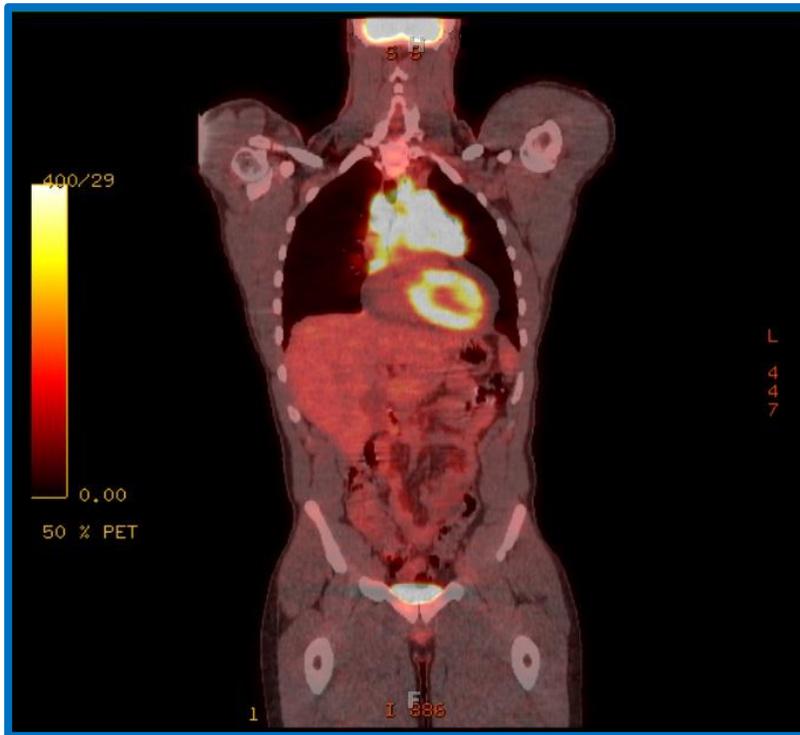


|| Case Presentation

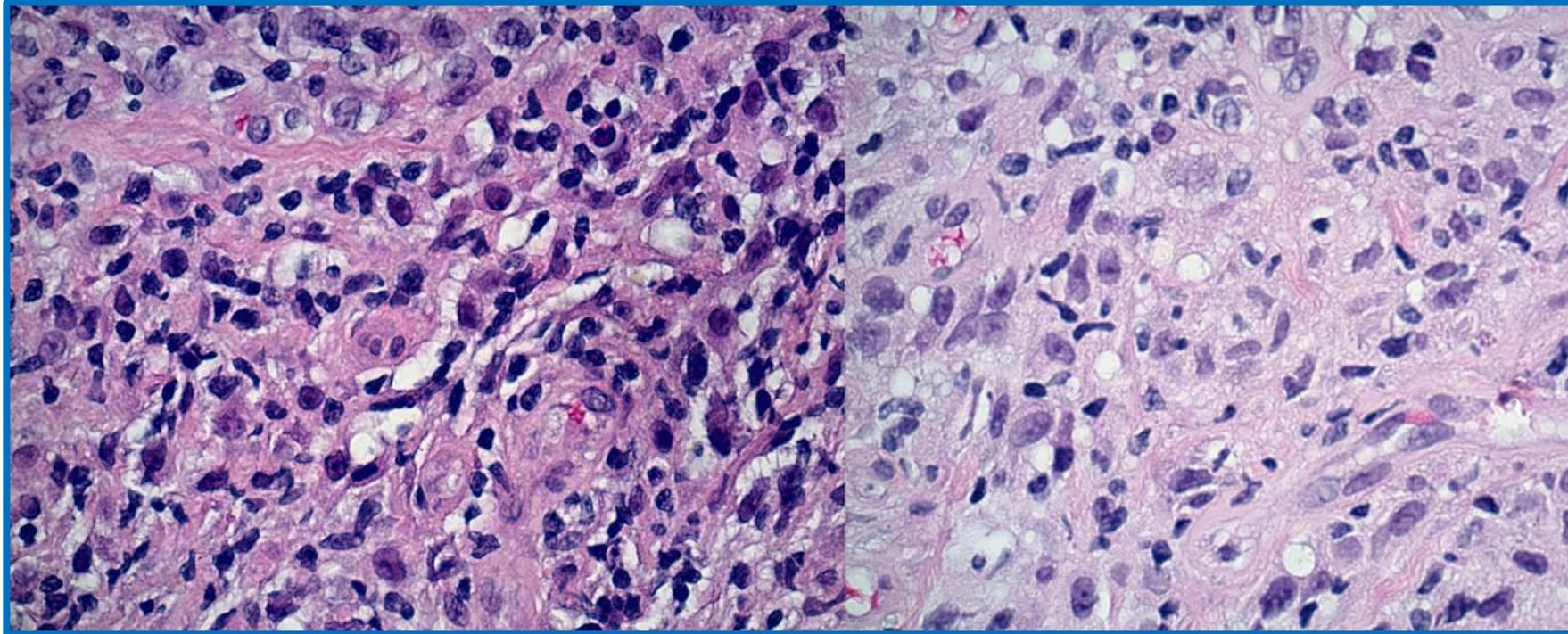
- A 28-year-old female with no PMH presents with several weeks of worsening dyspnea on exertion associated with chest pain as well as fatigue and night sweats.
- She denies any other symptoms of lymphadenopathy, fevers, rash, or weight loss. Her exam reveals clear breath sounds but distant heart sounds. Abdomen is soft with no organomegaly and there is no palpable lymphadenopathy.
- A CBC and CMP performed are unremarkable, though LDH is elevated at 422 U/L. A chest X-ray reveals a widened mediastinum, but no pulmonary infiltrates.

|| Case Presentation (Continued) ||

A CT of the chest reveals a 10.5 cm mediastinal mass as well as a moderate pericardial effusion. PET/CT demonstrates high metabolic activity in the mediastinal mass.

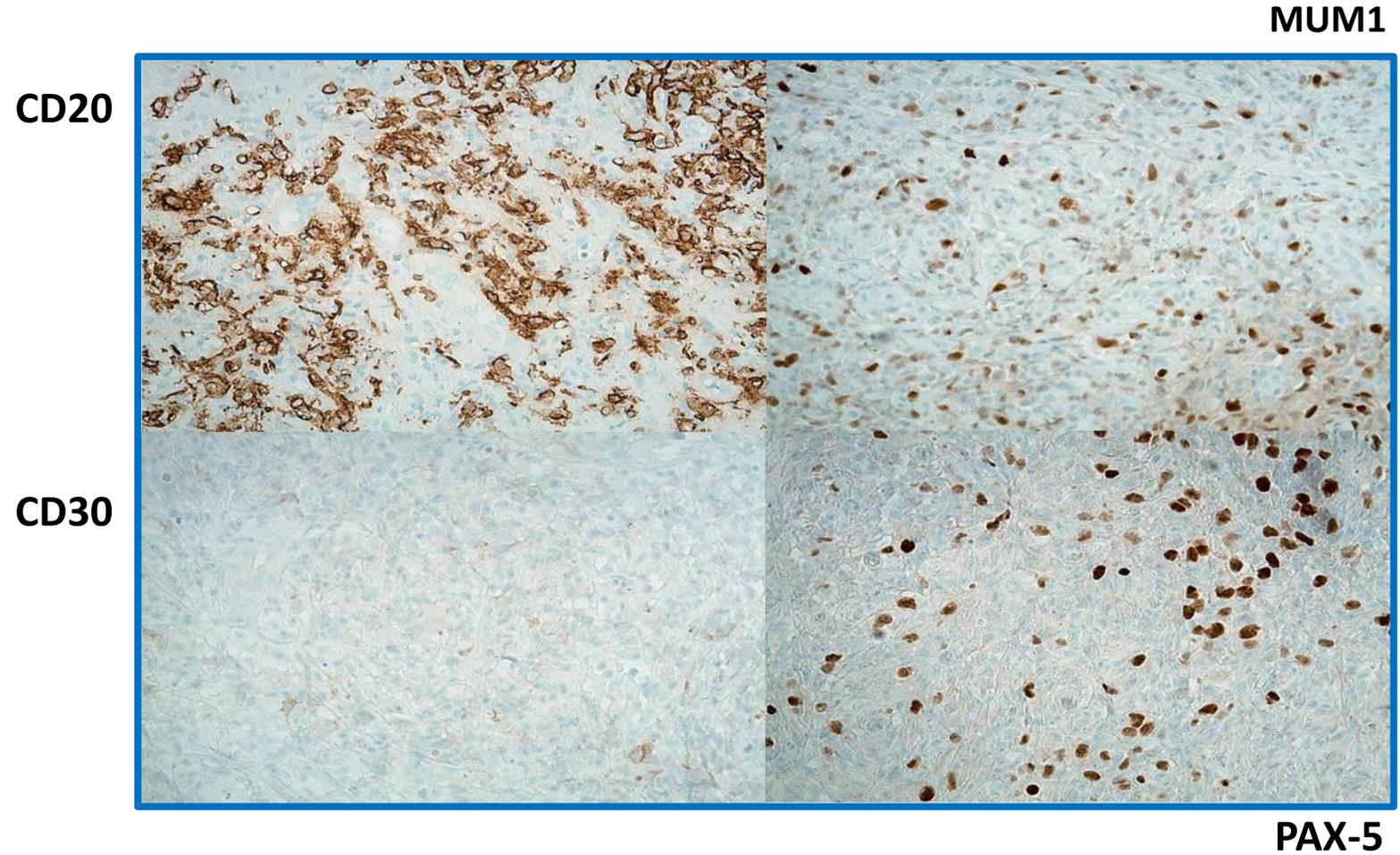


|| Core Needle Biopsy, Mediastinal Mass ||



A core needle biopsy shows atypical large lymphoid cells with irregular, vesicular nuclei and abundant, pale cytoplasm associated with delicate compartmentalizing fibrosis.

|| Immunohistochemistry



|| Diagnosis



- **Which of the following is the most likely diagnosis?**
 - A. Thymoma
 - B. Primary mediastinal (thymic) large B-cell lymphoma
 - C. Nodular sclerosis classical Hodgkin lymphoma
 - D. B-lymphoblastic leukemia/lymphoma
 - E. Diffuse large B-cell lymphoma

|| Diagnosis (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Thymoma
 - B. Primary mediastinal (thymic) large B-cell lymphoma**
 - C. Nodular sclerosis classical Hodgkin lymphoma
 - D. B-lymphoblastic leukemia/lymphoma
 - E. Diffuse large B-cell lymphoma

|| Diagnosis (Continued) ||

- **Gains in which chromosome are associated with PMBCL, and correspond to increased expression of JAK2 and PDL-1?**
 - A. 2p
 - B. 2q
 - C. 4p
 - D. 9p
 - E. 9q

|| Diagnosis (Continued) ||

- **Gains in which chromosome are associated with PMBCL, and correspond to increased expression of JAK2 and PDL-1?**
 - A. 2p
 - B. 2q
 - C. 4p
 - D. 9p**
 - E. 9q
- Disease specific amplification of the 9p24.1 chromosome region includes the JAK2 locus, which also induces increased expression of PD-L1.

|| Diagnosis (Continued) ||

- **Which of the following is expressed by IHC in PMBCL but typically not expressed in classical Hodgkin lymphoma?**
 - A. MUM1
 - B. CD30
 - C. CD20
 - D. PAX5
 - E. CD3

|| Diagnosis (Continued) ||

- Which of the following is expressed by IHC in PMBCL but typically not expressed in Hodgkin lymphoma?
 - A. MUM1
 - B. CD30
 - C. CD20**
 - D. PAX5
 - E. CD3
- PMBCL cells typically stain positive for pan-B-cell antigens (CD19, CD20, CD22, CD79a).
- The addition of the anti-CD20 monoclonal antibody rituximab to CHOP-like chemotherapy in PMBCL has been demonstrated to significantly improve response rates as well as survival.

|| Treatment



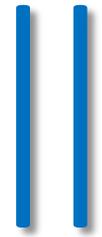
- **Which of the following factors may be used in the decision to omit consolidative mediastinal radiation therapy in PMBCL?**
 - A. Good risk IPI
 - B. Lack of pleural or pericardial effusions
 - C. Age under 30
 - D. Treatment with rituximab-containing regimen
 - E. Complete response to initial treatment as demonstrated by PET/CT

|| Treatment (Continued) ||

- **Which of the following factors may be used in the decision to omit consolidative mediastinal radiation therapy in PMBCL?**
 - A. Good risk IPI
 - B. Lack of pleural or pericardial effusions
 - C. Age under 30
 - D. Treatment with rituximab-containing regimen
 - E. Complete response to initial treatment as demonstrated by PET/CT**
- Data from multiple series suggest PMBCL patients who achieve a complete response to initial therapy have equally good outcomes without the need for radiotherapy.
- The use of FDG-PET as a marker to identify patients who may require consolidation radiation therapy has been proposed, and is being tested in one prospective randomized clinical trial [NCT01599559].

Companion Case for Chapter 35
Primary Mediastinal Large
B-Cell Lymphoma

*Andreas Saltos
and
Julio Chavez*



Clinical Case 13

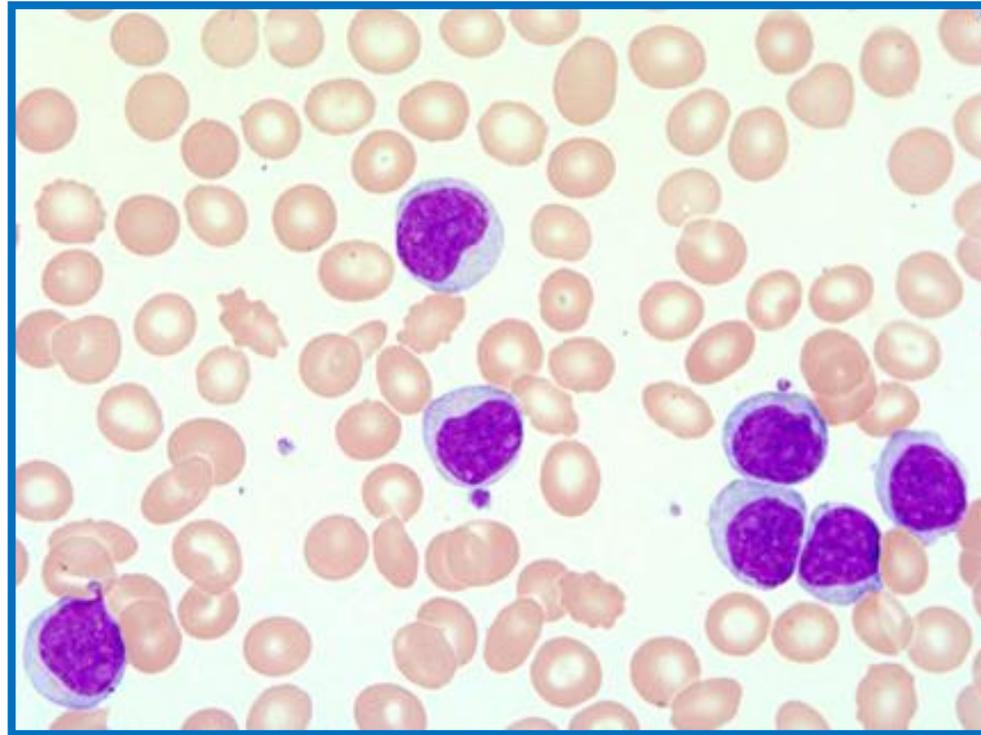


|| Case Presentation

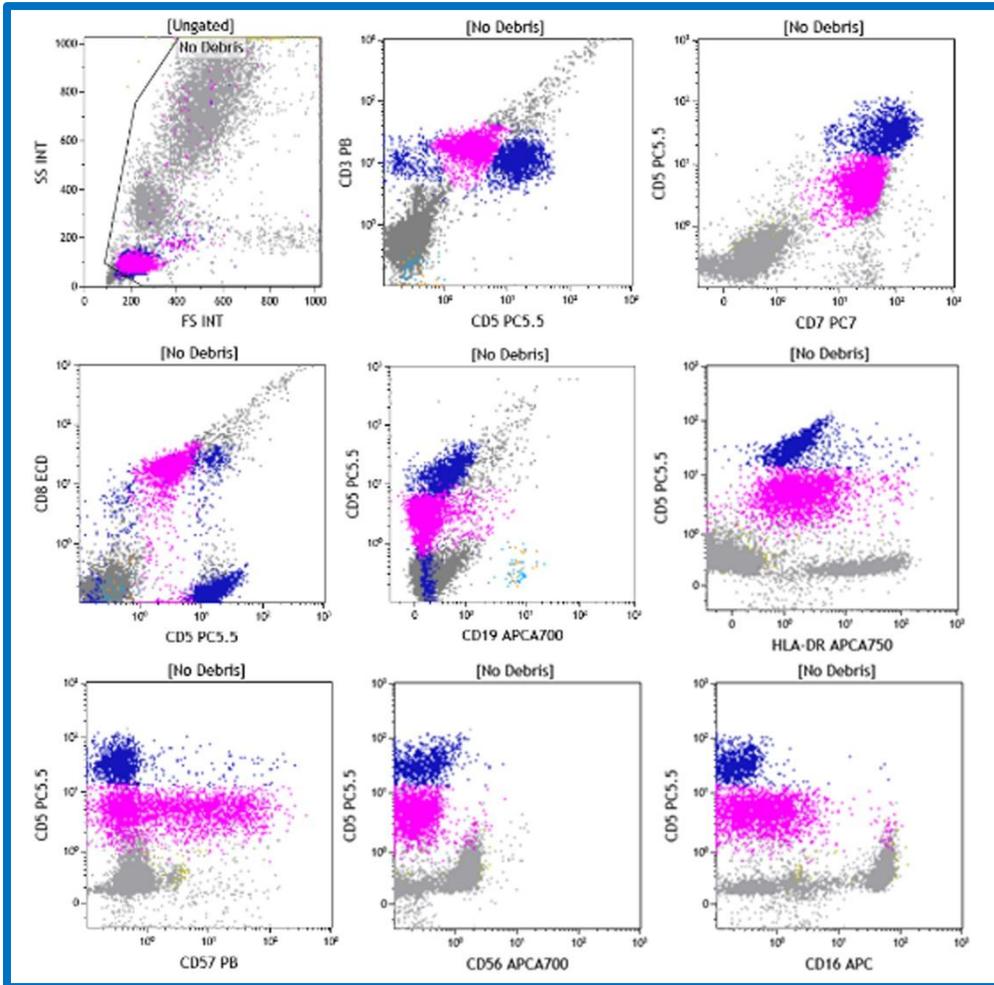
- A 57-year-old female with PMH of hypertension and hypothyroidism presents for her routine annual exam. She has some fatigue but is otherwise asymptomatic.
- A CBC performed reveals a WBC of 4.1 k/ μ L with a normal WBC differential, hemoglobin of 10.5 g/dL with MCV of 89 fL, and platelets of 121 k/ μ L. TSH, B12, and folate levels are within normal limits. She denied any other symptoms of lymphadenopathy, fevers, chills, or weight loss. Her exam is unremarkable.

|| Case Presentation (Continued) ||

The peripheral blood shows several large lymphocytes with reniform or round nuclei, abundant cytoplasm and azurophilic granules.



Flow Cytometry



The flow cytometry study reveals an abnormal population of T-cells (pink), expressing CD3, CD7, CD8, dim CD5, partial CD16, HLA-DR, and partial CD57 when compared with normal T-lymphocytes (blue). In this case, the abnormal T-cells accounts for 21% of the total events with an absolute count of 1264 cells/ μ L.

|| Treatment



- **What would be your next step?**
 - A. Start treatment with methotrexate.
 - B. Start treatment with cyclosporine.
 - C. Start treatment with cyclophosphamide.
 - D. Observe and repeat CBC with differential q3 months.
 - E. Observe and repeat CBC with differential, peripheral blood smear, flow cytometry, and T-cell gene rearrangements in 6 months.

|| Treatment (Continued) ||

- **What would be your next step?**
 - A. Start treatment with methotrexate.
 - B. Start treatment with cyclosporine.
 - C. Start treatment with cyclophosphamide.
 - D. Observe and repeat CBC with differential q3 months.
 - E. Observe and repeat CBC with differential, peripheral blood smear, flow cytometry, and T-cell gene rearrangements in 6 months.**
- Reactive T-cell large granular lymphocytosis secondary to a viral infection or aging needs to be excluded prior to establishing a diagnosis of T-LGL leukemia. A persistent duration of clonal LGL lymphocytosis that exceeds 6 months is required to make the diagnosis of T-LGL leukemia.

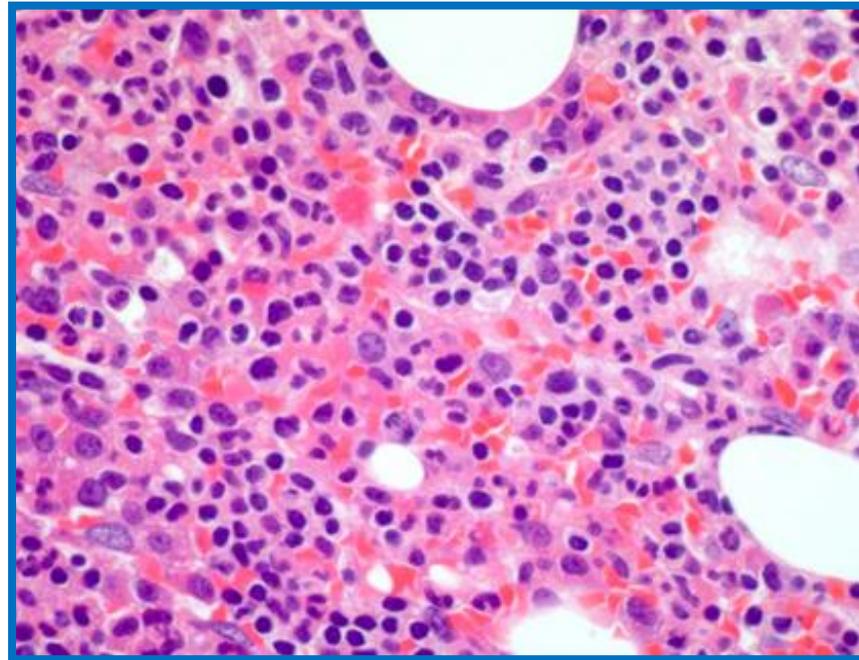
|| Follow-Up



- The patient returns to clinic 6 months later and now complains of worsening fatigue, weight loss, and night sweats over the past several months.
- A CBC at this time reveals a WBC of 2.5 k/ μ L with ANC of 610 cells/ μ L, hemoglobin of 8.5 g/dL with MCV of 87 fL, and platelet count of 105 k/ μ L.
- Flow cytometry and T-cell rearrangement analysis is similar to the analysis 6 months ago.

|| Bone Marrow Biopsy Findings ||

- A bone marrow biopsy is performed and demonstrates an interstitial and sinusoidal infiltrate by neoplastic lymphoid cells, which are significantly increased in number (H&E, x600)



|| Diagnosis



- **What is the most likely diagnosis?**
 - A. NK-cell LGL leukemia
 - B. T-cell LGL leukemia
 - C. Reactive LGL lymphocytosis
 - D. Peripheral T-cell lymphoma

|| Diagnosis (Continued) ||

- **What is the most likely diagnosis?**
 - A. Aggressive NK-cell leukemia
 - B. T-cell LGL leukemia**
 - C. Reactive T-LGL lymphocytosis
 - D. Peripheral T-cell lymphoma, NOS
- **The flow cytometry is characteristic for T-cell LGL leukemia. Note that aggressive NK-cell LGL leukemia is typically CD2+, surface CD3- and CD56+. Reactive LGL lymphocytosis is a benign transient condition that would not persist after 6 months.**

|| Treatment



- **How would you manage this patient?**
 - A. Observe and follow q 3–6 months with labs.
 - B. Start treatment with methotrexate.
 - C. Start treatment with CHOP.
 - D. Start treatment with prednisone.

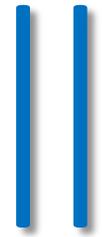
|| Treatment (Continued) ||

- **How would you manage this patient?**
 - A. Observe and follow q 3–6 months with labs.
 - B. Start treatment with methotrexate.**
 - C. Start treatment with CHOP.
 - D. Start treatment with prednisone.

For symptomatic patients who require treatment, methotrexate or cyclophosphamide are excellent first-line treatment options. Corticosteroid monotherapy is not effective in the treatment of LGLL.

Companion Case for Chapter 23
T-Cell Large Granular Lymphocytic
Leukemia

*Magali Van den Bergh
and
Lubomir Sokol*



Clinical Case 14



Case Presentation

A 56-year-old Guatemalan woman with a history of HTN and DM is referred from her primary care clinic after routine CBC for “fatigue and recent bruising” and showed:

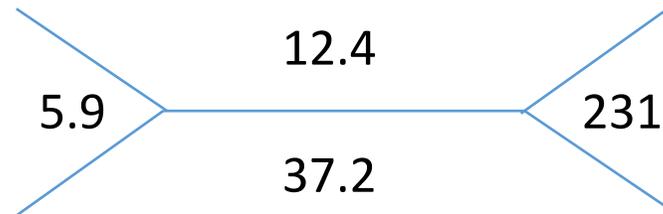


with 33% blasts, 48% lymphocytes and 19% neutrophils, 0% basophils and eosinophils. She endorses 20 lb weight loss over the past couple months as well as blurry vision. No hepatosplenomegaly or lymphadenopathy was appreciated on physical exam.

|| Previous CBC

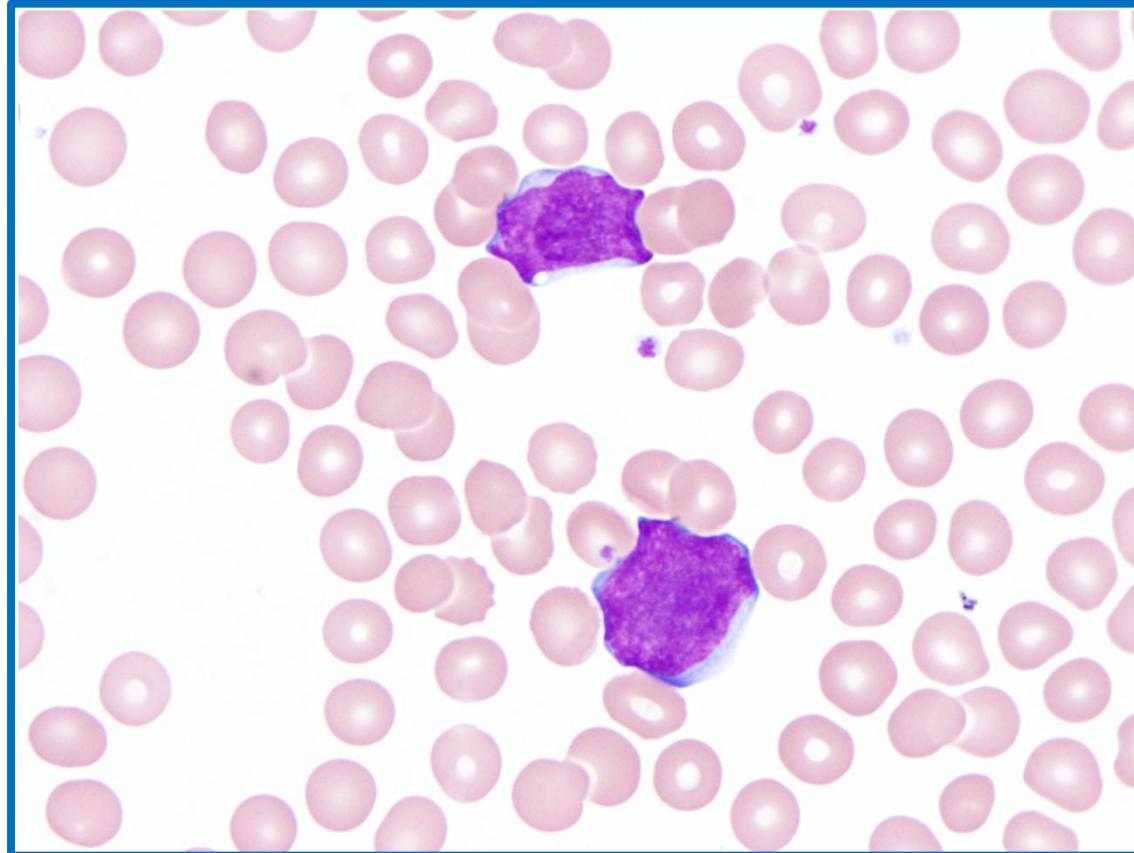


- Her PCP sends over her previous medical records where a CBC from 10 months ago shows:



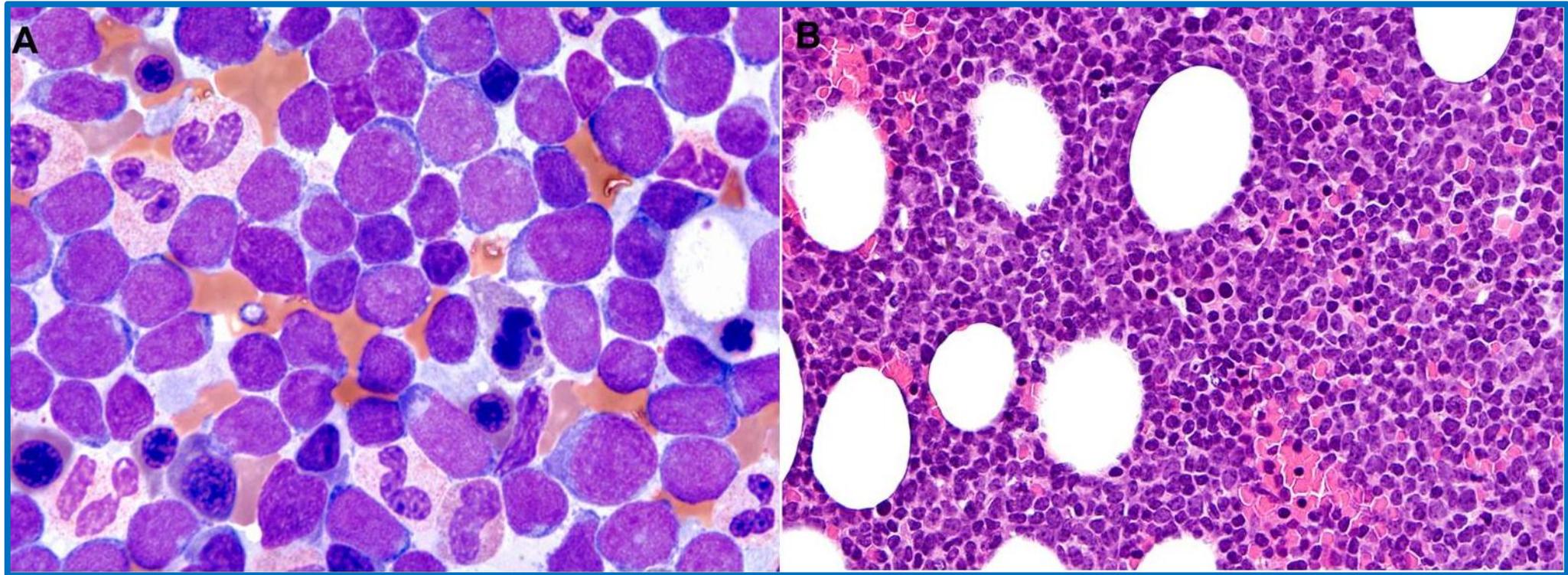
With a normal differential

Peripheral Blood Smear



The peripheral blood (PB) film includes two circulating lymphoblasts, uniform in size with fine chromatin, high N:C ratio, and scant cytoplasm (Wright stain, x1000).

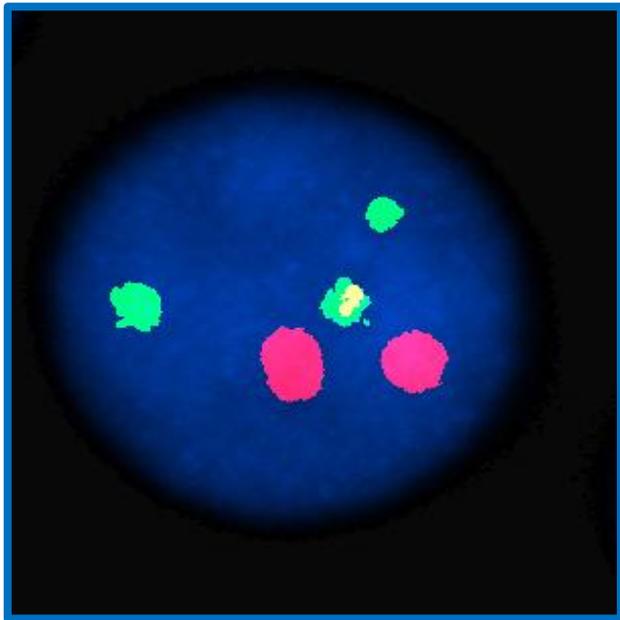
|| Bone Marrow Biopsy



The bone marrow aspirate and core biopsy show over 90% lymphoblasts, associated with scattered erythroid precursors and occasional granulocytes in the background (A, Wright-Giemsa x1000 and B, H&E, x400).

Flow Cytometry/FISH

- Flow cytometry shows the blasts coexpressed bright CD19, CD22 (cytoplasmic), CD79a, CD10, CD13, CD33 and TdT; negative for CD117.
- FISH was positive for $t(9;22)BCR-ABL1$ (Philadelphia chromosome positive).



Representative positive FISH for *BCR/ABL1* gene rearrangement, $t(9;22)(q34.1;q11.2)$.

BCR (22q11.2) is shown in green and *ABL1* (9q34) is shown in red. FISH shows two green signals and two red signals along with one fusion signal (yellow) that indicates the presence of *BCR/ABL* translocation.

|| Diagnosis



- **What is the most likely diagnosis given the following information?**
 - A. Acute myeloid leukemia
 - B. Chronic myelogenous leukemia, lymphoid blast phase
 - C. B-lymphoblastic leukemia/lymphoma, with t(9;22)(q34;q11.2)*BCR-ABL1*
 - D. B-lymphoblastic leukemia/lymphoma, NOS
 - E. Chronic lymphocytic leukemia/small lymphocytic lymphoma

|| Diagnosis (Continued) ||

- **What is the most likely diagnosis given the following information?**
 - A. Acute myeloid leukemia
 - B. Chronic myelogenous leukemia, lymphoid blast phase
 - C. B-lymphoblastic leukemia/lymphoma, with t(9;22)(q34;q11.2)*BCR-ABL1***
 - D. B-lymphoblastic leukemia/lymphoma, NOS
 - E. Chronic lymphocytic leukemia/small lymphocytic lymphoma

Differential Diagnosis: *BCR-ABL* B-ALL versus CML in Lymphoid Blast Crisis

- **What information already given in the case helps distinguish between the two?**
 - A. Flow cytometry and cytogenetic profile
 - B. Clinical presentation, age, gender
 - C. Lymphadenopathy, bone marrow morphology, and blast count
 - D. Previous CBC, current CBC, and time to count recovery following induction chemotherapy

Differential Diagnosis: *BCR-ABL* B-ALL versus CML in Lymphoid Blast Crisis (Continued)

- **What information already given in the case helps distinguish between the two?**
 - A. Flow cytometry and cytogenetic profile
 - B. Clinical presentation, age, gender
 - C. Lymphadenopathy, bone marrow morphology, and blast count
 - D. Previous CBC, current CBC, time to count recovery following induction chemotherapy**

Choice A: Flow cytometry and FISH will be the same in *BCR-ABL*+ B-ALL and CML in lymphoid blast phase (cells are of B-cell origin, T-cell lymphoid blast phase is very rare).

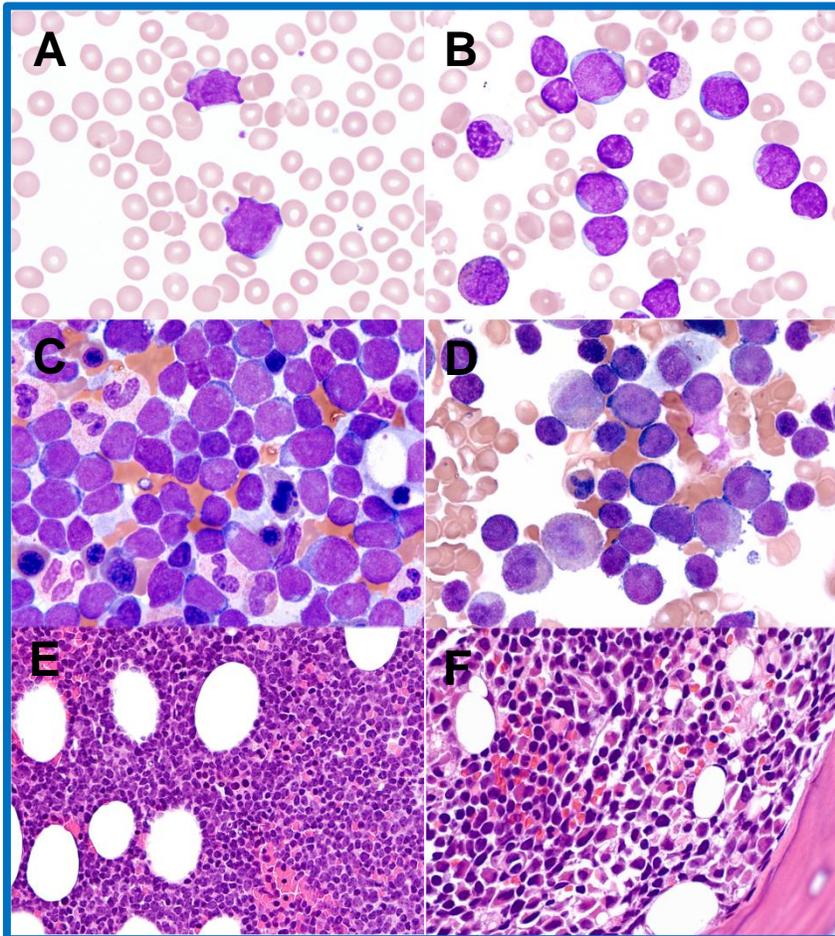
Choice B: This clinical presentation of a middle-aged Hispanic woman does not help differentiate between the two. Although CML is more common in this age group, both etiologies can be seen in the population.

Differential Diagnosis: *BCR-ABL* B-ALL versus CML in Lymphoid Blast Crisis (Continued)

Choice C: The lack of LAD and bone marrow morphology does not differentiate the two while the blast count is consistent with an acute process, which by definition both processes are.

Choice D: Answer D is the right answer. CML, when untreated, typically takes about 3 to 5 years to progress to the blast phase. This patient's CBC from 10 months ago was normal. CML is still coined as chronic granulocytic leukemia—referring to the granulocytic lineage, which are eosinophils, neutrophils, and basophils. Therefore, a degree of myeloid proliferation is typically seen on previous and current CBC of patients who present with blast crisis. These include the “myeloid bulge, absolute basophilia, and absolute eosinophilia. The “myeloid bulge” refers to the increased number of immature myeloid precursors in the peripheral blood than expected—elevated metamyelocytes to myelocytes. The equal meta:myelo ratio implies a process of increased process of *myeloid proliferation* with a *maturation arrest*, a hallmark of CML. Lastly, in a CBC of CML in blast crisis, typically, even in the setting of such high blast count and unregulated proliferation, the other lineage compartments (RBCs and platelets) are preserved while in an acute leukemic process such as ALL or AML, the bone marrow is destroyed and patients present with significant anemia and thrombocytopenia, as was the case in this patient. Lastly, because in CML blast phase the granulocyte precursors are part of the neoplastic clone, these cells are more sensitive to chemotherapy and thus, these patients often require longer to count recovery following induction therapy (~5–6 weeks).

Differential Diagnosis: *BCR-ABL+* B-ALL versus CML in Lymphoid Blast Crisis



In comparison to B-ALL (A,C,E), the images B, D, and F are representative of CML with lymphoid blast crisis. PB demonstrates a heterogeneous population of lymphoblasts, variable in size, with fine chromatin, prominent nucleoli, indistinct to a scant amount of cytoplasm (B, Wright-Giemsa stain, x1000). The bone marrow aspirate and core biopsy consist of lymphoblasts as well as a certain number of granulocytic precursors in a spectrum of maturation, occasional micromegakaryocytes, and myeloblasts (D, Wright-Giemsa, x1000 and F, H&E, x600).

|| Differential Diagnosis ||

- **What additional information could be obtained to help differentiate the two?**
 - A. *BCR-ABL1* real time (RT)-PCR transcript size
 - B. *BCR-ABL1* real time (RT)-PCR quantification
 - C. Cytogenetic analysis
 - D. Additional special stains (Silver, Giemsa etc.)

|| Differential Diagnosis (Continued) ||

- **What additional information could be obtained to help differentiate the two?**
 - A. ***BCR-ABL1* real time (RT)-PCR transcript size**
 - B. *BCR-ABL1* real time (RT)-PCR quantification
 - C. Cytogenetic analysis
 - D. Additional special stains (Silver, Giemsa etc.)

Choice A is the correct answer. The *BCR-ABL1* chromosome translocation results in different sized (kD) protein transcripts: p190, p210 and p230. The latter is exclusive to CML but the former two are typically found in varying prevalence in B-ALL and CML. p190 kD transcript, is seen in 50% of adult B-ALL, and is very rare in CML (although small amounts are not uncommon). In patients who harbor the p210 transcript, the presence of splenomegaly and/or a prolonged, prodromal phase of symptoms argue for a diagnosis of CML in blast crisis.

Choice B is incorrect because *BCR-ABL1* quantification is not used to differentiate between the two but used to assess the molecular response in CML patients.

Choice C is incorrect because cytogenetic analysis can detect the *BCR-ABL1* translocation, but cannot detect the various breakpoints.

Choice D is incorrect because additional special staining does not help differentiate between the two. Silver stains including Gomori-Methamine silver or Warthin Starry silver impregnation stains are used to assess for microbiological organisms.

Companion Case for Chapter 19

BCR-ABL1+ B-Lymphoblastic Leukemia

*Aneesha Hossain
and
Khaled el-Shami*



Clinical Case 15

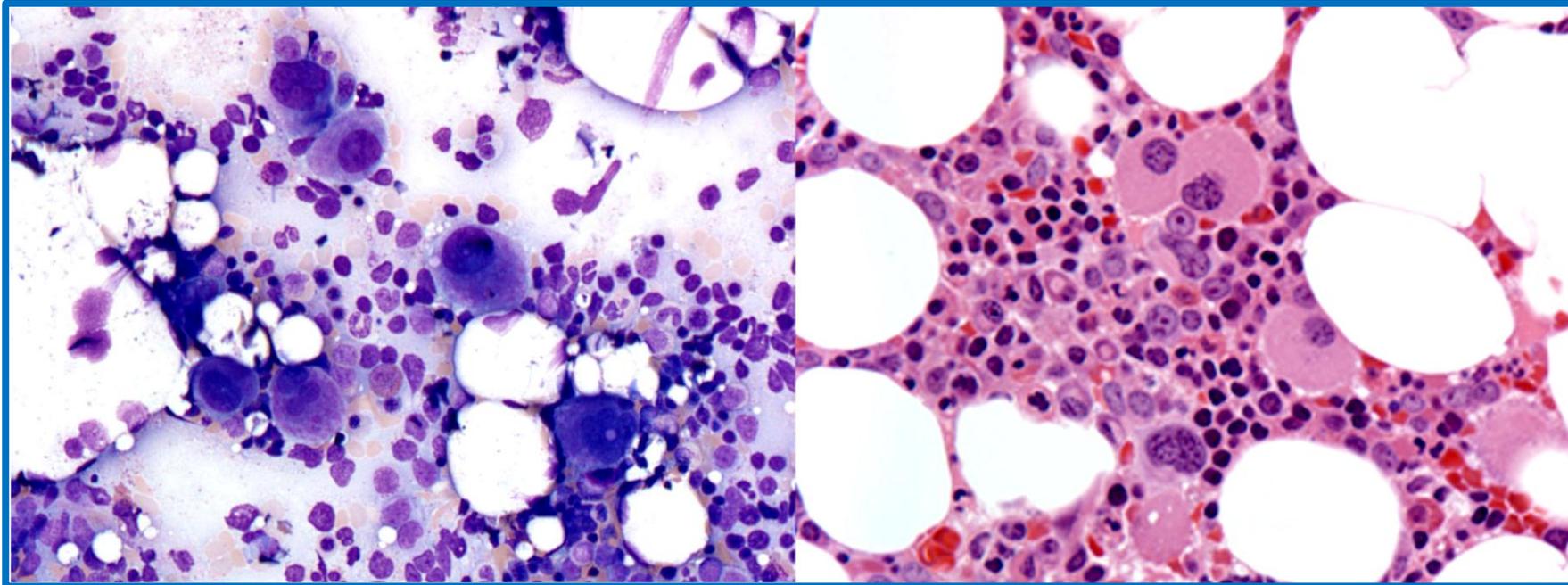


|| Case Presentation



- A 74-year-old woman with PMH of HTN presents for her annual H&P. She has been fatigued for the last few months and is attributing it to aging. Her complete blood cell count revealed a normal white blood cell count with mild neutropenia, hemoglobin of 7.9 g/dL with MCV of 115 fL, and platelet count of 456 k/ μ L. She denies lymphadenopathy, weight loss, and fever. Her physical exam is unrevealing.

|| BM Biopsy and Aspirate ||



Left panel. Wright-Giemsa stained bone marrow aspirate smears were cellular and particulate, consisting of strikingly abnormal megakaryocytes, which are smaller than normal, round to oval with hypolobated nuclei (Wright-Giemsa, x1000 total magnification). Right panel. The bone marrow biopsy shows a small cluster of dysplastic megakaryocytes displaying similar morphology to those noted in the bone marrow aspirate, which are admixed with a background of myeloid and erythroid precursors (H&E, x600).

|| BM Biopsy and Aspirate (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Refractory cytopenia with unilineage dysplasia (RCUD)
 - B. Refractory anemia with ring sideroblasts (RARS)
 - C. Refractory anemia with multilineage dysplasia (RCMD)
 - D. Refractory anemia with excess blasts (RAEB-1)
 - E. MDS associated with isolated del(5q)
 - F. MDS unclassifiable (MDS-U)

|| BM Biopsy and Aspirate (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Refractory cytopenia with unilineage dysplasia (RCUD)
 - B. Refractory anemia with ring sideroblasts (RARS)
 - C. Refractory anemia with multilineage dysplasia (RCMD)
 - D. Refractory anemia with excess blasts (RAEB-1)
 - E. MDS associated with isolated del(5q)**
 - F. MDS unclassifiable (MDS-U)

The dysplastic megakaryocytes from the BM aspirate and biopsy are characteristic for MDS patients with isolated del(5q) syndrome. In addition, the patient profile is typical of this particular MDS (elderly woman with macrocytic anemia, mild neutropenia, and thrombocytosis, which are all mediated via haploinsufficiency of genes in the common deleted region of 5q).

|| BM Biopsy and Aspirate (Continued) ||

- **Cytogenetics confirm isolated deletion of 5q (5q31) and no increase in BM myeloblasts (1%). What is the IPSS risk category of the patient?**
 - A. Low
 - B. Intermediate-1
 - C. Intermediate-2
 - D. High

|| BM Biopsy and Aspirate (Continued) ||

- **Cytogenetics confirm isolated deletion of 5q (5q31) and no increase in BM myeloblasts (1%). What is the IPSS risk category of the patient?**
 - A. Low
 - B. Intermediate-1**
 - C. Intermediate-2
 - D. High

The patient has lower risk disease. She has two cytopenias (neutropenia and anemia) and thus received 0.5 points del(5q) is good risk karyotype (0 points) and <5% blasts (0 points). Intermediate-1 risk disease is 0.5–1 points (see chapter).

|| Treatment



- **What is the standard of care treatment for patients with lower risk, del(5q) disease?**
 - A. Observation
 - B. Lenalidomide
 - C. Azacitidine
 - D. Anti-thymocyte globulin with cyclosporine

|| Treatment (Continued) ||

- **What is the standard of care treatment for patients with lower risk, del(5q) disease?**
 - A. Observation
 - B. Lenalidomide**
 - C. Azacitidine
 - D. Anti-thymocyte globulin with cyclosporine

Lenalidomide leads to transfusion independence in 67% of patients and also leads to complete cytogenetic remission in 61% of patients. Mean duration of response is >2 years. List A et al., *N Engl J Med* 2006; 355:1456-1465.

|| Treatment (Continued) ||

- **Haploinsufficiency of what gene is responsible for the mechanism of action of lenalidomide?**
 - A. Cereblon
 - B. *IKZF1*
 - C. *TRAF6*
 - D. Casein kinase 1A1

|| Treatment (Continued) ||

- **Haploinsufficiency of what gene is responsible for the mechanism of action of lenalidomide?**
 - A. Cereblon
 - B. *IKZF1*
 - C. *TRAF6*
 - D. Casein kinase 1A1**

Cereblon is a known binding partner of lenalidomide and functions as an E3 ubiquitin ligase. In MDS patients with deletion 5q, Casein kinase 1A1 (CK1 α) is located on the common deleted region of 5q. Lenalidomide leads to CK1 α degradation via bringing cereblon in contact with CK1 α and leads to synthetic lethality (*Nature*. 2015 Jul 9;523(7559):183-8). In addition, missense mutations of CK1 α occur in ~5% of del 5q patients (Bello et al., *BJH* 2015; Schneider et al., *Leukemia* 2014).

|| Treatment (Continued) ||

- **Mutations of what gene predict lack of response to lenalidomide?**
 - A. *ASXL1*
 - B. *CK1 α*
 - C. *SF3B1*
 - D. *TP53*

|| Treatment (Continued) ||

- **Mutations of what gene predict resistance to lenalidomide?**

A. *ASXL1*

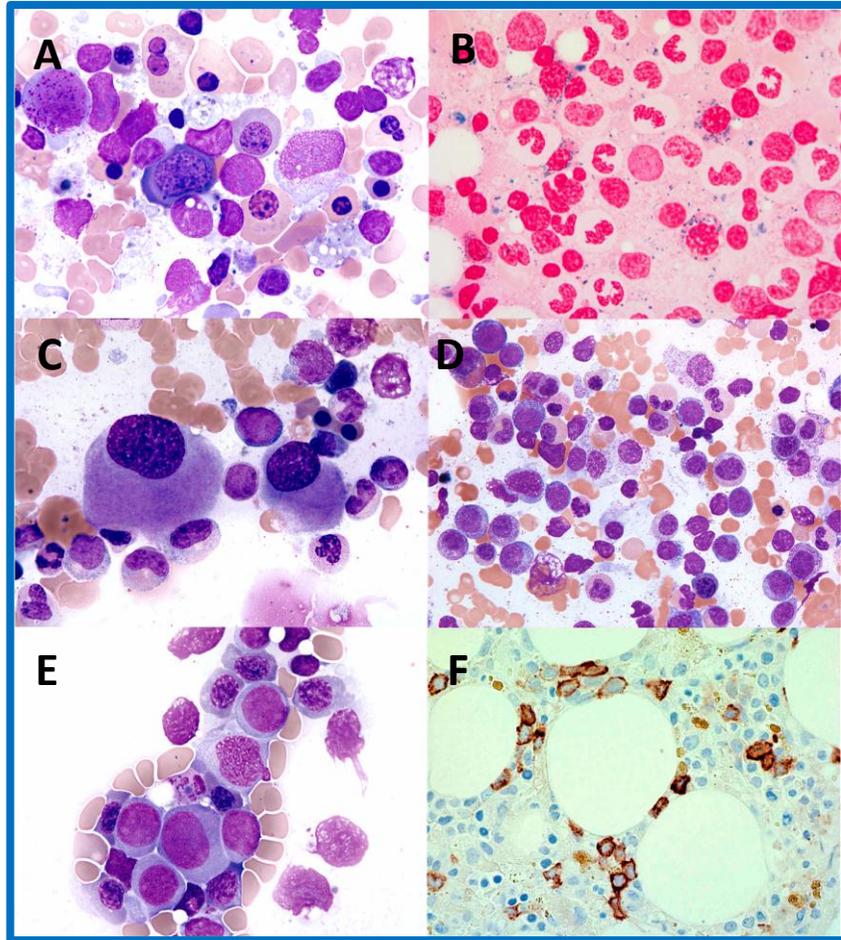
B. *CK1 α*

C. *SF3B1*

D. *TP53*

Primary resistance to lenalidomide has been linked to the presence of *TP53* mutations in lower risk del(5q) MDS. In an analysis of the French and Spanish compassionate treatment programs (n=107), cytogenetic response to lenalidomide in del(5q) MDS ranged from 0% to 12% in patients with mutated *TP53* compared to 73% in patients with wild-type *TP53*. Bally C et al. *Leukemia Research* 37:S25; Mallo M et al. (2013) 162(1):74-86. Jadersten M et al. (2011) 29(15):1971-9.

|| Treatment (Continued) ||



Representative figures from additional MDS patients

A bone marrow aspirate demonstrates significant dysplastic erythropoiesis including nuclear budding, cytoplasmic to nuclear maturation asynchrony, multinucleation and giant forms (A, Wright-Giemsa, x1000) accompanied by increased ring sideroblasts (>15/100nRBCs) (B, Prussian Blue, x1000) in an RARS patient.

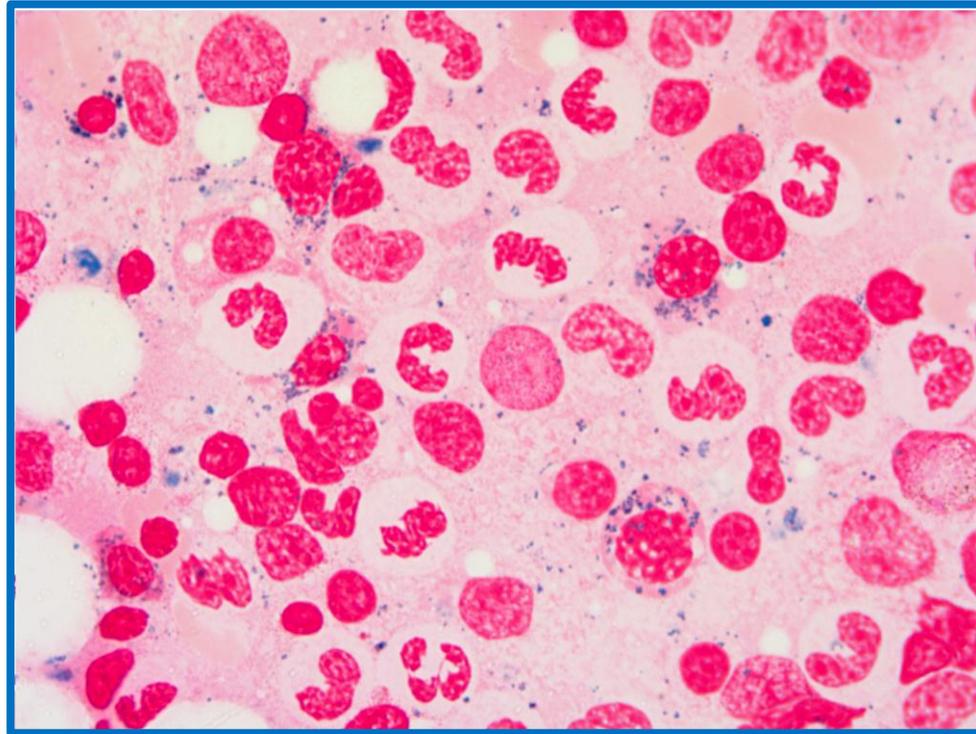
Dysmegakaryopoiesis is shown with small- to medium-sized megakaryocytes with single lobation, or micromegakaryocytes (C, Wright-Giemsa, x1000). Myeloid dysplasia is shown by bilobed, hypogranulated granulocytes or neutrophils (Pseudo-Pelger-Huët changes) along with myeloid preponderance and left-shifted maturation (D, Wright-Giemsa, x1000).

The bone marrow aspirate from a patient with refractory anemia with excess blasts shows clusters of blasts. The image illustrated foci of abnormal localization of immature precursors (ALIP) highlighted by CD34 IHC staining (Immunoperoxidase, x100).

|| Treatment (Continued) ||

○ **This histologic finding is tightly associated with which mutation?**

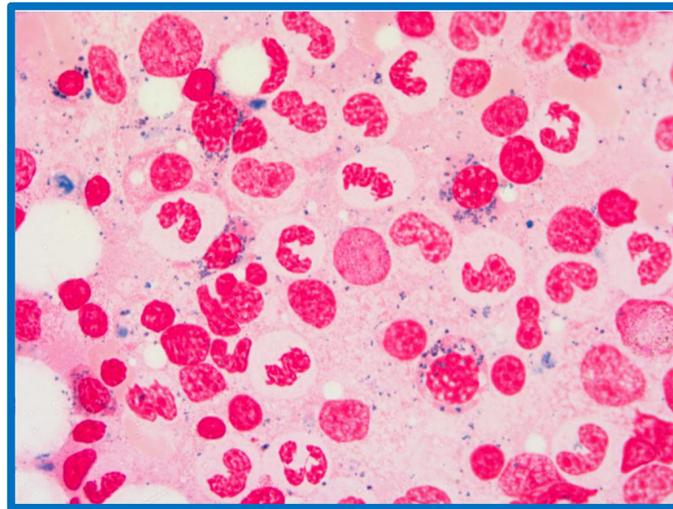
- A. *SF3B1*
- B. *SRSF2*
- C. *U2AF1*
- D. *ZRSR2*



|| Treatment (Continued) ||

○ **This histologic finding is tightly associated with which mutation?**

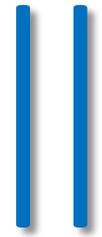
- A. *SF3B1*
- B. *SRSF2*
- C. *U2AF1*
- D. *ZRSR2*



SF3B1 mutation, although not 100% specific, is significantly associated with the presence of ring sideroblasts. In the WHO 2016 update, mutation of *SF3B1* will be diagnostic of RARS if there is at least 5% of RS/100 nucleated RBCs in BM given the striking genotype-phenotype correlation (*Blood* 2011, 118:6239-46). This is the only mutation in MDS to be associated with improved outcomes.

Companion Case for Chapter 9 Myelodysplastic Syndromes

*Joanna Grabska,
David A. Sallman,
and
Rami Komrokji*



Clinical Case 16



|| Case Presentation

- A 25-year-old African American male was admitted to the hospital with fever and fatigue of 1-month duration. He also reported night sweats, easy bruising on his arms, early satiety, and abdominal discomfort (LUQ). He lost approximately 15 lbs in the last 3 months. Examination was remarkable for hepatomegaly (8 cm below the costal margin) and splenomegaly (14 cm below the costal margin) without lymphadenopathy. Laboratory evaluation was notable for pancytopenia (WBC 3.8 k/ μ L, Hb 10 g/dL, PLT 50 k/ μ L), high LDH (800 U/L) and elevated liver associated enzymes (AST 120 U/L, ALT 137 U/L, total bilirubin 3.0 mg/dL, direct bilirubin 2.0 mg/dL). A CT scan of the abdomen confirmed hepato-splenomegaly.

|| Bone Marrow Biopsy ||

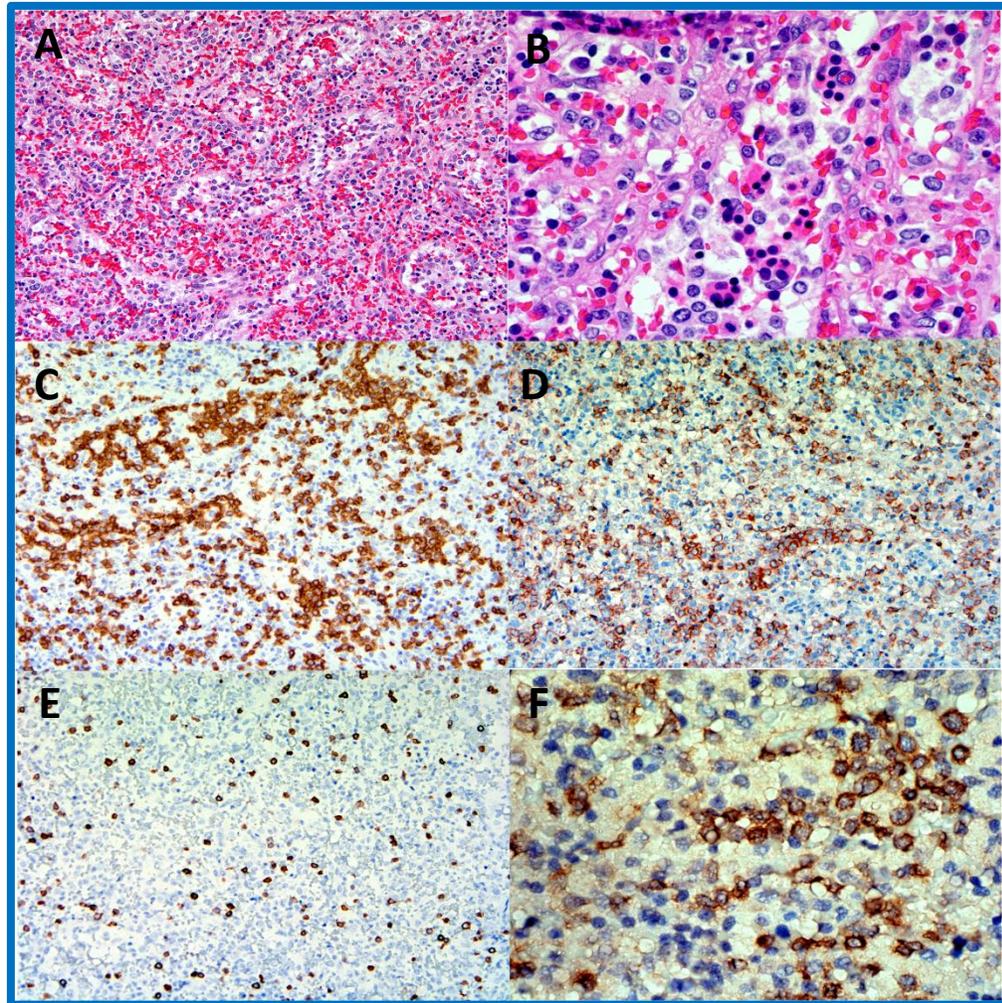
- This was followed by a bone marrow biopsy that reveals monotonous, medium-sized T-cells with scant pale cytoplasm, infiltrating within the sinuses of the spleen, liver, and bone marrow. Flow cytometric analysis shows the cells were CD2+, CD3+, CD7+, CD57+, $\gamma\delta$ TCR+, and CD4-, CD8-, CD56-, CD10-. Additional immunohistochemical results showed the cells were positive for the cytotoxic granules granzyme B, TIA1, and perforin. EBER-ISH (EBV-encoded RNA) was negative. PCR for T-cell receptor gene rearrangement confirmed clonality of $\gamma\delta$ genes. Cytogenetic analysis shows isochromosome 7q and trisomy 8.

|| Diagnostic Studies



- He subsequently undergoes liver biopsy that shows atypical sinusoidal lymphoid infiltrate that have the same immunophenotype as the bone marrow aspirate. Subsequently he undergoes splenectomy.

Splenectomy



A. Cross section of splenic parenchyma from splenectomy shows massive expansion of red pulp by atypical lymphoid cells, intermediate to large in size, dispersed chromatin, irregular nuclei and a small amount of cytoplasm (H&E x200). B. A high-power view highlights intrasinusoidal atypical lymphoid cells as well as increased macrophages engulfing many hematopoietic precursors (hemophagocytosis) (H&E, x600). C. Immunohistochemical stains highlight intrasinusoidal atypical lymphoid cells to be abnormal T-cells that are positive for CD2 (C, x200), CD3 (D, x200), and negative for CD5 (E, x200) and CD7 (image not shown). The infiltrate is TCR gamma-delta subtype (F, immunoperoxidase, x600).

|| Diagnosis



- **Which of the following is the most likely diagnosis?**
 - A. Peripheral T-cell lymphoma, NOS
 - B. Extranodal NK/T cell lymphoma, nasal type
 - C. T-cell large granular lymphocytic leukemia
 - D. Hepatosplenic T-cell lymphoma
 - E. Aggressive NK-cell leukemia

|| Diagnosis (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Peripheral T-cell lymphoma, NOS
 - B. Extranodal NK/T-cell lymphoma, nasal type
 - C. T-cell large granular lymphocytic leukemia
 - D. Hepatosplenic T-cell lymphoma**
 - E. Aggressive NK-cell leukemia

Although aggressive NK-cell leukemia (ANKCL) typically presents in middle-aged patients with common involvement of the peripheral blood, bone marrow, spleen, and liver, the diagnosis should be made with great caution in EBV-negative cases (90% of ANKCL are positive for EBV). Furthermore, T-cell receptor clonality cannot be established for ANKCL because the receptor is in germline status (see ANKCL chapter). Similarly, the diagnosis of extranodal NK/T-cell lymphoma, nasal type (see ENKTCL chapter), should be questioned if the presence of EBV cannot be established. The cells of ENKTCL are CD2+, surface CD3-, cytoplasmic CD3+, CD56+, with expression of cytotoxic granules including granzyme B, TIA1, and perforin. ENKTCL infiltrates in a diffuse or nodular pattern with extensive necrosis and apoptosis, due to angiocentric and angioinvasive behavior. Peripheral T-cell lymphoma, NOS may be considered in cases of a CD3+, CD56-/ lymphoma that lack EBV positivity and cytotoxic granules.

|| Treatment

- The patient was treated with six cycles of Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high dose methotrexate and cytarabine) with good response and reduction to 0.1% abnormal T-cell population.
- **What is the next line of treatment?**
 - A. Observation
 - B. Autologous hematopoietic cell transplant (auto-HSCT)
 - C. Allogeneic HCT (allo-HSCT)
 - D. Consolidation chemotherapy
 - E. Alemtuzumab

|| Treatment (Continued) ||

- **What is the next line of treatment?**
 - A. Observation
 - B. Autologous hematopoietic cell transplant (auto-HSCT)
 - C. Allogeneic HCT (allo-HSCT)**
 - D. Consolidation chemotherapy
 - E. Alemtuzumab

|| Outcome



- The patient undergoes pretransplant lumbar puncture, which is negative. He subsequently undergoes allo-HSCT with methotrexate and tacrolimus as GVHD prophylaxis. He is stable for 16 months when he presents with severe abdominal pain to the ED. A CT scan of the abdomen/pelvis reveals a colonic mass. He undergoes colonoscopy with biopsy.

|| Follow-Up

- A colonoscopic biopsy shows an infiltrate composed of sheets of abnormal small lymphoid cells that on IHC staining, express CD2, CD3, CD7, and CD56 and are negative for CD4, CD8, CD5, CD10, and CD30. Molecular studies identify a TCR gene rearrangement identical to the one previously characterized on both the bone marrow and liver biopsies. Staging studies shows no other sites of disease.
- **What is the treatment of this patient's relapsed disease?**
 - A. Pralatrexate
 - B. Alemtuzumab
 - C. HDAC inhibitors
 - D. Brentuximab vedotin
 - E. Any of the above

|| Follow-Up (Continued) ||

- **What is the treatment of this patient's relapsed disease?**
 - A. Pralatrexate
 - B. Alemtuzumab
 - C. HDAC inhibitors
 - D. Brentuximab vedotin
 - E. Any of the above**

|| Treatment of Relapsed HSTCL ||

- There is no standard therapeutic option for patients with relapsed or progressive disease although systemic chemotherapy utilizing an alternative first-line regimen can be done. Allo-HSCT is suitable for individual clinical use providing the patient does not undergo allo-HSCT after frontline therapy. However, relapsing disease is usually chemorefractory, and preference is for clinical trial if at all possible.
- The patient recently started on single agent Pralatrexate therapy.

|| Prognosis

- The prognosis of HSTCL is almost uniformly poor, and no prospective trials investigating treatment approaches are reported.
- This is especially true for relapsed/refractory cases.
- However, several novel agents such as the Aurora A kinase inhibitor alisertib and the Syk inhibitor entospletinib are currently under investigation.

Companion Case for Chapter 47 Hepatosplenic T-Cell Lymphoma

*Narendranath Epperla,
Apoorva Jayarangaiah,
and
Timothy S. Fenske*



Clinical Case 17



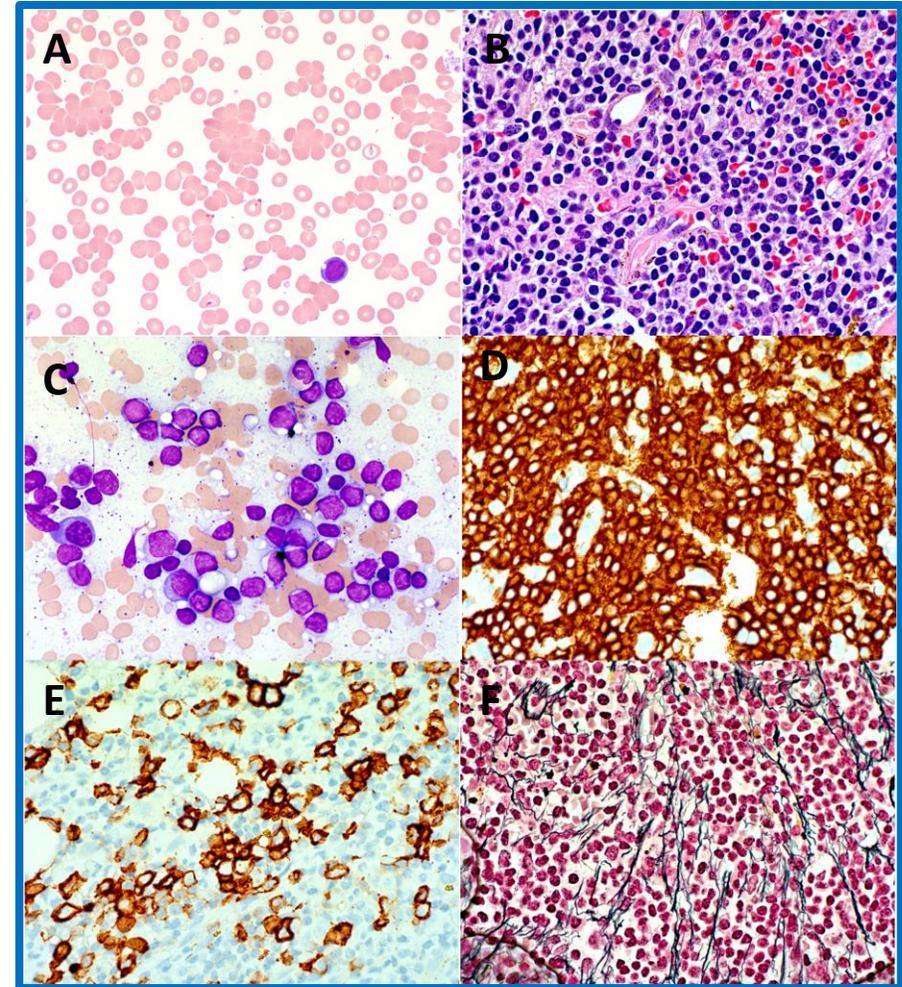
|| Case Presentation



- A 64-year-old White man with a PMH of hyperlipidemia and coronary artery disease presents with dyspnea on exertion and increasing fatigue. His CBC revealed a normal WBC count, Hgb of 10.5 g/dL with MCV of 89 fL, and a platelet count of 120 k/ μ L. His review of systems is negative for lymphadenopathy, weight loss, or fevers. His physical exam is unrevealing.

Bone Marrow Biopsy

A. Cold agglutination is identified in the patient's peripheral blood (Wright's, x1000 total magnification). B. The H&E stained bone marrow core biopsy shows peripheral sinusoidal to diffuse infiltration of atypical lymphoplasmacytic cells, occupying 80% of marrow cellularity (H&E, x600). C. The Wright-Giemsa stained bone marrow aspirate demonstrates sheets of plasmacytoid lymphocytes and occasional plasma cells (Wright-Giemsa, x600). D and E. Immunohistochemical stains show the atypical lymphoid infiltrate is positive for CD20 (diffuse) and CD138 (subset). F. A reticulin stain highlights moderate reticulin fibrosis in the lymphoid areas.



|| Flow Cytometry



- Flow cytometry shows CD19(+), CD20(+), and CD5(-) monoclonal cells. Further evaluation shows an IgM monoclonal protein present in his serum.
- **Which of the following is the most likely diagnosis?**
 - A. Marginal zone lymphoma
 - B. Chronic lymphocytic leukemia
 - C. Multiple myeloma (MM)
 - D. Waldenstrom macroglobulinemia (WM)

|| Diagnosis

- **Which of the following is the most likely diagnosis?**
 - A. Marginal zone lymphoma
 - B. Chronic lymphocytic leukemia
 - C. Multiple myeloma (MM)
 - D. Waldenstrom macroglobulinemia (WM)**

The clinical and pathologic picture are consistent with WM. Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma is typically CD5, CD10, and CD23 negative, but may be positive in 10% to 20% of WM cases and does not necessarily exclude the diagnosis of LPL/WM.

|| Treatment



- **Would you treat this patient?**
 - A. Yes
 - B. No
 - C. Not enough information

|| Treatment (Continued) ||

- **Would you treat this patient?**
 - A. Yes
 - B. No**
 - C. Not enough information

Clinical indications for initiation of therapy: *Blood* 2014, 125(9):1404-11.

- Recurrent fever, night sweats, weight loss, fatigue
- Hyperviscosity
- Lymphadenopathy that is either symptomatic or bulky (≥ 5 cm in maximum diameter)
- Symptomatic hepatomegaly and/or splenomegaly
- Symptomatic organomegaly and/or organ or tissue infiltration
- Peripheral neuropathy due to WM

Laboratory indications for initiation of therapy:

- Symptomatic cryoglobulinemia
- Cold agglutinin anemia
- Immune hemolytic anemia and/or thrombocytopenia
- Neuropathy related to WM
- Amyloidosis related to WM
- Hemoglobin ≤ 10 g/dL
- Platelet count $< 100 \times 10^9/L$

|| Follow-Up



Now the patient returns to you with symptoms of dyspnea on exertion and fatigue. You order additional tests that show:

Hgb: 8.5 g/dL

PLT: 102 k/ μ L

M-protein: 8.2 g/dL

The patient otherwise feels well. Review of systems other than the above symptoms is negative.

|| Additional Tests



- **What additional test should you order at this time?**
 - A. Cryocrit because you suspect cryoglobulinemia
 - B. Retinal exam because there is a possibility he may have hyperviscosity based on one of the lab results
 - C. Electromyelogram
 - D. Fat pad biopsy and Congo red testing of bone marrow

|| Additional Tests (Continued) ||

- **What additional test should you order at this time?**
 - A. Cryocrit because you suspect cryoglobulinemia (he has no symptoms)
 - B. Retinal exam because there is a possibility he may have hyperviscosity based on one of the lab results**
 - C. Electromyelogram (he has no symptoms of neuropathy)
 - D. Fat pad biopsy and Congo red testing of bone marrow (not the best answer here)

Retinal exam is indicated if IgM is $>3\text{g/dL}$ or hyperviscosity is suspected.

|| Additional Tests (Continued) ||

- **Additional testing shows viscosity of 4.8 cp. What is the next best step in management?**
 - A. There is no need for plasmapheresis because he is asymptomatic.
 - B. Start DRC (dexamethasone, rituximab and cyclophosphamide).
 - C. Start bortezomib first followed by bortezomib/rituximab to avoid IgM flare; monitor IgM level before rituximab is started.
 - D. A and C are correct.

|| Additional Tests (Continued) ||

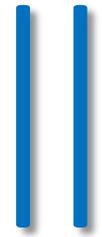
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 - A. There is no need for plasmapheresis because he is asymptomatic.
 - B. Start DRC (dexamethasone, rituximab and cyclophosphamide).
 - C. Start bortezomib first followed by bortezomib/rituximab to avoid IgM flare; monitor IgM level before rituximab is started.
 - D. A and C are correct.**

The patient is currently asymptomatic but his IgM level is greater than 5 g/dL; therefore, after starting bortezomib alone, serum IgM level should be checked prior to initiating rituximab therapy, as it can cause a flare leading to symptomatic hyperviscosity.

Companion Case for Chapter 27

Waldenström's Macroglobulinemia

*Joanna Grabska
and
Rachid Baz*



Clinical Case 18

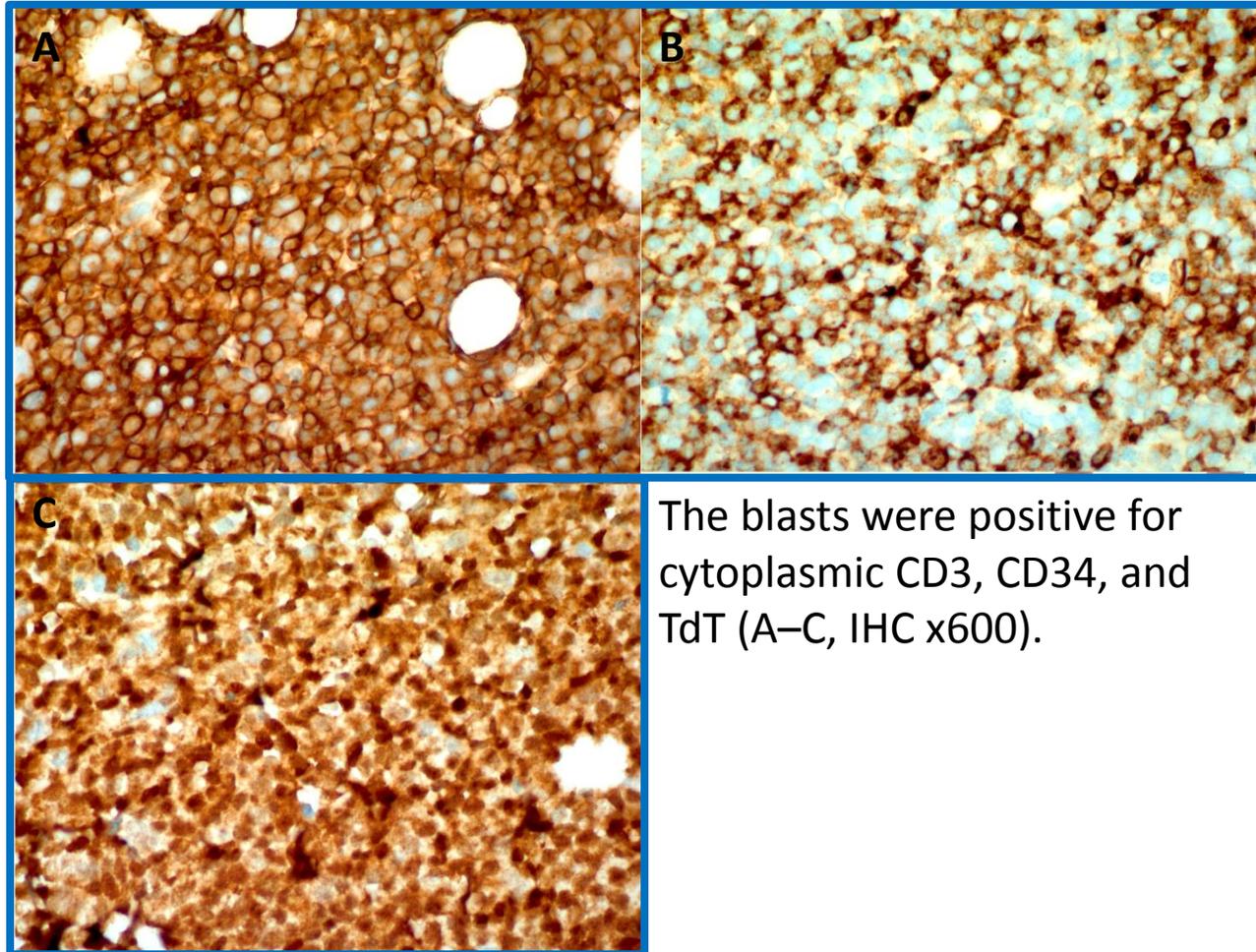


|| Case Presentation



- A 30-year-old healthy male presents to the emergency department complaining of fatigue, diffuse arthralgias, fever, vision changes, and mild confusion. He has no significant medical history and is very physically active. CBC reveals a hemoglobin of 8.5 g/dL, platelets 65 k/ μ L, and WBC 14.3 k/ μ L with 55% circulating blasts.
- A bone marrow biopsy and aspirate are performed that show 100% cellularity and 75% blasts. Immunohistochemistry (see following figure) is positive for cytoplasmic CD3, CD34, CD1a, and TdT. Cytogenetic analysis shows a normal male karyotype, 46,XY[20].

|| Case Presentation (Continued) ||



The blasts were positive for cytoplasmic CD3, CD34, and TdT (A–C, IHC x600).

|| Diagnosis

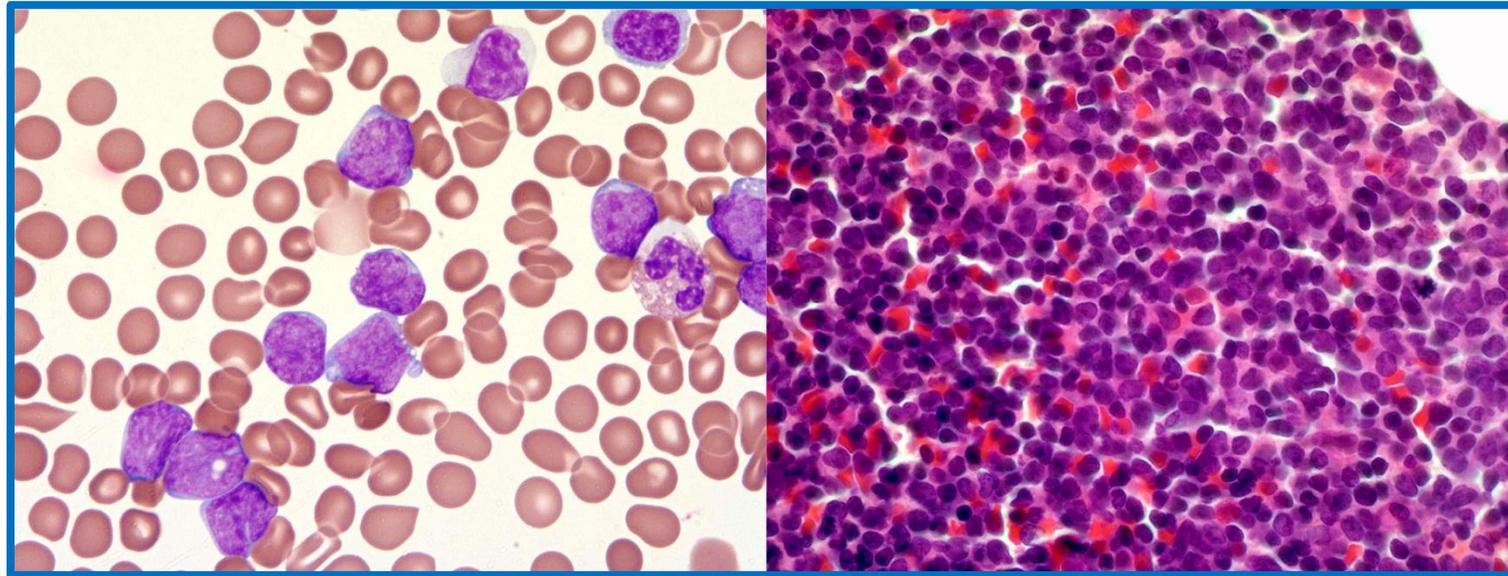
- **Which of the following is the most likely diagnosis?**
 - A. Acute myeloid leukemia
 - B. B-ALL
 - C. T-ALL
 - D. Acute undifferentiated leukemia

|| Diagnosis (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Acute myeloid leukemia
 - B. B-ALL
 - C. T-ALL**
 - D. Acute undifferentiated leukemia

The immunophenotypic findings are most consistent with an immature T-lineage phenotype, namely T-ALL. Cytoplasmic CD3 or surface CD3 positivity is considered relatively lineage specific for T-cell differentiation.

Peripheral Blood Smear and Bone Marrow Biopsy



The figures above demonstrate involvement of T-ALL in peripheral blood and bone marrow, respectively. The PB smear shows leukocytosis with blastosis consisting of immature precursors with delicate chromatin, prominent nuclei, irregular nuclear contours, and scant basophilic cytoplasm (left panel, Wright x1000). The bone marrow core biopsy is diffusely replaced by the blasts (right panel, H&E, x600)

|| Differential Diagnosis

- T-ALL should be differentiated from other acute leukemias, which is usually achieved on the basis of flow cytometry, immunophenotyping, and other ancillary studies.
- In particular, the specific B-lineage marker, CD19, as well as the myeloid marker MPO, can help rule out the possibility of mixed phenotype acute leukemia (see MPAL section and case).
- As noted previously, cytoplasmic CD3 (epsilon chain) or surface CD3 is a T-cell lineage-specific antigen.

|| Differential Diagnosis (Continued) ||

- **Which of the following should be performed in the diagnostic workup?**
 - A. Ultrasound of abdomen to evaluate for spleen size
 - B. Rheumatologic workup given diffuse arthralgias to r/o concomitant rheumatoid arthritis
 - C. Lumbar puncture with flow cytometry analysis
 - D. Molecular analysis of *CEBPA*, *NPM1*, *FLT3*, and *C-KIT*
 - E. All of the above

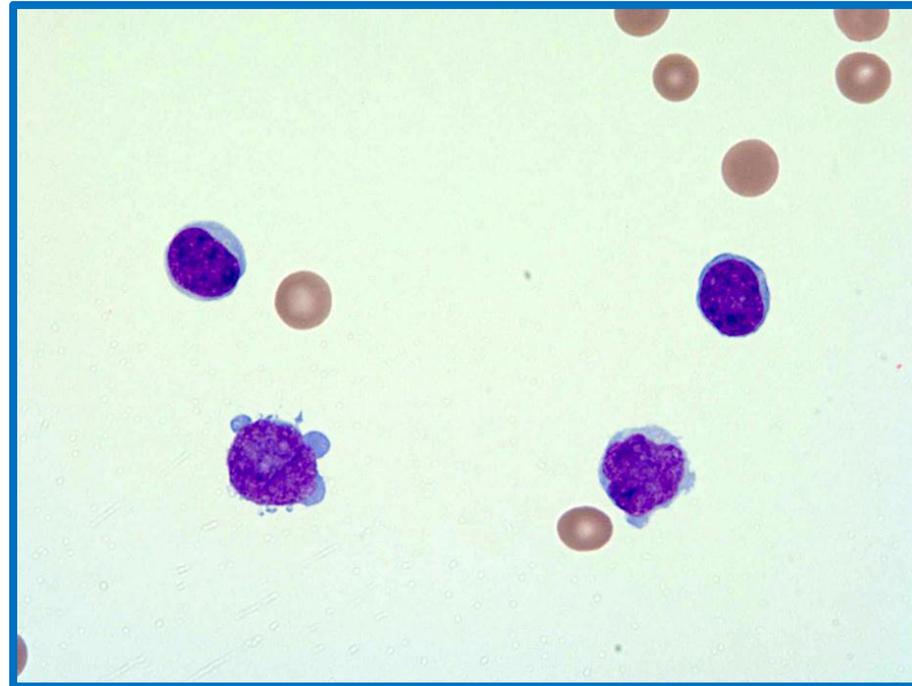
|| Differential Diagnosis (Continued) ||

- **Which of the following should be performed in the diagnostic workup?**
 - A. Ultrasound of abdomen to evaluate for spleen size
 - B. Rheumatologic workup given diffuse arthralgias to r/o concomitant rheumatoid arthritis
 - C. Lumbar puncture with flow cytometry analysis**
 - D. Molecular analysis of *CEBPA*, *NPM1*, *FLT3*, and *C-KIT*
 - E. All of the above

T-ALL can often have extramedullary involvement, including the testicular, CNS, and mediastinal regions.

|| Case Presentation

- A lumbar puncture is performed, and cytopsin preparation (Wright-Giemsa, x1000 total mag.) shows involvement of the CNS by ALL with flow cytometry showing a T-cell phenotype.



|| Case Presentation (Continued) ||

- **Which of the following poses the greatest risk of poor outcomes in this case?**
 - A. Patient age
 - B. Presenting WBC count
 - C. CNS involvement
 - D. Normal karyotype
 - E. All of the above

|| Case Presentation (Continued) ||

- **Which of the following poses the greatest risk of poor outcomes in this case?**
 - A. Patient age
 - B. Presenting WBC count
 - C. CNS involvement**
 - D. Normal karyotype and cytogenetic analysis
 - E. All of the above
- In adult T-ALL, favorable prognostic indicators include age <35, WBC count less than 100 k/ μ L, a cortical T immunophenotype. Certain mutations and complex cytogenetics have been associated with a poor prognosis. CNS involvement is generally considered an adverse prognostic feature.

|| Treatment



- **Which of the following treatments would be most appropriate for this patient?**
 - A. Cytarabine + doxorubicin
 - B. Pediatric ALL regimen
 - C. Nelarabine
 - D. Intrathecal chemotherapy + high dose methotrexate

|| Treatment (Continued) ||

- **Which of the following treatments would be most appropriate for this patient?**
 - A. Cytarabine + doxorubicin
 - B. Pediatric ALL regimen**
 - C. Nelarabine
 - D. Intrathecal chemotherapy + high dose methotrexate

Emerging data have shown that treatment intensification afforded by pediatric ALL regimens is tolerable to age of 40, and should be considered to manage systemic and CNS disease. Cytarabine + doxorubicin can be used to treat AML. Nelarabine can be considered in the relapsed/refractory setting. While CNS-directed therapy will be necessary for this patient, IT chemotherapy with high dose methotrexate would not adequately address his systemic disease.

|| Prognosis

- **A mutation in which of the following genes has been detected in over 50% of cases of T-ALL and is generally associated with a more favorable prognosis?**
 - A. *JAK 1*
 - B. *NOTCH1*
 - C. *FLT3*
 - D. *PTEN*
 - E. *KRAS*

|| Prognosis (Continued) ||

- **A mutation in which of the following genes has been detected in over 50% of cases of T-ALL and is generally associated with a more favorable prognosis?**
 - A. *JAK 1*
 - B. *NOTCH1***
 - C. *FLT3*
 - D. *PTEN*
 - E. *KRAS*

|| ETP-ALL



- **All of the following are true of early T-cell precursor acute lymphoblastic leukemia EXCEPT which one?**
 - A. ETP-ALL is an immunophenotypically defined group of T-ALLs that typically expresses CD1a, CD8, CD5, and at least one more myeloid or stem-cell markers (CD117, CD34, HLA-DR, CD13, CD33, CD11b, CD65).
 - B. ETP-ALL accounts for about 15% of all cases of T-ALL and is associated with a much poorer prognosis and higher treatment failure rate in both children and adults.
 - C. Activating mutations in genes involved in cytokine receptor and *RAS* signaling are frequently observed, such as *NRAS*, *KRAS*, and *FLT3*.
 - D. ETP-ALL is derived from “double-negative 1” (or DN1) type thymocytes, which may differentiate into T and myeloid lineages, but not the B-cell program.

|| ETP-ALL (Continued) ||

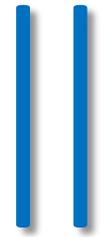
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 - B. ETP-ALL accounts for about 15% of all cases of T-ALL and is associated with a much poorer prognosis and higher treatment failure rate in both children and adults.
 - C. Activating mutations in genes involved in cytokine receptor and *RAS* signaling are frequently observed, such as *NRAS*, *KRAS*, and *FLT3*.
 - D. ETP-ALL is derived from “double-negative 1” (or DN1) type thymocytes, which may differentiate into T and myeloid lineages, but not the B-cell program.

ETP-ALL phenotypic markers typically include **absent** CD1a and CD8 expression, and either dim or negative CD5 expression, **and** at least one or more myeloid or stem-cell markers. This immunophenotypic profile is relatively characteristic of ETP-ALL subtype of T-ALL, and should be noted as patients are more likely to have relapsed disease and an overall poor prognosis.

Companion Case for Chapter 20

T-Lymphoblastic Lymphoma/Leukemia

Keri Maher
and
Ravitharan Krishnadasan



Clinical Case 19



|| Case Presentation

- A 57-year-old female presents with enlarging bilateral cervical and axillary lymphadenopathy. Lymph nodes have been waxing and waning in size over the previous 2 years and are painless and asymptomatic. She denies fevers, chills, night sweats, weight loss, or discomfort. Physical exam is unremarkable except for firm, nontender lymphadenopathy; no splenomegaly. CBC reveals Hgb 13.6 g/dL, WBC 4000 k/ μ L, Plt 260 k/ μ L. The peripheral smear was unremarkable.

|| Case Presentation (Continued) ||

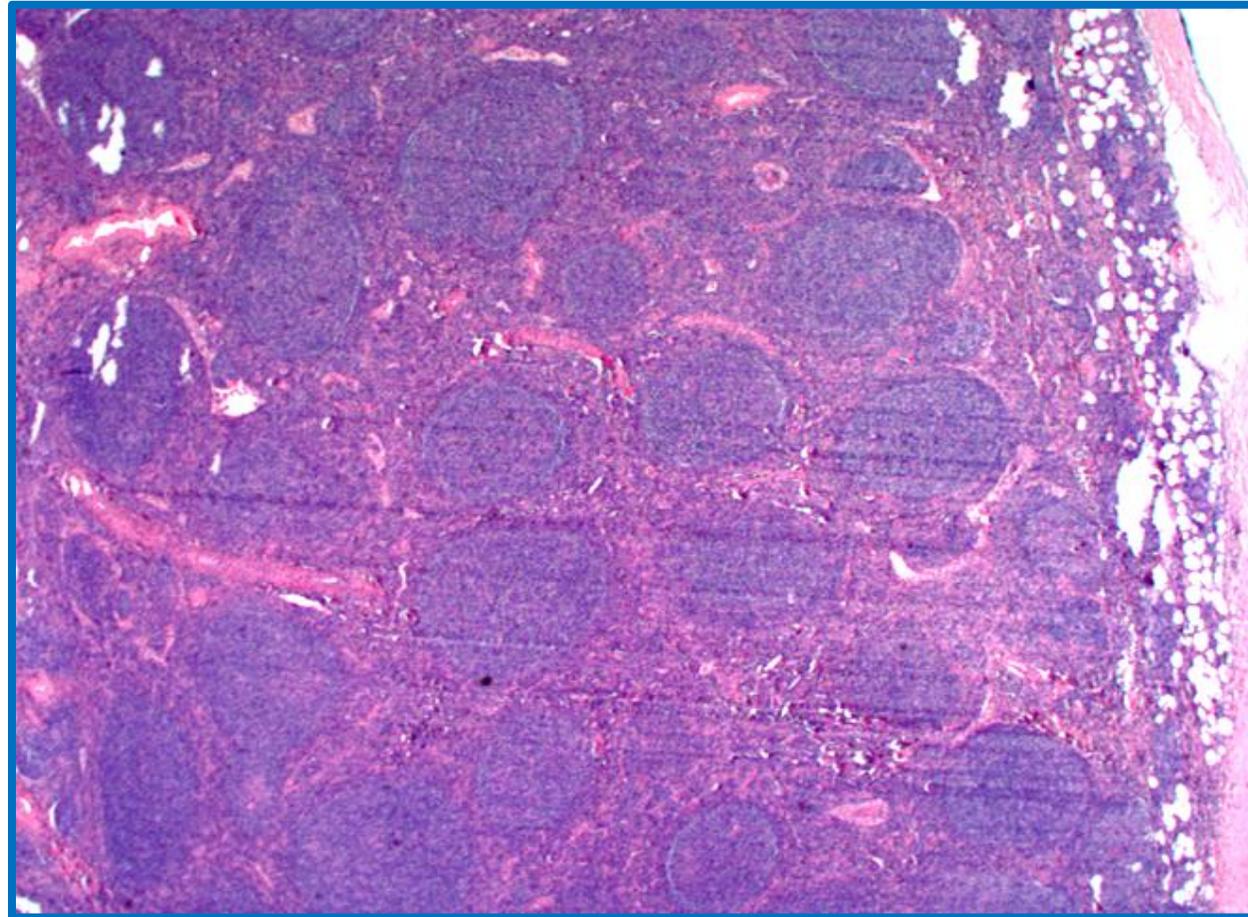
- **Which of the following is the best next step in evaluation?**
 - A. Whole body PET-CT scan
 - B. Bone marrow biopsy and aspiration
 - C. Fine needle aspiration of lymph node
 - D. Surgical excisional lymph node biopsy
 - E. Observation

|| Case Presentation (Continued) ||

- **Which of the following is the best next step in evaluation?**
 - A. Whole body PET-CT scan
 - B. Bone marrow biopsy and aspiration
 - C. Fine needle aspiration of lymph node
 - D. Surgical excisional lymph node biopsy**
 - E. Observation

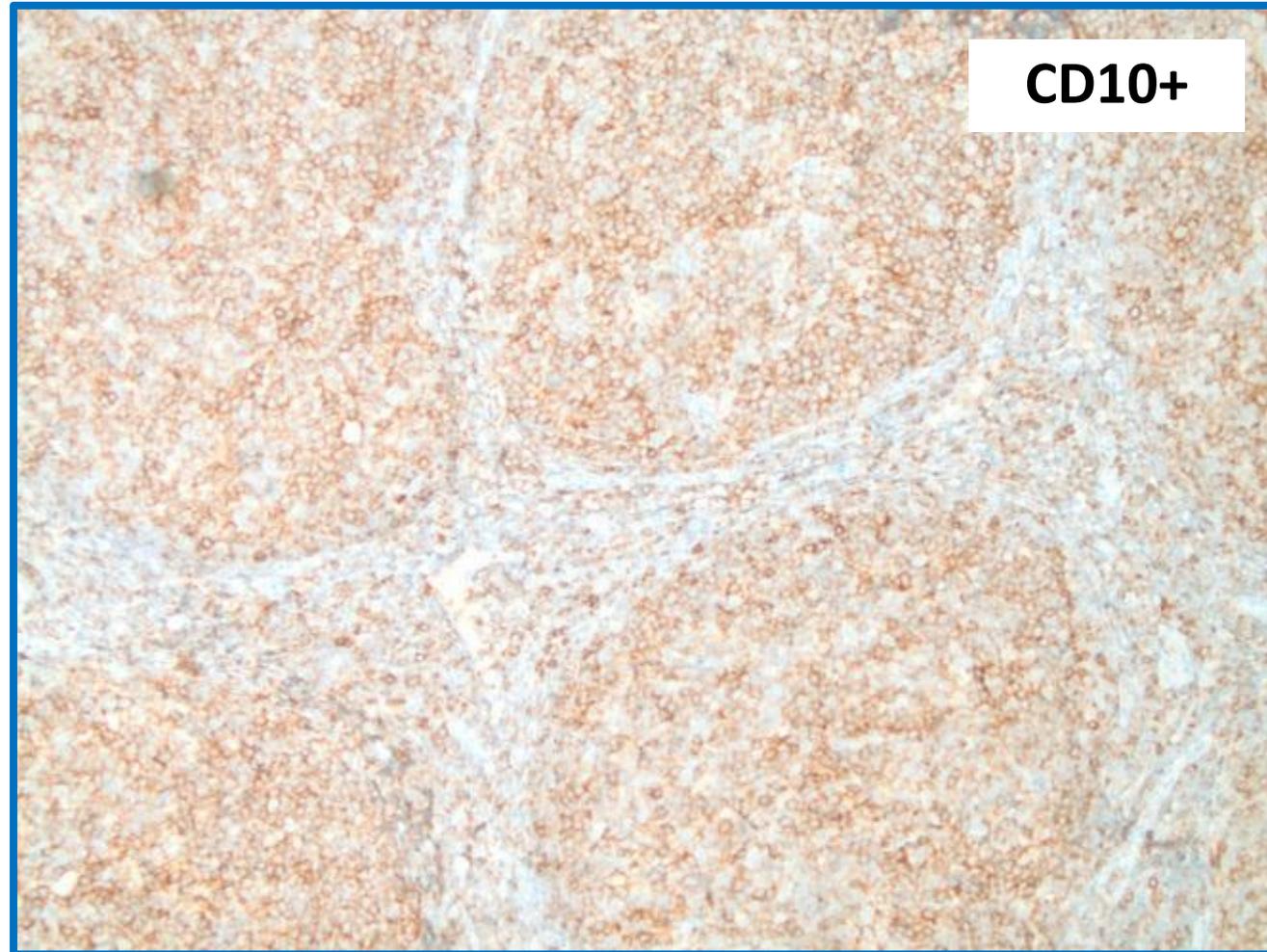
Observing LN architecture is critical in the diagnostic evaluation of non-Hodgkin lymphoma. If not possible (e.g., retroperitoneal LAD), core biopsy can be obtained.

|| Lymph Node Biopsy

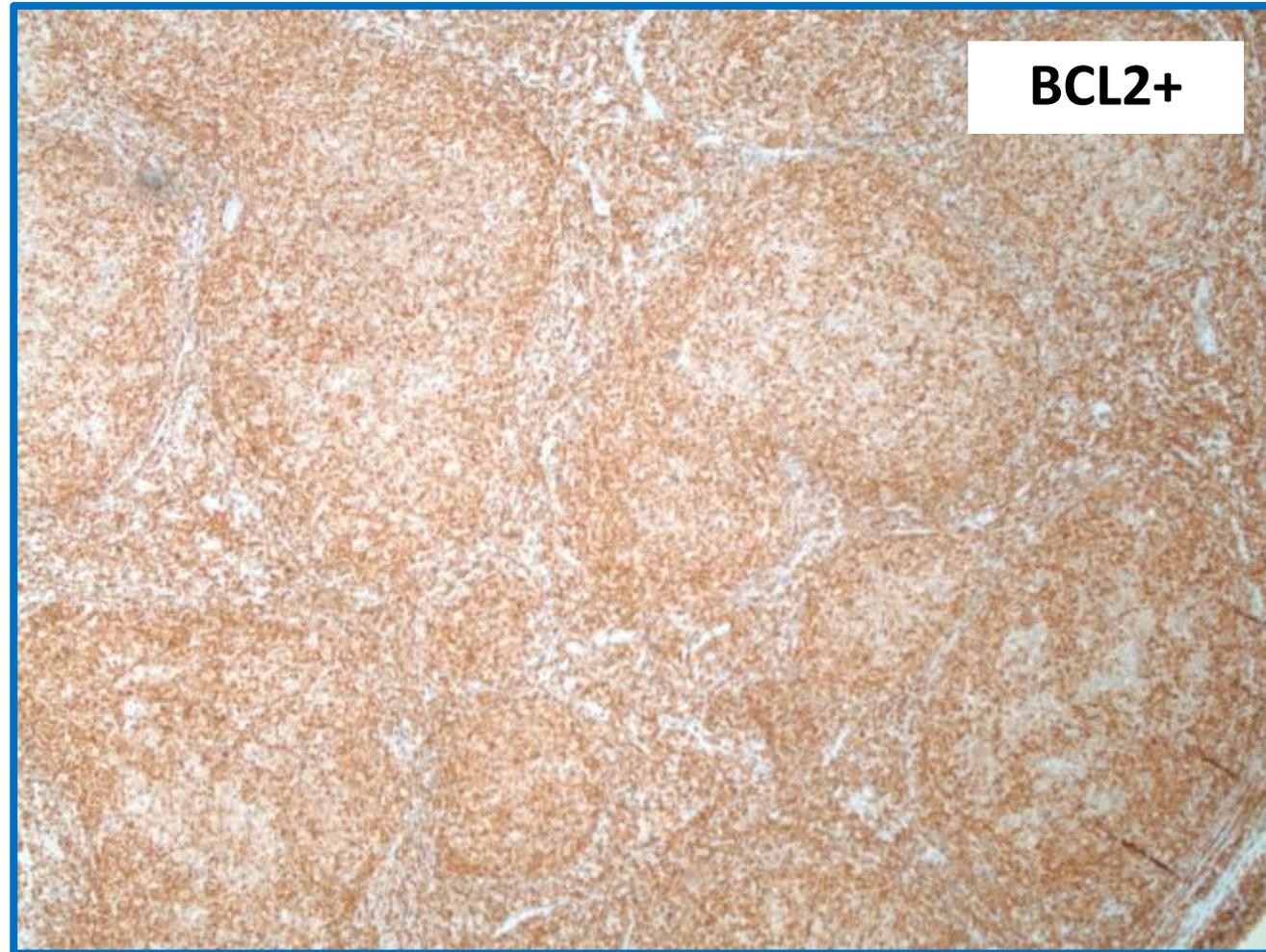


Uniformly densely packed follicles

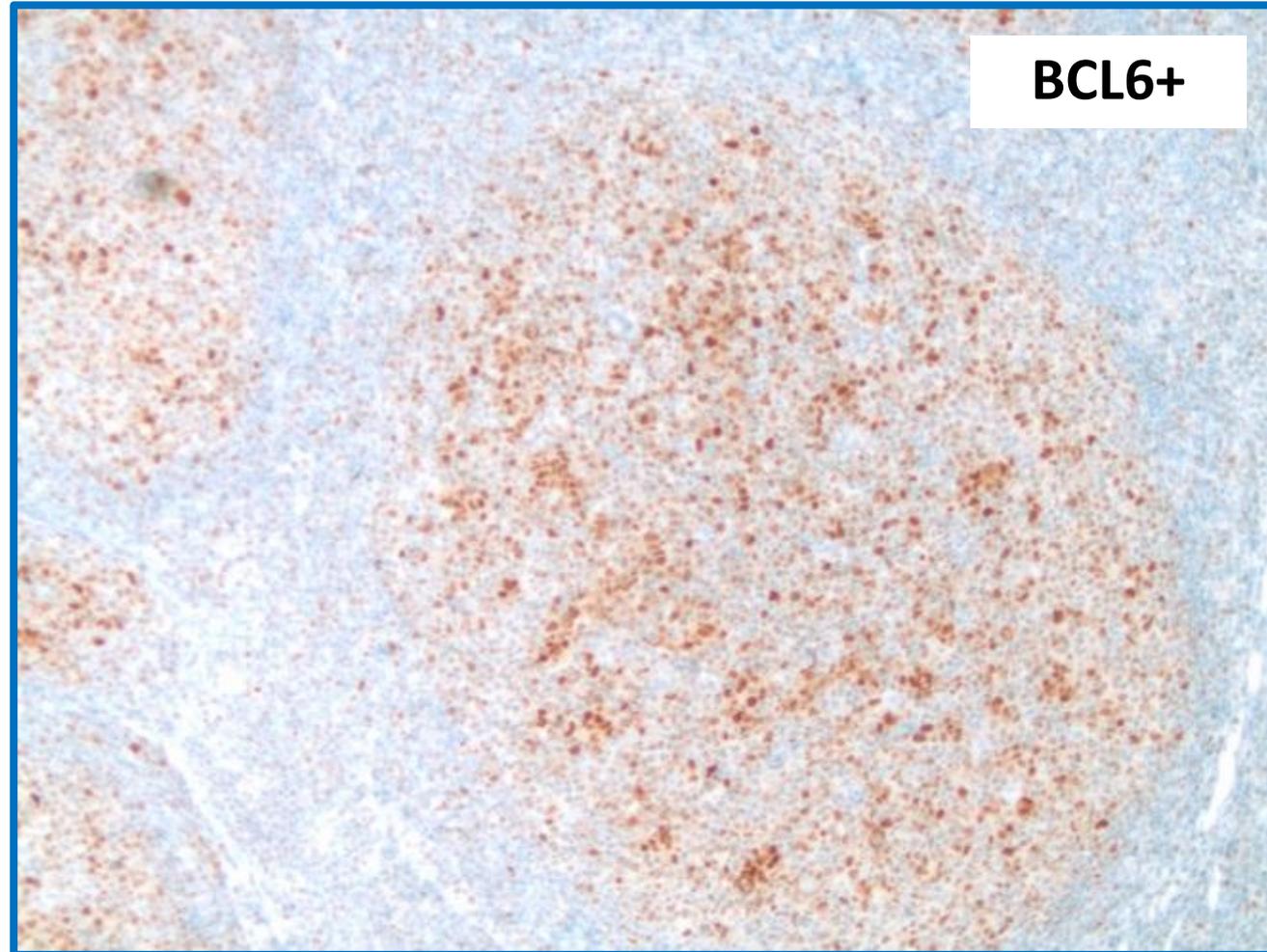
|| Lymph Node Biopsy (Continued) ||



|| Lymph Node Biopsy (Continued) ||



|| Lymph Node Biopsy (Continued) ||



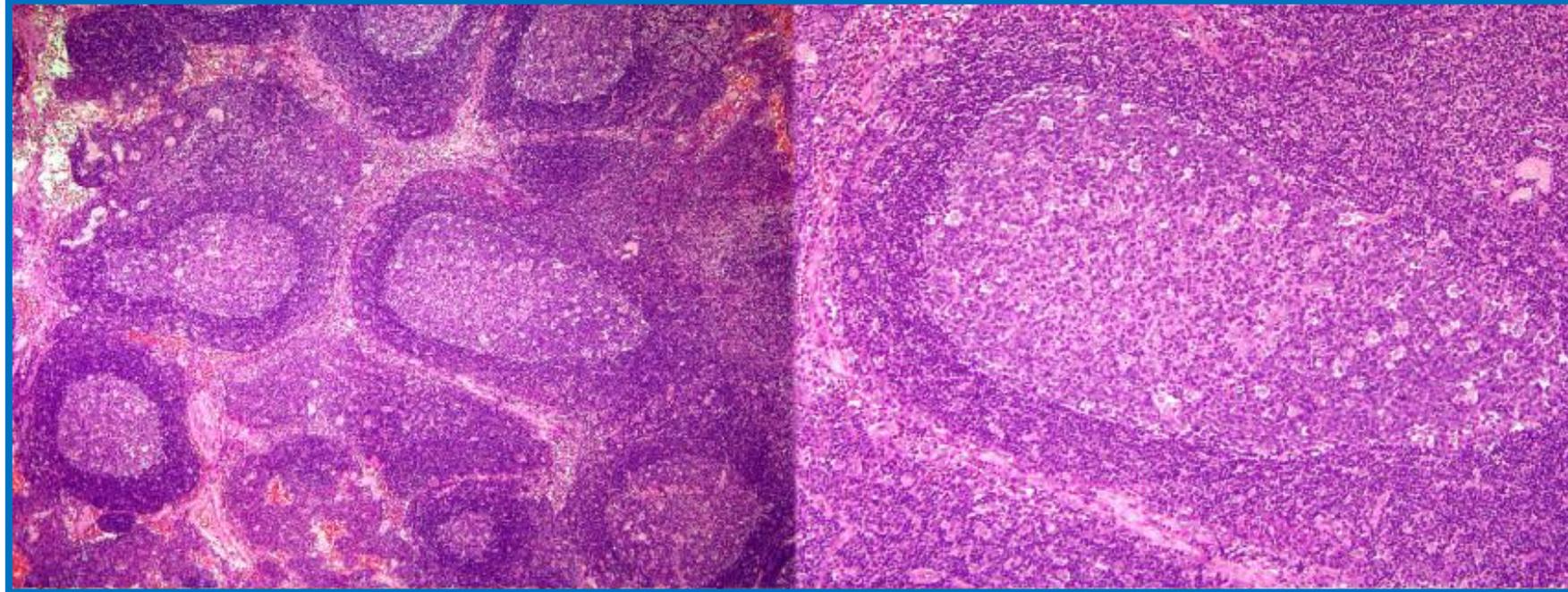
|| Lymph Node Biopsy (Continued) ||

- **Given the patient's history, lymph node biopsy morphology, and positive staining for CD10, BCL2, and BCL6, which of the following is the most likely diagnosis?**
 - A. Mantle cell lymphoma
 - B. Reactive follicular hyperplasia
 - C. Hodgkin lymphoma
 - D. Diffuse large B-cell lymphoma
 - E. Follicular lymphoma

|| Lymph Node Biopsy (Continued) ||

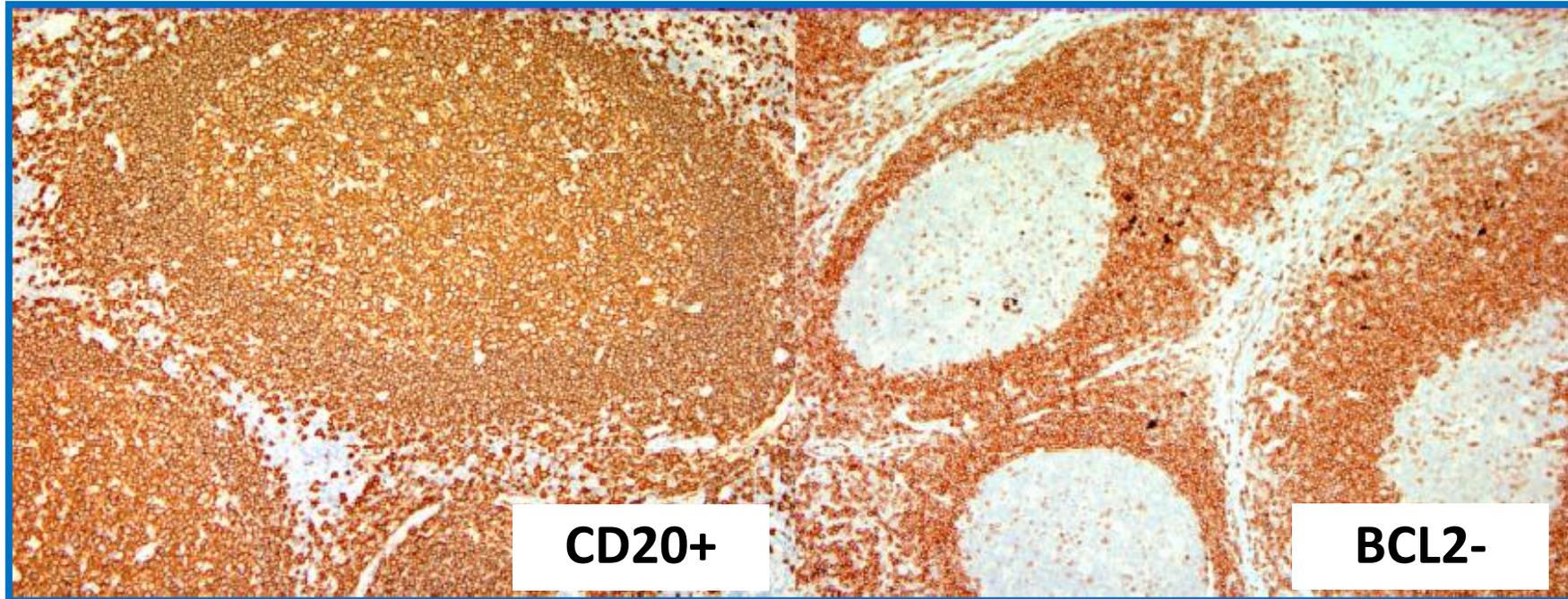
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 - A. Mantle cell lymphoma
 - B. Reactive follicular hyperplasia
 - C. Hodgkin lymphoma
 - D. Diffuse large B-cell lymphoma
 - E. Follicular lymphoma**

Reactive Follicular Hyperplasia (RFH)



In contrast to follicular lymphoma, RFH is characterized by multiple lymphoid follicles, variable in size and shape, with preserved mantle and marginal zones. The reactive follicle is composed of a heterogeneous population of centrocytes, centroblasts, immunoblasts, admixed tingible-body macrophages, and intact, normal polarization into pale and dark zones according to the dominant cell population.

Reactive Follicular Hyperplasia (RFH) (Continued)

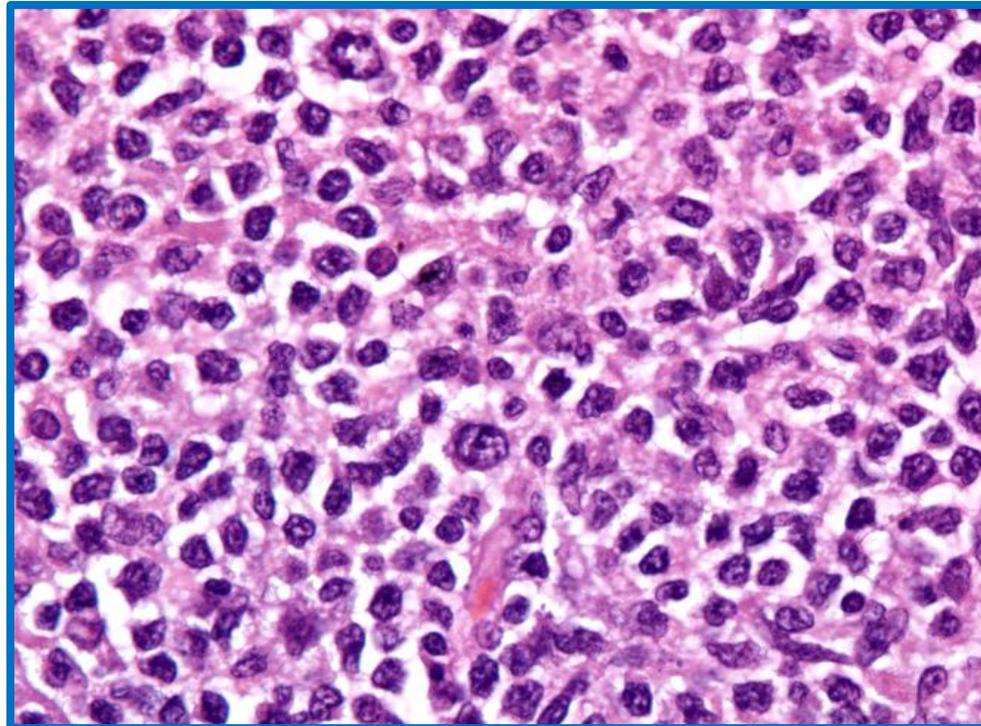


The follicle in RFH stains positive for CD20, and does not aberrantly coexpress BCL-2.

Follicular Lymphoma Grading

- Pathology reveals <15 centroblasts per high-power field. At which grade would you classify this lymphoma based on the WHO Grading System?

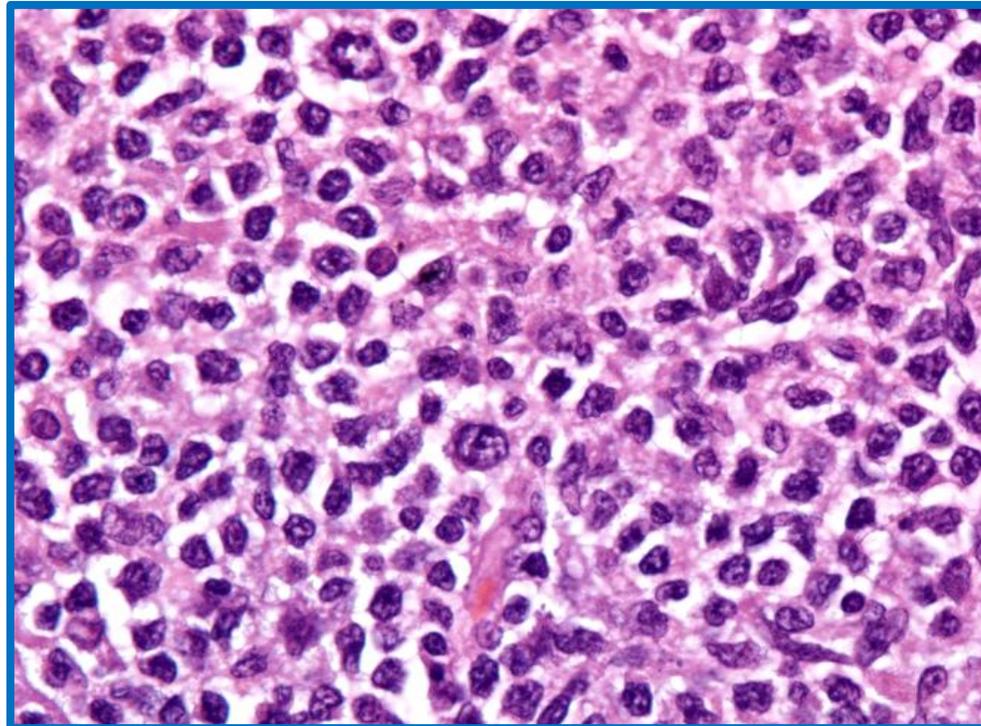
- A. Grade 1–2
- B. Grade 3a
- C. Grade 3b
- D. Grade 4



|| Follicular Lymphoma Grading (Continued) ||

- **Pathology reveals <15 centroblasts per high-power field. At which grade would you classify this lymphoma based on the WHO Grading System?**

- A. Grade 1–2
- B. Grade 3a
- C. Grade 3b
- D. Grade 4



WHO Follicular Lymphoma Grading System

Grade	Histology	Cell type
1	0–5 centroblasts/hpf	Follicular small cleaved
2	6–15 centroblasts/hpf	Follicular mixed
3a	>15 centroblasts/hpf with centrocytes present	Follicular large cell
3b	Solid sheets of centroblasts	Follicular large cell

hpf = high powered field

World Health Organization Follicular Lymphoma Tumor Grading System (2008).

|| Cytogenetics



- **Which of the following translocations is associated with follicular lymphoma?**
 - A. t(9;22)
 - B. t(14;18)
 - C. t(11;14)
 - D. t(15;17)
 - E. t(8;14)

|| Cytogenetics (Continued) ||

- Which of the following translocations is associated with follicular lymphoma?
 - A. t(9;22) (Ph+ B-ALL or CML)
 - B. t(14;18)**
 - C. t(11;14) (Mantle cell lymphoma)
 - D. t(15;17) (Acute promyelocytic leukemia)
 - E. t(8;14) (Burkitt lymphoma)

|| Staging



- **PET-CT reveals increased activity in the bilateral anterior cervical chain and right axillary lymph nodes. There is no evidence of involvement below the diaphragm. Using the Lugano Classification system, at what stage of follicular lymphoma is this patient?**
 - A. Stage I
 - B. Stage II
 - C. Stage III
 - D. Stage IV

|| Staging (Continued) ||

- **PET-CT reveals increased activity in the bilateral anterior cervical chain and right axillary lymph nodes. There is no evidence of involvement below the diaphragm. Using the Lugano Classification system, at what stage of follicular lymphoma is this patient?**
 - A. Stage I
 - B. Stage II**
 - C. Stage III
 - D. Stage IV

Lugano Classification System

Stage		Involvement	Extranodal status
Limited	I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
	II	≥2 nodal groups on same side of diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
	II bulky [#]	≥2 nodal groups on same side of diaphragm with “bulky” disease	N/A
Advanced	III	Nodes on both sides of diaphragm; nodes above the diaphragm with spleen involvement	N/A
	IV	Additional noncontiguous extralymphatic involvement	N/A

Extent of disease determined by PET-CT. Tonsils, Waldeyer’s ring, and spleen are considered nodal tissue.

[#] Whether Stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors

J Clin Oncol 2014;32(27):3059-67.

Follicular Lymphoma International Prognostic Index (FLIPI) Score and Overall Survival

Poor Prognostic Factors	FLIPI Score (Number of Factors*)	5-Year Overall Survival	10-Year Overall Survival
Age ≥ 60 years	0–1 = Low risk	91%	71%
LDH above normal			
Hemoglobin < 12 g/dL			
Ann Arbor Stage III or IV nodal sites > 4	2 = Intermediate risk	78%	51%
	≥ 3 = High risk	53%	36%

Blood. 2004;104(5):1258-1265.

|| Treatment



- **Which of the following is the best next step in treatment for her asymptomatic Stage II follicular lymphoma?**
 - A. Watchful waiting
 - B. Prednisone
 - C. Rituximab
 - D. R-CHOP
 - E. Total lymph node radiation

|| Treatment (Continued) ||

- **Which of the following is the best next step in treatment for her asymptomatic Stage II follicular lymphoma?**
 - A. Watchful waiting**
 - B. Prednisone
 - C. Rituximab
 - D. R-CHOP
 - E. Total lymph node radiation

|| Follow-Up and Management ||

Patient is closely observed for the following 2 years, and then presents with night sweats and new abdominal pain. Physical exam reveals enlarging cervical and axillary lymphadenopathy with new splenomegaly; PET-CT with stable axillary and cervical lymphadenopathy but new increased uptake in an enlarged spleen. She is physically fit with good performance status.

- **Which of the following would be an appropriate choice in management at this point?**
 - A. Continued watchful waiting
 - B. Rituximab, Cyclophosphamide, Vincristine, Prednisone
 - C. Bendamustine, Rituximab
 - D. Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
 - E. B, C, or D

|| Follow-Up and Management (Continued) ||

Patient is closely observed for the following 2 years, and then presents with night sweats and new abdominal pain. Physical exam reveals enlarging cervical and axillary lymphadenopathy with new splenomegaly; PET-CT with stable axillary and cervical lymphadenopathy but new increased uptake in an enlarged spleen. She is physically fit with good performance status.

- **Which of the following would be an appropriate choice in management at this point?**
 - A. Continued watchful waiting
 - B. Rituximab, Cyclophosphamide, Vincristine, Prednisone
 - C. Bendamustine, Rituximab
 - D. Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
 - E. **B, C, or D**

Frontline Treatment Regimens

Frontline Treatment: Asymptomatic Patients

Stage IA or Limited Stage IIA: Involved-site radiation therapy

Clinical observation if potential toxicity of radiation outweighs clinical benefit

Frontline Treatment: Symptomatic, Fit Patients

Bendamustine + rituximab (often preferred first-line therapy based on improved PFS and side effect profile). *Lancet*. 2013; 381:1203-1210. *Blood* 2014;123:2944-2952.

RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). *J Clin Oncol* 2004;22:4711-4716. *Blood* 2005;106:3725-3732.

RCVP (rituximab, cyclophosphamide, vincristine, prednisone). *J Clin Oncol* 2008;26:4579-4586.

Rituximab (375 mg/m² weekly for 4 doses). *J Clin Oncol* 2002;20:4261-4267. *Blood* 2001;97:101-106. *J Clin Oncol* 2010;28:4480-4484. *Lancet Oncology* 2014;15:424-435.

Frontline Treatment: Symptomatic, Elderly, or Unfit Patients

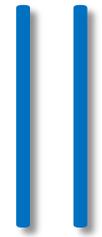
Rituximab (375 mg/m² weekly for 4 doses)

Single-agent alkylators (e.g., chlorambucil or cyclophosphamide) ± rituximab. *J Clin Oncol* 2003;21:5-15.

Companion Case for Chapter 38

Follicular Lymphoma

*Asha Balakrishnan
and
Celeste Bello*



Clinical Case 20

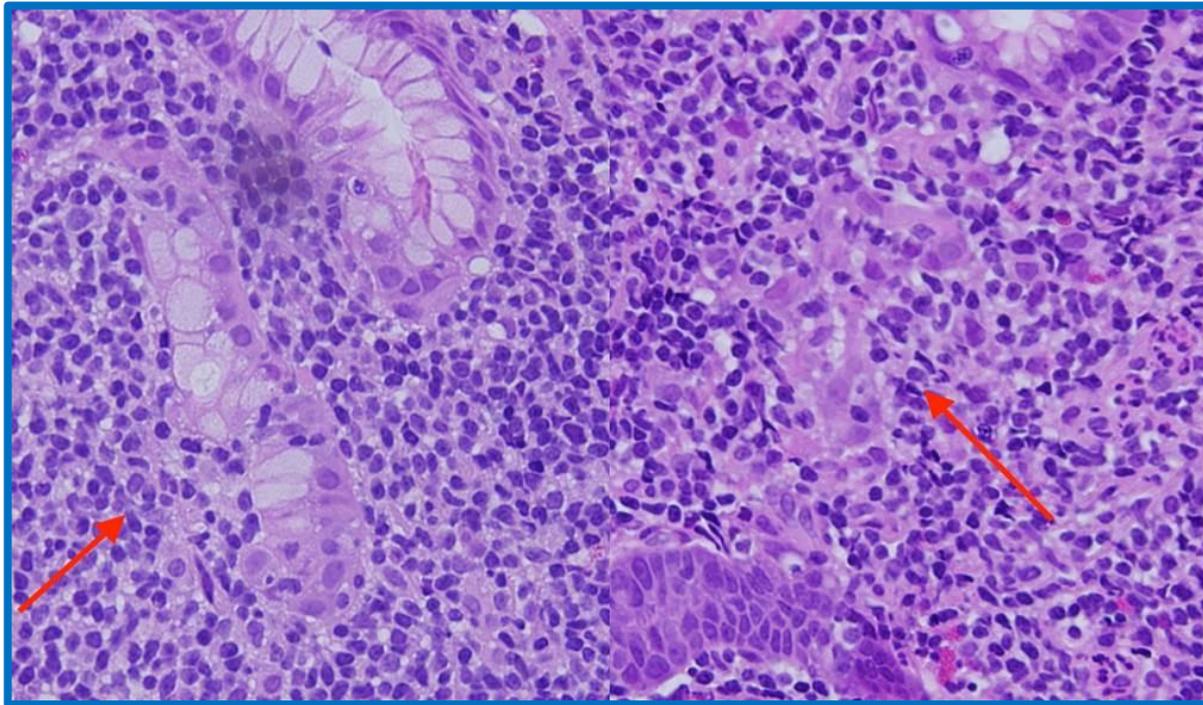


|| Case Presentation

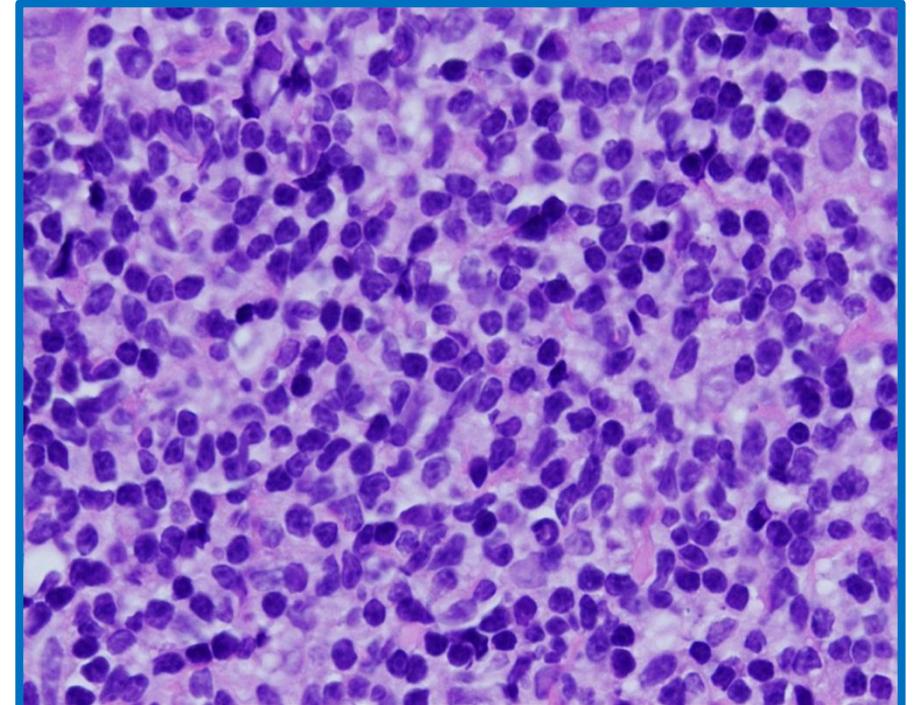
- A 62-year-old Caucasian woman presents with symptoms of worsening cough and workup including CT chest is suggestive of bilateral pulmonary scarring and upper esophageal wall thickening. She has a complaint of occasional heartburn but denies any dysphagia, weight loss, night sweats, or abdominal pain. The esophageal wall thickening is further evaluated with an EGD that reveals normal esophagus and evidence of chronic inflammation in the body and antrum of the stomach. These sites are biopsied. CT chest/abdomen/pelvis is negative for any evidence of metastatic disease. Her physical examination is normal and lab work is unremarkable with WBC count of 6.36 k/ μ L, Hgb 12.8 g/dL, HCT 40.5%, MCV 91.2 fL, and normal LDH and uric acid levels.

EGD - Biopsy from Body of the Stomach

Hematoxylin and eosin, x200 total magnification. Arrow= lymphoepithelial lesions



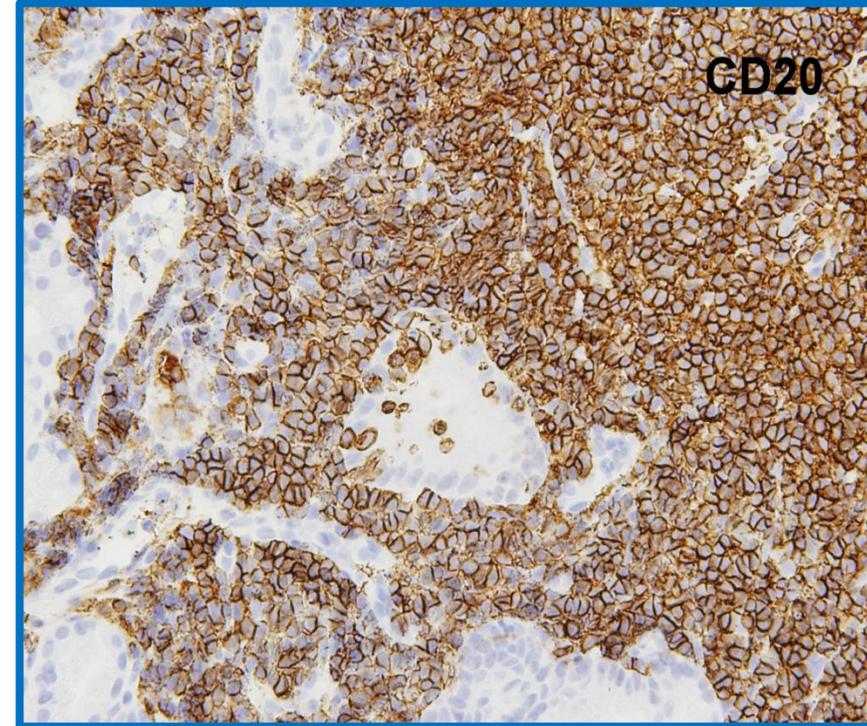
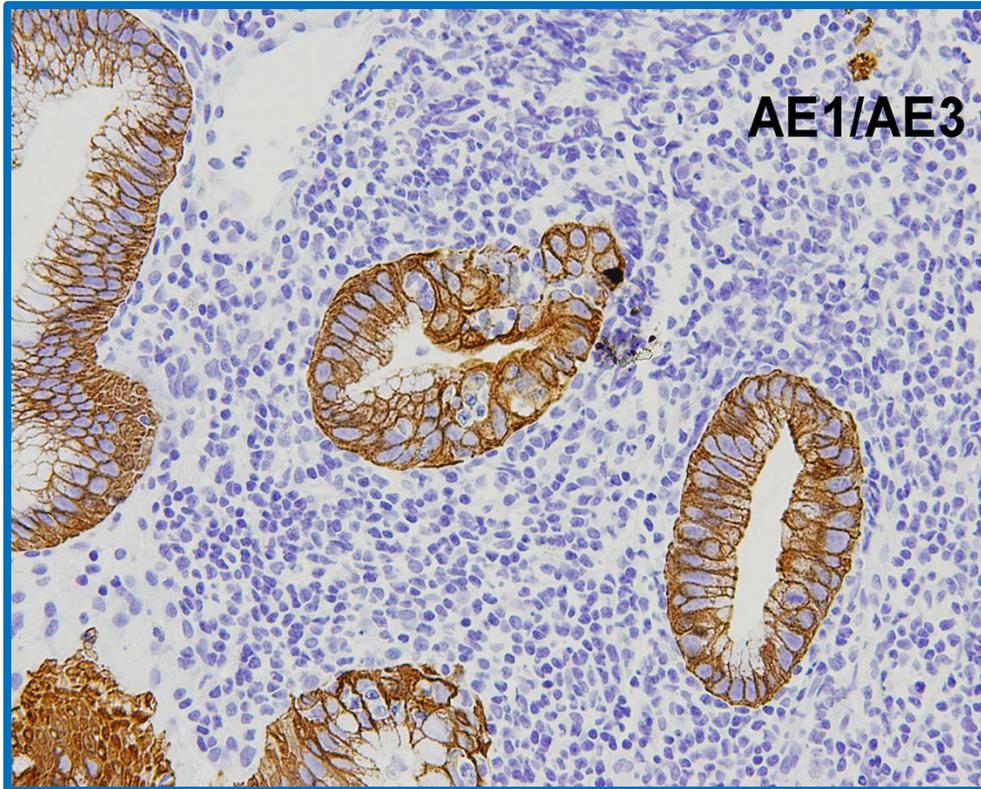
Hematoxylin and eosin, x400 total mag.



Pathology: There is proliferation of small- to intermediate-sized lymphoid cells. The cells have indented nuclei with inconspicuous nucleoli and abundant pale/clear cytoplasm, giving the cells a “monocytoid” appearance. The infiltrate often invades epithelial structures, forming lymphoepithelial lesions.

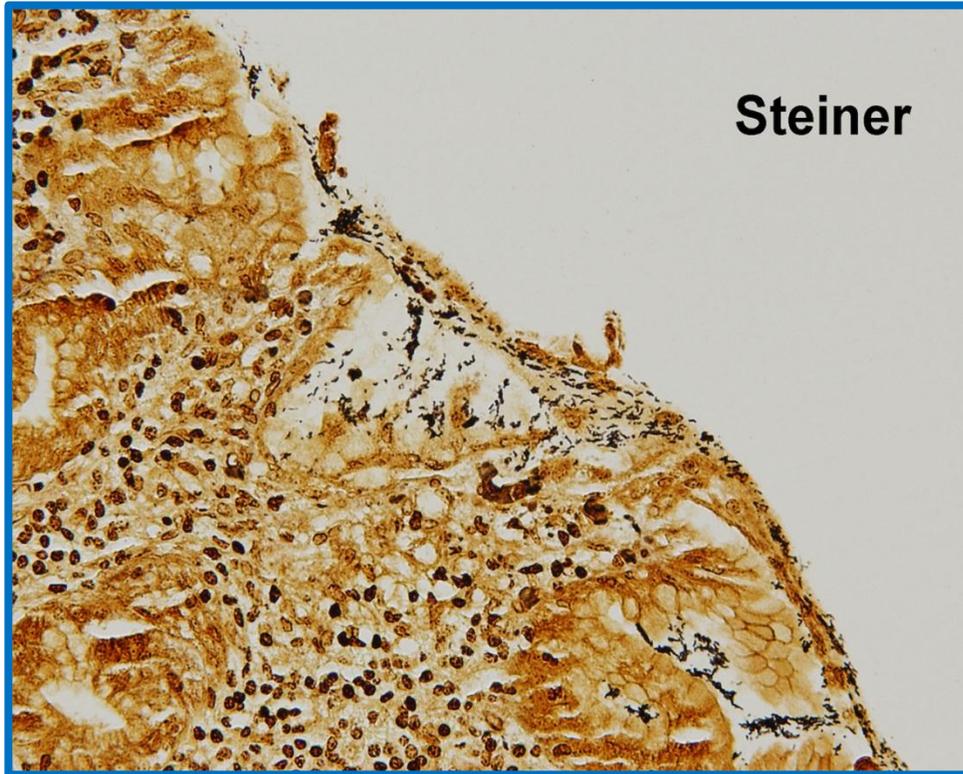
Special and IHC Staining

Pancytokeratin stain demonstrating a lymphoepithelial lesion

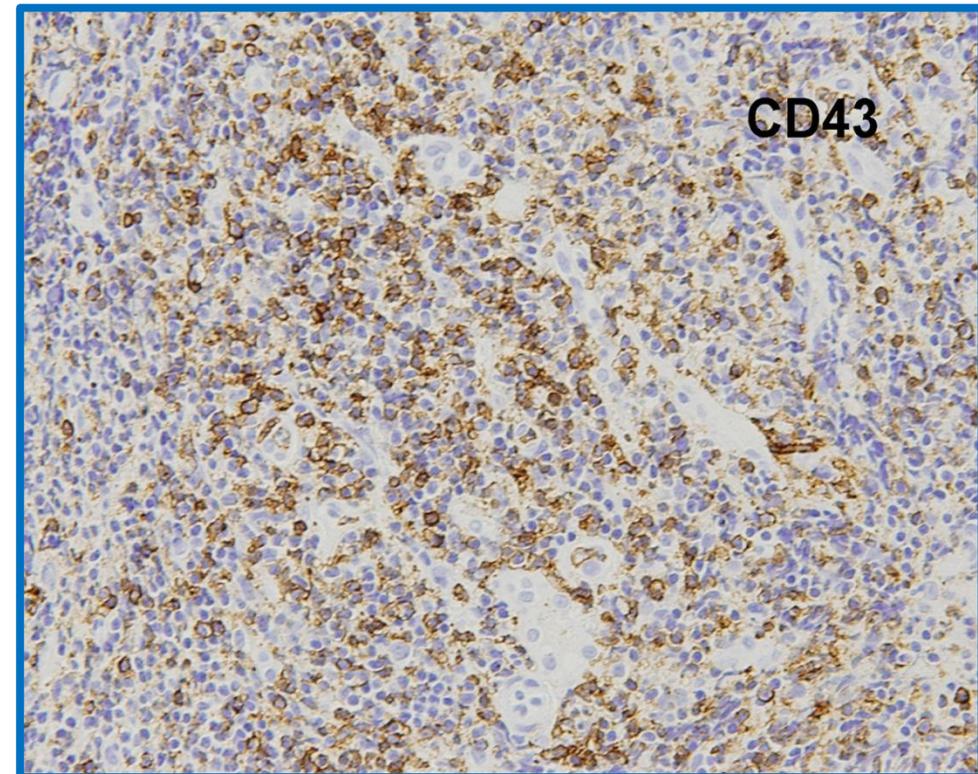


CD20: Shows the neoplastic infiltrate is strongly and diffusely positive for CD20, indicating B-cell lineage. Also, neoplastic lymphocytes are within the glandular epithelium at the center of the picture (lymphoepithelial lesion).

|| Special and IHC Staining (Continued) ||

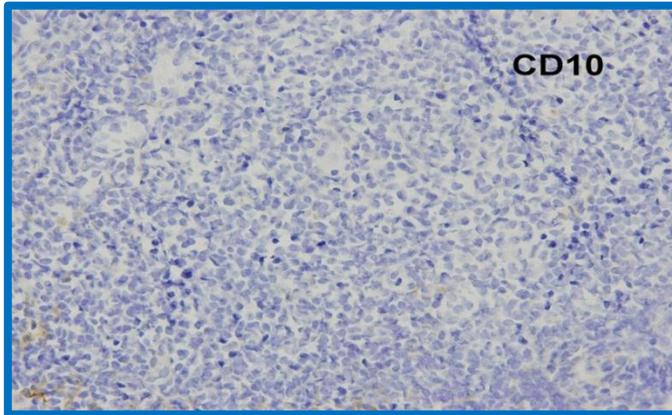


Steiner stain: Silver stain demonstrating *helicobacter-like* organisms

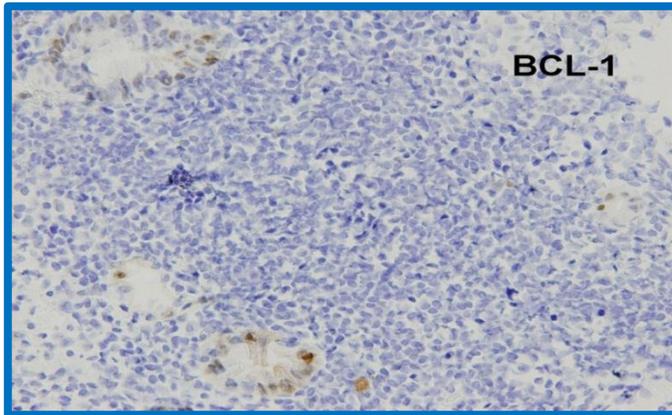


CD43 (Normal T-cell marker): Aberrant expression in a subset of the neoplastic infiltrate

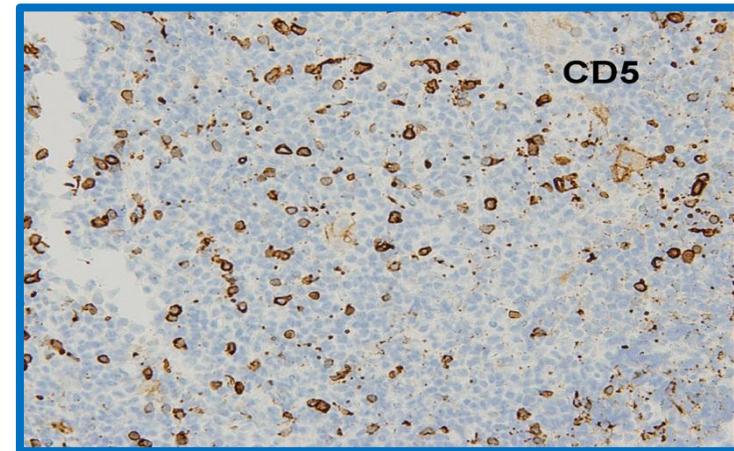
|| Special and IHC Staining (Continued) ||



CD10: Negative in the neoplastic infiltrate



BCL-1 (cyclin D1): Negative in the neoplastic infiltrate



CD5: Highlights background T cells;
Negative in the neoplastic infiltrate

|| Diagnosis

FLOW CYTOMETRY revealed: CD20+, CD19+, CD23+, CD3+(focal), CD43+ , CD10- , CD5- , BCL1-

Steiner silver special stain: positive for *helicobacter-like* organisms

Molecular analysis by PCR/FISH: positive for t(11;18)

- **Which of the following is the most likely diagnosis?**
 - A. Follicular lymphoma
 - B. Mantle cell lymphoma
 - C. Diffuse large B-cell lymphoma
 - D. Extranodal marginal zone lymphoma of mucosa-associated lymphoma tissue (MALT lymphoma)

|| Diagnosis (Continued) ||

- Which of the following is the most likely diagnosis?
 - A. Follicular lymphoma
 - B. Mantle cell lymphoma
 - C. Diffuse large B-cell lymphoma
 - D. **Extranodal marginal zone lymphoma of mucosa-associated lymphoma tissue (EN-MZL) or MALT lymphoma**

Diagnosis was made on the basis of:

- Clinical presentation—presented with symptoms of heartburn but largely had nonspecific symptoms
- Histopathological review of biopsy of tissue suggestive of lymphoepithelial lesions and IHC + for CD20 and CD43 and negative for CD5, CD10 and BCL-1
- Molecular analysis positive for t(11;18)

**Final diagnosis: MALT—Gastric location , *H. pylori* + and t(11;18)
Localized disease**

Differential Diagnosis

Extra-nodal marginal zone lymphoma (EN-MZL) needs to be distinguished from other indolent small B-cell lymphomas.

Lymphoma	CD19	CD20	CD5	CD10	CD23	Cyclin D1	Slg
MALT lymphoma	+	+	-	-	-	-	+
CLL/SLL	+	+(dim)	+	-	+	-	+(dim)
MCL	+	+	+	-	-	+	+
FL	+	+	-	+	-	-	+
LPL	+	+	-	-	-	-	+

CD20+ intensity and CD5- and CD10- help distinguish EN-MZL from CLL/SLL, MCL and FL.

To distinguish between LPL/WM and MZL: **MYD88 L265P** somatic mutation is widely prevalent in patients with Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL).

In a retrospective series, 123 patients with WM/LPL and MZL were enrolled and tested for Immunoglobulin heavy chain variable (IGHV) gene sequences and *MYD88* mutations. *MYD88* mutations were found in 67% of patients with WM/LPL (18/27) compared to 7% in patients with MALT, 4% splenic MZL, and 0% in nodal MZL.

|| Treatment



- **What is the best treatment plan ?**
 - A. Radiation therapy
 - B. *Helicobacter pylori* eradication with antimicrobials
 - C. Observation
 - D. Rituxan—either alone or in combination with other agents
 - E. Surgical excision
 - F. All of the above
 - G. Combination of above two treatments

|| Treatment (Continued) ||

- A. Radiation therapy
- B. Helicobacter pylori eradication antibiotics
- C. Observation
- D. Rituxan—either alone or in combination with other agents
- E. Surgical excision
- F. All of the above
- G. Combination of above two treatments**

Given that she has gastric MALT that is *H. pylori* positive, the first line of treatment will be with triple therapy (proton pump inhibitor + clarithromycin + amoxicillin). *H. pylori* eradication with antibiotics results in lymphoma regression in 70% to 95% of patients with localized disease. The 5-year OS rate with *H. pylori* eradication was 90% to 95% with a 5-year disease-free survival (DFS) and event-free survival (EFS) rate of 75% to 80%. There have been late relapses noted. Patients with t(11;18), t(1;14) or t(11;14) are associated with poor response to antibiotics. However, a trial of antibiotics is warranted, but if the patient is symptomatic (as in our case), treatment with radiation therapy should be initiated as first-line treatment .

|| Prognosis



- **What prognostic markers contribute to treatment response with antibiotics in this patient?**
 - A. t(11;18) translocation
 - B. Depth of involvement of tumor in the gastric wall as determined by EUS
 - C. Advanced disease—Stage IIIE/IV
 - D. A and B
 - E. A and C

|| Prognosis (Continued) ||

- **What prognostic markers contribute to treatment response with antibiotics in this patient?**
 - A. t(11;18) translocation
 - B. Depth of involvement of tumor in the gastric wall as determined by EUS
 - C. Advanced disease—Stage IIIE/IV
 - D. A and B**
 - E. A and C
- t(11;18) is the most common translocation implicated in the pathogenesis of MALT lymphoma and frequently detected in pulmonary and gastric MALT lymphomas. It has been associated with disseminated disease and resistance to antibiotics and so, if the patient is symptomatic, more aggressive therapy such as RT should be attempted as first-line.
- Endoscopic ultrasound (EUS) informs about the depth of involvement of gastric wall and presence of locally involved lymph nodes. EUS is useful in predicting the efficacy of *H. pylori* eradication treatment and the likelihood of response is related to depth of tumor invasion.
- Other poor prognostic factors are advanced disease and severely symptomatic patient.

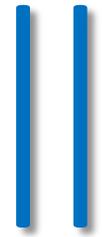
|| Current Patient Status and Follow-Up ||

- The patient receives involved-field radiation therapy (IFRT) to the body of the stomach (30 Grays/10 fractions) as first-line of treatment.
- She is followed up in 3 months after completion of RT with a repeat EGD, gastric biopsy, *and* testing for *H. pylori*.
- The biopsy reveals benign gastric tissue and *H. pylori* status is negative on biopsy.

Companion Case for Chapter 42

Mucosa-Associated Lymphoid Tissue Lymphoma

*Ridhi Gupta,
Matthew Mastrodomenico,
Nishan Tchekmedyian,
and
Saurabh Chhabra*



Clinical Case 21

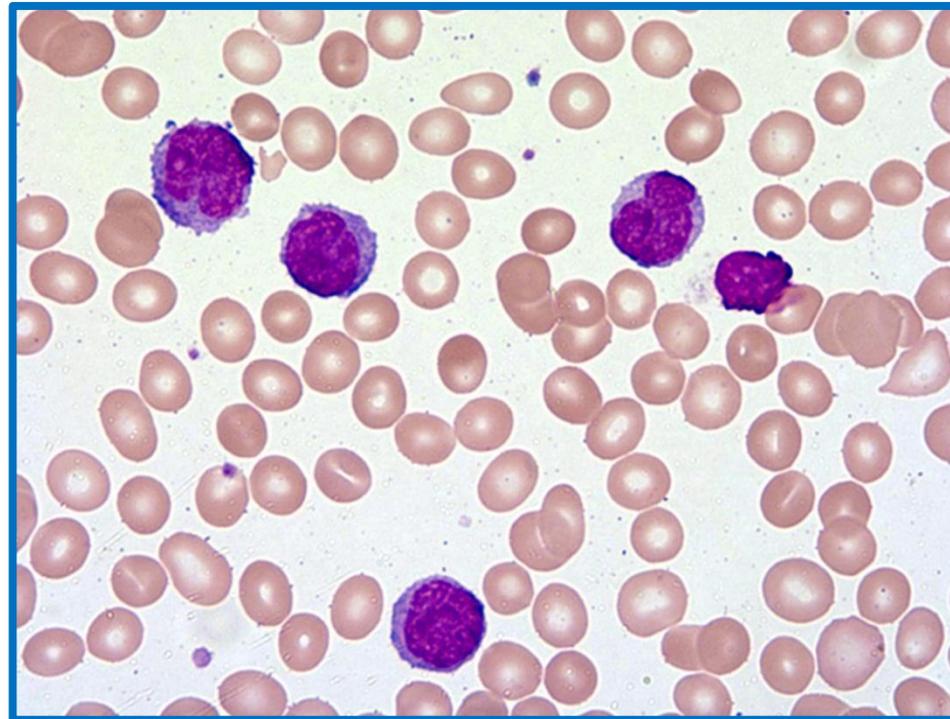


|| Case Presentation

- A-60-year-old male with PMH of coronary artery disease presents with severe fatigue and shortness of breath. He presented to hospital and had a CBC performed that reveals a WBC of 46.3 k/uL with 82% lymphocytes, hemoglobin of 4.9 g/dL with MCV of 109.5 fL, and platelets of 109 k/μL. He denies any other symptoms of lymphadenopathy, fevers, chills, or weight loss. His exam reveals splenomegaly with a palpable spleen 2 cm below costal margin.

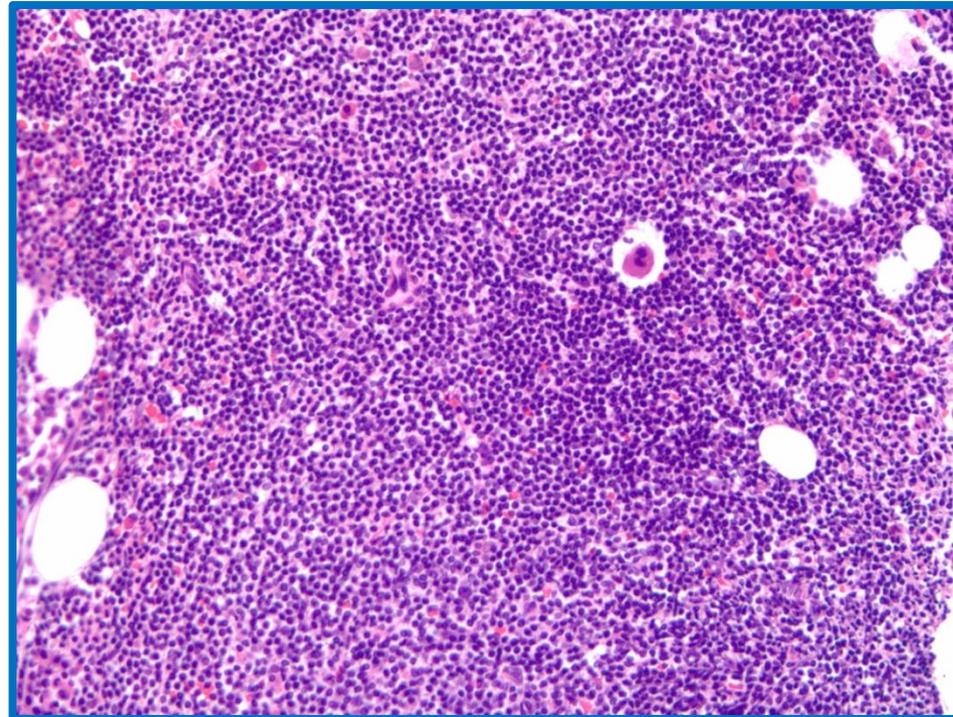
|| Case Presentation (Continued) ||

The peripheral blood shows several small lymphocytes with oval, lobated or convoluted nuclei, irregular nuclear cell borders, and a scant amount of amphophilic cytoplasm. Some lymphoid cells contain single prominent nuclei.



|| Bone Marrow Core Biopsy ||

The bone marrow core biopsy is markedly hypercellular and mostly effaced by sheets of small lymphocytes with round to oval nuclei, hyperchromasia, and scant amount of cytoplasm. Mitoses are rare. Few residual trilineage hematopoietic elements are present.



|| Flow Cytometry

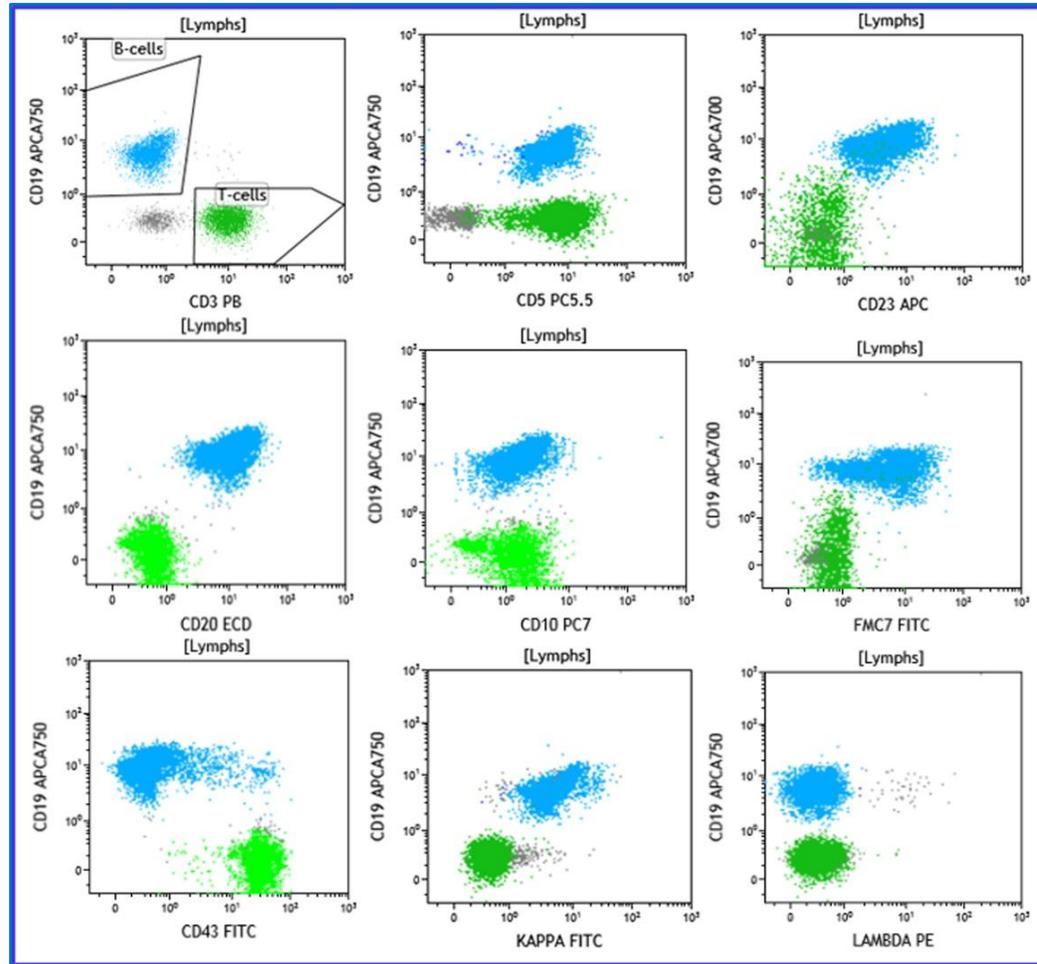


- Gating on lymphocyte region detects a distinct population of small lymphoid cells coexpressing CD19, CD5, CD23, FMC-7, moderate to bright CD20, and moderate surface kappa light chain. The neoplastic B-cells are negative for CD10 and surface lambda light chain and also reduced in CD43 expression.
- **Which of the following is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia
 - B. Chronic lymphocytic leukemia
 - C. Mantle cell lymphoma
 - D. B-lymphoblastic leukemia/lymphoma
 - E. Diffuse large B-cell lymphoma

|| Flow Cytometry (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia
 - B. Chronic lymphocytic leukemia**
 - C. Mantle cell lymphoma
 - D. B-lymphoblastic leukemia/lymphoma
 - E. Diffuse large B-cell lymphoma

Atypical CLL Immunophenotype



|| Atypical CLL Immunophenotype (Continued) ||

- Gating on lymphocyte region detects a distinct population of small lymphoid cells coexpressing CD19, CD5, CD23, FMC-7, moderate to bright CD20, and moderate surface kappa light chain, phenotypically most compatible with ATYPICAL chronic lymphocytic leukemia/small lymphocytic lymphoma. The neoplastic B-cells are negative for CD10 and surface lambda light chain and also reduced in CD43 expression.

|| Atypical CLL Immunophenotype (Continued) ||

- **This atypical immunophenotype is most consistent with what cytogenetic abnormality in CLL?**
 - A. 17p deletion
 - B. 11q deletion
 - C. Trisomy 12
 - D. 13q deletion
 - E. All of the above

|| Atypical CLL Immunophenotype (Continued) ||

- **This atypical immunophenotype is most consistent with what cytogenetic abnormality in CLL?**
 - A. 17p deletion
 - B. 11q deletion
 - C. Trisomy 12**
 - D. 13q deletion
 - E. All of the above
- Trisomy 12 can be seen in "atypical" CLL and often cells appear larger than the typical small lymphocytes that are seen in conventional CLL.
- Trisomy 12 is associated with brighter CD20 expression and expression of FMC-7 in the B-cell population.

|| Trisomy 12



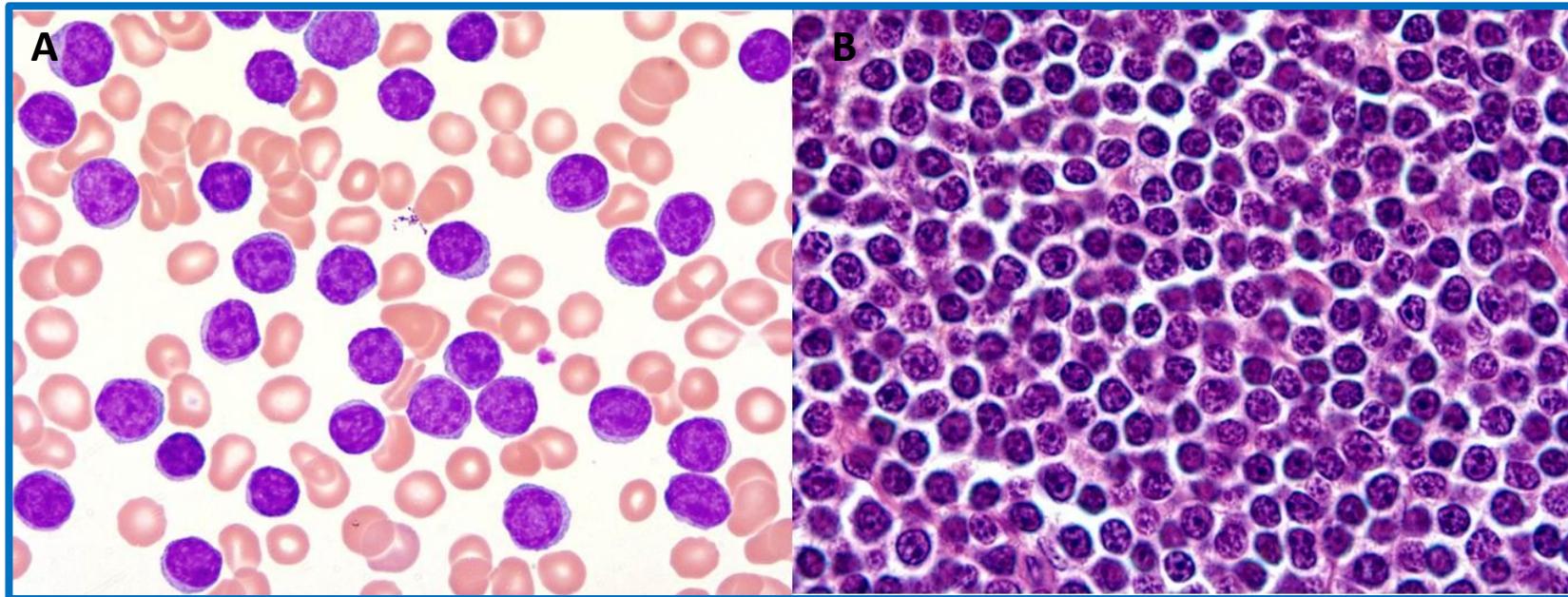
- **Trisomy 12 is associated with increased mutations in what gene?**
 - A. *TP53*
 - B. *NOTCH1*
 - C. *ATM*
 - D. *BIRC3*
 - E. *SF3B1*

|| Trisomy 12 (Continued) ||

- **Trisomy 12 in CLL is associated with increased mutations in what gene?**
 - A. *TP53*
 - B. *NOTCH1***
 - C. *ATM*
 - D. *BIRC3*
 - E. *SF3B1*

|| Typical CLL/SLL Morphology

In contrast to a representative case of atypical CLL, pictures below represent a case of typical CLL/SLL patients. A. Peripheral smear shows lymphocytosis consisting of small lymphocytes with round to oval nuclei, condensed chromatin with characteristic “fractured” or “earth-baked” or “soccer-ball” pattern, and scant cytoplasm. B, Lymph node biopsy shows sheets of monomorphic, neoplastic small lymphocytes with round to oval nuclei, clumped, mature chromatin, and scant cytoplasm. Mitotic figures are rare.



|| Differential Diagnosis

- Besides CD5, CLL and mantle cell lymphoma (MCL) express the B-cell antigens CD19 and CD20.
- Typical CLL also expresses CD23 without FMC-7 and shows characteristic dim expression of CD20 and dim surface immunoglobulin expression.
- MCL typically expresses bright CD20 and bright to moderate surface immunoglobulin(sIg), lacks CD23, and is FMC-7+.

|| Differential Diagnosis (Continued) ||

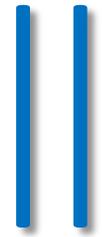
- **What test can be done to differentiate MCL from CLL/SLL?**
 - A. FISH for t(8;11)
 - B. FISH for t(8;14)
 - C. FISH for t(4;8)
 - D. FISH for t(4;11)
 - E. FISH for t(11;14)

|| Differential Diagnosis (Continued) ||

- **What test can be done to differentiate MCL from CLL/SLL?**
 - A. FISH for t(8;11)
 - B. FISH for t(8;14)
 - C. FISH for t(4;8)
 - D. FISH for t(4;11)
 - E. FISH for t(11;14)**
- In cases with variant phenotypes such as those lacking CD23 and/or showing FMC-7 positivity, accurate diagnosis often depends on testing for t(11;14)/IgH-CCND1, which should be positive in nearly all MCL cases and absent in CLL/SLL.

Companion Case for Chapter 39
Chronic Lymphocytic Leukemia/Small
Lymphocytic Lymphoma

*Ateefa Chaudhury
and
Javier Pinilla-Ibarz*



Clinical Case 22



|| Case Presentation



- A 56-year-old man is evaluated in the emergency room for fever and night sweats that have progressed over the past month and are now newly associated with dyspnea and severe fatigue.
- A CBC reveals pancytopenia and CT scan of the chest/abdomen/pelvis shows widespread lymphadenopathy. He is on cardiac monitor that reveals normal sinus rhythm.

|| Case Presentation (Continued) ||

- Labs ordered thus far reveal hyperkalemia at 5.9 mEq/L (*normal range: 3.7 to 5.2 mEq/L*), creatinine 1.5 mg/dL (*normal range: 0.7 to 1.2 mg/dL*), otherwise normal BMP including calcium and phosphorous. LDH is markedly elevated. He is pending admission and Oncology is consulted to evaluate the patient for likely malignancy.

|| Case Presentation (Continued) ||

- **What additional blood tests do you recommend at this time?**
 - A. TSH
 - B. Uric acid
 - C. Complete blood count
 - D. Peripheral smear

|| Case Presentation (Continued) ||

- **What additional blood tests do you recommend at this time?**
 - A. TSH
 - B. Uric acid**
 - C. Complete blood count
 - D. Peripheral smear

The patient has diffuse lymphadenopathy, pancytopenia, and elevated LDH which would all be consistent with an aggressive lymphoma. Therefore, the likelihood of tumor lysis syndrome (TLS) is very high. Furthermore, the patient has hyperkalemia and acute kidney injury (AKI), further suggesting TLS is possible. To continue the evaluation, uric acid should be tested.

|| Case Presentation (Continued) ||

The patient has elevated uric acid at 9 mg/dL (*normal range: 3.0 and 7.0 mg/dL*).

- **What TLS risk category applies to this case?**
 - A. Very low risk
 - B. Low risk
 - C. Intermediate risk
 - D. High risk

|| Case Presentation (Continued) ||

- **What TLS risk category applies to this case?**
 - A. Very low risk
 - B. Low risk
 - C. Intermediate risk
 - D. High risk**

The patient has three laboratory abnormalities, has elevated LDH and acute kidney injury, which is consistent with clinical TLS (especially in a patient with likely aggressive lymphoma).

|| Case Presentation (Continued) ||

- **What treatment do you recommend for this patient in terms of TLS?**
 - A. Hydration IV only, recheck labs next day
 - B. Hydration IV and Allopurinol, recheck labs next day
 - C. Hydration IV, Allopurinol, admit to Med/Surg bed, recheck labs BID
 - D. Hydration IV, Rasburicase, admit to telemetry, recheck labs in 8 hours
 - E. Hydration IV, Rasburicase, admit to ICU, recheck labs in 4 hours

|| Case Presentation (Continued) ||

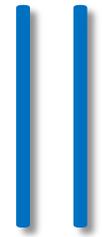
- **What treatment do you recommend for this patient in terms of TLS?**
 - A. Hydration IV only, recheck labs next day
 - B. Hydration IV and Allopurinol, recheck labs next day
 - C. Hydration IV, Allopurinol, admit to Med/Surg bed, recheck labs BID
 - D. Hydration IV, Rasburicase, admit to telemetry, recheck labs in 8 hours**
 - E. Hydration IV, Rasburicase, admit to ICU, recheck labs in 4 hours

Disease with high risk for TLS should be addressed as an inpatient. The patient should be treated with IV hydration, Rasburicase, and labs should be rechecked in 6 to 8 hours. He would also benefit from telemetry. The patient would also be started on allopurinol the following day.

Companion Case for Chapter 52

Tumor Lysis Syndrome

*Mintallah Haider,
Ateefa Chaudhury,
and
Michael Jaglal*



Clinical Case 23

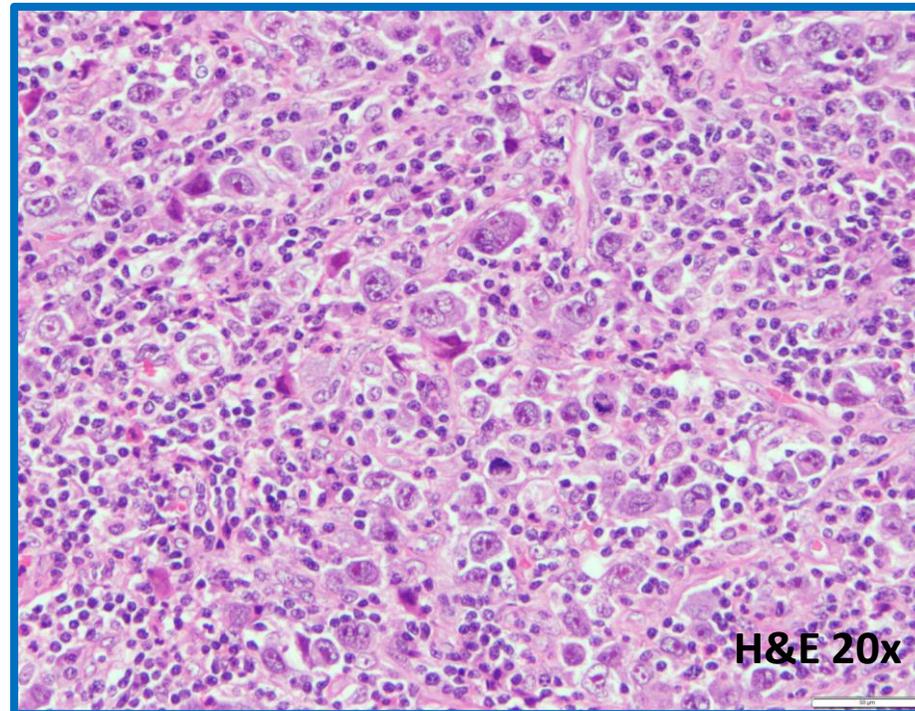


|| Case Presentation

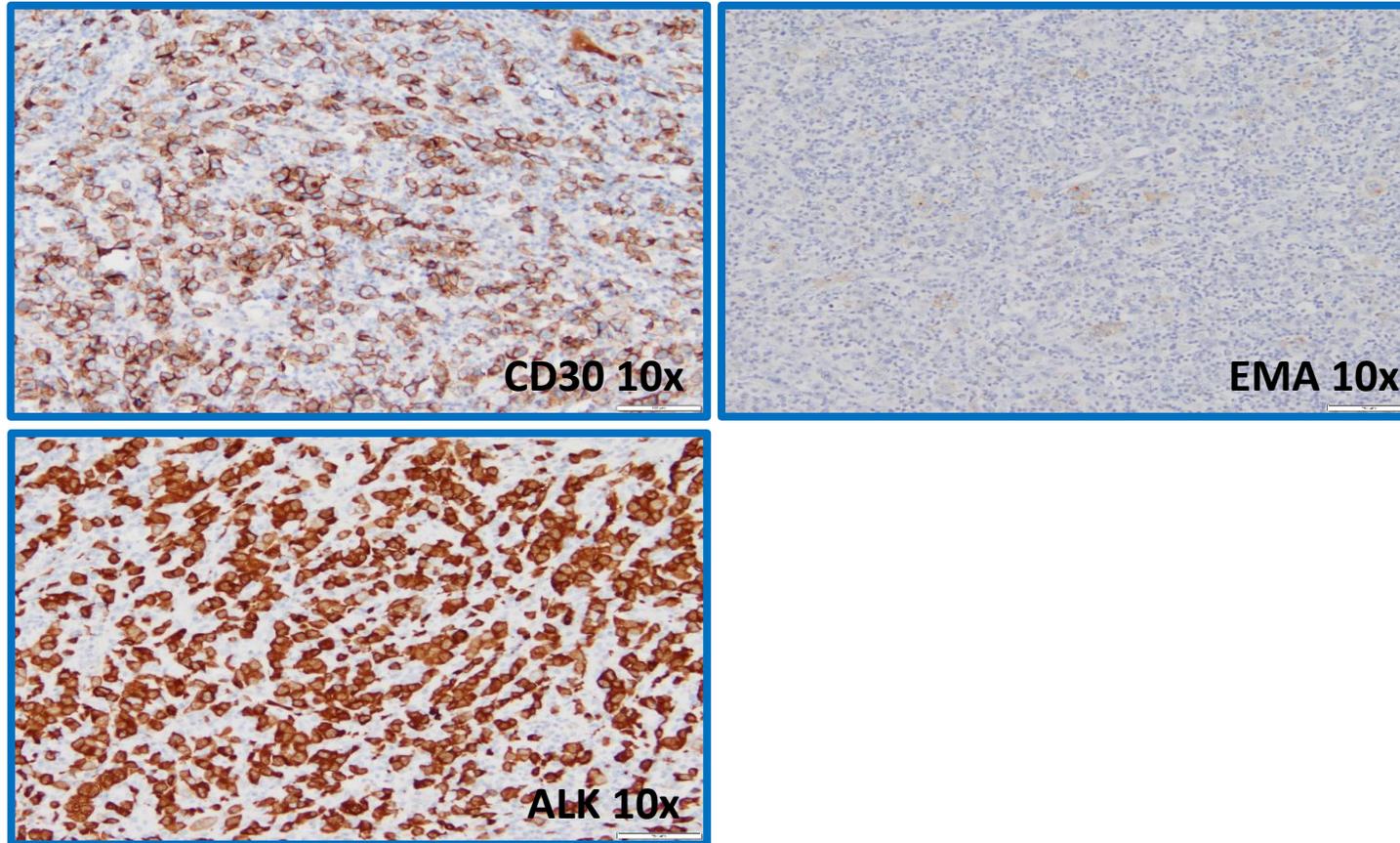
- A 25-year-old male with no significant past medical history presents with a 6-week history of fever, drenching night sweats, unintentional weight loss, and swollen painless lymph nodes of his neck and inguinal regions. Physical exam shows a thin male with bilateral cervical and inguinal lymphadenopathy. Abdominal exam is negative for organomegaly. A CBC showed a WBC of 8.6 k/ μ L with a normal differential, hemoglobin of 11.7 g/dL, MCV of 87 fL, and platelet count of 167 k/ μ L. The lactate dehydrogenase level is 346 U/L. Electrolytes and creatinine levels are within normal limits.

|| Lymph Node Extirpation ||

A biopsy of a cervical lymph node revealed sheets of large lymphoid cells surrounded by fibrous bands. The lymphoid cells had eccentric horseshoe- or kidney-shaped nuclei (“hallmark” cells) and intermediate nuclear:cytoplasmic ratio.



|| Immunohistochemical Studies ||



The neoplastic cells were negative for CD3.

|| Bone Marrow Core

- A bone marrow biopsy shows no morphologic or phenotypic evidence of lymphoproliferative disorder.

|| Bone Marrow Core (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Classical Hodgkin lymphoma (cHL), nodular-sclerosis
 - B. Diffuse large B-cell lymphoma (DLBCL)
 - C. Anaplastic large cell lymphoma, ALK positive (ALK+ ALCL)
 - D. Benign inflammatory infiltrate
 - E. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

|| Bone Marrow Core (Continued) ||

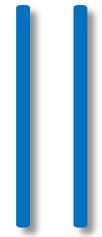
- **Which of the following is the most likely diagnosis?**
 - A. Classical Hodgkin lymphoma (cHL), nodular-sclerosis
 - B. Diffuse large B-cell lymphoma (DLBCL)
 - C. Anaplastic large cell lymphoma, ALK positive (ALK+ ALCL)**
 - D. Benign inflammatory infiltrate
 - E. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

|| Differential Diagnosis

- Classical Hodgkin lymphoma (cHL): cHL, particularly the nodular-sclerosis subtype, can morphologically be indistinguishable from ALK+ ALCL. Although cHL is B-cell derived, it usually doesn't express typical B-cell markers such as CD20 and CD45. Similar to ALCL, it expresses CD30. However in contrast to ALCL, cHL expresses weak PAX-5 and does not express EMA or ALK.
- ALK- ALCL: ALK- ALCLs have features similar to ALK+ ALCL but do not express ALK. ALK- ALCLs are genetically and clinically heterogeneous lymphomas seen usually in older adults.
- PTCL-NOS: The small cell variant of ALK+ ALCL can be misdiagnosed as PTCL-NOS. However, PTCL-NOS can express CD30, but is typically ALK and EMA negative.
- Benign inflammatory infiltrates: Histiocytic and small cell variants of ALK+ ALCL are more common in children and they are sometimes misdiagnosed as benign inflammatory infiltrates. Additional workup including immunohistochemical staining for CD30, EMA, and ALK is recommended.

Companion Case for Chapter 44
Anaplastic Large Cell Lymphoma, ALK
Positive

*Thomas Enzler
and
Changchun Deng*



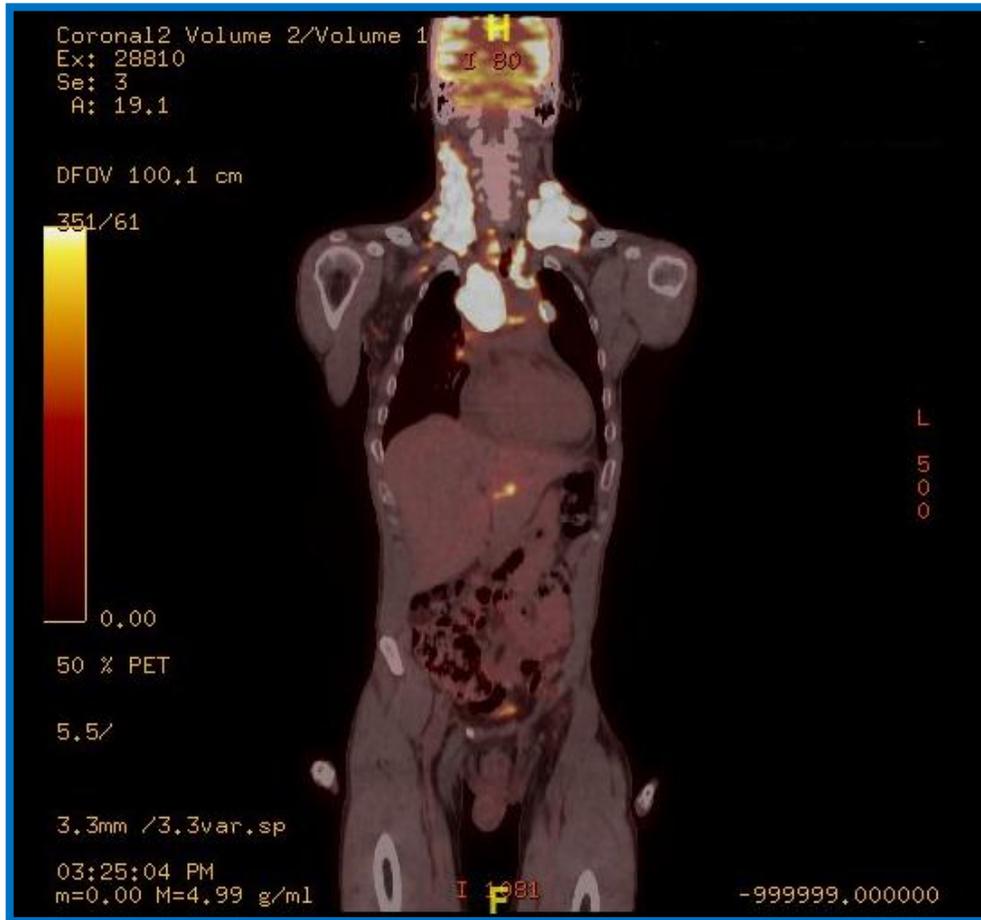
Clinical Case 24



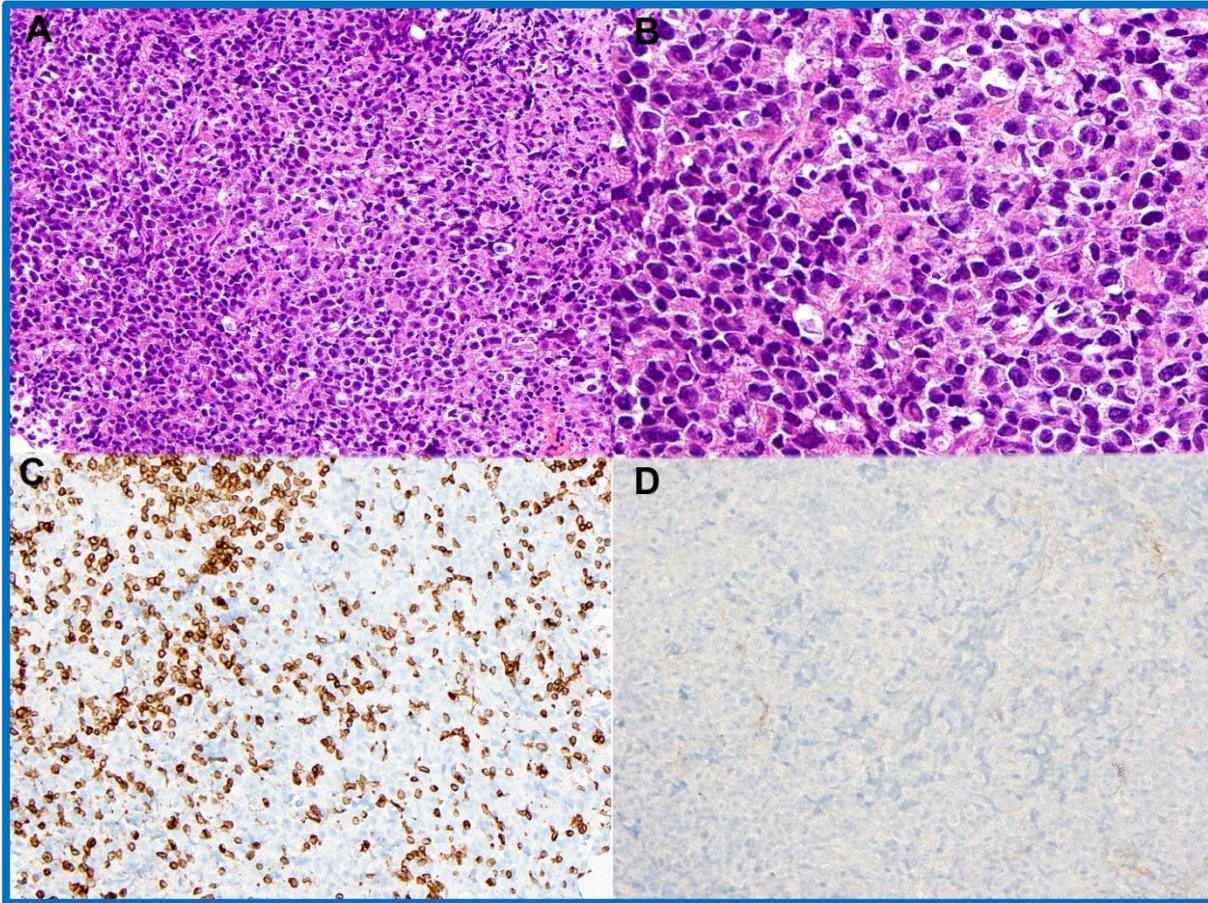
|| Case Presentation

- A 54-year-old woman with past medical history of hypertension presents to the ED complaining of progressive enlarging cervical and supraclavicular masses for the past 2 months, along with subjective fevers, orthopnea, and nocturnal diaphoresis. Her physical exam is positive for bilateral anterior cervical lymphadenopathy (LAD, largest LN was 4 x 5 cm), splenomegaly, and bilateral inguinal LAD. CBC reveals a WBC of 9.56 k/ μ L, Hgb 12 g/dL, MCV 101 fL, and platelet count of 156 k/ μ L with a normal WBC differential. A CMP is within normal limits; LDH 359 mg/dl and viral serologies are negative for hepatitis B/C and for HIV.
- CT scan of the neck, chest/abdomen, and pelvis reveals multiple enlarged bilateral cervical, supraclavicular, mediastinal, peripancreatic, retroperitoneal, and inguinal LAD.

|| PET-CT SCAN

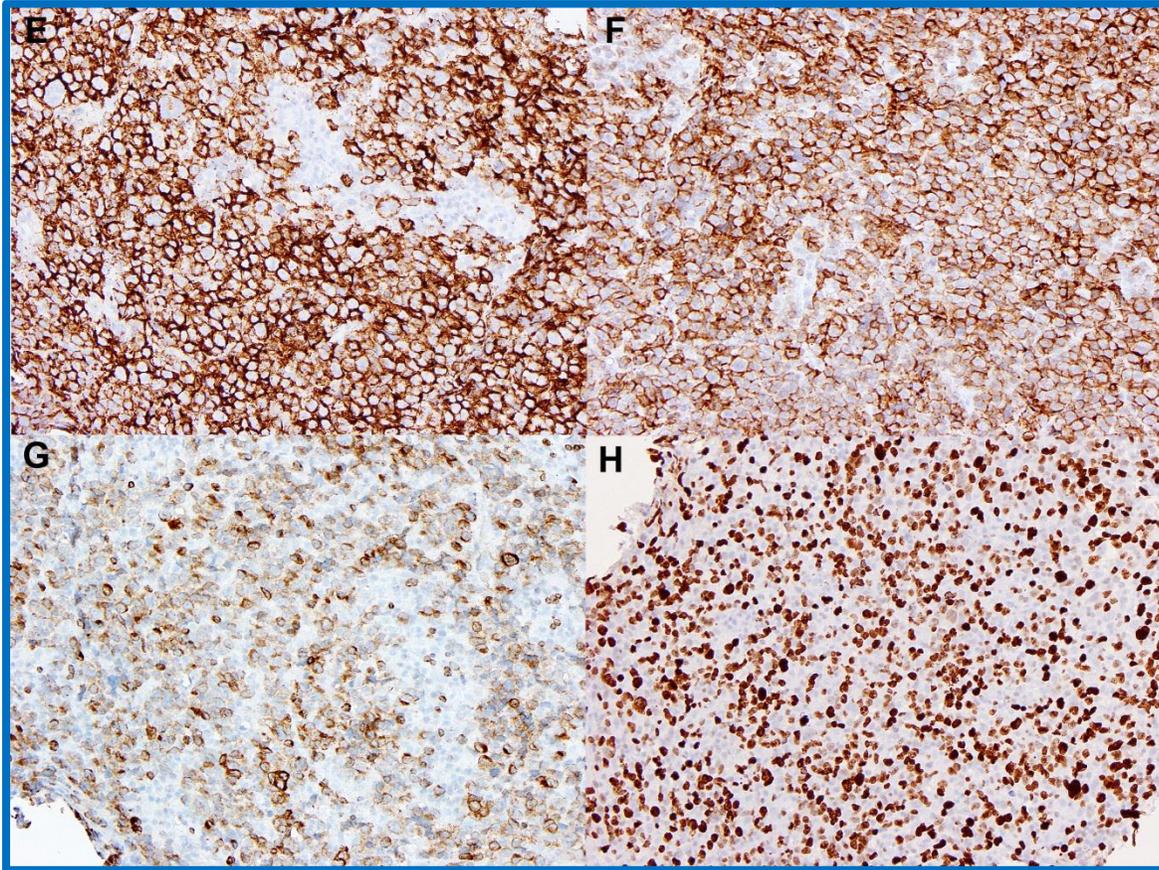


Left Supraclavicular Lymph Node Core Biopsy (1)



Sections show sheets of large atypical lymphoid cells with hyperchromatic nuclei, irregular nuclear contours, inconspicuous or small visible nuclei and variable amounts of eosinophilic cytoplasm (A & B, H&E, original magnification x200 and x400, respectively; C & D, immunoperoxidase, x200).

Left Supraclavicular Lymph Node Core Biopsy (2)



The atypical lymphoid cells are negative for CD3 and CD10, and positive for CD20, CD5 and BCL-2 (C through G, immunoperoxidase, x200). The Ki-67 proliferative index is high at approximately 80% (x200).

Left Supraclavicular Lymph Node Core Biopsy

Morphology and immunohistochemistry

- Diffuse infiltrate of large atypical lymphoid cells that are CD5(+), CD20(+), CD79a(+), PAX-5(+), BCL6(+), BCL2(+), CD23 (-), CD10(-), MUM-1(-) cyclin D1(-) and CD30(-). C-MYC shows 60% overexpression and the Ki-67 proliferative index is 80%.

Flow cytometry

- Flow cytometry identifies a population of kappa-restricted B-cells with CD19(+), variable CD20(+), CD22(+), CD5(+), CD10(-) and CD23(-).

Fluorescence in-situ hybridization (FISH)

- Normal for *BCL2*, *BCL6*, *IgH* and *c-MYC*

|| Bone Marrow Biopsy

- Diffuse infiltration with monoclonal B-cells with similar immunophenotype to the above LN biopsy
- **Which of the following is the most likely diagnosis?**
 - A. Mantle cell lymphoma
 - B. Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - C. B-lymphoblastic leukemia/lymphoma
 - D. Diffuse large B-cell lymphoma
 - E. Burkitt lymphoma

|| Bone Marrow Biopsy (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Mantle cell lymphoma
 - B. Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - C. B-lymphoblastic leukemia/lymphoma
 - D. Diffuse large B-cell lymphoma**
 - E. Burkitt lymphoma
- Primary CD5+ DLBCL comprises 5% to 10% of DLBCL and is characterized by older age at diagnosis, female preponderance, advanced stage, elevated LDH, more extranodal involvement, higher rates of CNS involvement, and inferior response to rituximab-based therapies.
- The main differential diagnoses are: CLL with Richter's transformation (usually loss of CD5 with persistent CD23 expression), mantle cell lymphoma (confirmed by cyclin D1 overexpression), intravascular large B-cell lymphoma, and secondary CD5+ DLBCL (acquired during DLBCL progression).

|| Treatment



- **Most of the primary CD5+ DLBCL belong to the activated B-cell (ABC) subtype. What first-line treatment would you recommend for a patient with stage IV DLBCL, ABC subtype?**
 - A. DA-EPOCH-R
 - B. R-CHOP
 - C. R-CHOP + lenalidomide (R2CHOP)
 - D. Clinical trial
 - E. R-CHOP + ibrutinib

|| Treatment (Continued) ||

- **Most of the primary CD5+ DLBCL belong to the activated B-cell (ABC) subtype. What first-line treatment would you recommend for a patient with stage IV DLBCL, ABC subtype?**
 - A. DA-EPOCH-R
 - B. R-CHOP**
 - C. R-CHOP + lenalidomide (R2CHOP)
 - D. Clinical trial
 - E. R-CHOP + ibrutinib
- ABC subtype DLBCL is associated with activated B-cell receptor (BCR) and upregulation of downstream Nuclear Factor Kappa B (NF- κ B).
- Multiple studies have demonstrated inferior clinical outcomes in patients with ABC subtype DLBCL when treated with frontline conventional chemoimmunotherapies (CIT).
- Even though several ongoing clinical trials have shown promising preliminary outcomes with novel CIT combinations (e.g., R-CHOP and ibrutinib), the current standard of care for first-line therapy of ABC-subtype DLBCL is R-CHOP.

|| Treatment (Continued) ||

- **The patient underwent treatment with six cycles of R-CHOP along with central nervous system (CNS) prophylaxis with intrathecal methotrexate and cytarabine. Which of the following is NOT an indication for CNS prophylaxis in DLBCL?**
 - A. Primary testicular involvement
 - B. Diffuse tonsillar infiltration
 - C. AIDS-related DLBCL with high LDH levels
 - D. Paranasal sinus involvement
 - E. Concurrent expression of MYC and BCL2 proteins

|| Treatment (Continued) ||

- **The patient underwent treatment with six cycles of R-CHOP along with central nervous system (CNS) prophylaxis with intrathecal methotrexate and cytarabine. Which of the following is NOT an indication for CNS prophylaxis in DLBCL?**
 - A. Primary testicular involvement
 - B. Diffuse tonsillar infiltration**
 - C. AIDS-related DLBCL with high LDH levels
 - D. Paranasal sinus involvement
 - E. Concurrent expression of MYC and BCL2 proteins
- CNS prophylaxis is recommended in the following situations: Systemic DLBCL with involvement of the testicle, epidural space, bone marrow, paranasal sinuses, kidney, adrenal gland, and/or ≥ 2 extranodal sites with elevated LDH. CNS prophylaxis is also recommended in HIV-related lymphomas or DLBCL with coexpression of MYC and BCL2.
- Therapeutic choices for CNS prophylaxis are: four to eight doses of IT methotrexate and/or cytarabine or systemic methotrexate (3–3.5 grams/m²) during the course of the treatment. Systemic methotrexate reaches higher intra-parenchymal drug concentration.

|| Gray Zone Lymphoma

- **Regarding “gray zone” lymphomas (GZL), which of the following statements is *false*?**
 - A. This tumor has overlapping molecular characteristics between classical Hodgkin lymphoma and primary mediastinal B-cell lymphoma.
 - B. Immunohistochemistry will usually show CD45(+), CD30(+), CD15(+), CD20(+), CD79a(+), CD10(-) and ALK(-).
 - C. GZL presents with a large mediastinal mass with or without supraclavicular lymph nodes, and is more common in males between the ages of 20 and 40 years.
 - D. ABVD without radiation therapy is the treatment of choice in order to avoid the risk of secondary malignancies.

|| Gray Zone Lymphoma (Continued) ||

- **Regarding gray zone lymphomas (GZL), which of the following statements is false?**
 - A. This tumor has overlapping molecular characteristics between classical Hodgkin lymphoma (cHL) and primary mediastinal B-cell lymphoma (PMBL).
 - B. Immunohistochemistry will usually show CD45(+), CD30(+), CD15(+), CD20(+), CD79a(+), CD10(-) and ALK(-).
 - C. GZL presents with a large mediastinal mass with or without supraclavicular lymph nodes, and is more common in males between the ages of 20 and 40 years.
 - D. ABVD without radiation therapy is the treatment of choice in order to avoid the risk of secondary malignancies.**
- Studies of gene expression profiling demonstrate overlap between PMBL and cHL and, interestingly, mediastinal gray zone lymphomas, with pathologic features that are intermediate and transitional between PMBL and classical Hodgkin lymphoma, nodular sclerosis subtype, have been described.
- If morphology is similar to PMBL, EBV+ and/or CD15+ and/or absence of CD20 suggest the diagnosis of GZL. If morphology is similar to cHL, strong CD20 positivity and other B-cell markers and absence of CD15 suggest the diagnosis of GZL.
- There is no consensus for the treatment of GZL. Rituximab-anthracycline containing therapy might be helpful, along with radiotherapy consolidation in localized disease (i.e., residual mediastinal mass).

|| Case Presentation

- **A 71-year-old woman with a past medical history of stage IV DLBCL, treated with R-CHOP x 6 and achieved a CR 6 years ago, presents with a 6-week history of an enlarging, painless, supraclavicular mass. Physical exam reveals 2.5 cm right supraclavicular lymphadenopathy (LAD). Otherwise, the physical exam is normal. A PET-CT scan demonstrates no other LAD or any other organ involvement, and laboratory workup is unremarkable.**

What would be the most appropriate therapy for this patient?

- A. Excisional biopsy
- B. Involved site radiation therapy (ISRT)
- C. R-ESHAP salvaged chemotherapy
- D. Rituximab monotherapy
- E. Fine needle aspiration (FNA) and follow-up in 3 months to review results

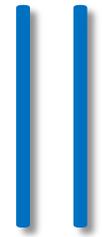
|| Case Presentation (Continued) ||

- **What would be the most appropriate therapy for this patient?**
 - A. **Excisional biopsy**
 - B. Involved site radiation therapy (ISRT)
 - C. R-ESHAP salvaged chemotherapy
 - D. Rituximab monotherapy
 - E. Fine needle aspiration (FNA) and follow-up in 3 months to review results
- Usually DLBCL relapses in the first 2 years after diagnosis, and late relapses can present with different histologic subtypes of NHL (e.g., follicular lymphoma). Excisional biopsy is always needed, since both prognosis and treatment options are different between DLBCL and indolent lymphomas. FNA should be avoided if at all possible for diagnosing DLBCL (either at initial presentation or possible relapse).
- Second-line rituximab-based chemotherapy (e.g., R-ESHAP) would be given if DLBCL is confirmed. ISRT can potentially be an option for localized relapsed disease (Stage I and non-bulky Stage II).
- Although rituximab monotherapy is a therapeutic option for follicular lymphoma, it is not recommended DLBCL.

Companion Case for Chapter 32

Diffuse Large B-Cell Lymphoma

*Jose Sandoval-Sus
and
Julio Chavez*



Clinical Case 25



|| General Outline

- Case Presentation
 - History
 - Pertinent laboratory values
 - Diagnosis
- Pathologic Entity
 - Pathophysiology
 - Management and treatment
- Therapeutic Plasma Exchange Yes/No
- Case Follow-up
 - Response to treatment

|| Patient Case #1

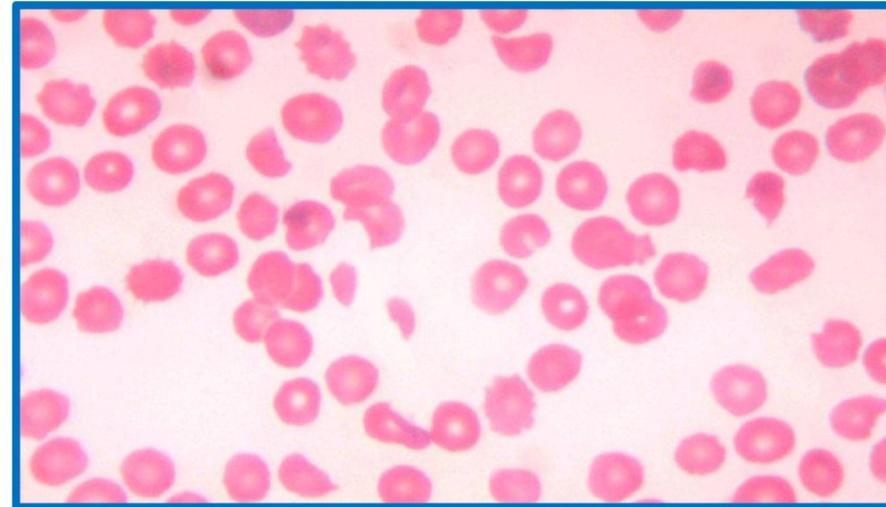


A 23-year-old woman complained of new-onset shortness of breath, dizziness, nausea, vomiting, and jaundice over the course of 1 week.

|| Laboratory Workup

Hemoglobin	6.1 g/dL
Hematocrit	26%
Platelets	7 k/ μ L
WBC	6.5 k/ μ L

LDH	1400 U/dL
Bilirubin, total	6.6 mg/dL
Bilirubin, direct	0.4 mg/dL
BUN	15 mg/dL
Creatinine	0.8 mg/dL



The peripheral smear showed a profound decrease in number of platelets, and few schistocytes including helmet forms.

Urgent Care Management

- **What is the next best step in management?**
 - A. Order ADAMTS-13 activity and await result (turn-around time ~3 days).
 - B. Wait for central catheter placement by IR and arrange plasmapheresis (earliest availability tomorrow morning).
 - C. Collect blood for ADAMTS-13 activity level and activity and empirically start plasma infusion, 2 Units FFP (fresh frozen plasma) q4h, while planning for plasmapheresis.
 - D. Start steroids therapy.
 - E. Start eculizumab.

Urgent Care Management

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 - C. Collect blood for ADAMTS-13 activity level and activity and empirically start plasma infusion, 2 Units FFP q4h, while planning for plasmapheresis.**
 - D. Start steroids therapy.
 - E. Start Eculizumab.

Initiating empiric and urgent therapeutic plasma exchange (TPE) treatment for suspected TTP is of paramount importance. The decision to treat is based on clinical judgment since ADAMTS-13 results are often not available for several days, and if the concern for the diagnosis of TTP is strong, then urgent TPE should be initiated while the diagnostic evaluation continues. **If there may be delay in planning for plasmapheresis, as a temporizing measure, plasma infusion should be initiated immediately.**

|| Lab Evaluation of TTP ||

Reference laboratory result for ADAMTS-13 sample taken prior to plasma infusion:

- ADAMTS-13 activity: <0.1 U/mL (reference range >0.56 U/mL)
- **Which assay for ADAMTS-13 measurement is not clinically helpful?**
 - A. Whole substrate assay ADAMTS-13 activity measurement
 - B. Peptide substrate or the FRETs-vWF73 assay
 - C. Plasma ADAMTS-13 antigen levels
 - D. Neutralizing ADAMTS-13 autoantibodies (inhibitor)

FRETs-vWF73: Fluorescence - Quenching Substrate for ADAMTS - 13

|| Lab Evaluation of TTP (Continued) ||

- **Which assay for ADAMTS-13 measurement is *NOT* clinically helpful?**
 - A. Whole substrate assay ADAMTS-13 activity measurement
 - B. Peptide substrate or the FRETs-vWF73 assay
 - C. Plasma ADAMTS-13 antigen levels**
 - D. Neutralizing ADAMTS-13 autoantibodies (inhibitor)

Currently, the fluorescence resonance energy transfer (FRETs-VWF73) assay is most widely used in the United States. It is a one-step assay and can be completed in 1 hour with excellent precision. It has excellent reproducibility (CV 6%). The FRETs-VWF73 based-assay has a detection limit between 1% and 5%. It also has excellent correlation when compared to the gold standard whole substrate assay (correlation coefficient >0.90).

Because assay sensitivity and specificity vary (both falsely high and low results), this should be recognized in the context of clinical decision making. For example, FRETs-VWF73 may give higher activity results (>10%, i.e., FALSE NEGATIVE) than gel-based VWF assays.

In acquired TTP ADAMTS-13 antigen levels is not helpful since it may be normal or reduced as a result of immune complex clearance and based on specificity of autoantibodies neutralizing or non-neutralizing.

|| Testing Limitations: Interference ||

- **Which of the following are known clinically significant interferences in the ADAMTS-13 activity assays? (There may be more than one answer.)**
 - A. Hyperbilirubinemia
 - B. Free plasma hemoglobin
 - C. Improper sample storage
 - D. Lipemic sample
 - E. Uremia

|| Testing Limitations: Interference (Continued) ||

- **Which of the following are known clinically significant interferences in the ADAMTS-13 activity assays?**
 - A. Hyperbilirubinemia**
 - B. Free plasma hemoglobin**
 - C. Improper sample storage**
 - D. Lipemic sample
 - E. Uremia

The FRETs-VWF73 method, the most commonly used in the United States, is affected by hyperbilirubinemia and free plasma hemoglobin.

In plasmas with bilirubin levels of 5.8 mg/dL or higher, the interference may cause a falsely severe ADAMTS-13 deficiency suggestive of idiopathic TTP in patients with other TMAs who have ADAMTS-13 activity in the lower range of normal. Since this degree of hyperbilirubinemia is not uncommon in patients with brisk hemolysis, this is a potential testing confounder.

Free hemoglobin at 0.2 g/dL or more may also falsely lower ADAMTS-13 activity.

Falsely low ADAMTS-13 activity is seen with enzyme degradation due to improper storage and handling.

Prognostic Value of ADAMTS-13

Activity

- **Which of the following statements is true?**
 - A. Patients with severe ADAMTS-13 deficiency are less likely to achieve a remission in response to TPE than those with nonsevere ADAMTS-13 deficiency.
 - B. The likelihood of relapse is less in patients with severe ADAMTS-13 deficiency than those with nonsevere ADAMTS-13 deficiency.
 - C. Neither of the above
 - D. Both of the above

Prognostic Value of ADAMTS-13 Activity (Continued)

○ Which of the following statements is true?

- A. Patients with severe ADAMTS-13 deficiency are less likely to achieve a remission in response to TPE than those with nonsevere ADAMTS-13 deficiency.
- B. The likelihood of relapse is less in patients with severe ADAMTS-13 deficiency than those with nonsevere ADAMTS-13 deficiency.
- C. Neither of the above**
- D. Both of the above

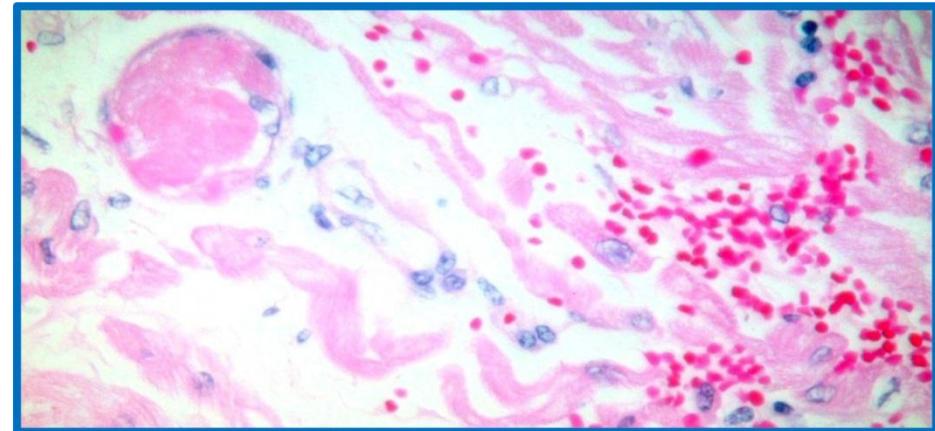
Patients with severe ADAMTS-13 deficiency (<10%) are more likely to have TTP and achieve a remission in response to TPE than those with nonsevere ADAMTS-13 deficiency (82-88% vs. 20%-75%). Patients with nonsevere ADAMTS-13 deficiency are more likely to have other types of TMA.

However, the likelihood of relapse is *greater* in patients with severe ADAMTS-13 deficiency than those with non severe ADAMTS-13 deficiency (40% versus 8%).

|| Mortality in TTP ||

On Day 3, during the third round of plasma exchange, the patient goes into cardiac arrest and Troponin I increased from 1.70 to 6.98.

- **Which of the following are the most recognized causes of mortality in TTP?
(There may be more than one answer.)**
 - A. Cardiac arrest
 - B. Acute myocardial injury
 - C. Acute renal failure
 - D. Respiratory failure



|| Mortality in TTP (Continued) ||

- **Which of the following are the most recognized causes of mortality in TTP?**
 - A. Cardiac arrest**
 - B. Acute myocardial injury**
 - C. Acute renal failure
 - D. Respiratory failure

The most common immediate causes of death in TTP include cardiac arrest and myocardial infarction. Cardiac injury is a common postmortem finding in TTP patients. The most common TTP-related findings at autopsy are thrombi/emboli and hemorrhages in heart, lung, brain, and kidney.

The patients can develop cardiac arrest and myocardial infarction but, clinically, there is pulmonary sparing and minimal-to-no kidney injury despite microthrombi observed throughout the kidney.

|| When Not to Do Plasmapheresis? ||

- **In which of the following TMAs should you NOT use plasma infusion or TPE with FFP as a replacement?**
 - A. Shiga-toxin associated-HUS (ST-HUS)
 - B. Membrane cofactor protein (MCP) deficiency
 - C. *S. pneumoniae* HUS (DAT+)
 - D. Post bone marrow transplant TMA
 - E. All of the above

|| When Not to Do Plasmapheresis? (Continued) ||

- In which of the following TMAs should you NOT use plasma infusion or TPE with FFP as a replacement?
 - A. Shiga-toxin associated-HUS (ST-HUS)
 - B. Membrane cofactor protein (MCP) deficiency
 - C. *S. pneumoniae* HUS (DAT+)
 - D. Post bone marrow transplant TMA
 - E. All of the above**

Because of the overlap in clinical presentation and high mortality among patients with TTP, there are some conditions where early initiation of TPE is ineffective and possibly harmful.

- TMA patients without severe ADAMTS-13 deficiency do not benefit from TPE. For example, Shiga-toxin associated-HUS (ST-HUS) has not been shown to respond to TPE; thus, it should not be attempted in these patients.
- Membrane cofactor protein (MCP) deficiency does not respond to TPE because MCP protein is not a plasma protein.
- In DAT positive *S. pneumoniae* HUS, plasma can actually be harmful and washed RBCs should be provided (see case 3).

|| Patient Case #2



A 63-year-old female with refractory multiple myeloma, currently with diffuse bone involvement, presented with new-onset shortness of breath lasting 4 to 5 days and with severe thrombocytopenia new-onset acute kidney injury, hematuria, and altered mental status. She denies fever.

|| Lab Results



- Hemoglobin/Hematocrit: 10.1 g/dL/30.7%,
- MCV: 83.4 fL, RDW: 18.5%
- Platelet count: 24 k/ μ L
- Total bilirubin increase in under 24 hrs from 1.4 to 3.5 (Indirect: 1.2 mg/dL, direct: 0.2 mg/dL)
- Elevated LDH: 832 U/dL \uparrow
- Low haptoglobin level: <15 mg/dL \downarrow
- Negative direct antiglobulin test (DAT), or direct Coombs test.

|| Lab Results (Continued) ||

- **Differential diagnosis includes (select all that apply):**
 - A. Pancytopenia due to marrow failure
 - B. Acute renal failure due to myeloma involvement of kidney
 - C. Altered mental status due to hyperviscosity
 - D. Acquired TTP
 - E. HUS due to unrecognized GI infection

|| Lab Results (Continued) ||

- **Differential diagnosis includes:**
 - A. Pancytopenia due to marrow failure**
 - B. Acute renal failure due to myeloma involvement of kidney**
 - C. Altered mental status due to hyperviscosity**
 - D. Acquired TTP**
 - E. HUS due to unrecognized GI infection**

All of the above!

The patient reached a platelet count of $100 \times 10^9/L$ for 4 consecutive days accompanied by normalizing LDH and improving neurological deficits and TPE was stopped.

The diagnosis of this challenging clinical presentation was established after 8 days upon return of ADAMTS-13 activity $<10\%$.

However, at day 15 since onset, platelet counts drop and LDH rise.

Patient was continued to be treated with plasma exchange with addition of rituximab.

|| Response Evaluation in TTP ||

- **Which of the following definitions of disease presentation apply to the patient?**
 - A. Relapse
 - B. Exacerbation
 - C. Durable treatment response
 - D. Refractory disease
 - E. None of these

|| Response Evaluation in TTP (Continued) ||

- **Which of the following definitions of disease presentation apply to the patient?**
 - A. Relapse
 - B. Exacerbation
 - C. Durable treatment response
 - D. Refractory disease
 - E. **None of these**

|| Response Evaluation in TTP (Continued) ||

There is standardization of disease definition, management, and response evaluation for TTP as follows:

Treatment response is defined as platelet count above $150 \times 10^9/L$ for 2 consecutive days accompanied by normal or normalizing LDH and stable or improving neurological deficits.

Durable treatment response is defined as treatment response that is lasting at least 30 days after discontinuation of plasma exchange.

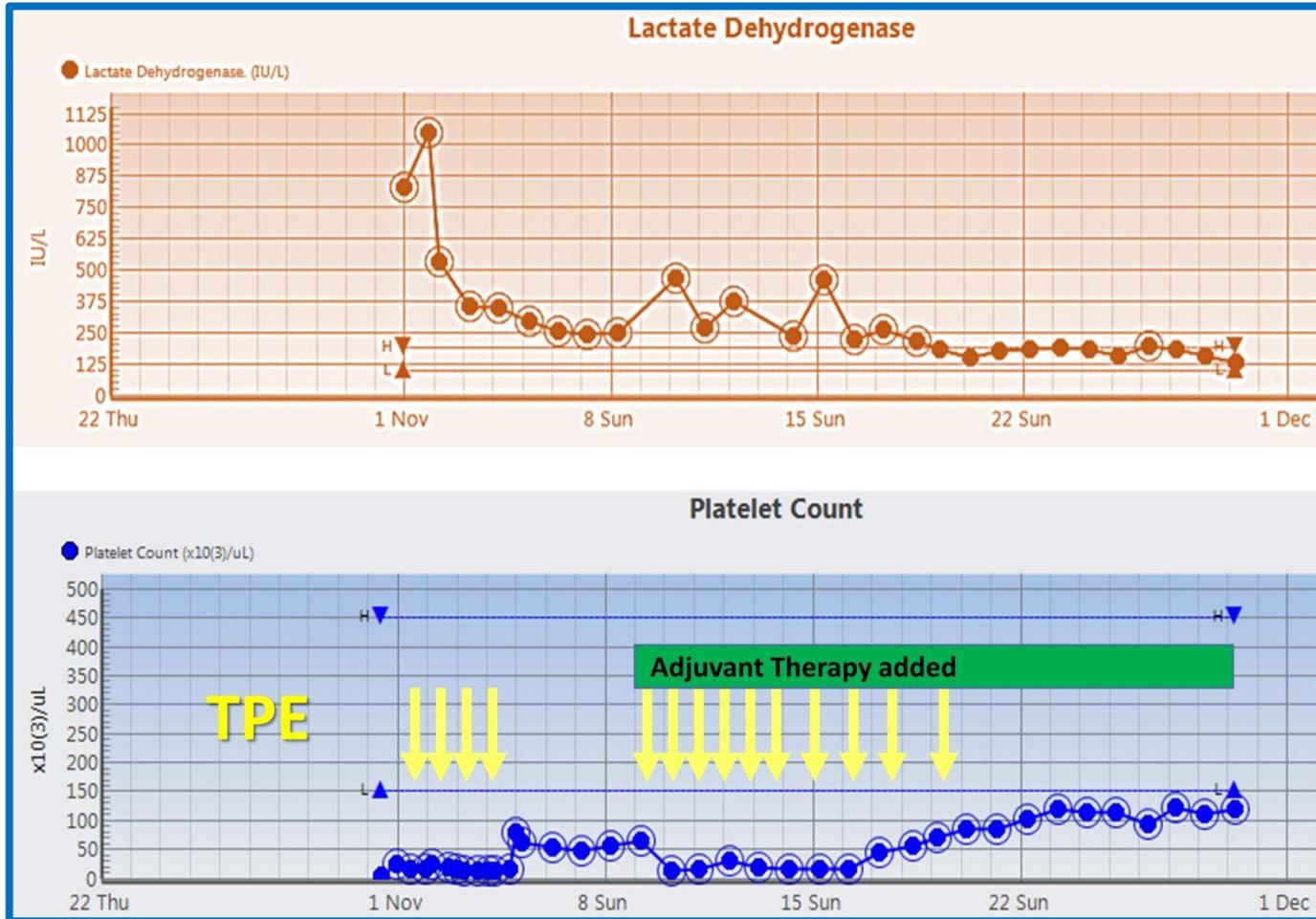
Relapse is recurrent disease 30 days or longer after reaching treatment response.

Exacerbation is defined as recurrent disease within 30 days after reaching treatment response.

Refractory disease occurs when there is no treatment response by day 30 and/or no durable treatment response by day 60.

Our patient's treatment was incorrectly and prematurely interrupted without reaching a stable platelet threshold for $>150 \text{ k/uL}$. Thus, although it seems like an "exacerbation," she does not fall into any of the standardized categories.

|| Patient's Response to Therapy ||



|| Adjuvant Therapy



While the majority (85%–90%) of patients respond to the plasmapheresis regimen, adjuvant therapies are needed in remaining cases.

- **Which of the following are available adjuvant therapies?**
 - A. Rituximab
 - B. Steroids
 - C. Splenectomy
 - D. Cyclosporine
 - E. All of above

|| Adjuvant Therapy (Continued) ||

○ **Which of the following are available adjuvant therapies?**

- A. Rituximab
- B. Steroids
- C. Splenectomy
- D. Cyclosporine
- E. **All of above**

While there are no RCTs showing efficacy of any adjuvant therapies yet, there are retrospective studies showing encouraging results for all of the above therapies.

- a. Use of TPE plus corticosteroids (prednisone 200 mg/dL) has been proposed to result in faster achievement of remission.
- b. Corticosteroids and rituximab may be effective for decreasing the duration of TPE required to achieve a remission; rituximab may also be effective to delay or prevent relapses.
- c. Recent experience with rituximab has also shown decreased mortality of less than 8% in patients refractory to TPE alone.
- d. Cyclosporine 2–3 mg/kg/day as an adjunct to TPE showed higher remission rates without disease exacerbation.
- e. Splenectomy has been used prior to rituximab era in refractory or relapsing TTP patients with mixed responses. with decreased relapses suggested. Splenectomy might be useful in reducing the B-cell mass capable of forming autoantibodies.

|| Patient Case #3



A 2-year-old male presented with pneumonia and a pleural effusion. No significant previous medical history. Laboratory findings were significant only for mild anemia 8.5 g/dL. He is started on antibiotics.

By day 3 post admission his CBC dramatically worsened:

Hemoglobin dropped from 8.5 g/dL to 3.3 g/dL.

Platelets dropped from 470 k/ μ L to 20 k/ μ L.

The peripheral smear was notable for decreased amount of large platelets, schistocytes and microspherocytes, and toxic granulations in the neutrophils.

Lactic dehydrogenase (LDH) was 5,000 U/L, total bilirubin 2.1 mg/dL, and direct bilirubin 0.8 mg/dL.

Creatinine increased from 0.5mg/dL to 1.5mg/dL, and the patient become oliguric.

Streptococcus pneumoniae was detected in the urine.

|| Congenital TTP



- **Upshaw-Schulman Syndrome, or an inherited deficiency of ADAMTS-13, can present at what age groups? (Select all that apply.)**
 - A. Neonatal age/Infancy
 - B. Early childhood
 - C. Teenage years
 - D. During adult age-group (>18 yrs)

Congenital TTP Due to Mutation of ADAMTS13 Gene

- **Upshaw-Schulman Syndrome, or an inherited deficiency Of ADAMTS-13, can present at what age groups?**
 - A. Neonatal age/Infancy**
 - B. Early childhood**
 - C. Teenage years**
 - D. During adult age-group (>18 yrs)**

All of the above!

It was traditionally believed that congenital TTP presents only at a very young age either during infancy or early childhood; but USS can occur even later in life. USS can be classified into two groups: **early onset** (<18 years of age) and **late onset** (>18 years of age). Early onset can occur either in the neonatal period (45%) when patients present with hyperbilirubinemia, likely requiring exchange transfusion, or in infancy or early childhood (29%). Late onset (or adult onset) generally is precipitated by stress (e.g., infection or pregnancy). The clinical syndrome might be dependent upon the baseline activity of the enzyme. USS patients with an activity of <2% may present with TTP in infancy (early onset group), and those with 3% to 9% activity who may develop TTP only upon exposure to infection or stress (e.g., pregnancy) and belong to the late onset group.

|| Clinical Vignette: What's There, What's Not? ||

- **The patient has all of the following except:**
 - A. MAHA
 - B. ARF
 - C. Streptococcal pneumonia
 - D. DAT positive HA
 - E. *Escherichia coli* 0157:H7 infection

Clinical Vignette: What's There, What's Not? (Continued)

- The patient has all of the following except:
 - A. MAHA
 - B. ARF
 - C. Streptococcal pneumonia
 - D. DAT positive HA
 - E. ***Escherichia coli 0157:H7 infection***

The patient has MAHA, thrombocytopenia, acute renal failure, and streptococcal pneumonia, but there is no evidence of *Escherichia coli* 0157:H7 infection, nor diarrhea as seen in a classical ST-HUS.

|| Clinical Vignette: What's There, What's Not? (Continued) ||

- **The most likely diagnosis is:**
 - A. TTP
 - B. DIC
 - C. ST-HUS
 - D. *Streptococcus pneumoniae-associated pHUS*
 - E. Atypical HUS
 - F. Evans syndrome

Clinical Vignette: What's There, What's Not? (Continued)

- The most likely diagnosis is:
 - A. TTP
 - B. DIC
 - C. ST-HUS
 - D. *Streptococcus pneumoniae*-associated pHUS**
 - E. Atypical HUS
 - F. Evans syndrome

Streptococcus pneumoniae-associated hemolytic uremic syndrome (SpHUS) is defined by the occurrence of acute hemolytic anemia, thrombocytopenia, and acute kidney injury in a patient with a *S. pneumoniae* infection. The majority of SpHUS patients have pneumonia and a low mortality rate in contrast to those with meningitis, who have a more severe clinical course. *S. pneumoniae* produces neuraminidase, thereby exposing the **Thomsen-Friedenreich antigen (T antigen)** on the surface of cell membranes. Thomsen-Friedenreich antigen exposure can result in hemolysis and direct endothelial injury leading to HUS phenotype. **Early identification of these patients is critical so that fresh frozen plasma may be avoided.** SpHUS often may be underdiagnosed because of overlapping features with DIC and the lack of strict diagnostic criteria. The epidemiology has changed with the emergence of different pneumococcal serotypes as newer pneumococcal vaccines have been introduced.

|| Clinical Vignette: What's There, What's Not? (Continued) ||

- **Which of the following laboratory findings is *not* present in patients with pneumococcal HUS?**
 - A. ADAMTS-13 deficiency
 - B. Schistocytes
 - C. Positive result of a Coombs test
 - D. Thomsen–Friedenreich (TF) antigen exposure
 - E. Hypocomplementemia

Clinical Vignette: What's There, What's Not? (Continued)

- Which of the following laboratory findings is *not* present in patients with pneumococcal HUS?
 - A. ADAMTS-13 deficiency
 - B. Schistocytes
 - C. Positive result of a Coombs test
 - D. Thomsen–Friedenreich (TF) antigen exposure
 - E. Hypo-complementemia

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Early identification of these patients is critical so that fresh frozen plasma may be avoided.

Management of Streptococcus Pneumonia-Associated HUS

- **Treatment of a patient with pneumococcal HUS should include:**
 - A. Transfusion of unwashed packed red blood cells (PRBCs)
 - B. Transfusion of washed packed red blood cells (PRBCs)
 - C. Plasmapheresis with albumin
 - D. Fresh frozen plasma Infusion
 - E. Transfusion of unwashed platelets
 - F. A & B
 - G. B & D
 - H. A & C
 - I. B & C

Management of Streptococcus Pneumonia-Associated HUS (Continued)

- **Treatment of a patient with pneumococcal HUS should include:**
 - A. Transfusion of unwashed packed red blood cells (PRBCs)
 - B. Transfusion of washed packed red blood cells (PRBCs)**
 - C. Plasmapheresis with albumin**
 - D. Fresh frozen plasma Infusion
 - E. Transfusion of unwashed platelets

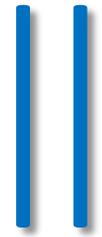
Answer, I = B & C: Early recognition of S pneumonia-associated HUS is important. Plasma or plasma-containing blood products may worsen the clinical course and worsen hemolysis, because most healthy individuals contain anti-T IgM in their serum. Therefore, use of **anti-T free blood products** (e.g., **plasmapheresis with 5% albumin replacement and transfusion of washed red blood cells**) is recommended.

Fluorescein-labelled peanut agglutinin confirms the presence of T antigen on tested cells or tissues. However, this assay is not routinely performed in many laboratories. The direct Coombs test, which is more readily available, detects (auto-) antibody binding to red blood cells, and is usually positive in these cases. It has been suggested that this test could be useful in detecting HUS early in cases of invasive *S. pneumonia* disease. However, there are no clear data on the specificity of the DAT in these cases.

Companion Case for Chapter 53

Thrombotic Microangiopathy

*Ruchika Goel,
Aaron Tobian,
and
Ljiljana V. Vasovic*



Clinical Case 26



|| Case Presentation



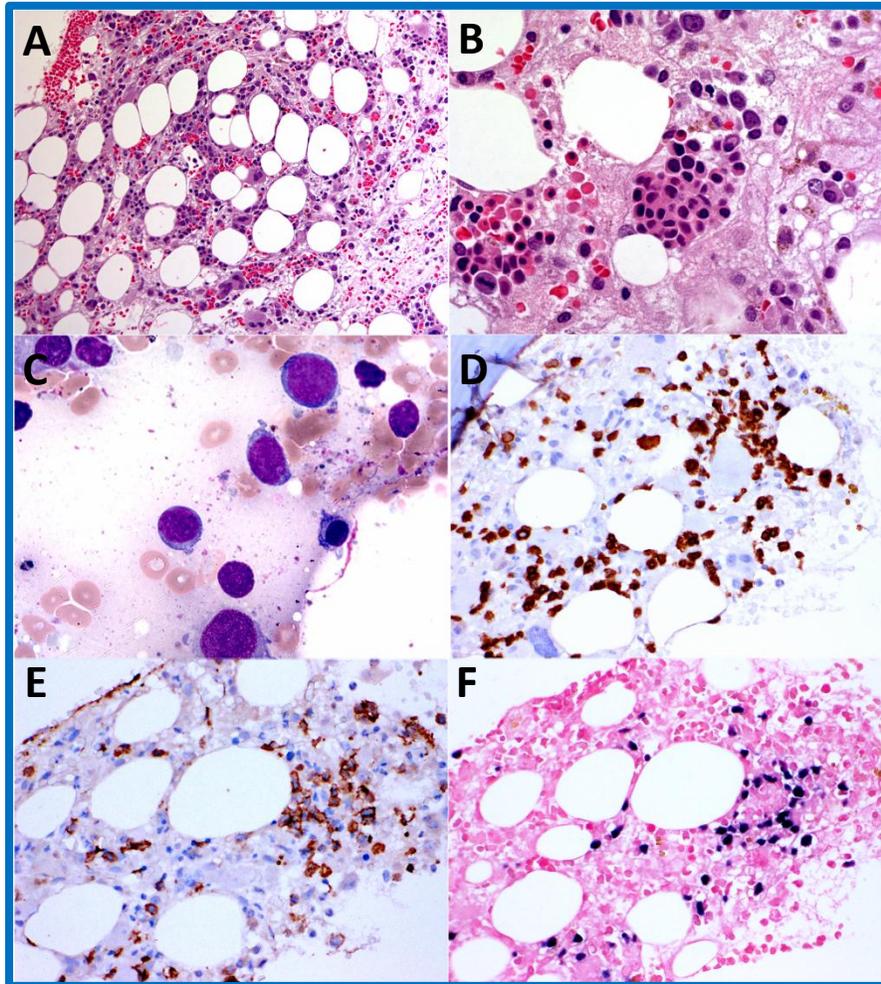
- A previously healthy 30-year-old man is brought to the emergency room with a 3-week history of progressive fatigue, fever, abdominal pain, and most recently yellowing of his eyes and skin. He has been treated with antibiotics for bronchitis without any improvement in fever.
- On exam, he appears acutely ill and vital signs reveal tachycardia, hypotension, and tachypnea.
- The patient is jaundiced and also shows significant hepatosplenomegaly.

|| Labs



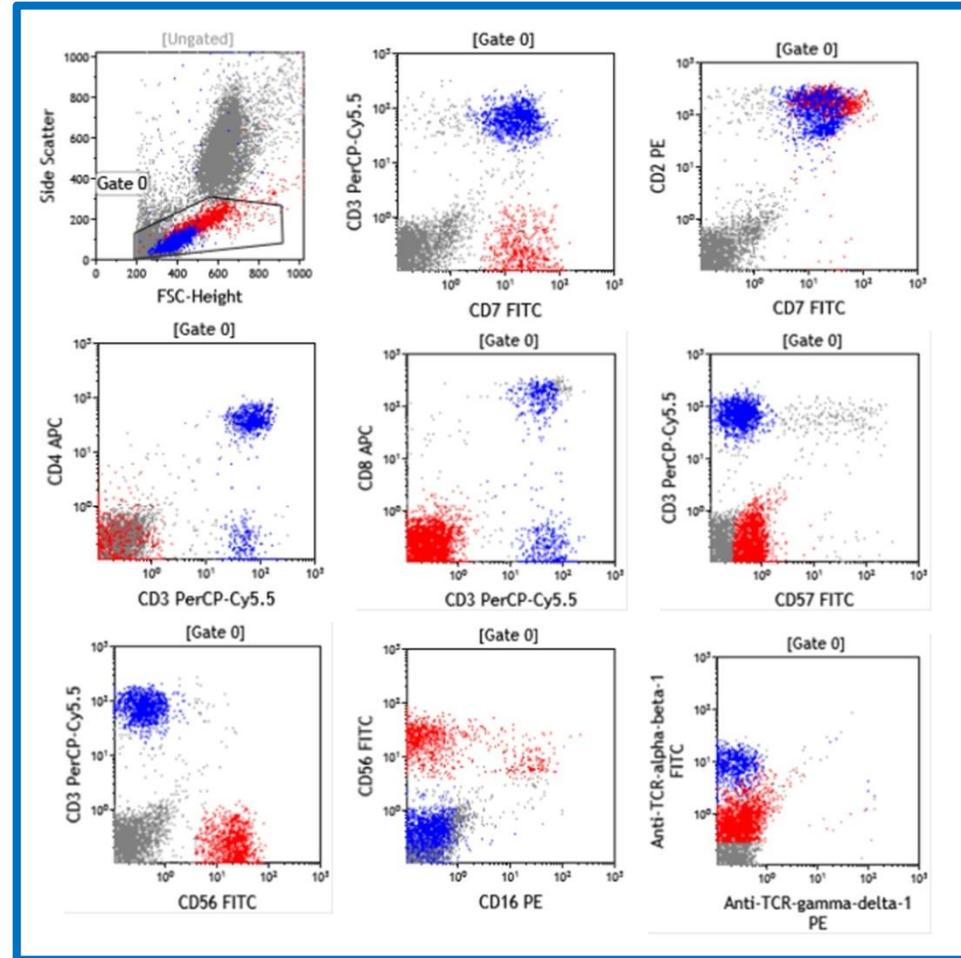
- The patient is found to have renal failure, transaminitis, and hyperbilirubinemia.
- In addition, the CBC reveals pancytopenia and circulating “atypical cells.”
- Blood cultures are obtained and are negative in the first 24 hours.
- Imaging study showed no lymphadenopathy or any mass involving extranodal sites.
- The patient was admitted to the ICU and hematology was consulted.

Bone Marrow Biopsy



Bone marrow core biopsy demonstrates disordered trilineage hematopoiesis associated with an interstitial atypical lymphoid infiltrate and increased phagocytic histiocytes (A, H&E, x200). B. A higher power view of the core biopsy revealed characteristic hemophagocytosis of numerous hematopoietic cells (H&E, x600). C. The bone marrow aspirate smear shows variably-sized atypical lymphoid cells, with high nuclear:cytoplasmic ratio, finely-granular or delicate chromatin, and scant basophilic cytoplasm (Wright Giemsa, x1000). D through F. Immunohistochemical stains show the atypical cells to be positive for cytoplasmic CD3 and CD56 (D and E. Immunoperoxidase, x400, respectively) and in-situ hybridization using EBC encoded RNA probe (EBER-ISH) showed the same cells to be positive for the hybridization signals, indicating EBV infection and/or reactivation (ISH, x400). Additionally, TCR gene rearrangement studies performed were germline status (not shown).

Flow Cytometry



|| Flow Cytometry (Continued) ||

- Flow cytometry performed on the bone marrow aspirate harvested from the patient disclosed a population of atypical larger cells, large (forward side scatter, or FSC, red) in contrast to mature T-cells (blue). These cells (red) coexpressed CD2, CD7, CD56, and CD16 (small subset) but lacked expression of surface CD3, CD4, CD8, CD57, and both TCR beta and TCR gamma.

|| Flow Cytometry (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Hepatosplenic T-cell lymphoma
 - B. Aggressive NK-cell leukemia
 - C. T-LGL leukemia
 - D. Extranodal NK/T-cell lymphoma

|| Flow Cytometry (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Hepatosplenic T-cell lymphoma
 - B. Aggressive NK-cell leukemia**
 - C. T-LGL leukemia
 - D. Extranodal NK/T-cell lymphoma

The clinical and pathologic picture is consistent with aggressive NK-cell leukemia. The presence of atypical cells with an NK-cell phenotype, lack of TCR gene rearrangement, presence of EBV infection/reactivation, and HLH all point toward the diagnosis of NK-cell leukemia. Although virtually all cases of extranodal NK/T-cell lymphoma, nasal type, show evidence of EBV infection/reactivation as well as TCR germline status, negative imaging findings and the presence of CD16 positivity, though small subset, by flow cytometry favors aggressive NK-cell leukemia. The clinical picture and CD57 argues against T-LGL leukemia. TCR-germline configuration, flow cytometric phenotype, and EBV positivity are not consistent with hepatosplenic T-cell lymphoma.

|| Flow Cytometry (Continued) ||

- **What additional blood tests will you order?**
 - A. EBV by PCR
 - B. Hepatitis titers
 - C. Coagulopathy tests
 - D. All of the above

|| Flow Cytometry (Continued) ||

- **What additional blood tests will you order?**
 - A. EBV by PCR
 - B. Hepatitis titers
 - C. Coagulopathy tests
 - D. All of the above**

The patient is high risk for coagulopathy, which would need correction and monitoring. Obtaining EBV PCR at baseline will help with monitoring during treatment as it can correlate with response as well as relapse. It is reasonable to rule out additional causes of acute liver failure including assessment for viral hepatitis (e.g., hepatitis A/B).

|| Flow Cytometry (Continued) ||

- **What treatment options will you discuss with the patient?**
 - A. The patient is too sick for treatment
 - B. Dose modified SMILE
 - C. 7+3 induction
 - D. CLAG-M

|| Flow Cytometry (Continued) ||

- **What treatment options will you discuss with the patient?**
 - A. The patient is too sick for treatment
 - B. Dose modified SMILE**
 - C. 7+3 induction
 - D. CLAG-M

Young patients should be treated through organ failure, hemophagocytic lymphohistiocytosis (HLH) and coagulopathy as this is the only chance for survival. The patient would benefit from SMILE*. Etoposide and dexamethasone will offer a treatment for HLH (treatment of the primary disease can lead to resolution of the HLH).

* SMILE Chemotherapy, 28-Day Cycle:

Methotrexate 2g/m² IV Day 1

Leucovorin 15mg IV/PO X4 Day 2,3,4

Ifosfamide 1500mg/m² IV Day 2,3,4

Mesna 300mg/m² IV X 3 Day 2,3,4

Dexamethasone 40mg daily IV/PO Day 2,3,4

Etoposide 100mg/m² IV Day 2,3,4

L-asparaginase 6000U/m² Day 8,10,12,14,16,18,20

G-CSF Day 6 to ANC > 500/ μ L

|| Flow Cytometry (Continued) ||

- **If the patient achieves a response, what is the next step?**
 - A. Consolidation with chemotherapy
 - B. Consolidation with allogeneic hematopoietic stem cell transplantation (allo-HSCT)
 - C. Observation with serial bone marrow biopsies
 - D. Liver transplant

|| Flow Cytometry (Continued) ||

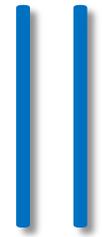
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 - A. Consolidation with chemotherapy
 - B. Consolidation with allogeneic hematopoietic stem cell transplantation (allo-HSCT)**
 - C. Observation with serial bone marrow biopsies
 - D. Liver transplant

Aggressive NK-cell leukemia has a high risk of relapse with extremely poor long-term outcomes. The patient should be referred to allo-HSCT during initial treatment to expedite evaluation with allogeneic HSCT being the next step in treatment if a partial or complete remission is achieved as long-term remissions have been described in this setting.

Companion Case for Chapter 24

Aggressive Natural Killer Cell Leukemia

*Mintallah Haider
and
Lubomir Sokol*



Clinical Case 27



|| Case Presentation

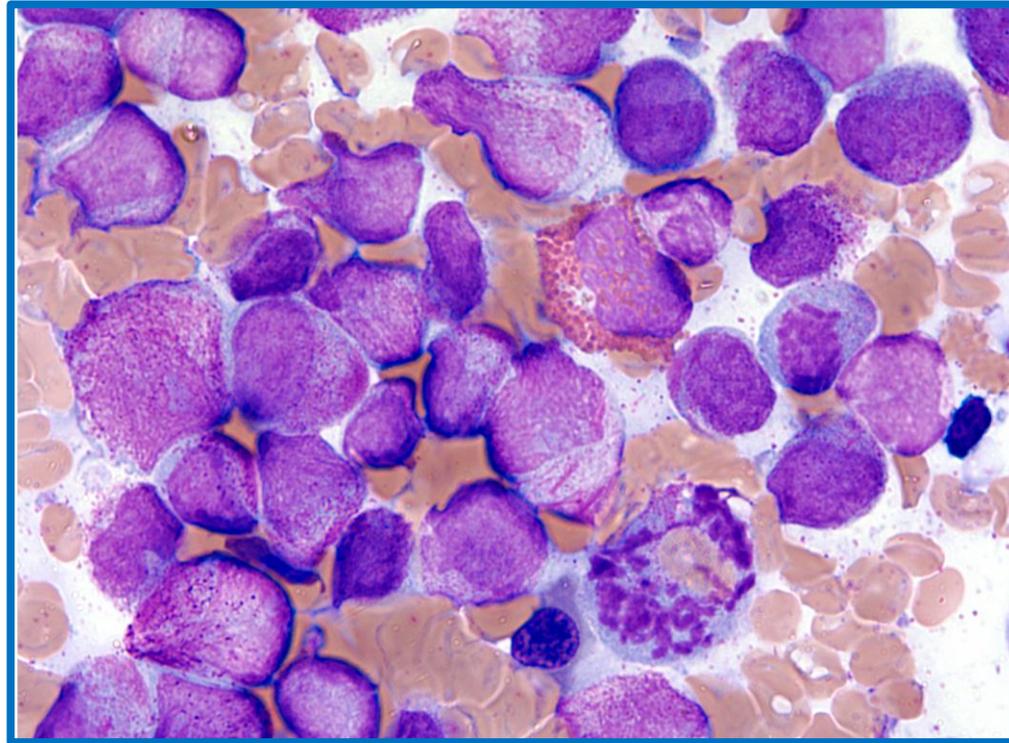
A 37-year-old female with a past medical history of HTN presents with a 1-month history of fatigue, fever, and malaise. She is also reporting prolonged menstrual bleeding.

Her labs are shown:

- WBC: 23.88 k/uL; Hgb 8.9 g/dL; Hct 25.8%; Plt: 32 k/uL
- PTT: 37s
- PT: 20s
- INR: 2.1
- Fibrinogen: 89 mg/dL

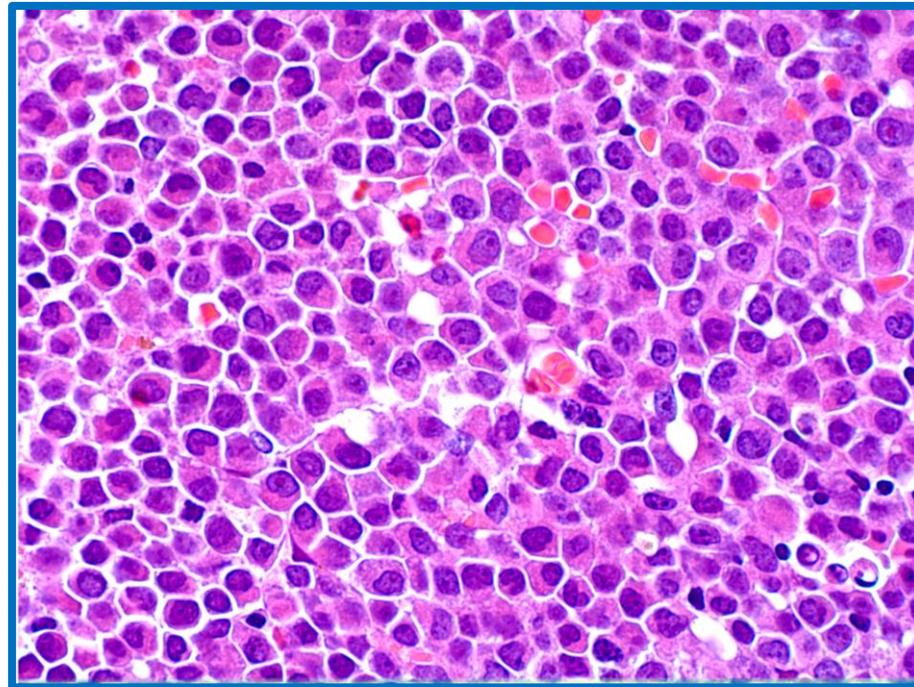
|| Case Presentation (Continued) ||

- The bone marrow aspirate reveals numerous promyelocytes rich in cytoplasmic azurophic granules or Auer rods.



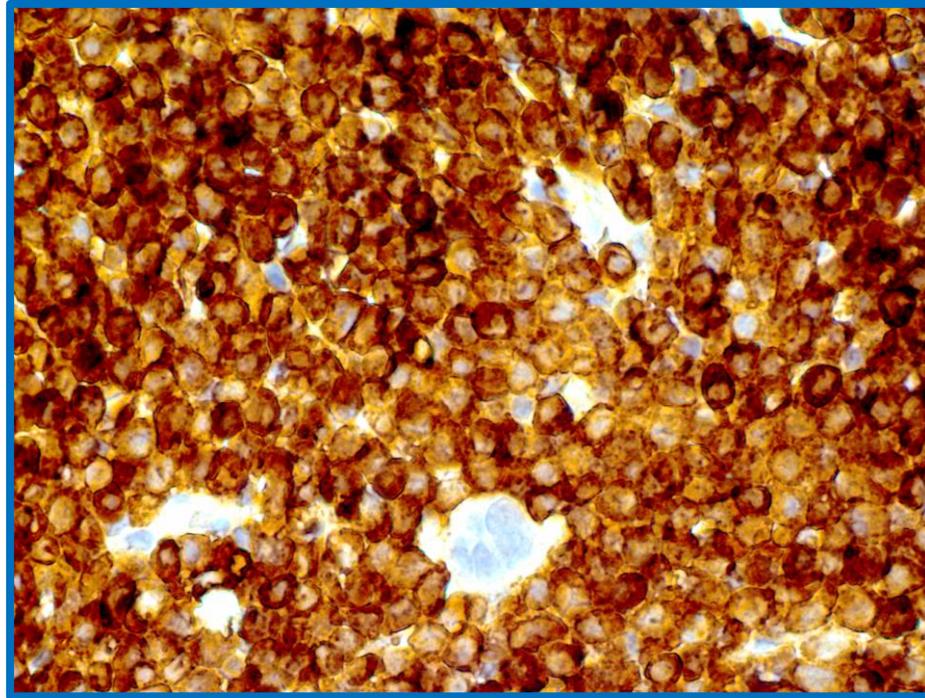
|| Case Presentation (Continued) ||

- A representative section of bone marrow core biopsy from the patient demonstrates sheets of promyelocytes with prominent nucleoli and abundant eosinophilic cytoplasmic granules (H&E, x200).



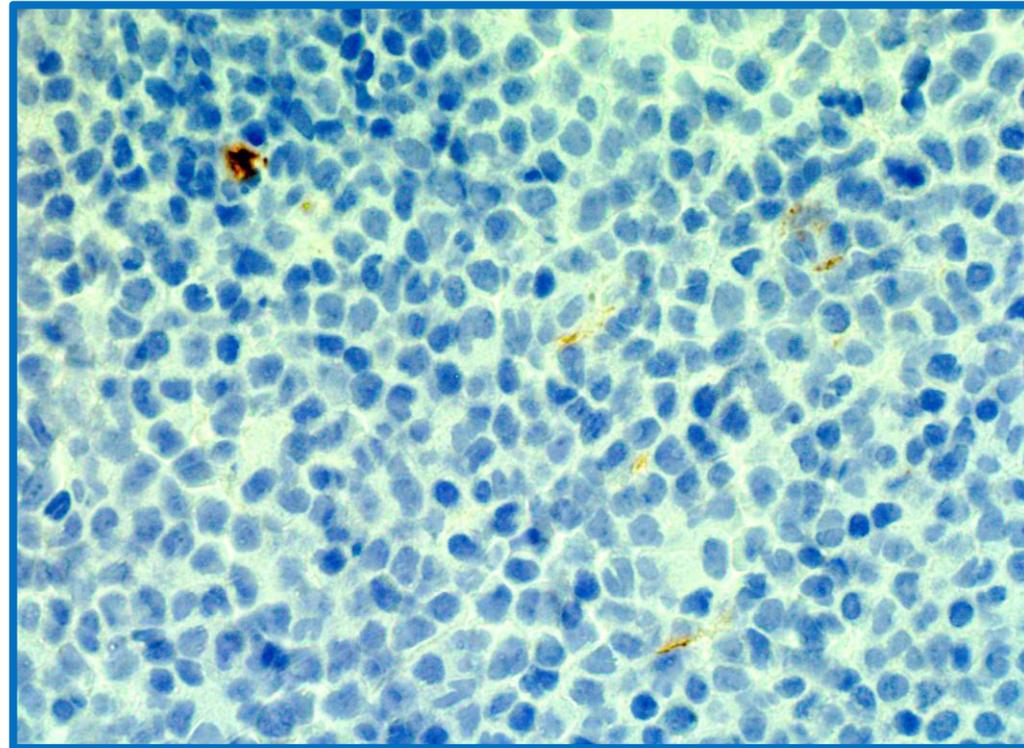
|| Case Presentation (Continued) ||

- These promyelocytes show strong myeloperoxidase immunoreactivity. (Immunoperoxidase, x200)



|| Case Presentation (Continued) ||

- CD34 stain is negative (immunoperoxidase, x200).



|| Flow Cytometry



- Positive for CD13, CD33, CD45, CD117
- Negative for: CD3, CD4 ,CD7, CD8, CD10, CD34, CD11b,CD11c, CD14, CD19,CD22 ,HLA-DR, CD56, CD61,CD79a, cytoplasmic CD3, CD22
MRD-1 negative

|| Flow Cytometry (Continued) ||

- **What is the most likely diagnosis?**
 - A. AML
 - B. APL
 - C. ALL
 - D. CML

|| Flow Cytometry (Continued) ||

- **What is the most likely diagnosis?**
 - A. AML
 - B. APL**
 - C. ALL
 - D. CML

The clinical picture along with the morphologic and immunophenotypic findings are compatible with the diagnosis of APL.

|| Flow Cytometry (Continued) ||

- **What is the most appropriate treatment?**
 - A. Daunorubicin + Cytarabine
 - B. ATRA + Idarubicin
 - C. ATRA + Arsenic Trioxide
 - D. ATRA

|| Flow Cytometry (Continued) ||

- **What is the most appropriate treatment?**
 - A. Daunorubicin + Cytarabine
 - B. ATRA + Idarubicin**
 - C. ATRA + Arsenic Trioxide
 - D. ATRA

The patient has high-risk APL based on WBC count $>10,000\text{k}/\mu\text{L}$. ATRA is required regardless of the treatment strategy.

For standard-risk APL, standard induction therapy is ATRA + ATO.

For high-risk APL, standard induction therapy involves a combination of ATRA + chemotherapy.

– *All-trans* retinoic acid $45\text{mg}/\text{m}^2$ in divided doses until clinical remission + Idarubicin $12\text{mg}/\text{m}^2$ on days 2,5,6,8.

or

– *All-trans* retinoic acid $45\text{mg}/\text{m}^2$ in divided doses until clinical remission + Daunorubicin $60\text{mg}/\text{m}^2$ X 3 days + Cytarabine $200\text{mg}/\text{m}^2$ X 7 days

|| Flow Cytometry (Continued) ||

Three days into therapy she develops cough, shortness of breath, and is now requiring O₂ supplementation, and peripheral edema.

- **What is the diagnosis?**
 - A. Pneumonia
 - B. ATRA differentiation syndrome
 - C. Fluid overload
 - D. PE

|| Flow Cytometry (Continued) ||

Three days into therapy she develops cough, shortness of breath, and is now requiring O₂ supplementation, and peripheral edema.

- **What is the diagnosis?**
 - A. Pneumonia
 - B. ATRA differentiation syndrome**
 - C. Fluid overload
 - D. PE

Symptoms of ATRA differentiation syndrome are dyspnea, weight gain, peripheral edema, congestive heart failure, and acute renal failure. Vigilant monitoring of APL patients treated with ATRA or ATO for these signs is imperative. DS is a potentially fatal complication of therapy and needs to be treated aggressively.

|| Flow Cytometry (Continued) ||

The patient is tolerating the induction regimen without further complications.

- **How is response to therapy assessed?**
 - A. Bone marrow biopsy and aspirate to assess morphological response and RT-PCR for *PML-RARA* after 2 weeks of induction therapy
 - B. Bone marrow to assess morphological response at 4 weeks into therapy
 - C. Bone marrow biopsy to assess morphological response and RT RT-PCR for *PML-RARA* at end of consolidation
 - D. By obtaining blood sample and establishing recovery of white blood cell count (WBC)

|| Flow Cytometry (Continued) ||

The patient is tolerating the induction regimen without further complications.

- **How is response to therapy assessed?**
 - A. Bone marrow biopsy and aspirate to assess morphological response and RT-PCR for *PML-RARA* after 2 weeks of induction therapy
 - B. Bone marrow to assess morphological response at 4 weeks into therapy
 - C. Bone marrow biopsy to assess morphological response and RT RT-PCR for *PML-RARA* at end of consolidation**
 - D. By obtaining blood sample and establishing recovery of white blood cell count (WBC)

To evaluate for remission, a bone marrow biopsy following count recovery is performed to confirm that blasts are <5%. Evaluation of molecular and morphological response after induction is not helpful, since many patients remain positive due to delayed maturation of the leukemic cells. Bone marrow biopsy and aspirate for RT PCR *PML-RARA* should be performed at completion of consolidation.

|| Flow Cytometry (Continued) ||

An 18-year-old male presents with low-risk APL who completed consolidation therapy with arsenic + all-trans retinoic acid (ATRA). Bone marrow biopsy and aspirate is performed and RT PCR for *PML-RARA* is detected.

- **What is the next best management?**
 - A. Reinduction with combination of ATRA and chemotherapy
 - B. Reinduction with 7+3 regimen
 - C. Repeat bone marrow biopsy and aspirate for PCR for *PML-RARA*
 - D. Send patient for hematopoietic stem cell transplantation

If PCR is positive, a repeat bone marrow within 4 weeks is required to confirm positive result. If repeat testing is positive, patient should be treated as relapse APL.

|| Flow Cytometry (Continued) ||

An 18-year-old male presents with low-risk APL who completed consolidation therapy with arsenic + all-trans retinoic acid (ATRA). Bone marrow biopsy and aspirate is performed and RT PCR for *PML-RARA* is detected.

- **What is the next best management?**
 - A. Reinduction with combination of ATRA and chemotherapy
 - B. Reinduction with 7+3 regimen
 - C. Repeat bone marrow biopsy and aspirate for PCR for *PML-RARA***
 - D. Send patient for hematopoietic stem cell transplantation

If PCR is positive, a repeat bone marrow within 4 weeks is required to confirm positive result. If repeat testing is positive, patient should be treated as relapse APL.

Companion Case for Chapter 16

Acute Promyelocytic Leukemia

*Leidy L. Isenalumhe
and
Jeffrey Lancet*

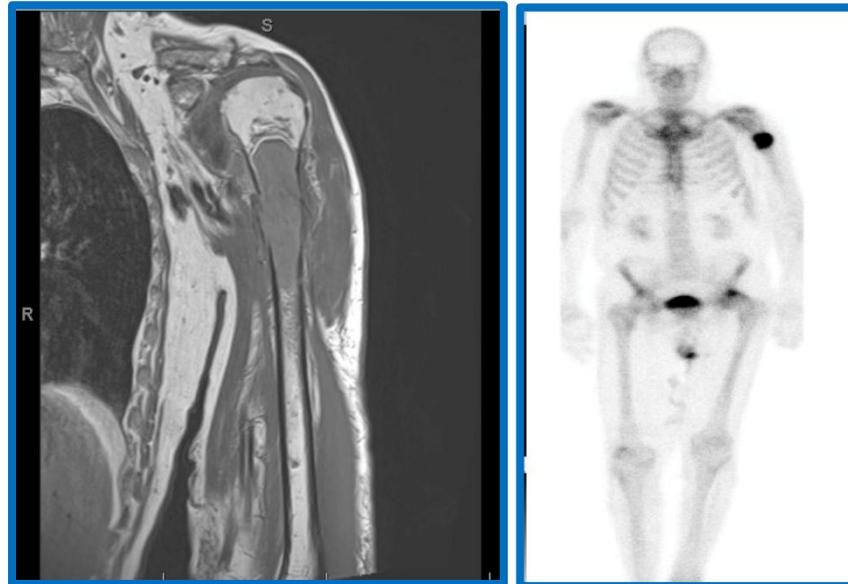


Clinical Case 28



|| Case Presentation

- A 71-year-old male with pmh of HTN and DM is seen by his PCP for routine follow-up. He reports progressive left shoulder pain for 3 weeks limiting his daily activities. On physical exam, there is significant restriction of movement and pain. A MRI shoulder shows a 9.2 x 3.2 cm lesion in the left humeral meta-diaphysis. Labs reveal normal blood counts, creatinine, calcium, lactate dehydrogenase, serum and urine protein electrophoresis, free light chain ratio. Skeletal survey shows no other bone lesions. Biopsy of humeral lesion shows a monoclonal plasma cell neoplasm. An iliac crest bone marrow biopsy is normal.



|| Case Presentation (Continued) ||

- **What is your treatment recommendation for this patient?**
 - A. Observation
 - B. Chemotherapy with bortezomib based regimen
 - C. Definitive radiation therapy for 45 Gy
 - D. Definitive radiation therapy for 30 Gy
 - E. Concurrent bortezomib based chemotherapy with radiation for 30 Gy

|| Case Presentation (Continued) ||

- **What is your treatment recommendation for this patient?**
 - A. Observation
 - B. Chemotherapy with bortezomib based regimen
 - C. Definitive radiation therapy for 45 Gy**
 - D. Definitive radiation therapy for 30 Gy
 - E. Concurrent bortezomib based chemotherapy with radiation for 30 Gy

The definitive dose of radiation therapy for solitary plasmacytoma is 40–50Gy divided over 4 weeks of therapy with local control rates of 90%–100% (*Int J Radiat Oncol Biol Phys*, 2006. 64(4):1013-7; *Radiother Oncol*, 1990. 17(4):293-303).

|| Case Presentation (Continued) ||

- **The patient gets radiation of his humerus lesions and achieves complete response. One year later, a serum protein electrophoresis and immuno-fixation showed a monoclonal IgA band of 1.2 g/dL. Free light chain ratio(FLCR) is noted to be 1.5 with elevated kappa chain. His complete blood count, serum calcium level, creatinine, immunoglobulin levels are noted to be normal. Skeletal survey shows no lytic lesions. Patient is diagnosed with monoclonal gammopathy of unknown significance and is recommended to be on surveillance. Which among the following is considered to be an adverse prognostic factor in patient's presentation?**
 - A. Age
 - B. IgA MGUS
 - C. M-Spike of 1.2g/dl
 - D. Elevated kappa chain with FLCR of 1.5

|| Case Presentation (Continued) ||

- **Which among the following is considered to be an adverse prognostic factor in patient's presentation?**
 - A. Age
 - B. IgA MGUS**
 - C. M-Spike of 1.2g/dL
 - D. Elevated kappa chain with FLCR of 1.5
- **Risk Factors**
 - Non IgG MGUS (as in our patient)
 - Serum M protein >1.5
 - Abnormal serum free light chain ratio (i.e., ratio of kappa to lambda free light chains <0.26 or >1.65)
- **Risk of Progression**
 - All three risk factors: 58% risk for progression in 20 years
 - Two of three risk factors: 37% risk for progression in 20 years
 - One of three risk factors: 20% risk for progression in 20 years
 - None: 5% risk for progression in 20 years

|| Case Presentation (Continued) ||

- **His repeat SPEP 2 years later shows a M-protein level of 1.2 and an involved to uninvolved free light chain ratio of 7. CBC, creatinine, and calcium levels are normal. He is recommend to undergo a bone marrow biopsy. His bone marrow biopsy shows 15% involvement with an abnormal clone of plasma cells. MRI shows no focal lesion. Cytogenetic analysis shows normal study. What is your management recommendation based on the above findings?**
 - A. Patient has multiple myeloma; recommend treatment with bortezomib based regimen.
 - B. Patient has high-risk smoldering myeloma; recommend treatment with lenalidomide and dexamethasone.
 - C. Patient has low-risk smoldering myeloma; recommend close surveillance.
 - D. Recommend no further treatment or surveillance considering patient's age and comorbidities.

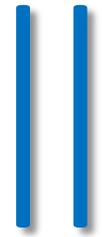
|| Case Presentation (Continued) ||

- **What is your management recommendation based on the above findings?**
 - A. Patient has multiple myeloma; recommend treatment with bortezomib based regimen.
 - B. Patient has high-risk smoldering myeloma; recommend treatment with lenalidomide and dexamethasone.
 - C. Patient has low-risk smoldering myeloma; recommend close surveillance.**
 - D. Recommend no further treatment or surveillance considering patient's age and comorbidities.

It is important to differentiate low-risk SMM from high-risk SMM given data of benefit of treatment in the latter group (*N Engl J Med*, 2013. 369(5):438-47) although treatment of this group should be under clinical trial. The above study defined high-risk SMM with plasma cells >10% and IgG level of ≥ 3 g per deciliter, an IgA level of ≥ 2 g per deciliter, or a urinary Bence Jones protein level of >1 g per 24 hours, or only one of the two criteria described above, plus at least 95% phenotypically aberrant plasma cells in the bone marrow plasma-cell compartment, with reductions in one or two uninvolved immunoglobulins of more than 25%, as compared with normal values.

Companion Case for Chapter 25
Monoclonal Gammopathy of
Unknown Significance, Smoldering
Myeloma, and Plasmacytomas

*Srinath Sundararajan,
Abhijeet Kumar,
Amit Agarwal,
and
Neha Korde*



Clinical Case 29

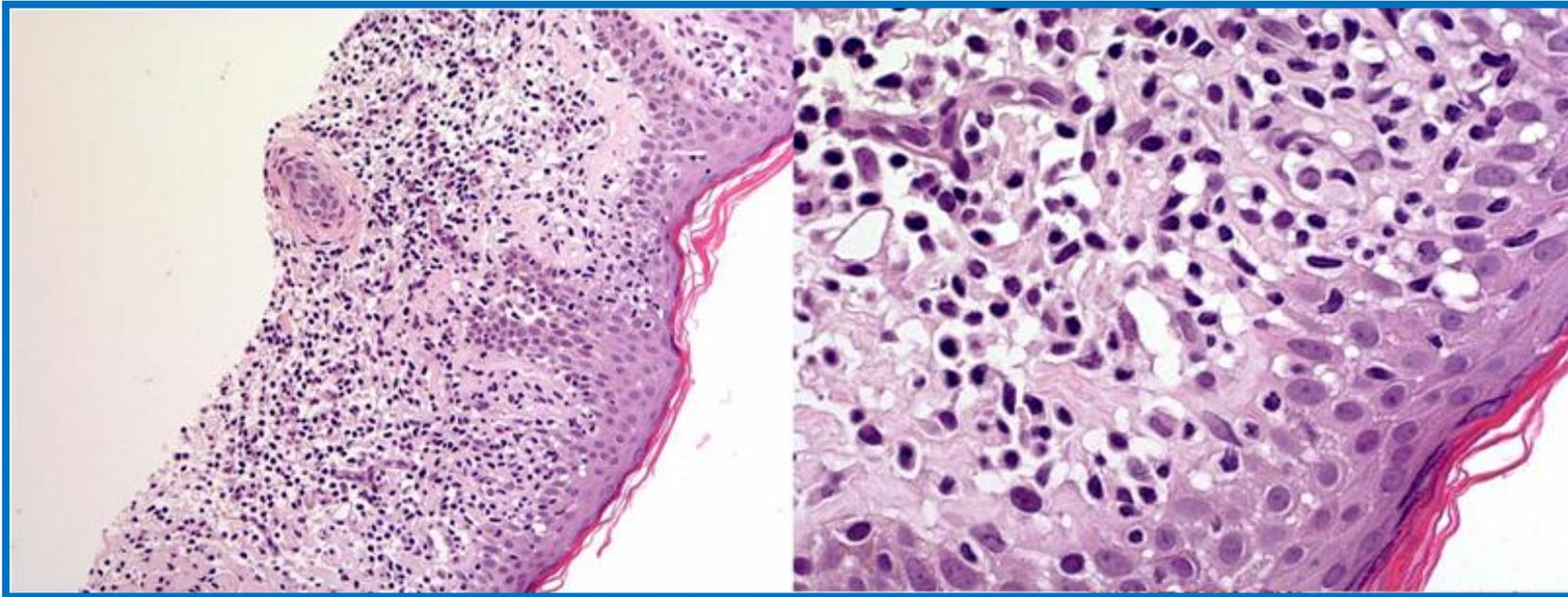


|| Case Presentation

- A 40-year-old gentleman with no significant medical history developed pruritus and hyperpigmented patches insidiously over the past year on his back. These lesions were waxing and waning in nature, with no apparent precipitating factor. He denied any recent travel, sick contacts, allergies, medication usage, recent fever/chills, night sweats, or loss of weight/appetite. His physical examination was notable for hyperpigmented patches occupying <10% of his total body surface area with no apparent lymphadenopathy or organomegaly. His CBC was normal.

|| Case Presentation (Continued) ||

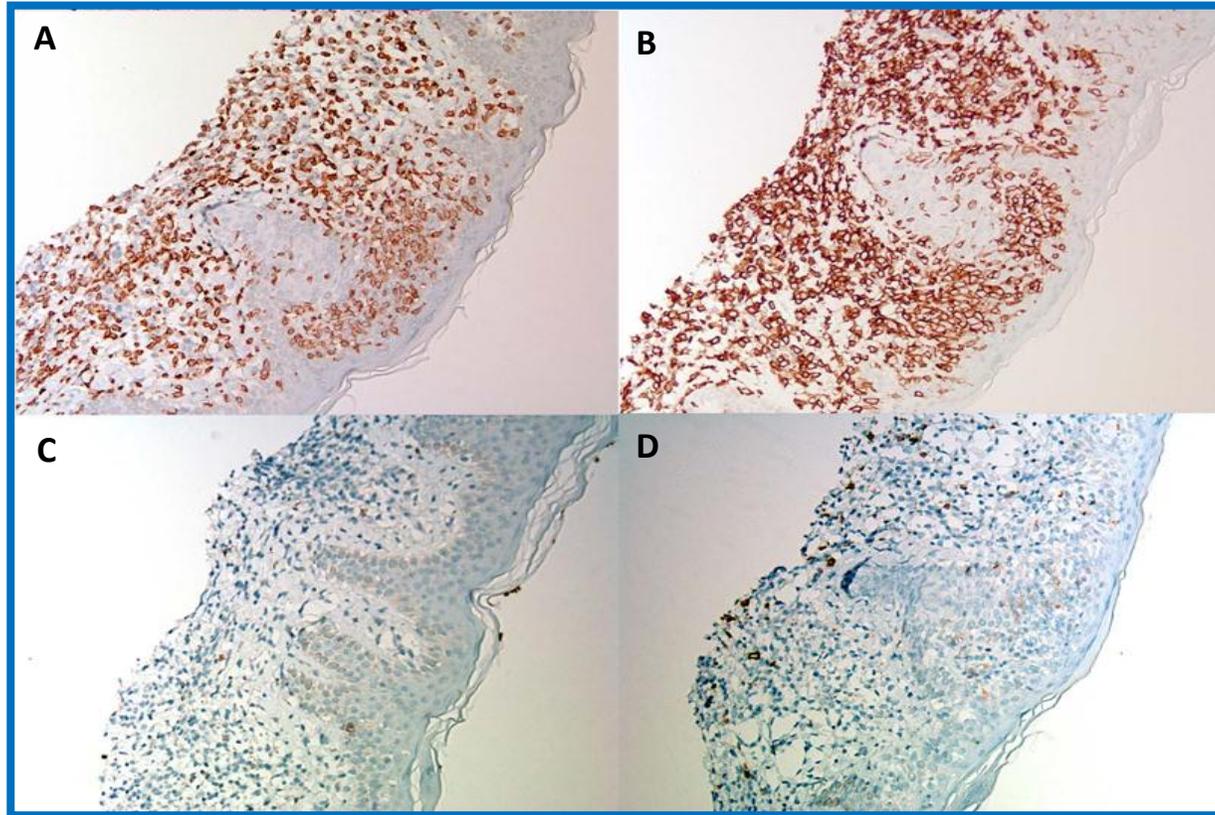
He recently underwent a skin biopsy of one of the hyperpigmented lesions that showed:



left panel: A shave biopsy of skin showed a subepidermal band-like infiltrate of atypical small lymphoid cells with epidermotropism (H&E, x200, total magnification).

right panel: Medium to high power view reveals these atypical lymphoid cells show irregular or cerebriform nuclei, condensed chromatin, and clear cytoplasm associated with spongiosis-like changes in the epidermis (H&E, x600, total magnification).

|| Case Presentation (Continued) ||



A battery of immunohistochemical stains showed the atypical lymphoid cells are T-cells (CD3) (A, x200, total magnification), frequently CD4+ (B, x200, total magnification) with a complete loss of surface CD7 expression (C, x200, total magnification) and CD8 (D, x200, total magnification).

|| Case Presentation (Continued) ||

- Imaging was negative for any other organ involvement and flow cytometry did not show any abnormal cells in the peripheral blood.
- **Which of the following is the correct diagnosis?**
 - A. Stage 1A mycosis fungoides
 - B. Stage 2A mycosis fungoides
 - C. Primary cutaneous anaplastic large cell lymphoma
 - D. Subcutaneous panniculitis-like T-cell lymphoma
 - E. Primary cutaneous small/medium CD4 positive T-cell lymphoproliferative disorder

|| Case Presentation (Continued) ||

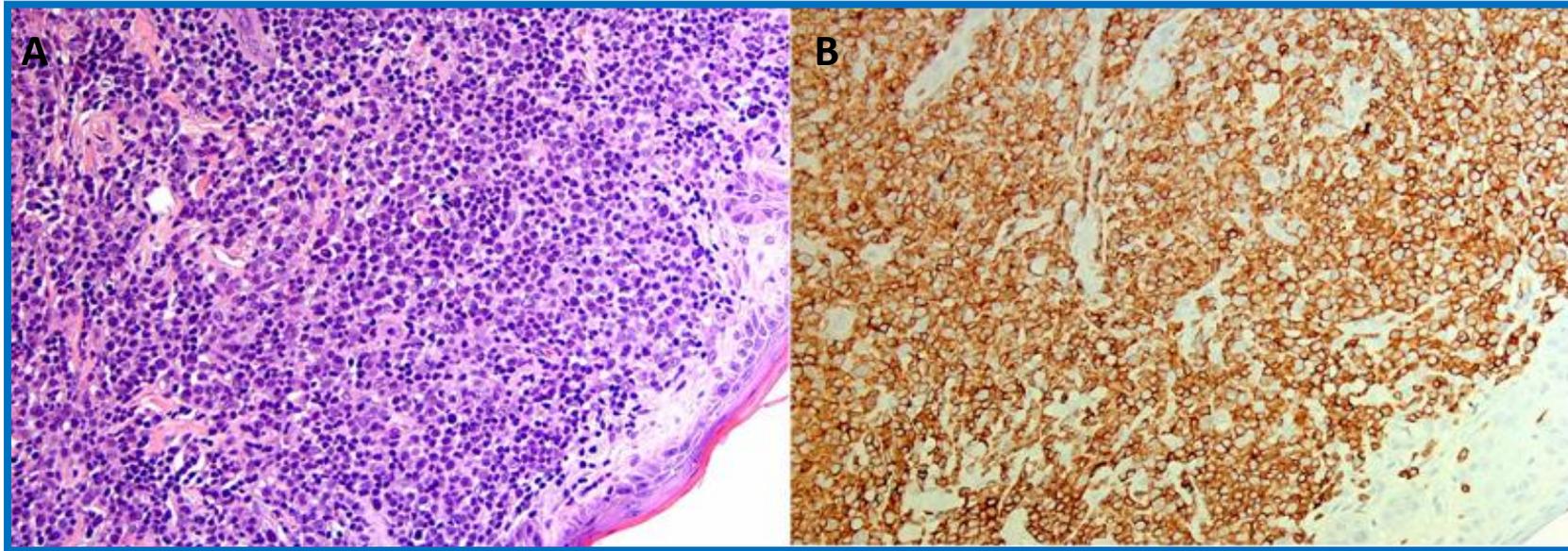
- **Which of the following is the correct diagnosis?**
 - A. **Stage 1A mycosis fungoides**
 - B. Stage 2A mycosis fungoides
 - C. Primary cutaneous anaplastic large cell lymphoma
 - D. Subcutaneous panniculitis-like T-cell lymphoma
 - E. Primary cutaneous small/medium CD4 positive T-cell lymphoproliferative disorder

Case Presentation (Continued)

The clinical and histologic features are compatible with Stage 1A MF (see Table). Sheets of large, lymphoid cells that are CD30 positive are seen in primary cutaneous anaplastic large cell lymphoma, and, by definition, evidence or a history of MF must be excluded before rendering such a diagnosis. Patients with subcutaneous panniculitis-like T-cell lymphoma present with multiple subcutaneous nodules, with characteristic “rimming” of malignant T-cells around adipocytes, highlighted by CD8 and TIA-1. Cytotoxic molecules (granzyme B, perforin, TIA-1) are not present in MF. Primary cutaneous small/medium CD4 positive T-cell lymphoproliferative disorder presents with isolated lesions on the face, head/neck, and are associated with a favorable prognosis. The lesion is composed of small/medium atypical T-cells (CD3+, CD4+, CD8-, CD30-), with focal areas of large pleomorphic cells (<30%). Epidermotropism may be focally seen, but MF should be excluded if significant epidermotropism is present.

Stage	Description	
I	A	<10% skin involvement; no lymph node involvement
	B	>10% skin involvement; no lymph node involvement
II	A	Skin involvement along with N1-N2 lymph node involvement
	B	Skin involvement along with one or more tumors >1 cm in size
III		Skin involvement >80% with low blood tumor burden (<1000 Sezary cells)/erythroderma/N1-N2 lymph node involvement
IV		High blood tumor burden (>1000 Sezary cells)/N3 lymph node involvement/visceral involvement

|| Case Presentation (Continued) ||



Representative section of a skin biopsy of the tumor stage of MF. There is confluent proliferation of atypical lymphoid cells involving subepidermal to dermal regions, including the full thickness of skin as well as adjacent tissue. The cellularity is composed of an admixture of small to large lymphoid cells with nuclear irregularity, hyperchromasia, and some with visible to prominent nuclei (A, H&E, x200). CD3 stain highlighted these infiltrating cells (B, immunoperoxidase, x200).

|| Case Presentation (Continued) ||

- **What is the preferred first-line therapy?**
 - A. Surgical resection
 - B. Gemcitabine-based chemotherapy
 - C. Electron beam therapy
 - D. Skin-directed therapy
 - E. Pralatrexate-based chemotherapy

|| Case Presentation (Continued) ||

- **What is the preferred first-line therapy?**
 - A. Surgical resection
 - B. Gemcitabine-based chemotherapy
 - C. Electron beam therapy
 - D. Skin-directed therapy**
 - E. Pralatrexate-based chemotherapy
- Generalized skin therapy with topical steroids or retinoids is the preferred mode of therapy for early-stage mycosis fungoides.

|| Case Presentation (Continued) ||

- **Which of the following chromosomal alterations is associated with poor prognosis in MF?**
 - A. 9p21
 - B. 8q24
 - C. 1q21-1q22
 - D. All of the above

|| Case Presentation (Continued) ||

- **Which of the following chromosomal alterations is associated with poor prognosis in MF?**
 - A. 9p21
 - B. 8q24
 - C. 1q21-1q22
 - D. All of the above**
- “Oncogenomic analysis of mycosis fungoides reveals major differences with Sézary syndrome”; January 1, 2009; *Blood*: 113 (1).

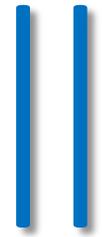
Companion Case for Chapter 46

Mycosis Fungoides

Achuta Kumar Guddati

and

Lubomir Sokol



Clinical Case 30



Case Presentation

A 66-year-old female with a past medical history of hypertension, well controlled on HCTZ 25 mg PO QD, presents to the emergency department with severe RUQ abdominal pain that had started earlier in the week. She also reports jaundice on the day of presentation. HR 89 beats/min, BP 155/90 mmHg, O2 100% on room air. Physical exam revealed mild scleral icterus. Abdominal exam showed hepatomegaly, significant tenderness to palpation of the RUQ and splenomegaly 3cm below the costal margin. Laboratory evaluation on presentation showed transaminitis (>5 times ULN), indirect hyperbilirubinemia, and increased LDH. Her complete blood count was as below.

CBC	
WBC	15 k/ μ L
Hgb	17.3 g/dL
HCT	51.9%
Platelets	654 k/ μ L
Neuts, abs	11.2 k/ μ L
Lymphs, abs	3.1 k/ μ L
Eos, abs	0.18 k/ μ L

|| Case Presentation (Continued) ||

An abdominal US with doppler was ordered, which showed obstruction in the hepatic veins consistent with Budd-Chiari syndrome. The patient was admitted to the hospital and started on anticoagulation with slow improvement of hepatic dysfunction and resolution of pain. Follow-up CBCs continued to demonstrate erythrocytosis, leukocytosis, and thrombocytosis. Hematology was consulted for evaluation, given her blood count abnormalities.

The hematologist orders a bone marrow biopsy, and the results are shown in Figure 1.

|| Case Presentation (Continued) ||

- A. Microscopic examination of a bone marrow core biopsy from a patient with PB shows markedly hypercellular (>90%) with panmyeloid hyperplasia (H&E, x40). B. A medium power field shows predominant erythroid hyperplasia with inverted myeloid to erythroid ratio, estimated at 1:1 to focally 1:2 (H&E, x200). C. Iron storage is markedly decreased (Prussian blue iron stain, x600). D. Reticulin stain shows no significant fibrosis in proliferation phase (reticulin stain, x600).
- E. A low power view of the earlier fibrotic phase bone marrow core biopsy shows retained hypercellularity including trilineage hematopoietic precursors, focally in spindly arrangement (H&E, x200). F and G. In the late phase of this disease, cellularity is reduced, particularly erythroid components while there is increase in mononuclear immature myeloid precursors admixed with atypical megakaryocytes (F, H&E, x600) in a background of dense reticulin fibrosis, 3+ of score 0–3 (G, reticulin, x600). Aspirate is often dry-tap. Increased myeloid blasts in touch imprint preparation are noted, particularly in accelerated phase (H, Wright-Giemsa, x1000).

Case Presentation (Continued)

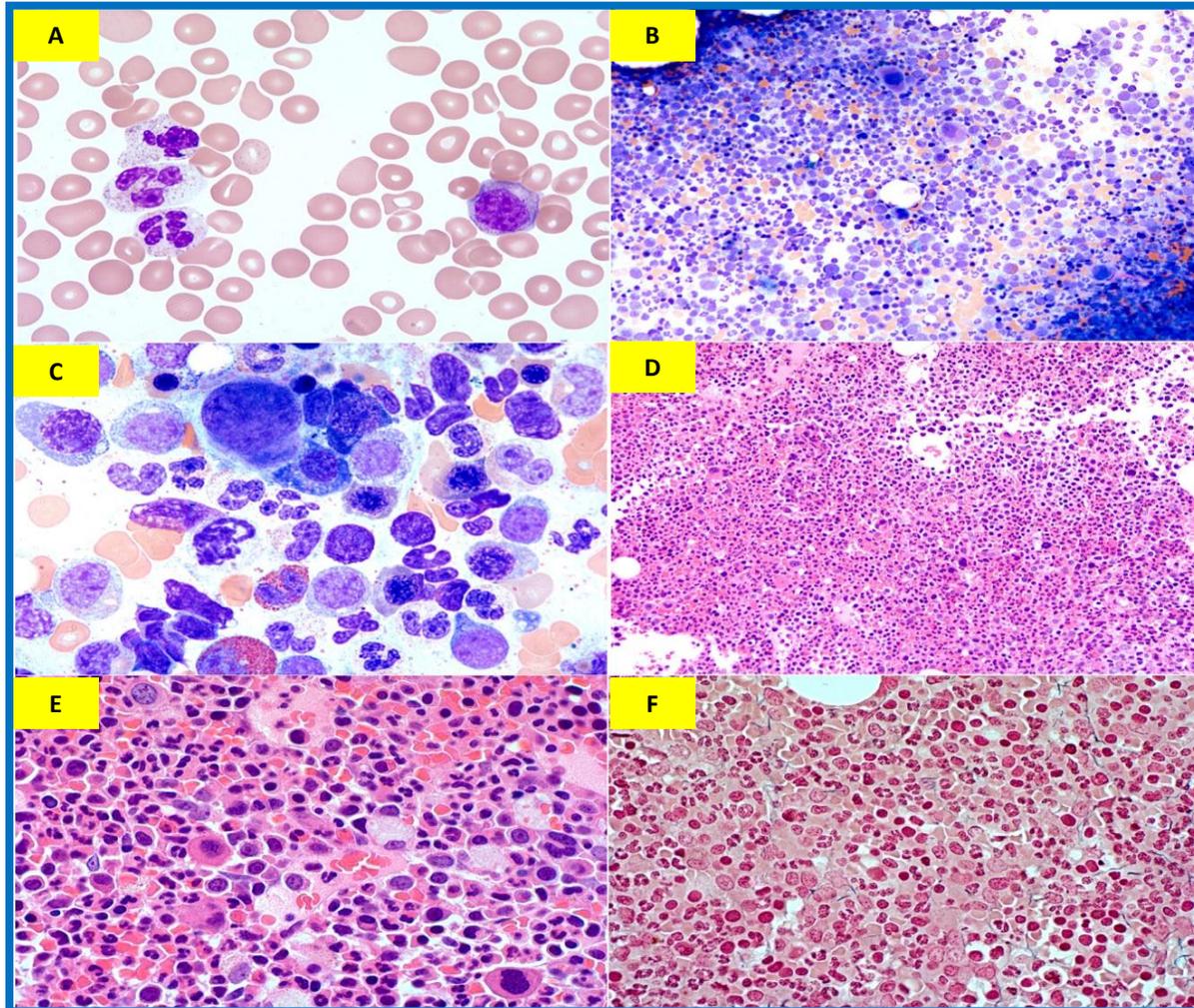


Figure 1. A peripheral blood smear (A, Wright-Giemsa, x600) shows leukocytosis but no circulating blasts, while the bone marrow aspirate smear (B, Wright-Giemsa, x400) shows panmyelosis (hyperplasia of all three hematopoietic lineages) and hyperplasia of pleomorphic megakaryocytes (B and C, Wright-Giemsa, x200 and x1000, respectively). Blasts are not increased, and dysplasia is not appreciated. A core biopsy of the patient shows marked hypercellularity (>90%) with hyperplasia of myeloid, erythroid, and megakaryocytic precursors, with megakaryocytes focally forming loose clusters and showing some pleomorphism (D and E, H&E, x200). Blasts are not increased, and a reticulin stain shows no significant fibrosis (F, reticulin, x200).

|| Case Presentation (Continued) ||

- **What is the most likely diagnosis?**
 - A. Polycythemia vera
 - B. Essential thrombocythemia (ET)
 - C. MDS
 - D. CMML

|| Case Presentation (Continued) ||

- **What is the most likely diagnosis?**
 - A. **Polycythemia vera (PV)**
 - B. Essential thrombocythemia (ET)
 - C. MDS
 - D. CMML

The clinical and pathologic features are compatible with PV. The bone marrow shows panmyelosis (hyperplasia of all three lineages) with accompanying variably sized megakaryocytes and are typically seen in the polycythemic phase. Blasts are not increased and there is no absolute monocytosis, in addition to no morphologic evidence of dyspoiesis, making MDS and CMML less likely. Essential thrombocythemia (ET) may mimic PV, especially in the early phase, due to megakaryocytic abnormalities and a subset of PV cases may present with thrombocytosis. However, even though uncommon cases of ET may have erythroid hyperplasia, panmyelosis is consistent with PV and not ET. PV megakaryocytes typically are hyperplastic with pleomorphism, but less often are bulbous or show atypia like those seen in ET.

|| Case Presentation (Continued) ||

- **What additional studies should be initially ordered in this patient to confirm the diagnosis?**
 - A. *JAK2* exon 12 mutation
 - B. *JAK2* V617F mutation
 - C. Serum erythropoietin level, *JAK2* V617F
 - D. *CALR* mutation

|| Case Presentation (Continued) ||

- **What additional studies should be initially ordered in this patient to confirm the diagnosis?**
 - A. *JAK2* exon 12 mutation
 - B. *JAK2* V617F mutation
 - C. Serum erythropoietin level, *JAK2* V617F**
 - D. Bone marrow biopsy

Based on the current WHO 2008 diagnostic criteria, the patient meets one major criterion based on her Hgb/Hct. Checking a serum EPO level and *JAK2* V617F mutation would be the first step to confirming PV.

Bone marrow morphology has been added to the proposed WHO 2016 diagnostic criteria in an effort to increase sensitivity by decreasing Hgb/Hct and to help differentiate PV with thrombocytosis from essential thrombocythemia (ET), which also has *JAK2* V617F mutation in 50% to 60% of cases.

|| Case Presentation (Continued) ||

Serum EPO level was 2 mIU/mL (*2.6–18.5 mIU/mL*). Mutation analysis was positive for a *JAK2* V617F mutation confirming the diagnosis of polycythemia vera.

- **What risk category would this patient be in, and what would be her prognosis?**
 - A. Low risk, median OS of >20 years
 - B. Intermediate risk, median OS of 15–20 years
 - C. High risk, median OS of 11 years

|| Case Presentation (Continued) ||

- **What risk category would this patient be in and what would be her prognosis?**
 - A. Low risk, median OS of >20 years
 - B. Intermediate risk, median OS of 15–20 years
 - C. **High risk, median OS of 11 years**

Mayo Clinic Prognostic Scoring System	
Age >67	5 points
Age 56–67 years	2 points
Leukocytes >15,000	1 point
Prior thrombosis	1 point

Risk Category	Points	Median OS
Low risk	0 points	28 years
Intermediate risk	1–2 points	19 years
High risk	≥3 points	11 years

|| Case Presentation (Continued) ||

- **What treatment is indicated for this patient?**
 - A. Low dose aspirin and phlebotomy
 - B. Low dose aspirin and hydroxyurea or PEG-interferon- α
 - C. Low dose aspirin, phlebotomy, and hydroxyurea or PEG-interferon- α
 - D. Warfarin, phlebotomy, and hydroxyurea or PEG-interferon- α

|| Case Presentation (Continued) ||

- **What treatment is indicated for this patient?**
 - A. Low dose aspirin and phlebotomy
 - B. Low dose aspirin and hydroxyurea or PEG-interferon- α
 - C. Low dose aspirin, phlebotomy, and hydroxyurea or PEG-interferon- α
 - D. Warfarin, phlebotomy, and hydroxyurea or PEG-interferon- α**

The patient is considered high risk based on her age, leukocytosis, and presenting thrombosis. Hydroxyurea or PEG-interferon- α and phlebotomy are indicated to a goal Hct of <45%. Given that patient has already had significant thrombosis, she should be treated with full dose anticoagulation.

|| Case Presentation (Continued) ||

Patient is started on weekly phlebotomy until Hct <45% and hydroxyurea is titrated up to a dose of 1,500 mg/day. She tolerates treatment with minimal side effects.

CBC at her 1-year follow-up showed a WBC of 4.3 k/ μ L, Hgb 13.6 g/dL, Hct 40.8%, and platelets of 580 k/ μ L.

Therapy was continued with no need of phlebotomies in the past 6 months.

|| Case Presentation (Continued) ||

Five years later, patient presented to clinic with complaints of increasing fatigue, shortness of breath, drenching night sweats almost every night, and 25-lb weight loss.

Vital signs were normal and physical exam revealed splenomegaly, 5cm below costal margin without any other abnormalities.

Her CBC showed a WBC of 2.3 k/ μ L, Hgb 9.6 g/dL, and platelets of 240 k/ μ L.

|| Case Presentation (Continued) ||

Bone marrow biopsy is obtained and confirms the diagnosis of post-PV myelofibrosis with 5% myeloblasts seen in the bone marrow (see image in next slide).

Cytogenetic studies demonstrate a normal female karyotype 46,XX.

Case Presentation (Continued)

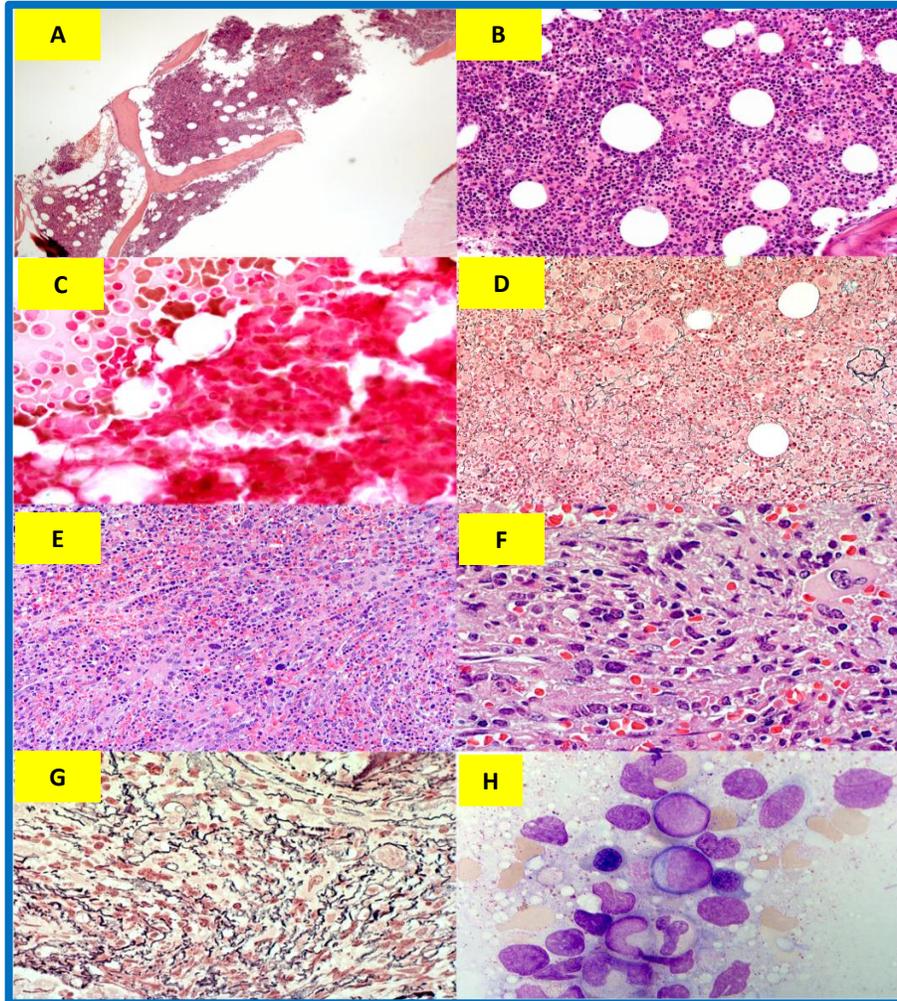


Figure 2. A. Microscopic examination of a bone marrow core biopsy from a patient with PV shows markedly hypercellular (>90%) with panmyeloid hyperplasia (H&E, x40). B. A medium power field shows predominant erythroid hyperplasia with inverted myeloid to erythroid ratio, estimated at 1:1 to focally 1:2 (H&E, x200). C. Iron storage is markedly decreased (Prussian blue iron stain, x600). D. Reticulin stain shows no significant fibrosis in the proliferation phase (reticulin stain, x600). A low power view of the earlier fibrotic phase bone marrow core biopsy shows retained hypercellularity including trilineage hematopoietic precursors, focally in spindly arrangement (E, H&E, x200).

In the last phase of PV, cellularity is reduced, particularly erythroid components while there is increase in mononuclear immature myeloid precursors admixed with atypical megakaryocytes (F, H&E, x600) in a background of dense reticulin fibrosis, 3+ of score 0–3 (G, reticulin, x600). Aspirate is often dry-tap. Increased myeloid blasts in touch imprint preparation are noted, particularly in accelerated phase of PV (H, Wright Giemsa, x1000).

|| Case Presentation (Continued) ||

- **What is the next step in treatment of this patient?**
 - A. Continue hydroxyurea and phlebotomies.
 - B. Continue hydroxyurea and start ruxolitinib.
 - C. Discontinue hydroxyurea and start ruxolitinib.
 - D. Refer for allogeneic hematopoietic cell transplant evaluation.
 - E. Both C and D

|| Case Presentation (Continued) ||

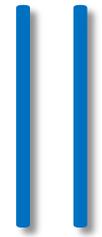
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 - B. Continue hydroxyurea and start ruxolitinib.
 - C. Discontinue hydroxyurea and start ruxolitinib.
 - D. Refer for allogeneic hematopoietic cell transplant evaluation.
 - E. Both C and D**

Based on current prognostic criteria, patient is an intermediate-2 risk given her age, hemoglobin, and constitutional symptoms. Hydroxyurea should be discontinued based on her cytopenias and Ruxolitinib started to improve constitutional symptoms and splenomegaly. Given the relatively poor prognosis, the patient should be referred early for bone marrow transplant evaluation.

Companion Case for Chapter 2

Polycythemia Vera

*Liliana Bustamante
and
Kenneth Zuckerman*



Clinical Case 31



|| Case Presentation



- A 24-year-old woman with no medical history presented with a marble-sized lymph node in her supraclavicular area with a sense of fullness in her upper chest wall with no pain. She denies fevers, chills, weight loss, change in appetite, or fatigue.

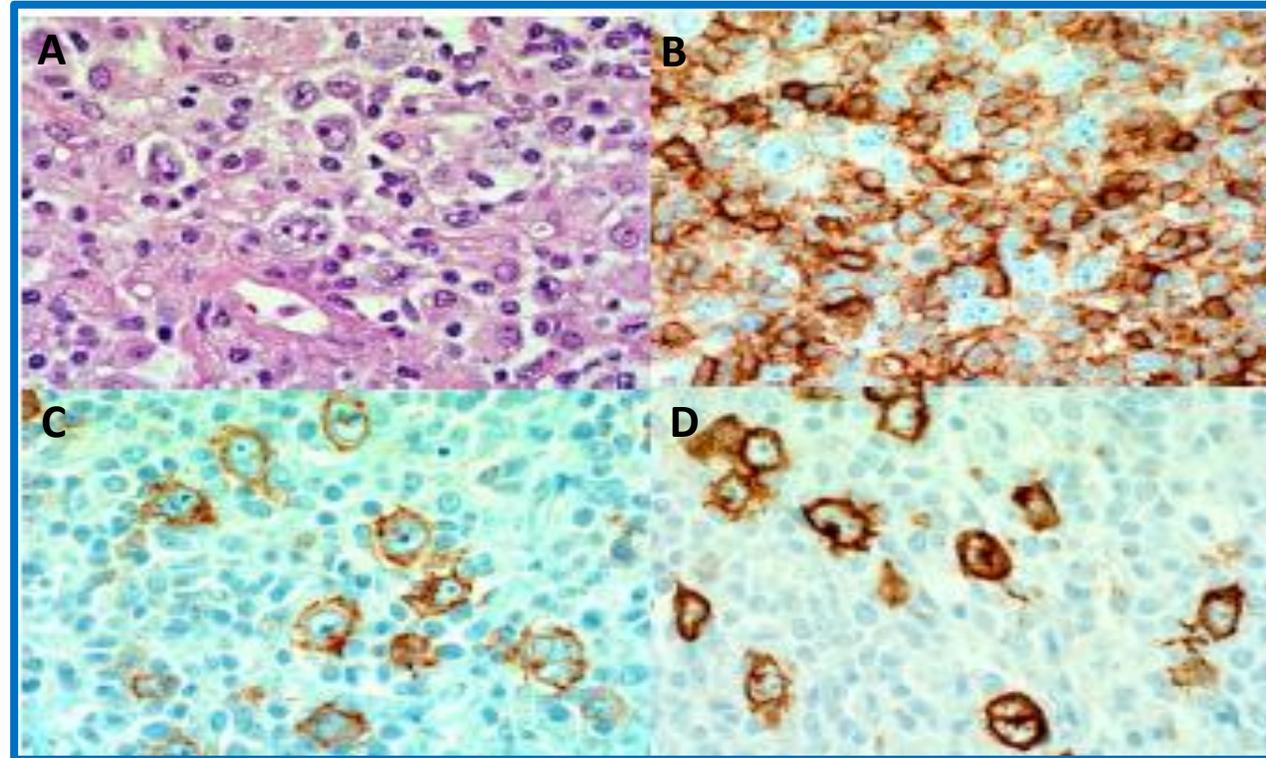
|| Case Presentation (Continued) ||

- Computed tomography (CT) scan of soft tissue of neck showed a large conglomerate lymph node mass located in the right supraclavicular region extending through the thoracic inlet into the right paratracheal region, measuring approximately 9 x 5 x 4 cm in size.

|| Case Presentation (Continued) ||

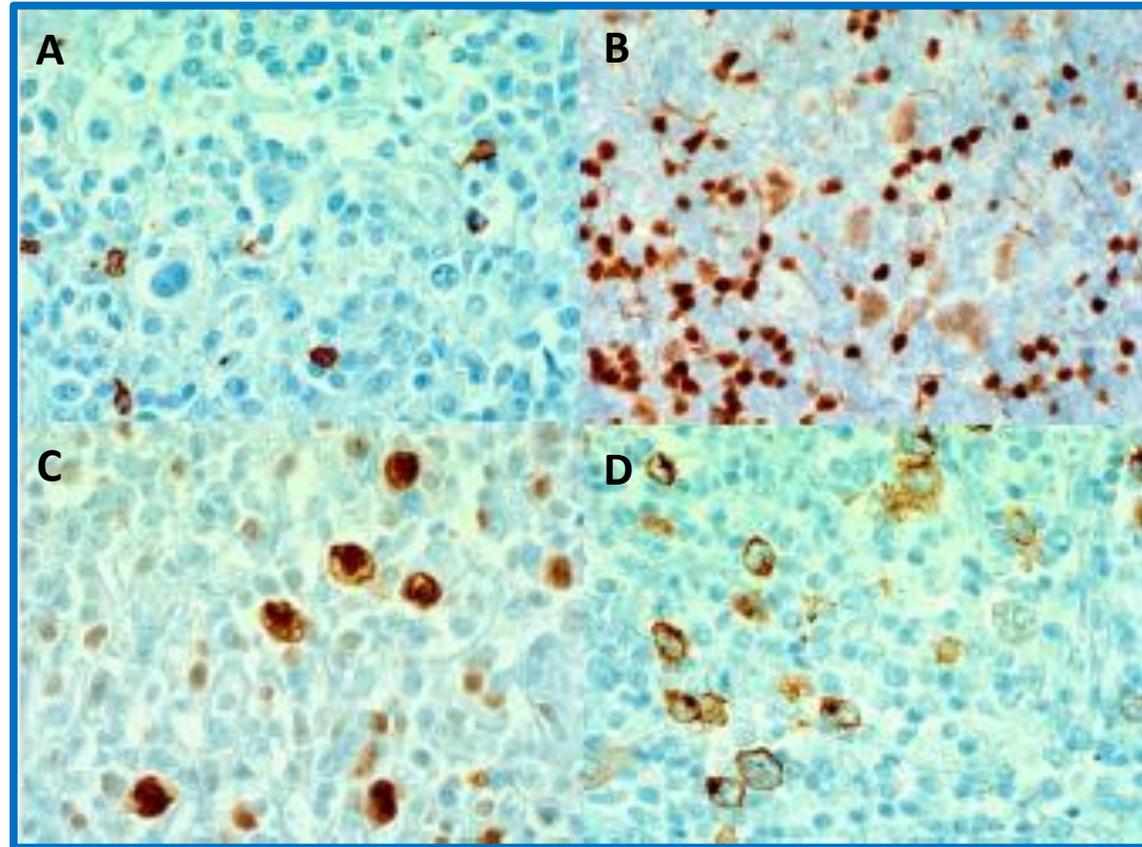
- Excisional biopsy of the right supraclavicular mass showed effacement of the lymph node architecture by a nodular infiltrate composed of scattered large, atypical cells with prominent, brightly eosinophilic nucleoli, focally binucleated, and abundant cytoplasm, admixed with a background of small lymphocytes, histiocytes, and eosinophils (see next slide).

|| Case Presentation (Continued) ||



- Immunohistochemical (IHC) staining shows the atypical large cells are negative for CD45 (B), and CD3 highlights background small T-cells. The large cells are staining positive for CD15 (C) and CD30 with characteristic membranous and Golgi enhancement pattern (D).

|| Case Presentation (Continued) ||



- The large atypical cells were negative for CD20 (A), weakly positive for PAX-5 (B), strongly positive for MUM-1 (C). EBV-latent membrane protein 1 was positive (EBV-LMP, D).

|| Case Presentation (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Nodular lymphocyte predominant Hodgkin lymphoma
 - B. Nodular sclerosis classical Hodgkin lymphoma
 - C. Anaplastic large cell lymphoma
 - D. Primary mediastinal (thymic) large B-cell lymphoma

|| Case Presentation (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Nodular lymphocyte predominant Hodgkin lymphoma
 - B. Nodular sclerosis classical Hodgkin lymphoma**
 - C. Anaplastic large cell lymphoma
 - D. Primary mediastinal (thymic) large B-cell lymphoma

|| Differential Diagnosis

- Nodular lymphocyte predominant Hodgkin lymphoma is CD20 and CD45 positive while negative for CD15 and CD30.
- Anaplastic large cell lymphoma is a T-cell neoplasm that stains negative for CD15 and positive for CD30 (see Chapter 44).
- Primary mediastinal (thymic) large B-cell lymphoma will express pan B-cell antigens, CD19 and CD20, while typically weakly expressing CD30 and rarely expressing CD15. It also will usually demonstrate compartmentalizing fibrosis as opposed to the broad fibrotic bands seen in NSCHL.

|| Differential Diagnosis (Continued) ||

- **The presence of which of the following phenotypes suggests the diagnosis of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) over classical Hodgkin lymphoma (cHL)?**
 - A. CD20-, CD15+, CD30+
 - B. CD20+, CD15-, CD30-
 - C. CD20+, CD15+, CD30+
 - D. Presence of Reed-Sternberg cells

|| Differential Diagnosis (Continued) ||

- **The presence of which of the following phenotypes suggests the diagnosis of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) over classical Hodgkin lymphoma (cHL)?**
 - A. CD20-, CD15+, CD30+
 - B. CD20+, CD15-, CD30-**
 - C. CD20+, CD15+, CD30+
 - D. Presence of Reed-Sternberg cells
- NLPHL expresses CD20 and is usually negative for the markers CD15 and CD30.
- Reed-Sternberg cells can be seen in both NHLPL and cHL.
- EBV infection/reactivation is not a feature of NHLPL.

|| Differential Diagnosis (Continued) ||

- **Which of the Hodgkin lymphomas has the highest incidence of EBV positivity?**
 - A. Nodular lymphocyte predominant Hodgkin lymphoma
 - B. Nodular sclerosis classical Hodgkin lymphoma
 - C. Mixed cellularity classical Hodgkin lymphoma
 - D. Lymphocyte-depleted classical Hodgkin lymphoma
 - E. Lymphocyte-rich classical Hodgkin lymphoma

|| Differential Diagnosis (Continued) ||

- **Which of the Hodgkin lymphomas has the highest incidence of EBV positivity?**
 - A. Nodular lymphocyte predominant Hodgkin lymphoma
 - B. Nodular sclerosis classical Hodgkin lymphoma
 - C. Mixed cellularity classical Hodgkin lymphoma**
 - D. Lymphocyte-depleted classical Hodgkin lymphoma
 - E. Lymphocyte-rich classical Hodgkin lymphoma
- About 75% of all cases of mixed cellularity cHL harbor the EBV infection. NSCHL shows the least prevalence of EBV positivity.

|| Differential Diagnosis (Continued) ||

- **Which of the following IHC patterns is typical of PAX-5 in HRS cells of classical Hodgkin lymphoma?**
 - A. Cytoplasmic, strong
 - B. Cytoplasmic, weak
 - C. Membranous with Golgi enhancement
 - D. Nuclear, strong
 - E. Nuclear, weak

|| Differential Diagnosis (Continued) ||

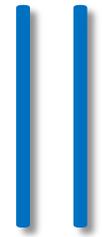
- **Which of the following IHC patterns is typical of PAX-5 in HRS cells of classical Hodgkin lymphoma?**
 - A. Cytoplasmic, strong
 - B. Cytoplasmic, weak
 - C. Membranous with Golgi enhancement
 - D. Nuclear, strong
 - E. **Nuclear, weak**

PAX-5, or B-cell specific activator protein (BSAP), is a transcription factor found in B-cells. PAX-5 will stain Reed-Sternberg cells within a weak nuclear pattern, which allows one to readily identify these cells in cHL cases. CD30 stains in a characteristic membranous and Golgi pattern.

Companion Case for Chapter 29

Hodgkin Lymphoma

*Anju Nair
and
Micah Burch*



Clinical Case 32



|| Case Presentation

A 37-year-old Caribbean male presents with increasing neck mass for 2 months. Physical exam reveals hard, fixed retroauricular, submental and occipital lymph nodes. Abdominal exam shows massive hepatosplenomegaly.

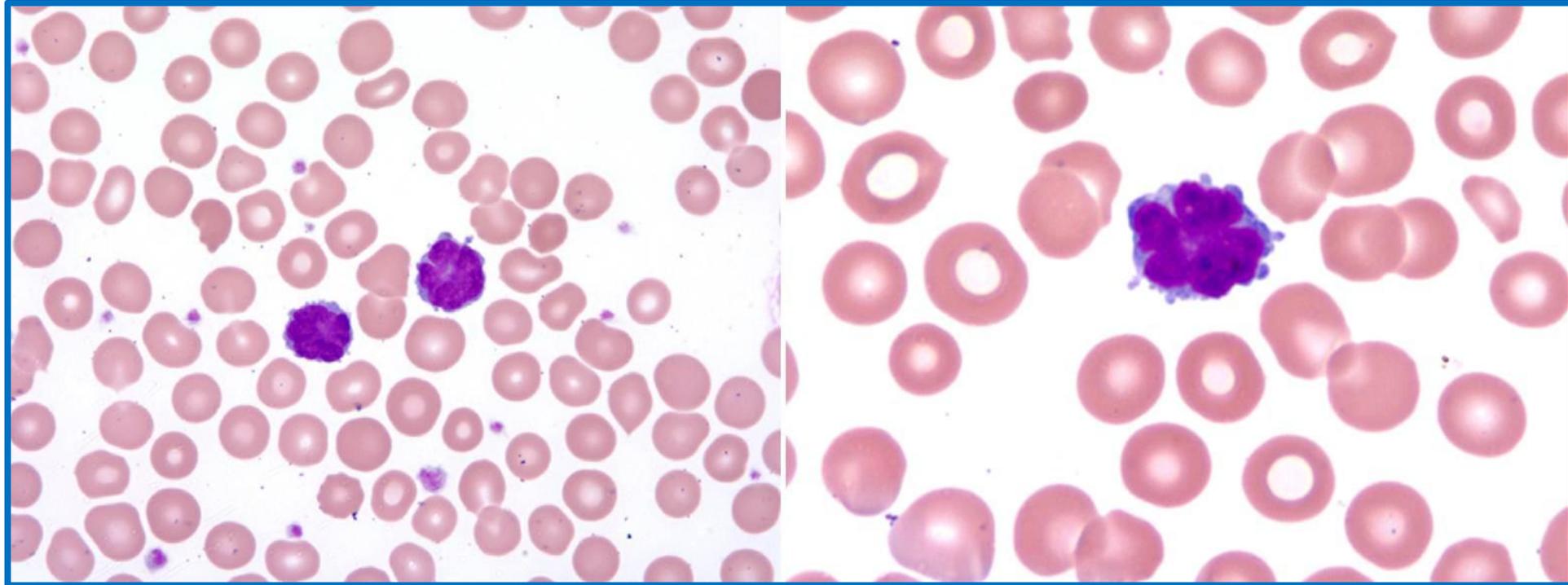
CBC shows:

WBC: 139.2 k/ μ L; Hgb: 13.1 g/dL; Platelets: 261 k/ μ L

Differential:

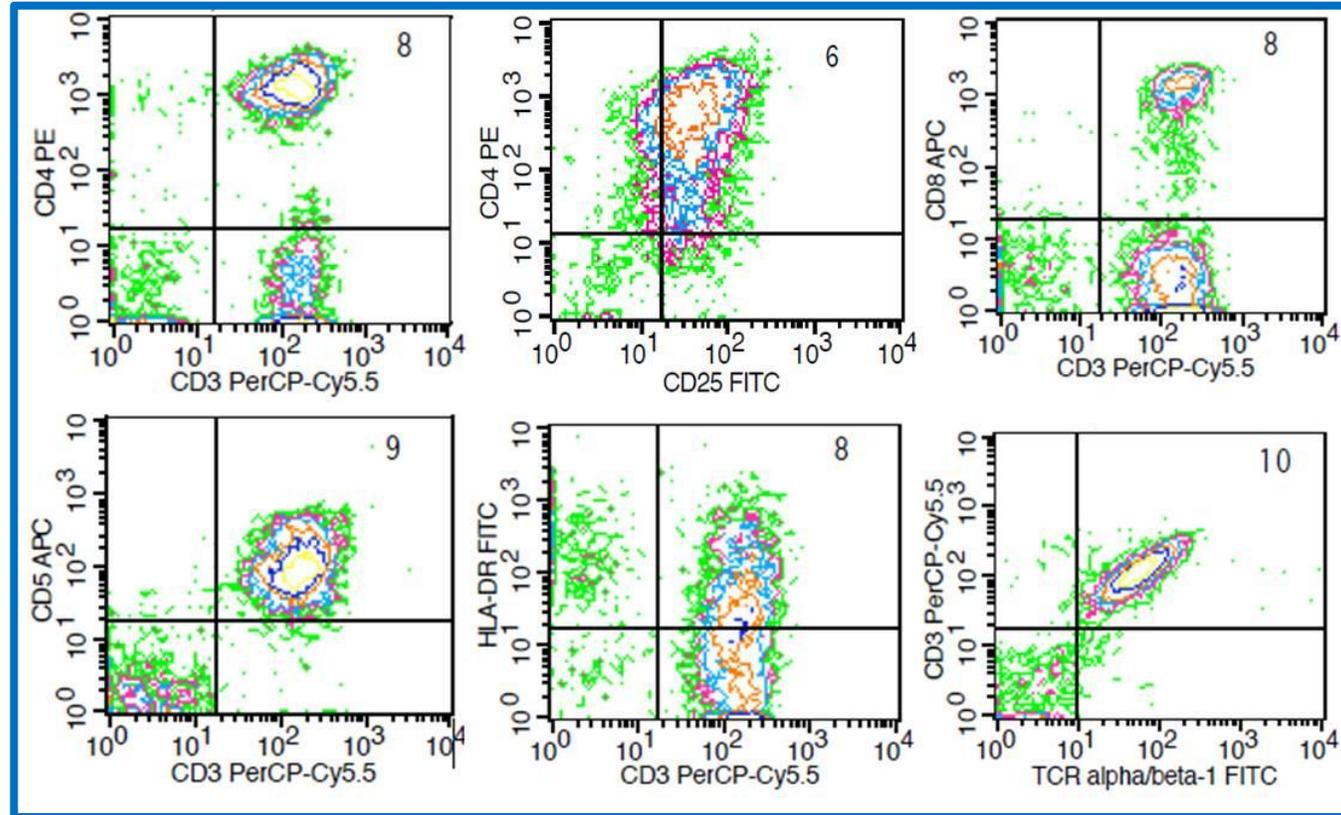
Neutrophils: 5%; Lymphocytes: 70%; Atypical Lymphocytes: 15%; Monocytes: 10%

Peripheral Blood Smear



Several circulating atypical lymphoid cells were identified in a peripheral blood smear. The cells showed hyperchromasia, markedly irregular nuclear contours with lobated nuclei, and abundant basophilic cytoplasm.

Peripheral Blood Flow Cytometry



Flow cytometric analysis shows a clonal T-cell population expressing CD3, CD4, CD5, CD25, HLA-DR(dim), TCR $\alpha\beta$, and negative for CD8.

|| Biopsy Results

Occipital lymph node biopsy:

Monotypic atypical lymphocytes, small to medium in size. Pleomorphic nuclear features in the form of irregular contours.

Immunohistochemistry shows the atypical cells are positive for CD3, CD4, CD5, CD8, CD25, FOXP3, and negative for CD7, CD8, CD30, and ALK1.

HTLV-1 serology is positive.

|| Question



- **What is the most likely diagnosis?**
 - A. Mantle cell lymphoma
 - B. Adult T-cell leukemia/lymphoma
 - C. Sézary syndrome
 - D. Anaplastic large cell lymphoma, ALK negative

|| Question (Continued) ||

- **What is the most likely diagnosis?**
 - A. Mantle cell lymphoma
 - B. Adult T-cell leukemia/lymphoma**
 - C. Sézary syndrome
 - D. Anaplastic large cell lymphoma, ALK negative
- The peripheral smear shows characteristic flower T-cells. Flow cytometry confirms a clonal CD4 positive T-regulatory phenotype. The presence of positive HTLV-1 serology indicates this patient likely has adult T-cell leukemia/lymphoma.

|| Question (Continued) ||

- **What would *not* be an appropriate treatment regimen for this patient?**
 - A. R-CHOP
 - B. Dose-adjusted EPOCH
 - C. Interferon alfa + zidovudine
 - D. LSG-15

|| Question (Continued) ||

- **What would *not* be an appropriate treatment regimen for this patient?**
 - A. R-CHOP**
 - B. Dose-adjusted EPOCH
 - C. Interferon alfa + zidovudine
 - D. LSG-15
- The optimal first-line chemotherapy treatment regimens include CHOP and EPOCH. LSG-15 is an aggressive Japanese chemotherapy regimen that has shown improved survival as compared to standard chemotherapy regimens. Interferon-alfa and zidovudine is an optimal regimen for acute type ATLL and had improved overall survival as compared to chemotherapy in one meta-analysis.
- ATLL is a mature T-cell neoplasm, and thus rituximab (CD20 antibody) would not be indicated in this patient.

|| Question (Continued) ||

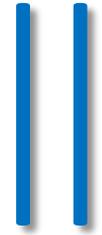
- **In which of the following ethnic groups is ATLL more prevalent?**
 - A. Ashkenazi Jewish
 - B. Hispanic
 - C. Japanese
 - D. Caucasian

|| Question (Continued) ||

- **In which of the following ethnic groups is ATLL more prevalent?**
 - A. Ashkenazi Jewish
 - B. Hispanic
 - C. Japanese**
 - D. Caucasian
- ATLL is endemic in southern Japan, the Caribbean basin, Central/South America, tropical Africa, and northern Iran.

Companion Case for Chapter 43 Adult T-Cell Leukemia/Lymphoma

*Nikhil Mukhi
and
Lubomir Sokol*



Clinical Case 33

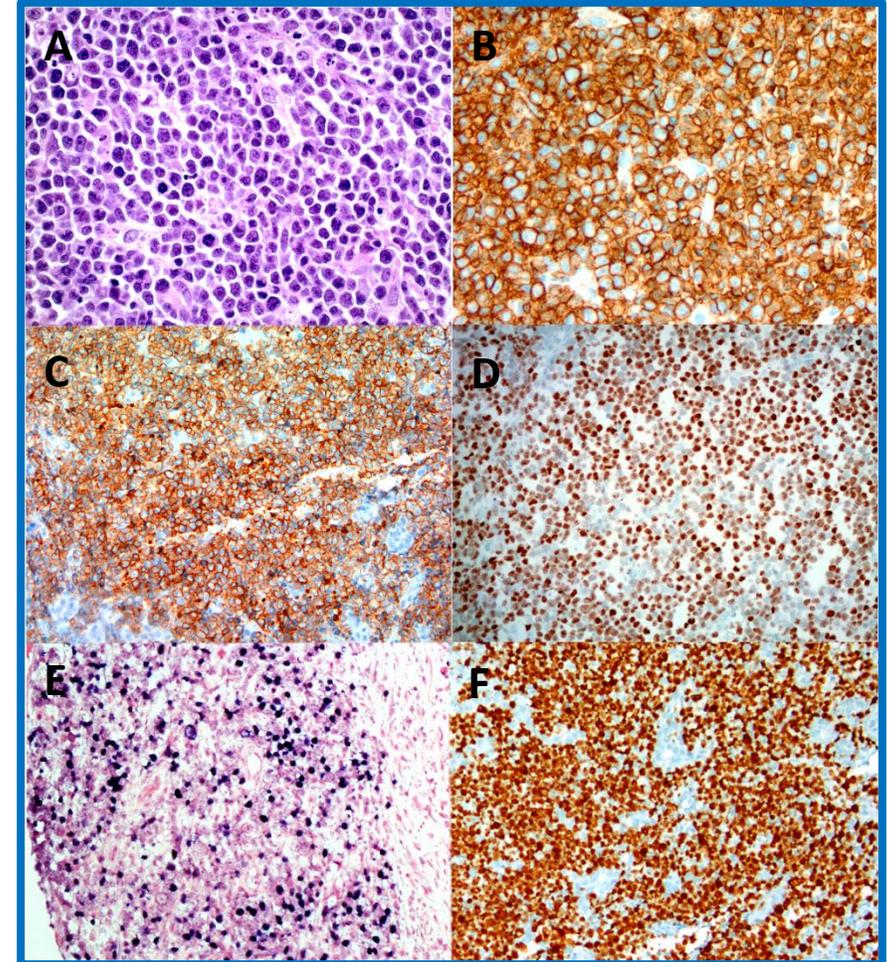


|| Case Presentation #1

- A 35-year-old male presents to his primary care provider for the evaluation of persistent fevers, night sweats, 15-lb weight loss, headaches, and cough for the past 2 months. He admits to high-risk sexual behavior and IV drug use. Vital signs are normal. Physical exam is notable for bitemporal wasting as well as cervical, axillary, and inguinal lymphadenopathy. CBC showed a hemoglobin of 10.5 g/dL. Other parameters were normal. CMP was within normal limits. LDH was 756 UI/L. An HIV test was positive. The CD4 count was 156 cells/ μ L with a viral load of 789,000 copies/mL.

Excisional Lymph Node Biopsy

- A. The H&E section of an enlarged axillary lymph node showed complete effacement of the normal nodal architecture and replacement by sheets of large atypical lymphoid cells with dispersed or hyperchromatic chromatin, high nuclear:cytoplasmic ratio, and amphophilic cytoplasm (H&E, x400).
- B-D. Immunohistochemical stains demonstrate the atypical cells were positive for CD20(B), CD10 (C), and BCL-6 (D) (immunoperoxidase, x400, x200, and x200, respectively).
- E. EBER-ISH (in situ hybridization) was positive (ISH, x200).
- F. Ki-67 showed a high proliferation rate, estimated at 90% (immunoperoxidase, x200).



|| Excisional Lymph Node Biopsy (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Marginal zone lymphoma
 - B. Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - C. Diffuse large B-cell lymphoma
 - D. Classical Hodgkin lymphoma
 - E. Primary effusion lymphoma

|| Excisional Lymph Node Biopsy (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Marginal zone lymphoma
 - B. Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - C. Diffuse large B-cell lymphoma**
 - D. Classical Hodgkin lymphoma
 - E. Primary effusion lymphoma

The overall morphologic and immunohistochemical results are compatible with a diagnosis of DLBCL. Marginal zone lymphoma is a subtype of small mature B-cell neoplasm, and is typically CD10 negative with a low proliferation rate, in most cases. CLL/SLL is not CD10 positive, and, the clinical features and morphologic findings in this case point toward an AIDS-defining lymphoma. The Reed-Sternberg cells of classical Hodgkin lymphoma are large; however, their immunophenotype includes CD45-, CD20-, CD30+, CD15-/+, PAX-5 (weak, nuclear), and MUM-1+, and cytologically are not compatible with the presented case. Patients with primary effusion lymphoma (PEL) typically present without increased lymphadenopathy, and, as the name suggests, effusions containing atypical large B-cells. PEL cells lack pan-B-cell markers such as CD20 and CD19, and the presence of EBV and/or HHV8 infection is generally seen.

|| Excisional Lymph Node Biopsy (Continued) ||

- **Which virus is typically associated with this disease in the setting of HIV?**
 - A. EBV
 - B. HCV
 - C. HHV8
 - D. HTLV-1
 - E. Parvovirus

|| Excisional Lymph Node Biopsy (Continued) ||

- **Which virus is typically associated with his disease in the setting of HIV?**
 - A. EBV
 - B. HCV
 - C. HHV8
 - D. HTLV-1
 - E. Parvovirus
- About two-thirds of all lymphoma cases in the setting of HIV infection are associated with EBV. HHV8 is typically associated with PEL.

|| Excisional Lymph Node Biopsy (Continued) ||

- **What would be a reasonable chemotherapy option for this patient?**
 - A. R-CHOP
 - B. R-hyperCVAD
 - C. R-DA-EPOCH
 - D. SC-EPOCH-RR
 - E. R-CDE

|| Excisional Lymph Node Biopsy (Continued) ||

- **What would be a reasonable chemotherapy option for this patient?**
 - A. R-CHOP
 - B. R-HyperCVAD
 - C. R-DA-EPOCH**
 - D. R-ICE
 - E. R-CDE
- Although the optimal first-line therapy choice has yet to be proven, a pooled analysis of patients treated with R-CHOP versus R-EPOCH suggested an improvement in EFS and OS with the latter. R-ICE would be a reasonable second-line option. R-CDE is generally considered to have activity though inferior to R-CHOP and R-EPOCH. R-HyperCVAD can be considered for Burkitt lymphoma.

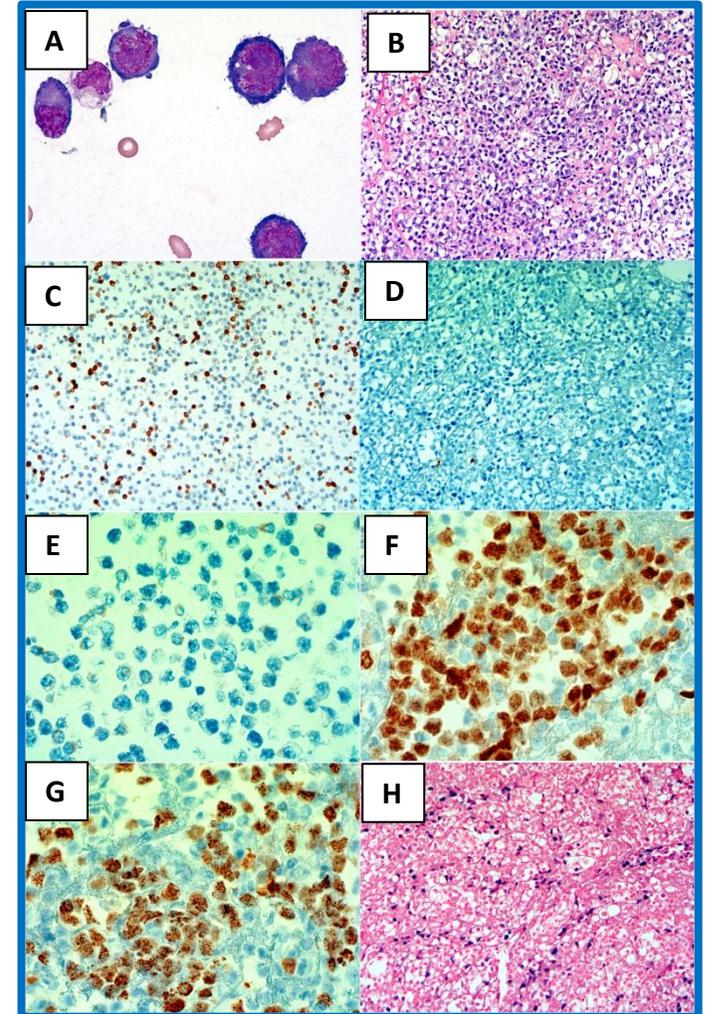
|| Case Presentation #2



- A 31-year-old newly diagnosed HIV-positive male presents with a 3-month history of cough, fever, weight loss, and drenching night sweats. Two weeks prior to admission, he developed right-sided chest pain, worsened by inspiration and difficulty in breathing.
- On examination he was tachypneic. He had decreased breath sounds bilaterally and dullness to percussion to the mid-chest. Chest x-ray revealed bilateral pleural effusions. He subsequently underwent a thoracentesis.

Case Presentation #2 (Continued)

- A. Cytospin preparation from the thoracentesis revealed many large atypical lymphoid cells (shown in contrast to the adjacent monocyte/histiocyte) with markedly irregular nuclear contours, one to multiple prominent nucleoli, and deeply basophilic cytoplasm (Wright-Giemsa, x1000).
- B. The cell clot showed a collection of large, atypical lymphoid cells with hyperchromatic nuclei, similar to those present in image A, intermingled with fibrin and many histiocytes (oval nuclear, smooth nuclear contour, low nuclear to cytoplasmic ratio, and containing foamy or vacuolated cytoplasm) in the background (H&E, x200).
- Immunohistochemical stains show the neoplastic cells are negative for CD3 (C, x200), CD20 (D, x200), PAX5 (E, x600), and positive for MUM1 (F, x600) and HHV8 (G, x600).
- H. A subset of the neoplastic cells were positive for EBV by in situ hybridization with EBV encoded RNA probe (EBER-ISH) (x200).



|| Case Presentation #2 (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Marginal zone lymphoma
 - B. Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - C. Burkitt lymphoma
 - D. Classical Hodgkin lymphoma
 - E. Primary effusion lymphoma

|| Case Presentation #2 (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Marginal zone lymphoma
 - B. Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - C. Burkitt lymphoma
 - D. Classical Hodgkin lymphoma
 - E. Primary effusion lymphoma**

The overall clinical, morphologic, and immunohistochemical results are compatible with primary effusion lymphoma (PEL). PEL cells are CD45 positive, but lack pan-B-cell antigens such as CD20 and CD19, and the presence of EBV and/or HHV8 infection is generally seen. Marginal zone lymphoma is a subtype of small mature B-cell neoplasm, and is typically CD5/CD10 negative with a low proliferation rate and demonstrates absence of EBV/HHV8, in most cases. CLL/SLL is another subtype of small, mature B-cell neoplasm; however, the clinical features and morphologic findings in this case point toward an AIDS-defining lymphoma. Burkitt lymphoma is considered a neoplasm of medium-sized, monomorphic B-cells with a typical “starry-sky” background containing tingible-body macrophages due to increased apoptosis and high mitotic activity. Although a subset of Burkitt lymphoma cases is associated with EBV infection, HHV8 is generally not observed. Reed-Sternberg cells of classical Hodgkin lymphoma are large; however, their immunophenotype includes CD45-, CD20-, CD30+, CD15-/+, PAX-5 (weak, nuclear), and MUM-1+, and cytologically are not compatible with presented case.

|| Case Presentation #2 (Continued) ||

- **Which two viruses are present in the majority of PEL cases?**
 - A. EBV and HBV
 - B. HBV and HCV
 - C. HHV8 and EBV
 - D. HTLV-1 and EBV
 - E. Parvovirus and EBV

|| Case Presentation #2 (Continued) ||

- **Which two viruses are present in the majority of PEL cases?**
 - A. EBV and HBV
 - B. HBV and HCV
 - C. HHV8 and EBV**
 - D. HTLV-1 and EBV
 - E. Parvovirus and EBV
- HHV8 is present in 100% of cases with PEL. Coinfection with EBV is very common (~90% of cases, although it can be absent particularly in patients without immunodeficiency).

|| Case Presentation #2 (Continued) ||

- **In considering treatment for this patient, which agent should be *avoided*?**
 - A. Adriamycin—as it has been linked to increased risk of cardiomyopathy in the HIV population versus the non-HIV population.
 - B. Cyclophosphamide—as it has been linked to further worsening of immune recovery in HIV patients.
 - C. Methotrexate—as it can accumulate to toxic levels at the primary site of disease.
 - D. Rituximab—as it has been associated with increased death in HIV patients due to baseline immunosuppression.

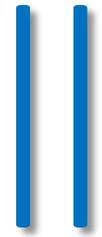
|| Case Presentation #2 (Continued) ||

- **In considering treatment for this patient, which agent should be *avoided*?**
 - A. Adriamycin—as it has been linked to increased risk of cardiomyopathy in the HIV population versus the non-HIV population.
 - B. Cyclophosphamide—as it has been linked to further worsening of immune recovery in HIV patients.
 - C. Methotrexate—as it can accumulate to toxic levels at the primary site of disease.**
 - D. Rituximab—as it has been associated with increased death in HIV patients due to baseline immunosuppression.

Companion Case for Chapter 37

HIV-Related Lymphomas

*Danny Nguyen,
Nishan Tchekmedyian,
and
Jeremy Abramson*



Clinical Case 34



|| Case Presentation



- A 69-year-old man develops reddish-purple macules on his chest.
- Over the next 2 months, he notes the macules grow in size and progress to plaques and nodules. The lesions spread from his chest to his back, arms, and, abdomen, also becoming more violaceous.
- ROS was positive for progressive fatigue that began at the same time as the skin lesions.
- Exam revealed a good performance status (KPS=90) and no lymphadenopathy or splenomegaly. Skin findings were as described.

|| Case Presentation (Continued) ||

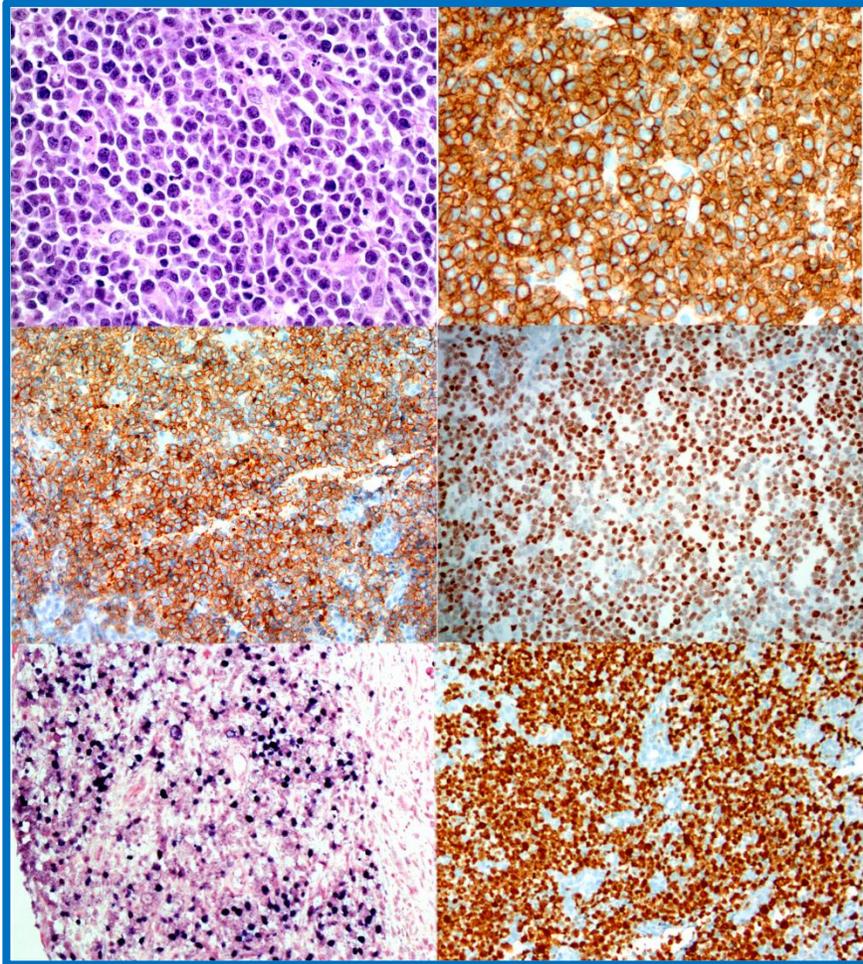
- **What is the next appropriate step in diagnosis?**
 - A. Perform skin biopsy only.
 - B. Perform bone marrow biopsy as this is a manifestation of acute myeloid leukemia.
 - C. Perform skin biopsy followed by bone marrow biopsy depending on the results.
 - D. A and B

|| Case Presentation (Continued) ||

- **What is the next appropriate step in diagnosis?**
 - A. Perform skin biopsy only.
 - B. Perform bone marrow biopsy as this is a manifestation of acute myeloid leukemia.
 - C. Perform skin biopsy followed by bone marrow biopsy depending on the results.**
 - D. A and B

While the skin manifestations described in this case are likely the result of a hematologic neoplasm, other diagnoses should be ruled out by performing a skin biopsy first.

|| Skin Biopsy Results ||



- A punch biopsy of skin showed a dense subepidermal and dermal infiltrate of immature cells with oval to irregular nuclei, fine (immature) chromatin, inconspicuous nucleoli, and high N:C ratio (A, H&E, x600). The infiltrate is immunophenotypically positive for CD4, CD56, CD123, and TCL1 (B through D, immunoperoxidase, x600). The proliferation index was high (80%–90%) as shown by Ki-67 (F, immunoperoxidase, x200).

|| Skin Biopsy Results (Continued) ||

- **What is the diagnosis?**
 - A. Peripheral T-cell lymphoma, NOS
 - B. Blastic plasmacytoid dendritic cell neoplasm
 - C. Acute myeloid leukemia
 - D. Cutaneous T-cell lymphoma

|| Skin Biopsy Results (Continued) ||

- **What is the diagnosis?**

- A. Peripheral T-cell lymphoma, NOS

- B. Blastic plasmacytoid dendritic cell neoplasm**

- C. Acute myeloid leukemia

- D. Cutaneous T-Cell lymphoma

Although the morphology shows numerous immature cells with blast-like chromatin, the immunophenotype is compatible with BPDCN (positive for CD4, CD56, CD123 and BDCA2 or TCL-1).

|| Skin Biopsy Results (Continued) ||

- **What is the median survival of this disease?**
 - A. Less than 6 months
 - B. 12 to 14 months
 - C. 2 to 5 years
 - D. Most patients are cured

|| Skin Biopsy Results (Continued) ||

- **What is the median survival of this disease?**
 - A. Less than 6 months
 - B. 12 to 14 months**
 - C. 2 to 5 years
 - D. Most patients are cured

The median outcome of BPDCN is only 12 to 14 months due to its aggressiveness upon relapse after induction chemotherapy.

|| Case Progression



- After receiving the diagnosis of BPDCN, the patient had a bone marrow biopsy and CT scan showing no evidence of marrow, lymphoid, or organ involvement. He presents for treatment recommendations.

|| Case Progression (Continued) ||

- **What is the best therapy to recommend?**
 - A. Standard AML induction therapy (i.e., 7+3)
 - B. Standard ALL induction therapy (HyperCVAD, etc.)
 - C. Low-dose cytarabine or decitabine/azacytadine
 - D. Clinical trial

|| Case Progression (Continued) ||

- **What is the best therapy to recommend?**
 - A. Standard AML induction therapy (i.e., 7+3)
 - B. Standard ALL induction therapy (HyperCVAD, etc.)
 - C. Low-dose cytarabine or decitabine/azacitadine
 - D. Clinical trial**

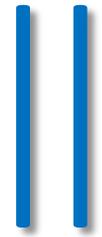
There is no standard treatment for BPDCN. AML or ALL-type regimens are commonly used for younger patients. BPDCN does not usually respond to low-dose therapy. A clinical trial of a new drug, SL-401, is underway in BPDCN.

|| Case Follow-Up

- The patient was enrolled on protocol NCT02113982, a non-randomized, open-label, multicenter study of SL-401. This drug is interleukin-3 (IL-3) conjugated to diphtheria toxin. BPDCN expresses high levels of CD123, the IL-3 receptor, and SL-401 therefore delivers diphtheria toxin to the malignant cells.
- The patient achieved a rapid clearance of his skin lesion after a single cycle of SL-401. He is continuing on the study as he is being considered for a hematopoietic stem cell transplantation.

Companion Case for Chapter 17
Blastic Plasmacytoid Dendritic Cell
Neoplasm

*Justin Taylor,
Ateefa Chaudhury,
and
Andrew A. Lane*



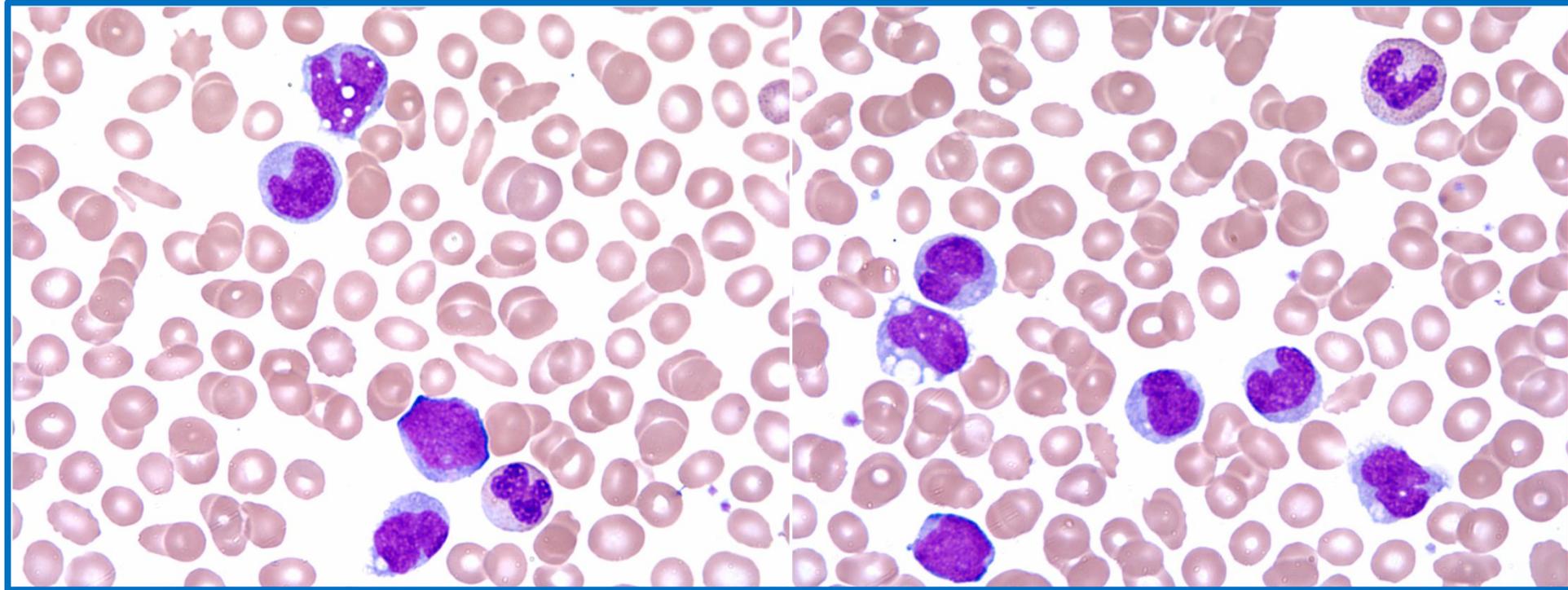
Clinical Case 35



|| Case Presentation

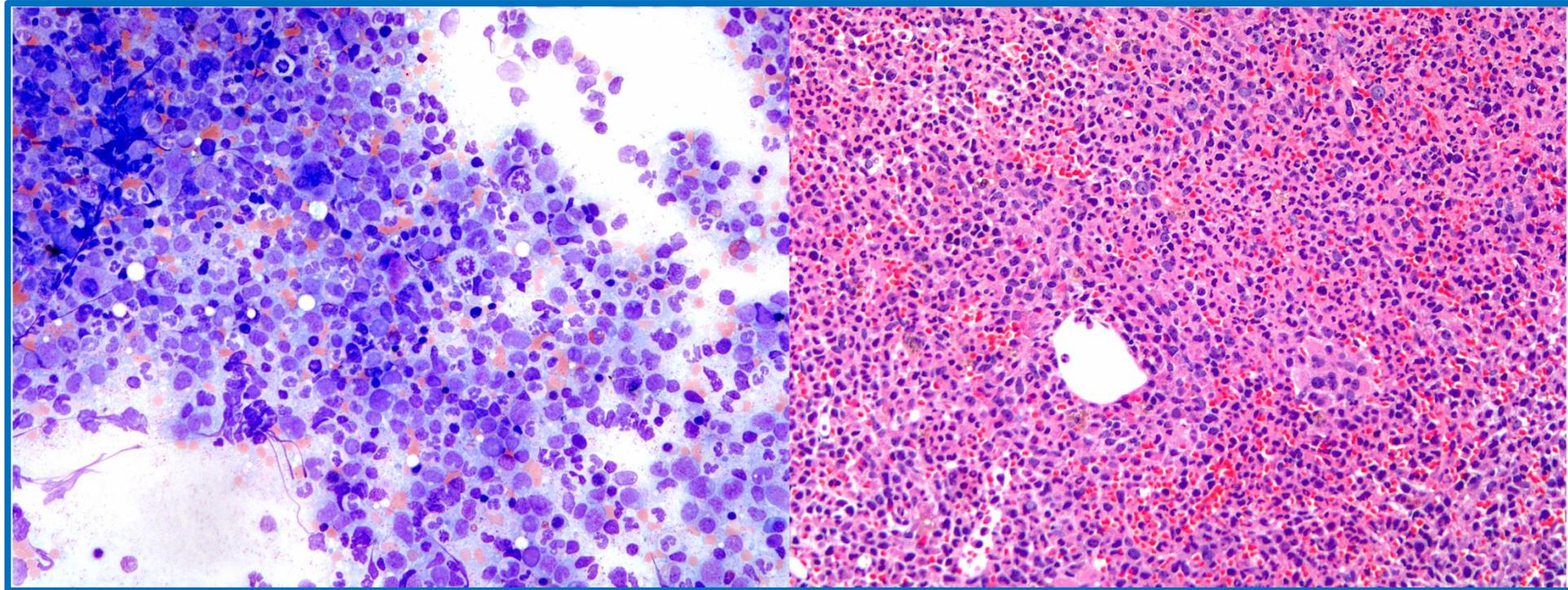
- A 65-year-old male with PMH of hypertension and hyperlipidemia presented to his primary clinic with fatigue and dyspnea on exertion worsening over the past 3 months associated with anorexia and a sensation of abdominal fullness. He denied any other symptoms of lymphadenopathy, fevers, chills, or weight loss.
- His exam revealed mild conjunctival pallor and splenomegaly with a palpable spleen 6 cm below costal margin.
- A CBC revealed a WBC of 20 k/ μ L, a WBC differential of 57% neutrophils, 12% lymphocytes, 25% monocytes, 2% metamyelocytes, 1% myelocytes, 1% blasts, and 2% basophils, hemoglobin of 8 g/dL with MCV of 85 fL, and platelet count of 80 k/ μ L.

Peripheral Smear



Peripheral blood films from the patient demonstrate moderate to severe leukocytosis with a predominantly mature monocytosis, dysplastic neutrophils (i.e., hypogranulation) and occasional circulating myeloblasts (Wright's stain, x1000).

|| Bone Marrow Aspirate/Core ||



The bone marrow aspirate smear and core biopsy from the same patient show marked hypercellularity with myeloid hyperplasia and <5% blasts, dysplastic megakaryocytes including micromegakaryocytes or hypolobated megakaryocytes, and overt mature monocytosis (Left panel, Wright-Giemsa, x200; Right panel, Hematoxylin and Eosin (H&E), x200).

|| Additional Studies



- Flow cytometry showed a small population of blasts coexpressing CD34 and CD117, <5%.
- Fish confirmed the absence of *BCR-ABL*, and probes were also negative for *PDGFRA* and *PDGFRB* abnormalities.
- Cytogenetics showed isolated loss of the Y chromosome.
- Molecular studies demonstrated a *SRSF2* mutation.

|| Additional Studies (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia
 - B. Chronic lymphocytic leukemia
 - C. Chronic myelomonocytic leukemia
 - D. Acute monocytic leukemia
 - E. Myeloproliferative neoplasm

|| Additional Studies (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia
 - B. Chronic lymphocytic leukemia
 - C. Chronic myelomonocytic leukemia**
 - D. Acute monocytic leukemia
 - E. Myeloproliferative neoplasm

CMML is a diagnosis of exclusion. After excluding causes for a reactive monocytosis, one can entertain a diagnosis of CMML. The patient has clear morphologic evidence of myelodysplasia, and given an absolute monocytosis on his CBC (although we do not know if it's been persistent >3 months), detection of *SRSF2* mutation by molecular methods, and exclusion of *BCR-ABL*, *PDGFRA* and *PDGFRB*-mutated myeloid neoplasms, CMML is the most appropriate answer. The blasts in this case are <20%; therefore, criteria for AML is not met.

|| Additional Studies (Continued) ||

- **What is his risk based on the cytogenetic findings?**
 - A. Low
 - B. Intermediate
 - C. High

|| Additional Studies (Continued) ||

- **What is his risk based on the cytogenetic findings?**

- A. Low**

- B. Intermediate

- C. High

Based on the Spanish cytogenetic risk stratification system (Such et al., 2013; doi:10.1182/blood-2012-08-452938):

Low: normal karyotype or isolated loss of Y chromosome

Intermediate: all other abnormalities

High: trisomy 8, chromosome 7 abnormalities, or complex karyotype

Survival at 5 years was 35% for low risk, 26% for intermediate risk, and 4% for higher risk (P < .001).

|| Additional Studies (Continued) ||

- **Which additional molecular abnormality would have increased his risk for AML transformation and worse survival?**
 - A. *TET2*
 - B. *NRAS*
 - C. *RUNX1*
 - D. *ASXL1*

|| Additional Studies (Continued) ||

- **Which additional molecular abnormality would have increased his risk for AML transformation and worse survival?**
 - A. *TET2*
 - B. *NRAS*
 - C. *RUNX1*
 - D. *ASXL1***

Data has shown that mutations of *ASXL1* correlated with an evolution to AML transformation, and that median OS was lower in *ASXL1*-mutated groups compared to wild-type status patients that was observed and validated by multivariable analyses. (See Chapter 13; *Br J Haematol* 2010 Nov;151(4):365-75); *Leukemia* 2014;28:2206-12; *J Clin Oncol*, 31(19), 2428-36).

|| Additional Studies (Continued) ||

- **The best next step in the management of this patient is:**
 - A. Observation
 - B. Treatment with ruxolitinib
 - C. Treatment with a hypomethylating agent
 - D. Supportive care with ESAs, HU, and transfusions as needed
 - E. Evaluation for allogeneic hematopoietic stem cell transplantation

|| Additional Studies (Continued) ||

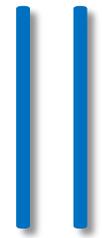
- **The best next step in the management of this patient is:**
 - A. Observation
 - B. Treatment with ruxolitinib
 - C. Treatment with a hypomethylating agent**
 - D. Supportive care with ESAs, HU, and transfusions as needed**
 - E. Evaluation for allogeneic hematopoietic stem cell transplantation**

Any of **C. through E.** are reasonable, reflecting the difficulty in management of CMML patients and lack of definitive therapies. Given that his primary problems are symptoms from splenomegaly and anemia, **D.** is reasonable. **C.** would also be a good approach that could potentially induce remission and improve the counts. Even though he is currently in the lower risk spectrum, given his younger age, assessment of donor status and a discussion about transplantation is also reasonable as he is unlikely to live >10 years without it. However, response to primary therapy should be assessed first, and if he does well with options **C.** or **D.** he could be observed closely on therapy, with stronger consideration of transplant at any sign of progression.

Companion Case for Chapter 13

Chronic Myelomonocytic Leukemia

*Alexandra Gomez
and
Justin M. Watts*



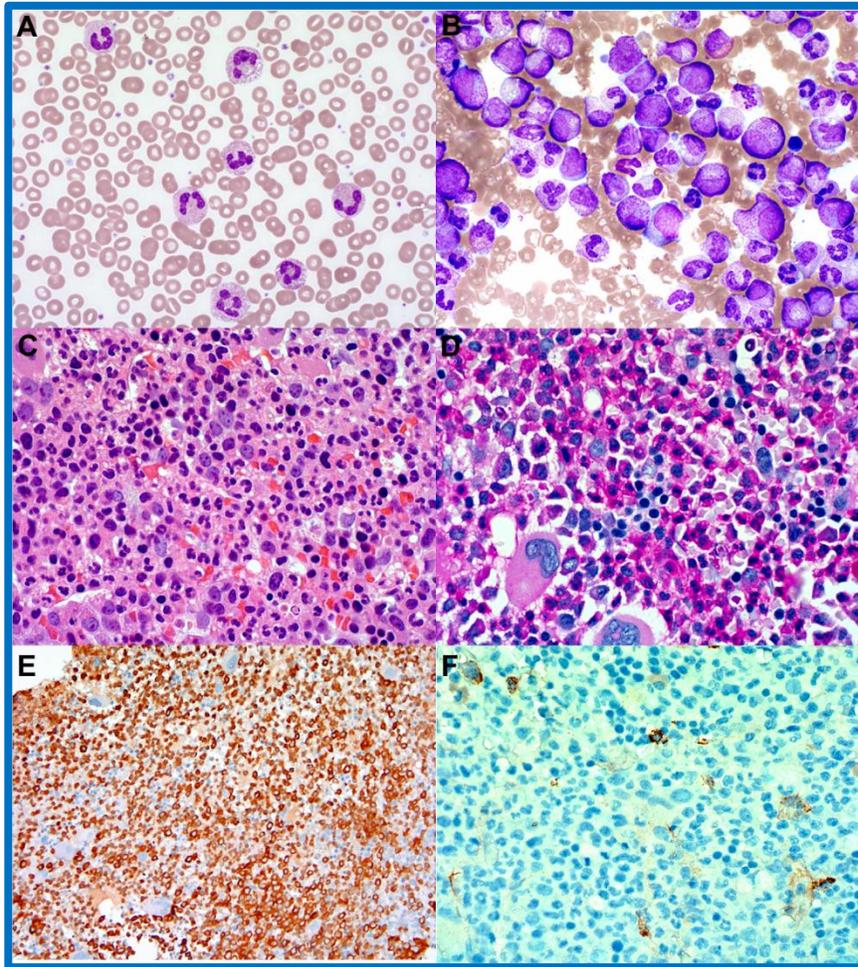
Clinical Case 36



|| Case Presentation

- A 76-year-old man with no past medical history presents with severe fatigue and easy bruising. A CBC revealed a WBC count of 56.3 k/ μ L with 15% lymphocytes, 90% neutrophils, 0% basophils, and 1% eosinophils, hemoglobin of 13.9 g/dL, MCV of 85 fL, and platelet count of 65 k/ μ L. No blasts were detected, and no metamyelocytes were noted on the differential. Accompanying symptoms included abdominal fullness and early satiety. However, he denied any additional constitutional symptoms. Examination reveals splenomegaly and purpura over the arms and legs consistent with his complaint of easy bruising.
- He undergoes a bone marrow aspiration and biopsy as shown.

Bone Marrow



A. Peripheral blood film reveals leukocytosis with predominant granulocytosis (Wright stain, x600). B. Bone marrow aspirate shows myeloid preponderancy with increased segmented and band-form neutrophils and mild left-shifted maturation (Wright-Giemsa stain, x600). C and D. Bone marrow core biopsy with Hematoxylin and Eosin (H&E) stain (C) and periodic acid–Schiff (PAS) stains (D) demonstrating a significant increased myeloid to erythroid ratio (Wright-Giemsa stain, x200). E. Myeloperoxidase stain highlights primarily myeloid precursors over 80% of the total marrow cellularity, indicating myeloid hyperplasia (immunoperoxidase, x200). F. Occasional CD34 positive blasts are identified (Immunoperoxidase, x600).

|| Bone Marrow (Continued) ||

- *BCR-ABL* testing, *PDGFR* testing, and *FGFR1* testing were all negative.
- **Which of the following is the most likely diagnosis?**
 - A. Chronic neutrophilic leukemia
 - B. Chronic myelogenous leukemia
 - C. Polycythemia vera
 - D. Chronic lymphocytic leukemia
 - E. Myelodysplastic syndrome

|| Bone Marrow (Continued) ||

- *BCR-ABL* testing, *PDGFR* testing, and *FGFR1* testing were all negative.
- **Which of the following is the most likely diagnosis?**
 - A. Chronic neutrophilic leukemia**
 - B. Chronic myelogenous leukemia
 - C. Polycythemia vera
 - D. Chronic lymphocytic leukemia
 - E. Myelodysplastic syndrome

|| Mutations



- **The presence of which mutations exclude the diagnosis of CNL?**
 - A. *BCR-ABL*
 - B. *PDGFRA*
 - C. *PDGFRB*
 - D. *FGFR1*
 - E. All of the above

|| Mutations (Continued) ||

- **The presence of which mutations exclude the diagnosis of CNL?**
 - A. *BCR-ABL*
 - B. *PDGFRA*
 - C. *PDGFRB*
 - D. *FGFR1*
 - E. **All of the above**

|| Mutations (Continued) ||

- **Which of the following molecular abnormalities is a potentially targetable agent and unique to CNL?**
 - A. *JAK2*
 - B. *BCR-ABL*
 - C. *CSF3R*
 - D. *MPL*
 - E. *CALR*

|| Mutations (Continued) ||

- **Which of the following molecular abnormalities is a potentially targetable agent and unique to CNL?**
 - A. *JAK2*
 - B. *BCR-ABL*
 - C. *CSF3R***
 - D. *MPL*
 - E. *CALR*

|| Differential Diagnosis

- CNL is a diagnosis of exclusion and the presence of *BCR-ABL1*, *PDGFR*, and *FGFR1* imply a diagnosis of an alternative myeloproliferative disorder.
- Essential thrombocythemia, myelodysplastic syndromes, primary myelofibrosis, polycythemia vera, and myelodysplastic syndrome/myeloproliferative neoplasm overlap syndrome must be ruled out.
- *CSF3R* mutation occurs in 60% to 100% of reported cases of CNL and may eventually become part of the WHO criteria in the diagnosis CNL.

|| Differential Diagnosis (Continued) ||

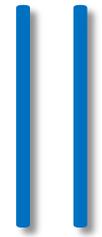
- **The use of which of the following medications has been demonstrated to improve thrombocytopenia in CSF3R mutated patients?**
 - A. Hydroxyurea
 - B. Interferon
 - C. Standard 7+3 Induction
 - D. Ruxolitinib
 - E. Imatinib

|| Differential Diagnosis (Continued) ||

- **The use of which of the following medications has been demonstrated to improve thrombocytopenia in CSF3R mutated patients?**
 - A. Hydroxyurea
 - B. Interferon
 - C. Standard 7+3 Induction
 - D. Ruxolitinib**
 - E. Imatinib
- While all of the above have been used to manage CNL, only Ruxolitinib has demonstrated efficacy in improving cytopenias in patients harboring the *CSF3R* mutation, which occurs in between 60% to 100% of CNL patients.

Companion Case for Chapter 6 Chronic Neutrophilic Leukemia

*Saman Nematollahi,
Shweta Jain,
and
Utkarsh Acharya*



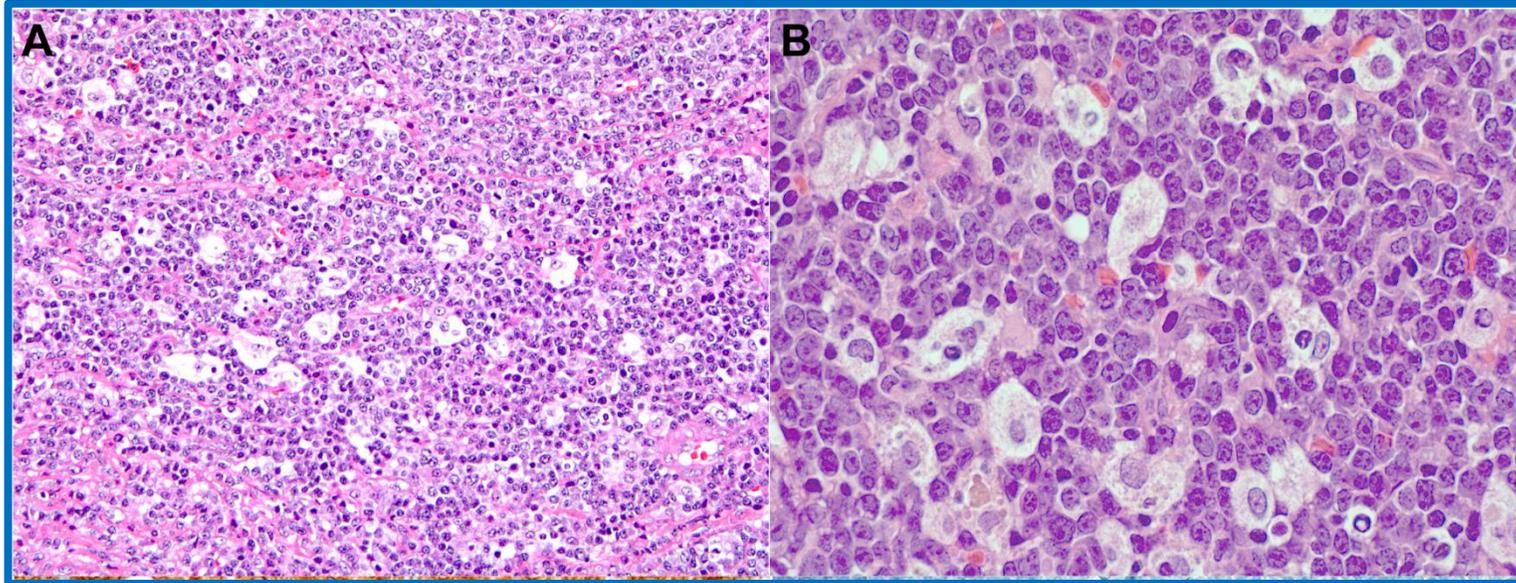
Clinical Case 37



|| Case Presentation

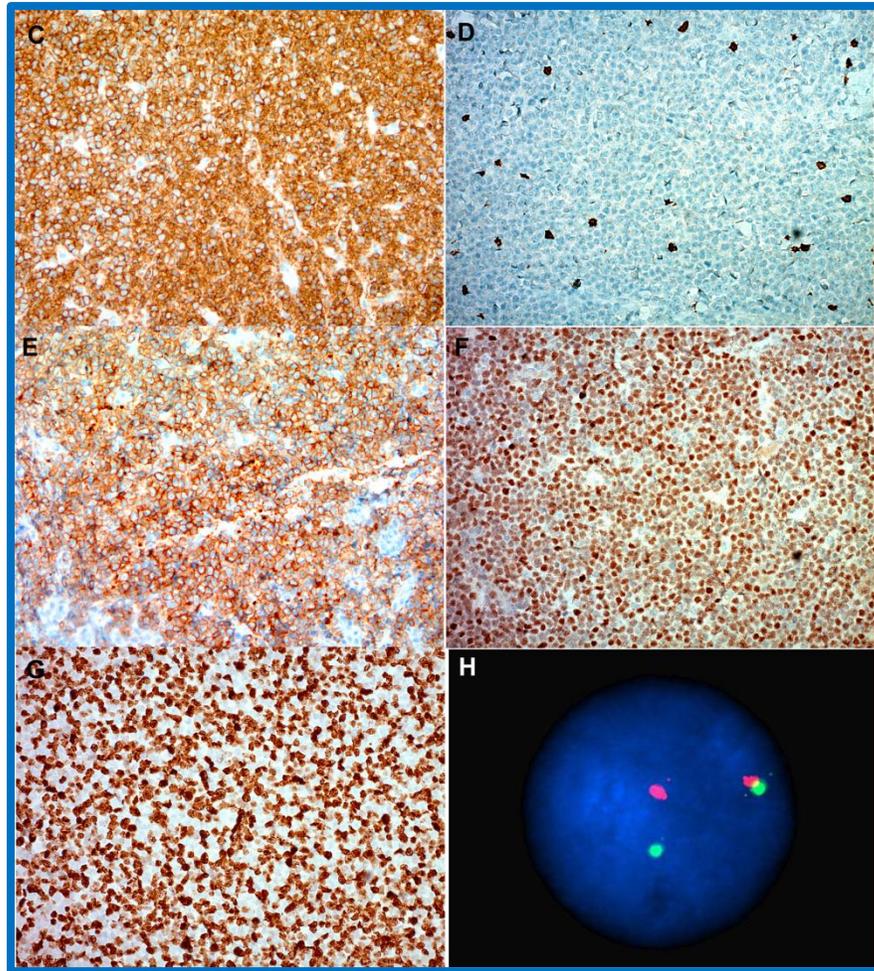
- A 25-year-old man with no significant past medical history presents with fever, worsening abdominal pain, nausea, and vomiting for the past 2 weeks. Clinical examination revealed a firm epigastric mass of 5.0 x 5.0 cm. Initial complete blood counts and metabolic panel were entirely within normal limits. A computed tomography (CT) scan of the abdomen with contrast showed diffuse infiltrative lesion of the stomach wall with multiple enlarged lymph nodes in celiac axis and retroperitoneal region. A CT guided biopsy of celiac lymph node was performed. The biopsy tissue histology is reviewed below.

|| Case Presentation (Continued) ||



- Microscopic examination revealed sheets of atypical lymphoid cells associated with increased tingible-body/phagocytizing macrophages in the background forming a “starry sky” pattern (A, H&E, x200). Cytologically, the atypical lymphoid cells are uniformly medium in size, and exhibit a high nuclear to cytoplasmic ratio, usually more than one nucleoli and scant cytoplasm (B, H&E, x600).

|| Case Presentation (Continued) ||



- A panel of immunohistochemical staining highlights the atypical lymphoid cells to be CD20(+) (C, x200), BCL-2(-)(D, x200), CD10 (+)(E, x200) and BCL-6 (+) (F, x200) with a high proliferation fraction of nearly 100% (G, Ki-67, immunoperoxidase, x200). FISH analysis using c-MYC break-apart probe identifies abnormal separated green and red signals (H).

|| Case Presentation (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Diffuse large B-cell lymphoma
 - B. Mantle cell lymphoma, blastoid variant
 - C. Burkitt lymphoma
 - D. Follicular lymphoma
 - E. B-lymphoblastic leukemia/lymphoma

|| Case Presentation (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Diffuse large B-cell lymphoma
 - B. Mantle cell lymphoma, blastoid variant
 - C. Burkitt lymphoma**
 - D. Follicular lymphoma
 - E. B-lymphoblastic leukemia/lymphoma

|| Differential Diagnosis

- Both Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL) express pan B-cell antigens including CD19, CD20, CD 22, CD79a, and PAX-5; however, they show different cytologic features.
- Burkitt lymphoma usually lacks CD5, bcl-2, and CD23 while mantle cell lymphoma typically expresses CD5 and nuclear staining for cyclin D1 will be present in nearly 95% of cases.

|| Differential Diagnosis (Continued) ||

- B-lymphoblastic leukemia/lymphoma expresses CD19, CD10, PAX-5, and TdT with variable expression of CD20 and CD34.
- Follicular lymphoma shows a nodular proliferation of follicles composed of centrocytes and centroblasts, and often coexpresses BCL-2, distinguishing it from Burkitt lymphoma.

|| Differential Diagnosis (Continued) ||

- **Which translocation of the *c-MYC* oncogene on the long arm of chromosome 8 is the most common translocation partner seen in Burkitt lymphoma on FISH studies?**
 - A. Translocation of *c-MYC* with Ig heavy chain gene (*IgH*) on chromosome 14q32
 - B. Translocation of *c-MYC* with kappa light chain gene (*IgK*) on chromosome 2p12
 - C. Translocation of *c-MYC* with lambda light chain gene (*IgL*) on chromosome 22q11

|| Differential Diagnosis (Continued) ||

- **Which translocation of the *c-MYC* oncogene on the long arm of chromosome 8 is the most common translocation partner seen in Burkitt lymphoma on FISH studies?**
 - A. Translocation of *c-MYC* with Ig heavy chain gene (*IgH*) on chromosome 14q32
 - B. Translocation of *c-MYC* with kappa light chain gene (*IgK*) on chromosome 2p12
 - C. Translocation of *c-MYC* with lambda light chain gene (*IgL*) on chromosome 22q11
- FISH or cytogenetic analysis are used to detect t(8;14), seen in nearly 80% of Burkitt lymphoma.

|| Differential Diagnosis (Continued) ||

- **The presence of which genetic rearrangement will help differentiate diffuse large B-Cell lymphoma (DLBCL) from Burkitt lymphoma?**
 - A. FISH for t(8;11)
 - B. FISH for t(11;14)
 - C. FISH for t(14;18)
 - D. FISH for t(8;21)

|| Differential Diagnosis (Continued) ||

- **The presence of which genetic rearrangement will help differentiate diffuse large B-Cell lymphoma from Burkitt lymphoma?**
 - A. FISH for t(8;11)
 - B. FISH for t(11;14)
 - C. FISH for t(14;18)**
 - D. FISH for t(8;21)

|| Differential Diagnosis (Continued) ||

- **The presence of which genetic rearrangement will help differentiate mantle cell lymphoma (MCL) from Burkitt lymphoma?**
 - A. FISH for t(8;11)
 - B. FISH for t(11;14)
 - C. FISH for t(14;18)
 - D. FISH for t(8;21)

|| Differential Diagnosis (Continued) ||

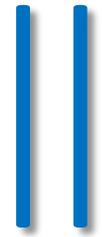
- **The presence of which genetic rearrangement will help differentiate mantle cell lymphoma (MCL) from Burkitt lymphoma?**
 - A. FISH for t(8;11)
 - B. FISH for t(11;14)**
 - C. FISH for t(14;18)
 - D. FISH for t(8;21)

The t(11;14)(q13;32) between *IgH* and cyclin D1 is present in almost all cases of MCL.

Companion Case for Chapter 31

Burkitt Lymphoma

*Anju Nair
and
Micah Burch*



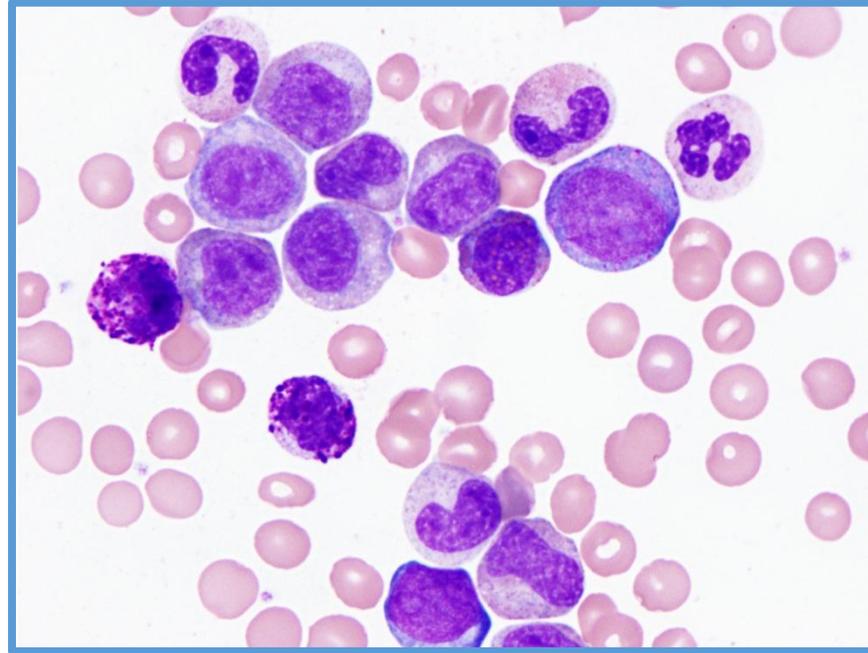
Clinical Case 38



|| Case Presentation

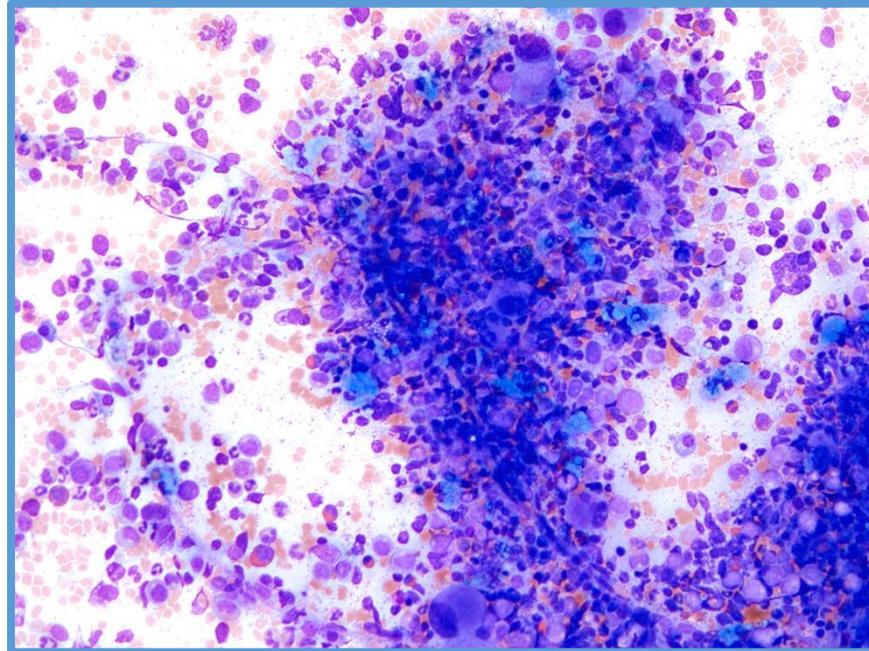
- A 62-year-old male presents to the primary care physician with weakness, fatigue, and pruritus.
- Review of symptoms: Positive for early satiety and abdominal discomfort.
- Physical exam: Positive for nontender, splenomegaly 12 cm below the ribs. Nontender hepatomegaly of 6 cm below the ribs was also seen. No lymphadenopathy noted.
- Labs: Initial bloodwork revealed WBC of 80 k/ μ L with differential of 3% blasts, 9% myelocytes, 3% metamyelocytes, 59% segmented neutrophils, 4% eosinophils, 3% basophils, 6% monocytes, and 13% lymphocytes. Hemoglobin 12.5 g/dL. Hematocrit 34%. Platelets 290 k/ μ L. He was referred to a hematologist who performed a bone marrow aspiration and biopsy.

Peripheral Smear



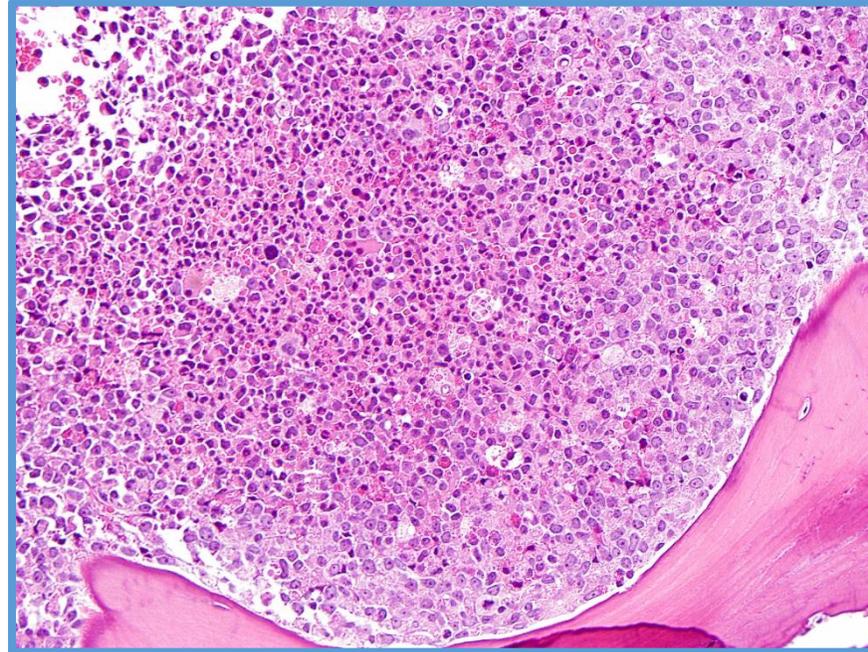
A peripheral blood smear shows leukocytosis with left-shifted granulocytic maturation including predominantly metamyelocytes and myelocytes and occasional circulating blasts (often 1%–2%), and often accompanied with basophilia (Wright Giemsa, x1000).

|| Bone Marrow Aspirate ||



Bone marrow aspirate shows hypercellularity, myeloid preponderance with mild left-shifted maturation, increased sea-blue histiocytes, and numerous small or micromegakaryocytes (Wright Giemsa, x1000). Blasts were <2%.

|| Bone Marrow Biopsy ||



Bone marrow core biopsy exhibits myeloid hyperplasia, increased myeloid to erythroid ratio up to 20:1, thickened peritrabecular myeloid cuffs (often >3–5 layers), and associated with many histiocytes and micromegakaryocytes in the background (H&E, x200).

|| Question 1



- **Which of the following is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia, blast phase
 - B. Chronic myelogenous leukemia, chronic phase
 - C. Chronic myelogenous leukemia, accelerated phase
 - D. Leukemoid reaction
 - E. Primary myelofibrosis

|| Question 1 (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia, blast phase
 - B. Chronic myelogenous leukemia, chronic phase**
 - C. Chronic myelogenous leukemia, accelerated phase
 - D. Leukemoid reaction
 - E. Primary myelofibrosis

The overall clinical and pathologic findings are suggestive of chronic myelogenous leukemia, chronic phase. The bone marrow aspirate contained less than 2% blasts, excluding the accelerated and blast phases (see CML chapter). Most patients with CML present in the chronic phase, although some patients may initially present with accelerated or blast crisis, in which case, the blast percentage would be 10% to 19% in the PB or >20% in the PB (or of the nucleated cells in the BM), respectively. Although patients with a leukemoid reaction can have significant leukocytosis exceeding 50 k/uL, basophilia should be absent. Primary myelofibrosis is also a myeloproliferative neoplasm, but is characterized by bizarre appearing, clustered megakaryocytes, and prominent reticulin fibrosis.

|| Differential Diagnosis for CML ||

- Leukemoid reaction: Elevated leukocyte alkaline phosphatase (LAP) score, infectious etiology should be sought
- CMML: Monocytosis (>1000 cells/ μL) with at least 10% of the total WBC, Philadelphia chromosome negative
- Atypical CML: Philadelphia chromosome negative, characterized under MDS/MPN category
- AML: difficult to differentiate from blast crisis phase of CML, usually Philadelphia chromosome positivity, splenomegaly and basophilia favors CML

|| Question 2



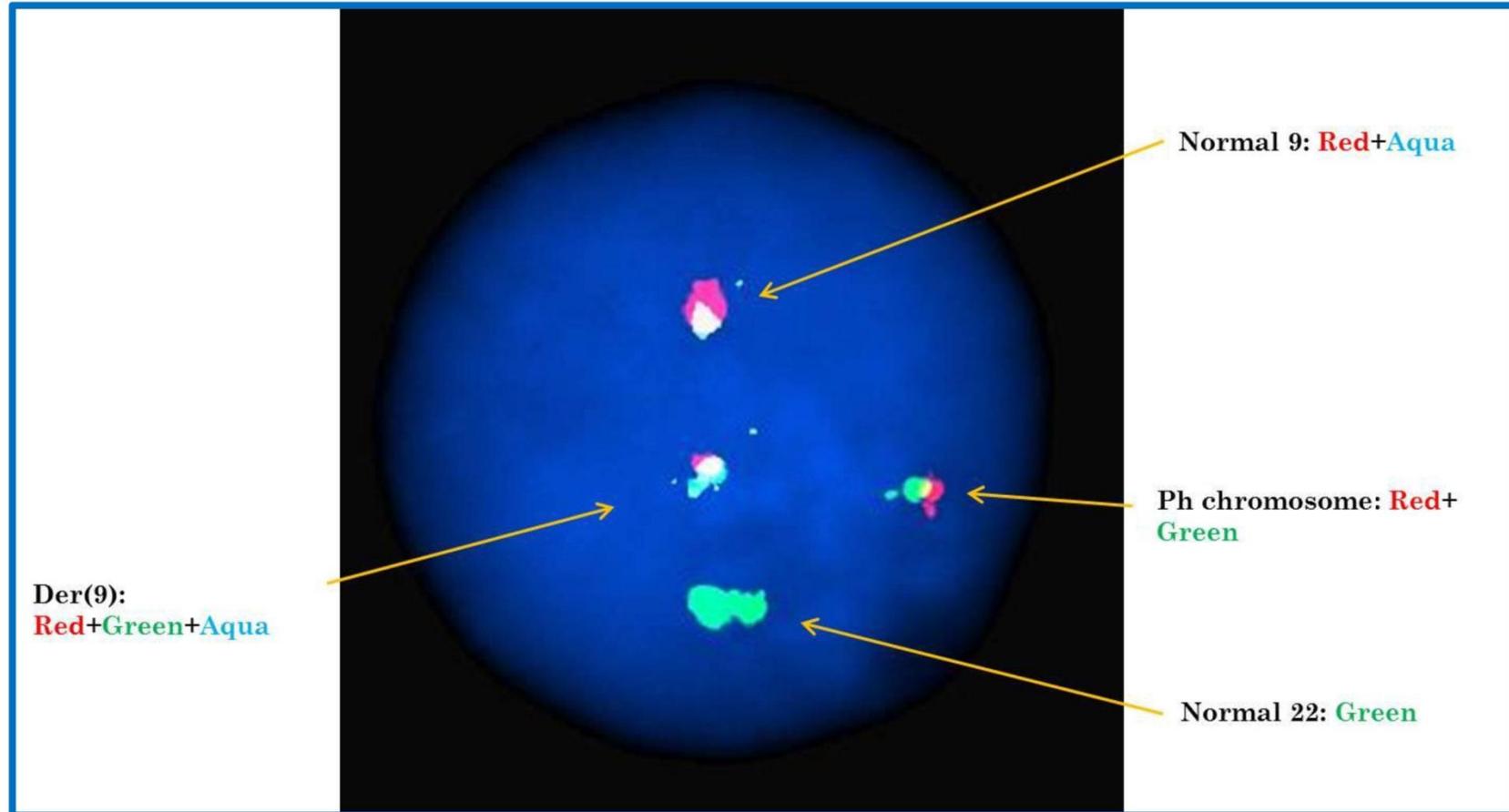
- **What test should be ordered initially to diagnose CML?**
 - A. Peripheral smear evaluation
 - B. *BCR-ABL1* kinase domain mutation analysis
 - C. FISH for t(9;22)(q34.1;q11.2)*BCR-ABL1*
 - D. Bone marrow biopsy and aspirate evaluation
 - E. Flow cytometry on bone marrow specimen

|| Answer

- **What test should be ordered initially to diagnose CML?**
 - A. Peripheral smear evaluation
 - B. *BCR-ABL1* kinase domain mutation analysis
 - C. FISH for t(9;22)(q34.1;q11.2)*BCR-ABL1***
 - D. Bone marrow biopsy and aspirate evaluation
 - E. Flow cytometry on bone marrow specimen

FISH testing will detect all fusion transcripts (i.e., p190, p210, p230). qRT-PCR for *BCR-ABL1* transcript can also be sent for each transcript but if p210 is sent alone, one can miss these more uncommon transcript variants.

|| Typical Positive BCR/ABL1 FISH



|| Question 4



- **Which mutation in the *BCR-ABL1* fusion protein is resistant to all TKIs except ponatinib?**
 - A. F359V
 - B. E255K
 - C. Y253H
 - D. T315I

|| Answer

- Which mutation in the *BCR-ABL1* fusion protein is resistant to all TKIs except ponatinib?
 - A. F359V
 - B. E255K
 - C. Y253H
 - D. T315I**

Besides ponatinib, omacetuxine mepesuccinate has activity against T315I mutant CML. These patients should be referred for bone marrow transplant if eligible.

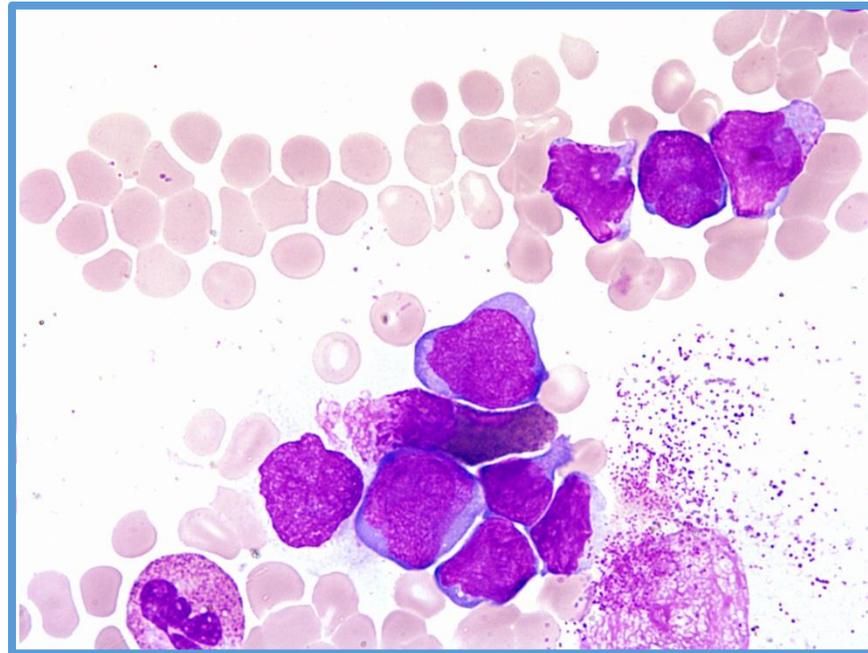
|| Question 5

- **Our patient was placed on dasatinib and was stable for 6 months with WBC in the range of 10 to 15 k/ μ L. However, on a follow-up visit his lab work revealed WBC of 32 k/ μ L. Flow cytometry of the peripheral blood was consistent with blast phase CML (BP-CML). Bone marrow biopsy confirms BP-CML with 40% myeloblasts. What should be the initial appropriate next step?**

- A. Check *BCR-ABL1* transcript levels by qRT-PCR.
- B. Order tyrosine kinase domain mutation analysis.
- C. Change TKI to imatinib.
- D. Continue dasatinib for 3 months and reassess.

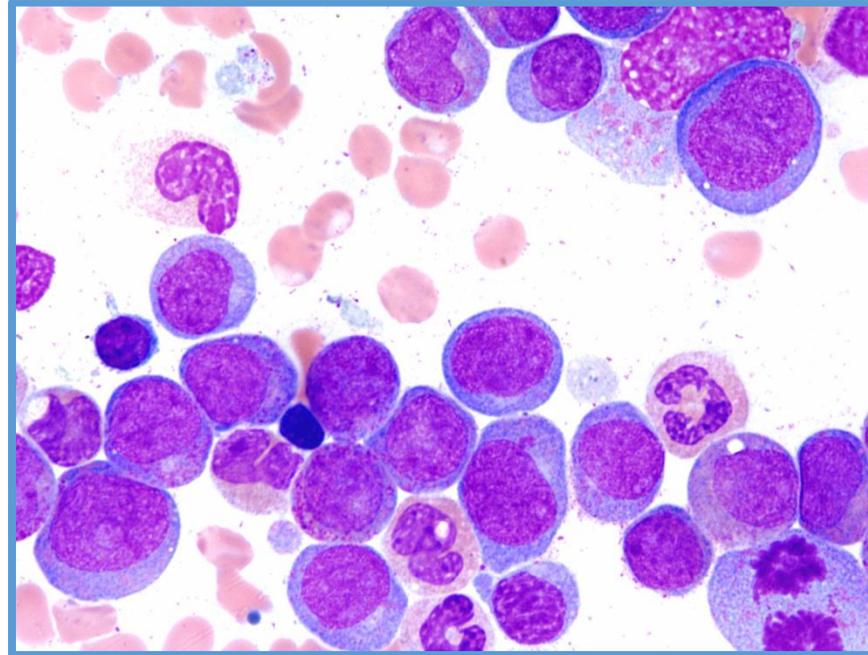
(Peripheral smear, bone marrow biopsy and aspirate are shown on the next slides.)

Peripheral Smear



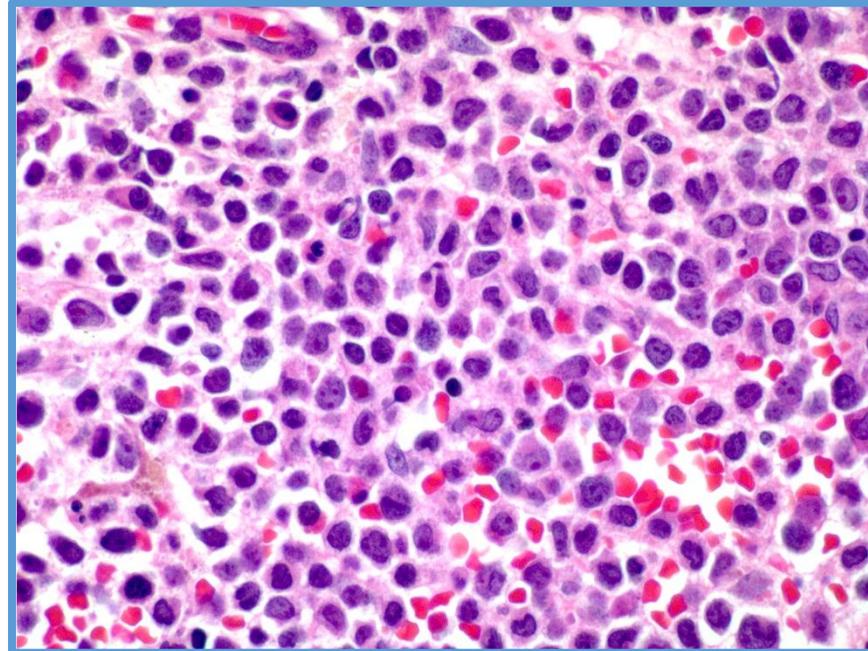
Peripheral blood smear also shows leukocytosis and increased blasts >20%, mainly myeloblasts with fine chromatin, oval to irregular nuclei, and some containing cytoplasmic azurophilic cytoplasm (Wright Giemsa, x1000).

|| Bone Marrow Aspirate ||



Bone marrow aspirate shows findings similar to peripheral blood with $>20\%$ myeloblasts and some maturing myeloid precursors. Megakaryocytes are decreased in number (Wright Giemsa, x1000).

|| Bone Marrow Biopsy ||



Bone marrow core biopsy displays increased myeloblasts interspersed with background early phase myeloid precursors. Megakaryocytes and erythroid precursors are diminished (H&E, x600).

|| Answer

- **Our patient was placed on dasatinib and was stable for 6 months with WBC in the range of 10 to 15 k/ μ L. However, on a follow-up visit his labwork revealed WBC of 32 k/ μ L. Flow cytometry of the peripheral blood was consistent with BP-CML (myeloblasts). Bone marrow biopsy confirms BP-CML with 40% blasts. What should be the initial appropriate next step?**
 - A. Check *BCR-ABL1* transcript levels by qRT-PCR.
 - B. Order tyrosine kinase domain mutation analysis.**
 - C. Change TKI to imatinib.
 - D. Continue dasatinib for 3 months and reassess.

|| Question 6



- **Tyrosine kinase domain mutational analysis reveals T315I mutation at this time. What should be the treatment plan?**
 - A. Continue dasatinib and refer to BMT service.
 - B. Change to nilotinib, refer to BMT service.
 - C. 7+3 induction, ponatinib, refer to BMT service.
 - D. Single agent ponatinib treatment, refer to BMT service.

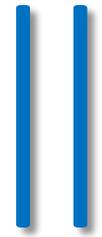
|| Answer

- **Tyrosine kinase domain mutational analysis reveals T315I mutation at this time. What should be the treatment plan?**
 - A. Continue dasatinib and refer to BMT service.
 - B. Change to nilotinib, refer to BMT service.
 - C. 7+3 induction, ponatinib, refer to BMT service.
 - D. Single agent ponatinib treatment, refer to BMT service.**

Given the presence of T315I mutation, his TKI therapy should be switched to ponatinib. He should be referred to BMT service given clonal evolution.

Companion Case for Chapter 5 Chronic Myelogenous Leukemia

*Chetasi Talati
and
Javier Pinilla-Ibarz*



Clinical Case 39

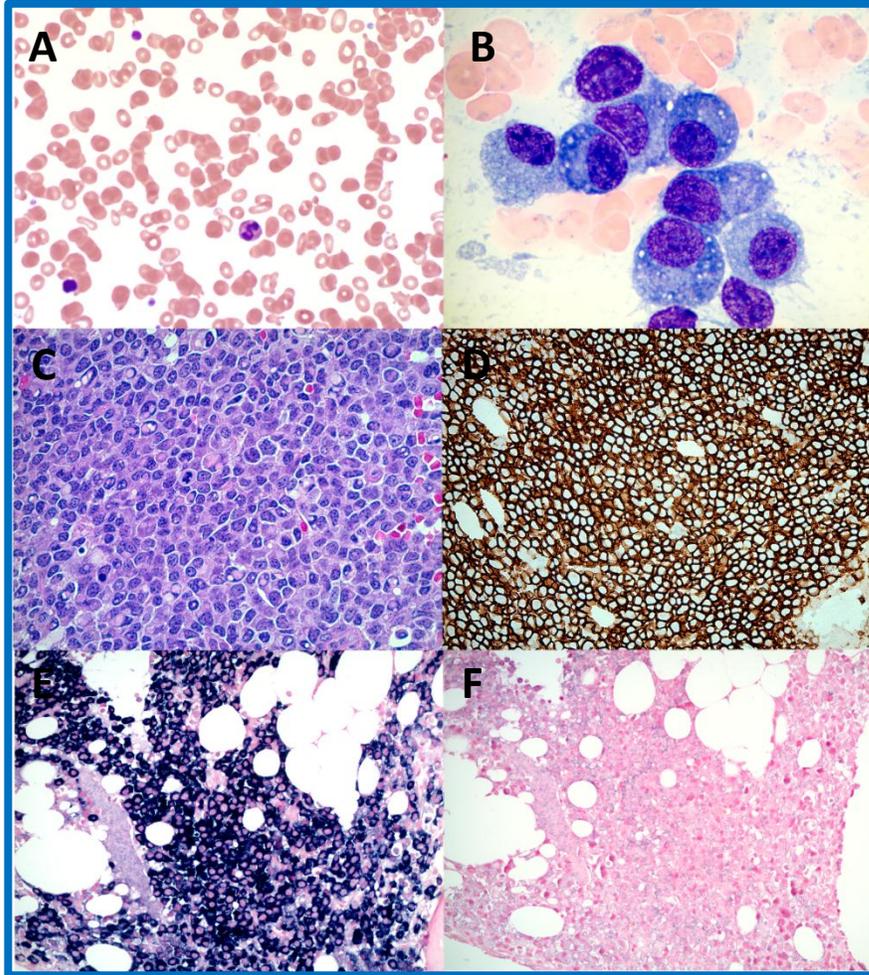


|| Case Presentation



- A previously healthy 61-year-old man presents with an elevated serum total protein identified on routine lab work. Further evaluation reveals an IgG kappa monoclonal gammopathy of 3.8 g/dL. Bone marrow biopsy reveals involvement by 65% kappa-restricted plasma cells. His hemoglobin is mildly decreased at 11 g/dL with normal serum creatinine and calcium. A skeletal survey is normal, and a subsequent PET/CT scan is negative for occult bone lesions.

Bone Marrow Biopsy



The peripheral blood film showed rouleaux formation (A). The bone marrow aspirate smear included atypical plasma cells with eccentrically located round to oval nuclei, prominent nucleoli, and abundant basophilic cytoplasm with or without cytoplasmic immunoglobulin inclusions (B). The bone marrow core biopsy showed a diffuse infiltrate of atypical plasma cells with Dutcher bodies (nuclear inclusions) or Russell bodies (cytoplasmic inclusions) (C) and are CD138+ (D). In situ hybridization with light chain probes demonstrates kappa light chain restriction without lambda light chain expression (E and F, respectively).

|| Cytogenetics/FISH

- Normal Male Karyotype: 46,XY[20]
- FISH: Monosomy 13, +1q21, and t(4;14)
- **Which of the following is an indication to initiate therapy for this patient?**
 - A. M-spike >3 g/dL
 - B. Hgb <12 g/dL
 - C. Clonal bone marrow plasma cells >60%
 - D. Elevated β 2-microglobulin
 - E. t(4;14) identified by FISH

|| Cytogenetics/FISH (Continued) ||

- **Which of the following is an indication to initiate therapy for this patient?**
 - A. M-spike >3 g/dL
 - B. Hgb <12 g/dL
 - C. Clonal bone marrow plasma cells >60%**
 - D. Elevated β 2-microglobulin
 - E. t(4;14) identified by FISH
- Indications for treatment include end-organ dysfunction attributable to multiple myeloma: hemoglobin <10 g/dL, or >2g/dL below baseline; GFR <40 ml/min or creatinine >2.0 mg/dL; lytic bone lesions >5mm, or corrected calcium >11 mg/dL. In addition high disease burden predicting inevitable progression to symptomatic disease is also an indication to start treatment: $\geq 60\%$ clonal bone marrow plasma cells or free light chain ratio ≥ 100 .

|| Cytogenetics/FISH (Continued) ||

- **Which of the following is not a high-risk cytogenetic feature among patients with multiple myeloma?**
 - A. del(17p)
 - B. t(4;14)
 - C. t(14;16)
 - D. 1q21 amplification
 - E. t(11;14)

|| Cytogenetics/FISH (Continued) ||

- Which of the following is not a high-risk cytogenetic feature among patients with multiple myeloma?
 - A. del(17p)
 - B. t(4;14)
 - C. t(14;16)
 - D. 1q21 amplification
 - E. **t(11;14)**

|| Case Presentation



- The patient is hesitant to start treatment in the absence of symptoms. As such, he is monitored with serial labs and regular clinic visits. At a follow-up visit 12 months later, his hemoglobin is now 9.4 g/dL without other identifiable causes for anemia. His serum calcium and creatinine remain normal. He also reports worsening fatigue.

|| Case Presentation (Continued) ||

- **Which of the following would NOT be an appropriate induction regimen for this patient?**
 - A. Lenalidomide-bortezomib-dexamethasone
 - B. Bortezomib-cyclophosphamide-dexamethasone
 - C. Lenalidomide-dexamethasone
 - D. Bortezomib-dexamethasone
 - E. Melphalan-prednisone-thalidomide

|| Case Presentation (Continued) ||

- **Which of the following would NOT be an appropriate induction regimen for this patient?**
 - A. Lenalidomide-bortezomib-dexamethasone
 - B. Bortezomib-cyclophosphamide-dexamethasone
 - C. Lenalidomide-dexamethasone
 - D. Bortezomib-dexamethasone
 - E. Melphalan-prednisone-thalidomide**
- Melphalan may limit the ability to collect stem cells, as such melphalan containing regimens are not recommended for transplant-eligible patients with multiple myeloma. Furthermore, MPT was inferior to lenalidomide and dexamethasone in a phase III trial of transplant-ineligible patients.

|| Case Presentation (Continued) ||

- **The patient starts therapy with lenalidomide-bortezomib-dexamethasone. Which of the following adjunctive agents should he also receive?**
 - A. Aspirin
 - B. Acyclovir
 - C. Zolendronic acid
 - D. PRN antiemetic
 - E. All of the above

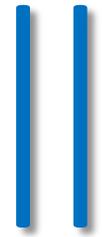
|| Case Presentation (Continued) ||

- **The patient starts therapy with lenalidomide-bortezomib-dexamethasone. Which of the following adjunctive agents should he also receive?**
 - A. Aspirin
 - B. Acyclovir
 - C. Zolendronic acid
 - D. PRN antiemetic
 - E. All of the above**
- Patients receiving IMiDs require DVT prophylaxis with aspirin, or LMWH if high risk. Patients receiving proteasome inhibitors require VZV prophylaxis with acyclovir. All patients receiving active treatment for myeloma should receive zolendronic acid, provided they have adequate renal function.

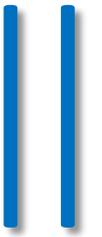
Companion Case for Chapter 26

Multiple Myeloma

*Patrick Griffin
and
Rachid Baz*



Clinical Case 40



|| Case Presentation

- **A 72-year-old asymptomatic male with a history of well-controlled hypertension, hyperlipidemia, and NSAID-associated gastrointestinal bleeding presents for a routine physical examination. A CBC was performed that revealed a WBC count of 10.5 k/ μ L, hemoglobin of 13.3 g/dL, MCV of 90 fL, and platelet count of 672 k/ μ L. Prior laboratory studies from the past year showed platelet counts of 250 k/ μ L and 320 k/ μ L. Physical examination is negative for hepatosplenomegaly. At this point, which of the following is the most likely diagnosis?**
 - A. Polycythemia vera
 - B. Reactive thrombocytosis
 - C. Essential thrombocytosis
 - D. Primary myelofibrosis

|| Case Presentation (Continued) ||

- **A 72-year-old asymptomatic male with a history of well-controlled hypertension, hyperlipidemia, and NSAID-associated gastrointestinal bleeding presents for a routine physical examination. A CBC was performed that revealed a WBC count of 10.5 k/ μ L, hemoglobin of 13.3 g/dL, MCV of 90 fL, and platelet count of 672 k/ μ L. Prior laboratory studies from the past year showed platelet counts of 250 k/ μ L and 320 k/ μ L. Physical examination is negative for hepatosplenomegaly. At this point, which of the following is the most likely diagnosis?**
 - A. Polycythemia vera
 - B. Reactive thrombocytosis**
 - C. Essential thrombocytosis
 - D. Primary myelofibrosis

Reactive thrombocytosis is the most common cause of thrombocytosis. A thorough history and labs should be obtained to evaluate for reversible causes.

|| Case Presentation (Continued) ||

- **What is the next step in management of this patient?**
 - A. No further evaluation
 - B. Bone marrow biopsy and aspiration
 - C. Observation with serial CBCs
 - D. Initiation of treatment for thrombocytosis

|| Case Presentation (Continued) ||

- **What is the next step in management of this patient?**
 - A. No further evaluation**
 - B. Bone marrow biopsy and aspiration
 - C. Observation with serial CBCs
 - D. Initiation of treatment for thrombocytosis

Patients who are asymptomatic and without risk factors could be observed with serial blood counts every 6 to 12 months.

|| Case Presentation (Continued) ||

- **Which of the following are causes of reactive thrombocytosis?**
 - A. Iron deficiency anemia
 - B. Malignancy
 - C. Chronic infections
 - D. Acute blood loss or post splenectomy
 - E. Drugs
 - F. Myelodysplastic syndromes/myeloproliferative neoplasms
 - G. All of the above

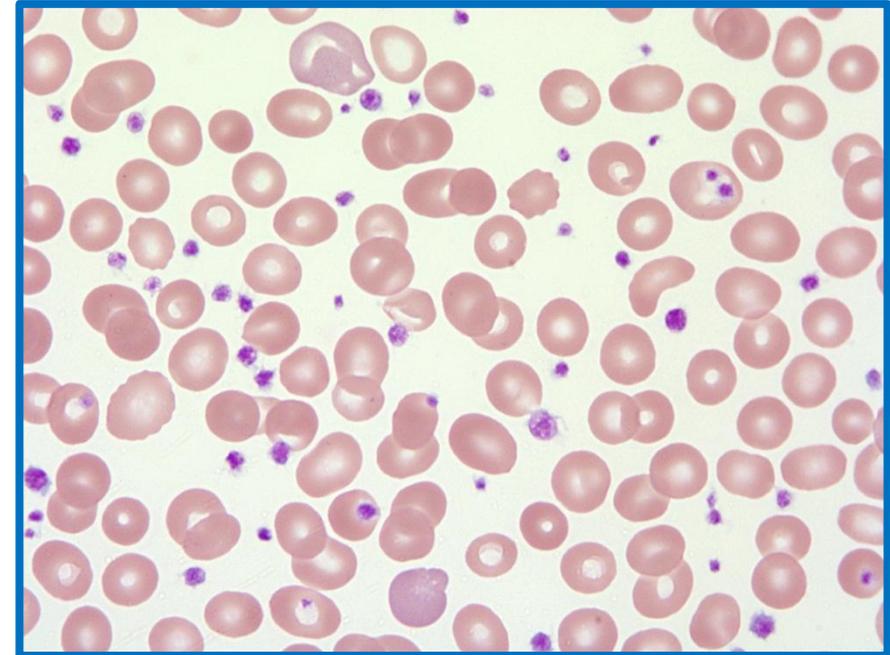
|| Case Presentation (Continued) ||

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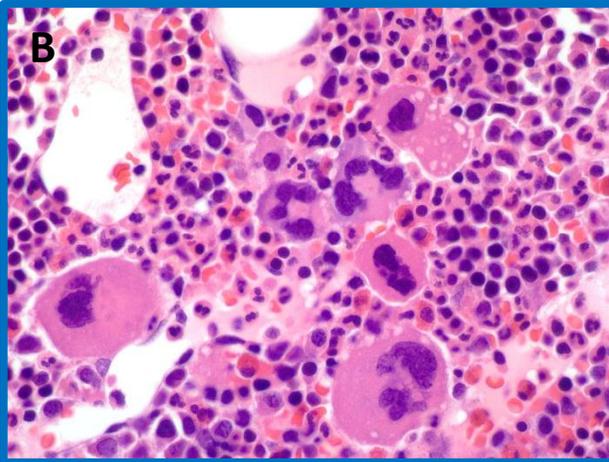
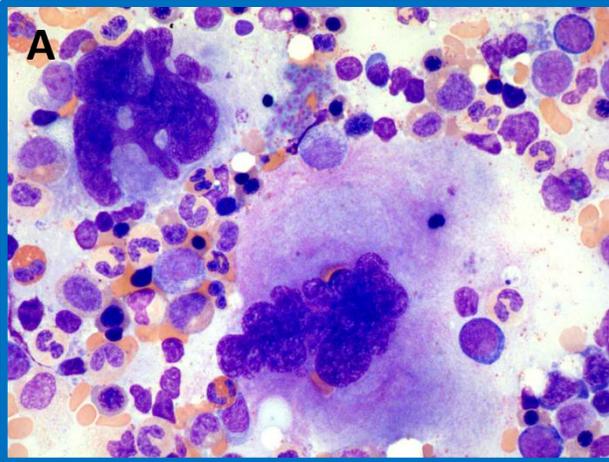
All are known causes of reactive thrombocytosis.

|| Case Presentation (Continued) ||

He underwent close monitoring for 2 years with serial CBCs that showed persistent thrombocytosis ranging from 570 k/ μ L to >1 million/ μ L (see figure). The peripheral blood smear demonstrates normocytic and normochromic RBCs with mild anisopoikilocytosis. Morphologically, platelets are slightly variable in size and shape (Wright stain, x1000). Bone marrow biopsy and aspiration was performed (next slide).



Case Presentation (Continued)



- Microscopic examination of the bone marrow aspirate revealed mainly megakaryocytic hyperplasia. Large, hyperlobated (i.e., “staghorn” nuclei) megakaryocytes, and megakaryocytes with irregularly shaped nuclei were noted (A, Wright-Giemsa, x1000 total magnification). The H&E section of bone marrow core biopsy showed increased megakaryocytes primarily enlarged in size with C-shaped nuclei (B, H&E, x600 total magnification). FISH for *BCR-ABL* and PCR for *JAK2 V617F* are negative.

- **Which of the following is the most likely diagnosis?**
 - A. Polycythemia vera
 - B. Essential thrombocythemia
 - C. Chronic myelogenous leukemia
 - D. Primary myelofibrosis

|| Case Presentation (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Polycythemia vera
 - B. Essential thrombocythemia**
 - C. Chronic myelogenous leukemia
 - D. Primary myelofibrosis

The overall morphologic findings are consistent with the diagnosis of essential thrombocythemia. In patients who are negative for *JAK2* and *MPL* mutation, *CALR* mutation analysis should be done to help confirm clonality with latter being found in 67% of patients with ET. The bone marrow findings and *BCR-ABL* negativity exclude CML, *BCR-ABL1* positive. The morphologic features of this bone marrow (“staghorn” nuclei megakaryocytes, lack of significant fibrosis) are not consistent with primary myelofibrosis, which should have atypical megakaryocytes with hyperchromatic, irregular lobulated nuclei (i.e., “cloud-like” nuclei). Post-ET or post-PV myelofibrosis are complications of ET or PV, respectively, and present with organomegaly and constitutional symptoms such as weight loss, early satiety, abdominal pain.

|| Case Presentation (Continued) ||

- **Which of the following is the most common cytogenetic and molecular alteration seen in essential thrombocytosis?**
 - A. *CALR* exon 9 mutation
 - B. *JAK2* V617F
 - C. *MPL* S505N
 - D. del(20q)
 - E. *MPL* W515L

|| Case Presentation (Continued) ||

- **Which of the following is the most common cytogenetic and molecular alteration seen in essential thrombocythosis?**
 - A. *CALR* exon 9 mutation
 - B. *JAK2* V617F**
 - C. *MPL* S505N
 - D. del(20q)
 - E. *MPL* W515L

JAK2 is found in approximately 60% of ET patients.

|| Case Presentation (Continued) ||

- **What are the criteria associated with increased risk of thrombosis in patients with essential thrombocytosis?**
 - A. Age >60 years
 - B. History of thrombosis
 - C. Cardiovascular risk factors
 - D. Presence of *JAK2* V617F
 - E. All of the above

|| Case Presentation (Continued) ||

- **What are the criteria associated with increased risk of thrombosis in patients with essential thrombocytosis?**
 - A. Age >60 years
 - B. History of thrombosis
 - C. Cardiovascular risk factors
 - D. Presence of *JAK2* V617F
 - E. All of the above**

IPSET-thrombosis study evaluated multiple risk factors that increase the risk of thrombosis in ET and four of the above listed factors were identified to increase the risk of thrombosis.

|| Case Presentation (Continued) ||

- **He was classified as intermediate risk based on the IPSET criteria and the decision was made to start treatment. What would be the initial choice of therapy?**
 - A. Anagrelide and low dose aspirin
 - B. Hydroxyurea and low dose aspirin
 - C. Pegylated interferon and low dose aspirin
 - D. Busulfan
 - E. A, B or C

|| Case Presentation (Continued) ||

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 - A. Anagrelide and low dose aspirin
 - B. Hydroxyurea and low dose aspirin
 - C. Pegylated interferon and low dose aspirin
 - D. Busulfan
 - E. A, B or C**

Most common first-line therapy is hydroxyurea and low dose aspirin. Anagrelide or pegylated interferon with aspirin are alternative options. Busulfan is a second-line therapy.

|| Case Presentation (Continued) ||

- **He was started on hydroxyurea 1,000 mg/day resulting in an excellent platelet response (<450 k/ μ L). Six weeks into therapy, he developed two episodes of acute febrile reaction that were attributed to hydroxyurea. What is the next best treatment option?**
 - A. Reduce the dose of hydroxyurea
 - B. Discontinue hydroxyurea and start anagrelide
 - C. Discontinue hydroxyurea and start pegylated interferon
 - D. Monitor without further treatment
 - E. B or C

|| Case Presentation (Continued) ||

- **He was started on hydroxyurea 1,000 mg/day resulting in an excellent platelet response (<450 k/ μ L). Six weeks into therapy, he developed two episodes of acute febrile reaction that were attributed to hydroxyurea. What is the next best treatment option?**
 - A. Reduce the dose of hydroxyurea
 - B. Discontinue hydroxyurea and start anagrelide
 - C. Discontinue hydroxyurea and start pegylated interferon
 - D. Monitor without further treatment
 - E. B or C**

Anagrelide or pegylated interferon are reasonable options after intolerance to hydroxyurea. Pegylated interferon may be poorly tolerated in the elderly. It is the treatment of choice in pregnant patients.

|| Case Presentation (Continued) ||

- **He was started on anagrelide. At 3-month follow-up visit, he reported severe fatigue and recurrent palpitations. CBC showed a WBC count of 13.7 k/ μ L, hemoglobin of 14 g/dL, and platelet count of 1,669,000/ μ L. What is the next best step in the management of his disease?**
 - A. Discontinue anagrelide and start hydroxyurea
 - B. Discontinue anagrelide and monitor
 - C. Reduce the dose of anagrelide
 - D. Discontinue anagrelide and start pegylated interferon
 - E. Discontinue anagrelide and start busulfan
 - F. A or D
 - G. A or E

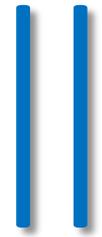
|| Case Presentation (Continued) ||

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 - A. Discontinue anagrelide and start hydroxyurea
 - B. Discontinue anagrelide and monitor
 - C. Reduce the dose of anagrelide
 - D. Discontinue anagrelide and start pegylated interferon
 - E. Discontinue anagrelide and start busulfan
 - F. A or D
 - G. A or E**

Hydroxyurea could be reinitiated after a discussion based on the risks of side effects and recurrence of prior symptoms. Alternatively, busulfan could be used.

Companion Case for Chapter 3 Essential Thrombocythemia

*Susmitha Apuri
and
Kenneth Zuckerman*



Clinical Case 41

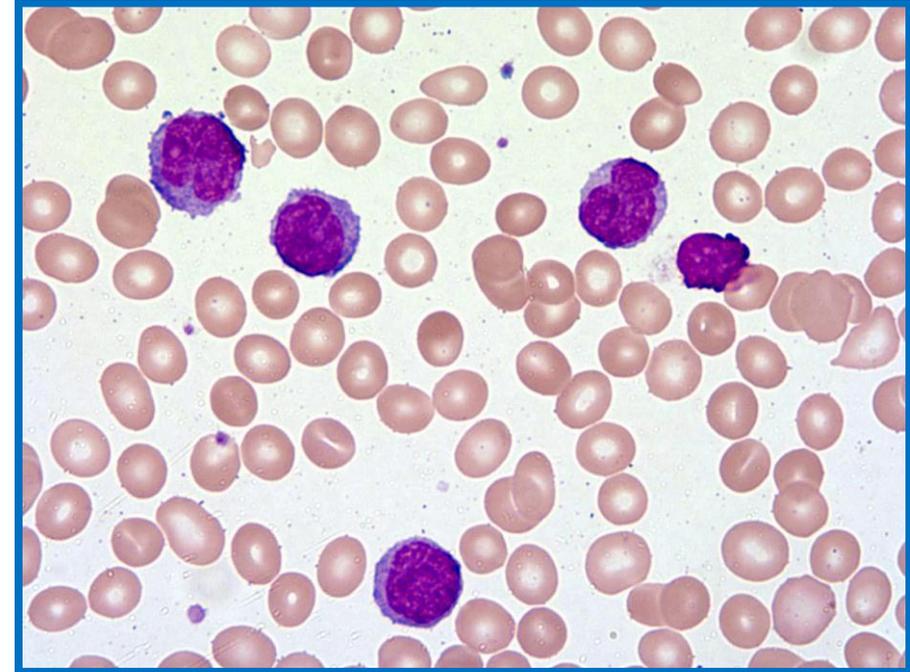


|| Case Presentation

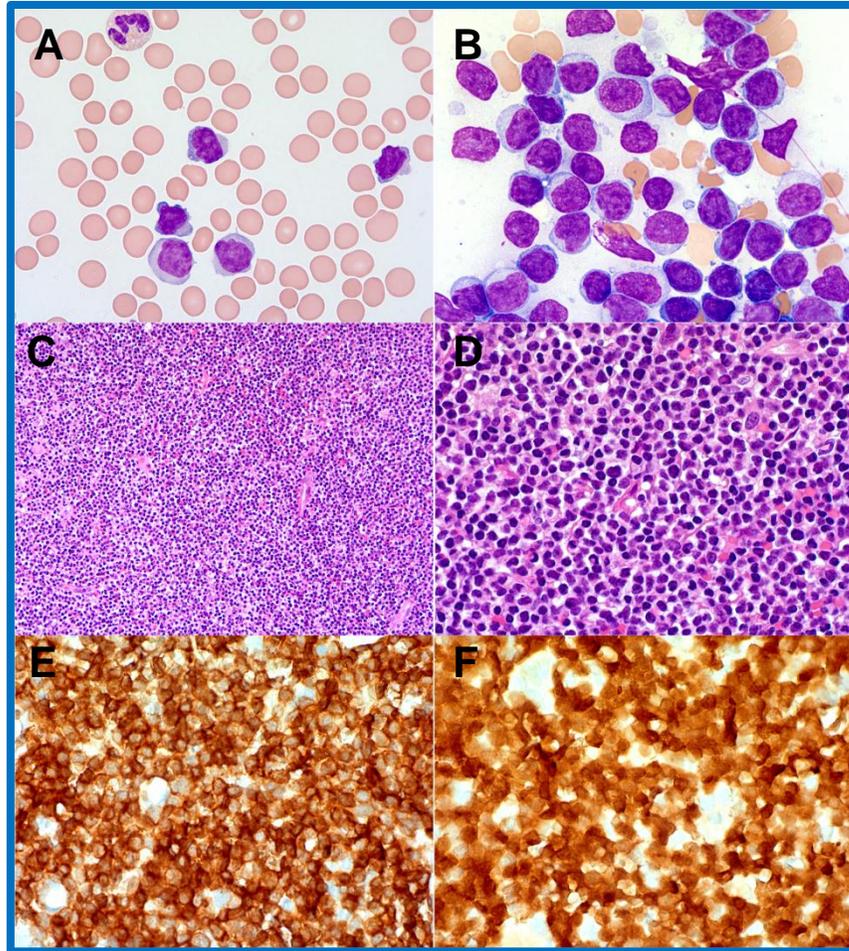
- A 72-year-old African American male is hospitalized for elevated WBC of $56 \times 10^9/L$ with 90% atypical lymphocytes. The patient complained of SOB which was attributed to bilateral pleural effusions. He was seen by his PCP 1 year ago when his WBC count was $19 \times 10^9/L$ with 70% lymphocytes. He was referred to a hematologist but he did not follow up.

|| Case Presentation (Continued) ||

The peripheral blood smear showed several medium-sized lymphocytes with condensed chromatin, a single prominent nucleolus, and intensely basophilic nongranular cytoplasm. There were cytoplasmic protrusions or “blebs.” The majority of nuclei were round to oval.

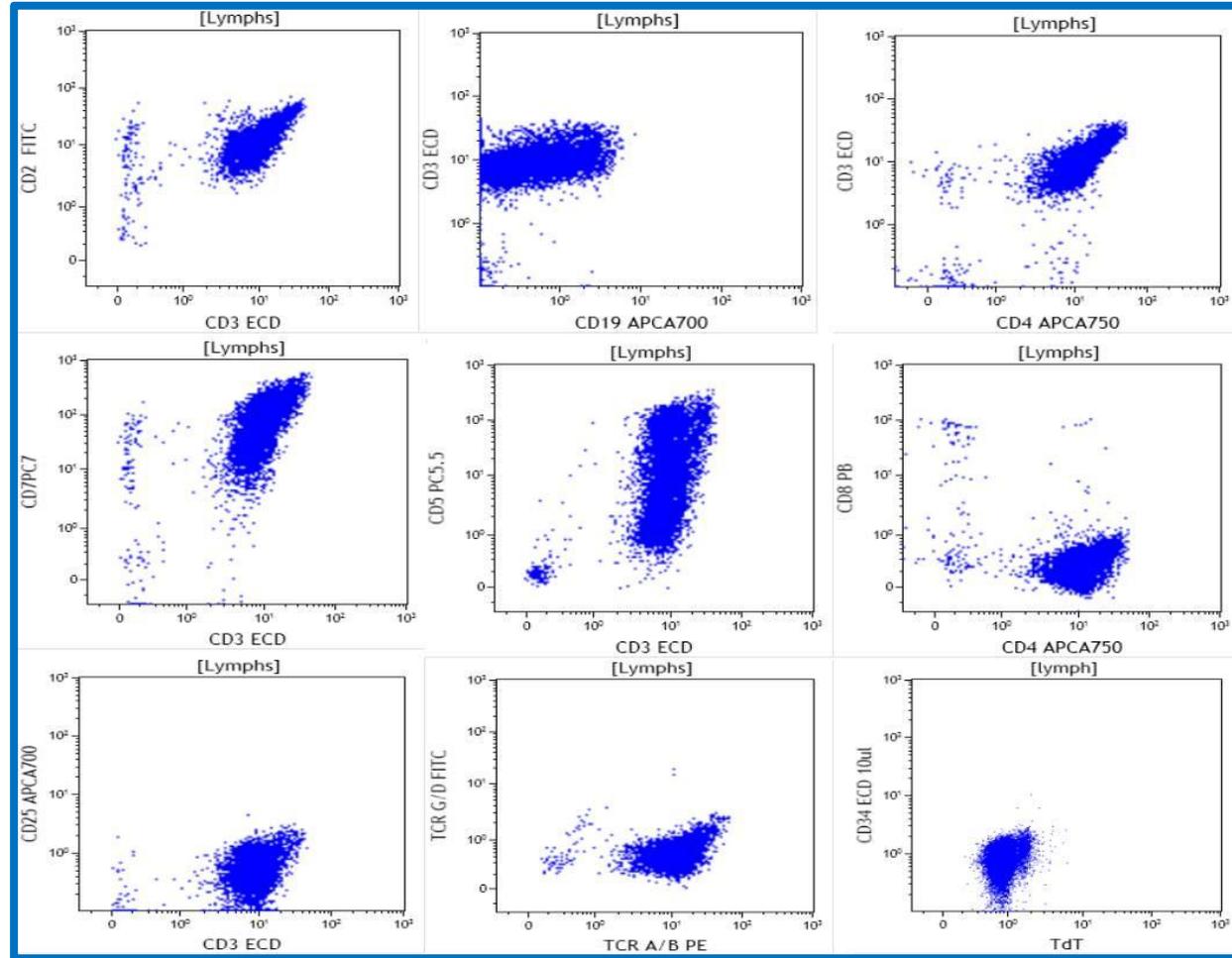


Peripheral Blood and Bone Marrow



Peripheral blood smear shows atypical lymphocytosis. The atypical lymphoid cells largely display condensed chromatin, prominent nucleoli, and a certain amount of amphophilic cytoplasm, compatible with prolymphocytes (A, x1000 total magnification). Touch imprint of bone marrow core biopsy reveals sheets of atypical lymphocytes with morphologic features similar to those in peripheral blood (B, x1000). Bone marrow core biopsy reveals a diffuse infiltrate of small- to medium-sized atypical lymphoid cells, covering nearly 80% to 90% of marrow cellularity. Normal trilineage hematopoietic progenitors are decreased in number (C and D, x200 and 600, respectively). Immunostains show the atypical lymphoid cells are positive for CD3 and TCL1 (E and F, x600, respectively).

Flow Cytometry



|| Flow Cytometry (Continued) ||

- The flow cytometry on the peripheral blood is positive for CD2, CD3, CD4, CD5, CD7, CD26, and CD52 (negative for CD19 and CD25). Cytogenetics show a complex karyotype including an inversion of chromosome 14 and isochromosome 8q. Fluorescence in situ hybridization also reveals 11q23 deletion and 17p13 loss.
- **Which of the following is the most likely diagnosis?**
 - A. Sezary syndrome
 - B. Chronic lymphocytic leukemia
 - C. T-cell prolymphocytic leukemia
 - D. T lymphoblastic leukemia/lymphoma
 - E. Hairy cell leukemia

|| Flow Cytometry (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Sezary syndrome
 - B. Chronic lymphocytic leukemia
 - C. T-cell prolymphocytic leukemia**
 - D. T lymphoblastic leukemia/lymphoma
 - E. Hairy cell leukemia

|| Flow Cytometry (Continued) ||

- **Which of the following is the most common cytogenetic abnormality in T-PLL?**
 - A. Inversion of chromosome 14
 - B. t(X;14)
 - C. t(8;8)
 - D. 11q23 deletion

|| Flow Cytometry (Continued) ||

- **Which of the following is the most common cytogenetic abnormality in the T-PLL?**
 - A. Inversion of chromosome 14**
 - B. t(X;14)
 - C. t(8;8)
 - D. Del(12p13)

|| Inversion of Chromosome 14 ||

- **This cytogenetic abnormality leads to activation of which protooncogene?**
 - A. ATM
 - B. RAS
 - C. TCL1
 - D. N-myc

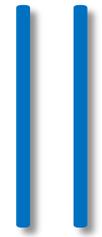
|| Inversion of Chromosome 14 (Continued) ||

- **This cytogenetic abnormality leads to activation of which protooncogene?**
 - A. ATM
 - B. RAS
 - C. TCL1**
 - D. N-myc

Companion Case for Chapter 22

T-Cell Prolymphocytic Leukemia

*Abhijeet Kumar,
Srinath Sundararajan,
and
Ravitharan Krishnadasan*



Clinical Case 42



|| Case Presentation #1



You are seeing a 30-year-old female in clinic. She has a history of iron deficiency anemia with her pregnancy 8 years ago. She was seen by her primary care physician after complaining of nausea, vomiting, and diarrhea for 2 days. A complete blood count performed by her primary care physician was notable for neutropenia, lymphopenia, and thrombocytopenia. She was therefore referred to you.

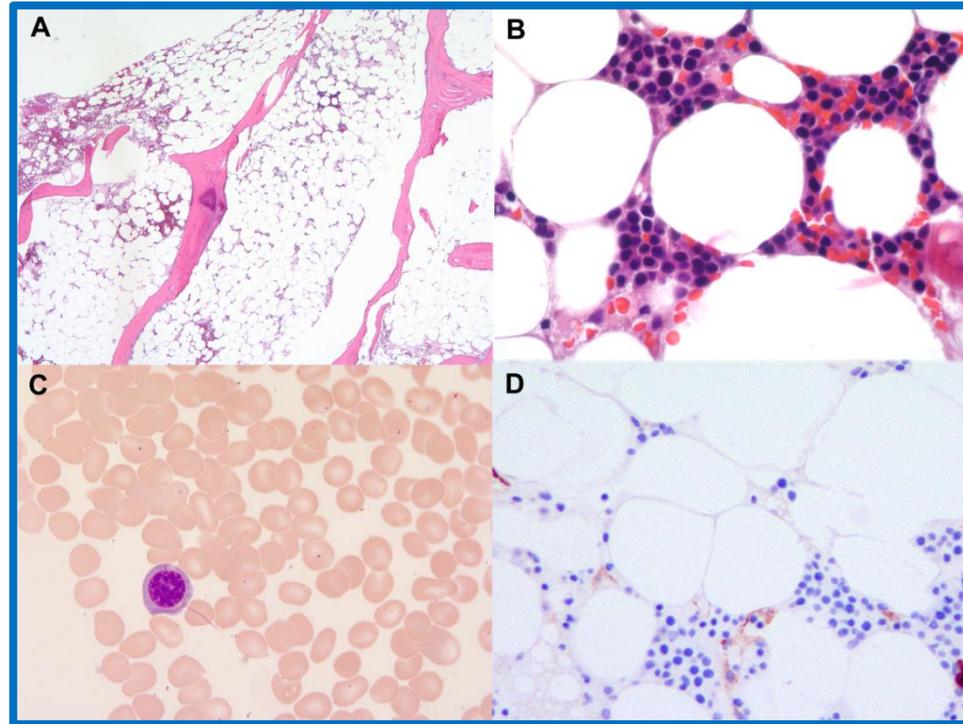
Her initial symptoms have resolved, and she is not complaining of fevers, chills, fatigue, weight loss, night sweats, dyspnea, or chest pain. She has no history of NSAID use, autoimmune diseases, or heavy metal/toxic exposures.

On physical exam, she has conjunctival pallor and is tachycardic, but she does not have petechiae, bruising, or hepatosplenomegaly. Her exam is otherwise normal.

Her CBC in clinic shows a total white count of $2.06 \text{ k}/\mu\text{L}$, absolute neutrophil count $1.08 \text{ k}/\mu\text{L}$, platelet count of $93 \text{ k}/\mu\text{L}$, and a hemoglobin of $9.7 \text{ g}/\text{dL}$. Additional laboratory evaluation was notable for normal B12 and folate levels. ANA, rheumatoid factor, monoclonal protein, and HIV serology were negative. Serologic testing for Hepatitis B and C was normal.

|| Case Presentation #1 (Continued) ||

The bone marrow results are shown below.



The bone marrow core is markedly hypocellular (5%) (A, H&E, x40) with a couple of small islands of erythroid precursors that show essentially normal morphology in the core (B, H&E, x600). The CD34 stain shows no CD34 positive blasts (Immunoperoxidase, x200). The aspirate smear is essentially acellular (C, Wright Giemsa, x1000). CD34 IHC is also shown with no increase in blasts (D, immunoperoxidase, x400).

|| Case Presentation #1 (Continued) ||

The bone marrow biopsy reveals a hypocellular marrow (5% cellularity) with trilineage hematopoiesis and no increase in reticulin fibrosis. It shows normal iron storage, and no ring sideroblasts or dyspoiesis of the myeloid, megakaryocytic, or erythroid lineages. Blasts are <1% of the differential count.

- **The patient should be diagnosed with what condition?**
 - A. Aplastic anemia
 - B. Hypoplastic MDS
 - C. PNH
 - D. Diamond blackfan anemia

|| Case Presentation #1 (Continued) ||

The bone marrow biopsy reveals a hypocellular marrow (5% cellularity) with trilineage hematopoiesis and no increase in reticulin fibrosis. It shows normal iron storage, and no ring sideroblasts or dyspoiesis of the myeloid, megakaryocytic, or erythroid lineages. Blasts are <1% of the differential count.

- **The patient should be diagnosed with what condition?**
 - A. **Aplastic anemia**
 - B. Hypoplastic MDS
 - C. PNH
 - D. Diamond blackfan anemia

|| Case Presentation #1 (Continued) ||

- **The patient was diagnosed with aplastic anemia. How would you manage this patient?**
 - A. Combination cyclosporine, horse antithymocyte globulin and cyclophosphamide
 - B. Combination cyclosporine and horse antithymocyte globulin
 - C. Conservative management
 - D. Referral for consideration of allogeneic stem cell transplantation

|| Case Presentation #1 (Answer) ||

Answer: C

The patient meets diagnostic criteria for aplastic anemia. However, she meets criteria for moderate disease, without severe cytopenias, and a marrow that is 25% cellular. She can be managed conservatively. Choices B and D would be appropriate options in the setting of severe disease. Choice A is associated with unacceptable toxicities when compared in a randomized trial against standard therapy (cyclosporine and ATG). Therefore, Choice A is not recommended for treatment in severe aplastic anemia.

|| Case Presentation #2



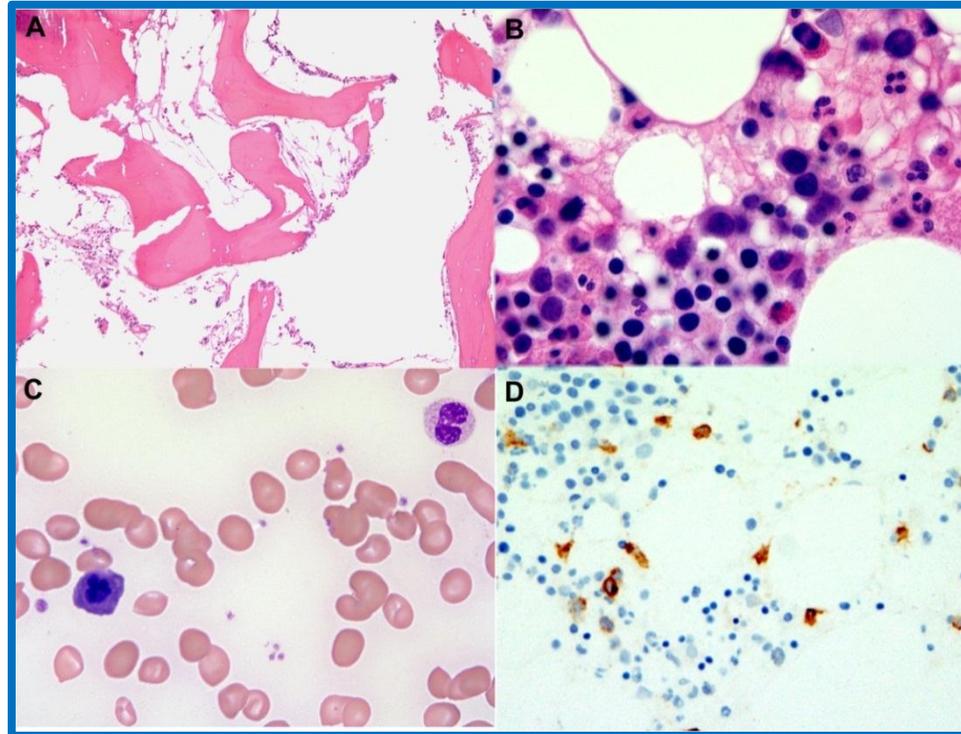
You are seeing a 47-year-old female in clinic who has a history of autoimmune disease (Hashimoto's thyroiditis, seronegative arthritis, and episcleritis) that has been previously treated with remicade for 2 years. She presents to clinic for fatigue and bruising of her arms and legs for 9 months. She denies fevers, chills, night sweats, rectal bleeding, or gingival bleeding.

On physical exam, she has obvious bruising on her forearms. She has no hepatosplenomegaly or petechiae.

In clinic, her complete blood count showed a white blood cell count of 2.83 k/ μ L, hemoglobin of 10.9 g/dL, and platelet count of 18 k/ μ L.

She undergoes a bone marrow biopsy and aspiration.

|| Case Presentation #2 (Continued) ||



Core biopsy shown on low power (A, H&E, x40 total magnification) and higher power revealing revealed micro- and hypolobated megakaryocytes associated with loosely formed erythroid precursors, few granulocytes, and scattered blasts (B, H&E, x600). A erythroid precursor with nuclear irregularity or budding along with a hyposegmented neutrophil was identified in the aspirate and acellular aspirate smear (C, Wright-Giemsa, x600) and CD34 IHC shows 5% blasts (D, immunoperoxidase, x400).

|| Case Presentation #2 (Continued) ||

The core biopsy is 5% to 10% cellular. Blasts are 5% of the total cellularity. Flow cytometry shows a PNH clone comprising 2% of the total cellularity. Cytogenetic studies are limited, but show del(13q) in 3/6 metaphases. FISH shows del(13q) in 25% of the cells.

- **What is the best diagnosis?**
 - A. Myelofibrosis
 - B. Aplastic anemia
 - C. Myelodysplastic syndrome
 - D. PNH

|| Case Presentation #2 (Answer) ||

Answer: C

These morphologic and immunohistochemical findings are compatible with hypoplastic MDS. MDS is typically associated with hypercellular bone marrow samples. In this case, however, despite being hypocellular, morphologic evidence of dysplasia supports a diagnosis of hypoplastic MDS, de novo or secondary. The megakaryocytes are small, hypolobated, and hypogranular, and erythroid dysplasia is also seen. An increase in blasts is also evident by CD34 IHC. Though flow cytometry shows a small PNH clone, the patient does not have other evidence of hemolytic anemia. Small PNH clones are commonly found in cases of aplastic anemia and MDS. PNH is discussed further in a separate chapter.

|| Case Presentation #3

A 69-year-old male is returning to your clinic for anemia. He was diagnosed 3 years ago with aplastic anemia when he presented for fatigue. A bone marrow biopsy confirmed his diagnosis, and he was treated with cyclosporine and ATG. He achieved a complete response and was transfusion independent until recently. He since has developed worsening anemia and thrombocytopenia requiring transfusions every 1 to 2 weeks.

He is otherwise healthy, and he is taking medications only for hypertension. His physical examination is notable for tachycardia and conjunctival pallor.

|| Case Presentation #3 (Continued) ||

A CBC shows a white count of 2.74 k/ μ L, hemoglobin of 7.9 g/dL, and a platelet count of 8 k/ μ L.

A repeat bone marrow biopsy shows 5% cellularity. There are no dysplastic features, and blasts are not increased. There is no increased storage iron, ring sideroblasts, or reticulin fibers. FISH for deletions in 5q, 7q, 11q, and 13q are negative, and cytogenetic analysis shows a normal male karyotype, 46 XY, in 20/20 metaphases.

|| Case Presentation #3 (Continued) ||

- **What is the most likely diagnosis?**
 - A. Acute myeloid leukemia
 - B. Myelodysplastic syndrome
 - C. Myelofibrosis
 - D. Relapsed aplastic anemia

|| Case Presentation #3 (Answer) ||

Answer: D

The most appropriate diagnosis is relapse of aplastic anemia. This will happen in 10% of patients who were previously treated with cyclosporine and ATG. The results of the bone marrow biopsy rule out acute leukemia, myelofibrosis, and MDS.

|| Case Presentation #3 (Continued) ||

- **What therapy or therapies would be appropriate for treating this patient?**
 - A. Retreatment with ATG/cyclosporine/prednisone
 - B. Alemtuzumab
 - C. Eltrombopag
 - D. Allogeneic stem cell transplantation
 - E. Only A and C
 - F. Only B and C
 - G. All of the above

|| Case Presentation #3 (Answer) ||

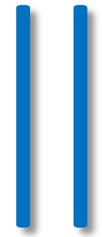
Answer: G

There is no standardized treatment for relapsed aplastic anemia. Certainly, allogeneic transplantation in this patient with minimal comorbid conditions can be considered. In addition, retreating him with ATG/cyclosporine/steroids is an option since he had an initial response 3 years ago. Relapsed disease can also be treated with eltrombopag (an oral thrombopoietin receptor agonist) or alemtuzumab.

Companion Case for Chapter 10

Aplastic Anemia

*Michael Shafique
and
Rami Komrokji*



Clinical Case 43

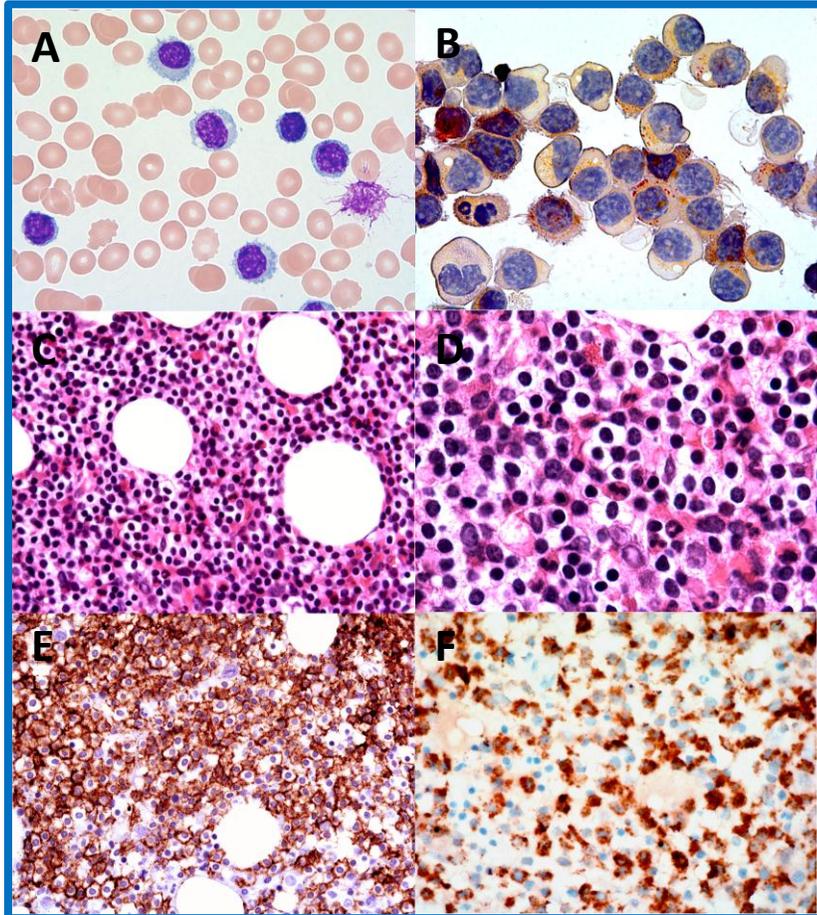


|| Case Presentation



- A 52-year-old man is referred from his primary care physician with newly diagnosed leukopenia with a WBC count ranging from 1.9 to 2.6 k/ μ L. He has some mild fatigue but is otherwise asymptomatic.
- Exam reveals a good performance status (KPS = 90). He has no lymphadenopathy or hepatomegaly, but significant splenomegaly with the spleen tip measuring 8.0 cm below the costal margin.
- Other laboratory tests reveal anemia and thrombocytopenia. The LDH level is normal.

Peripheral Blood Smear & Bone Marrow Aspirate/Biopsy



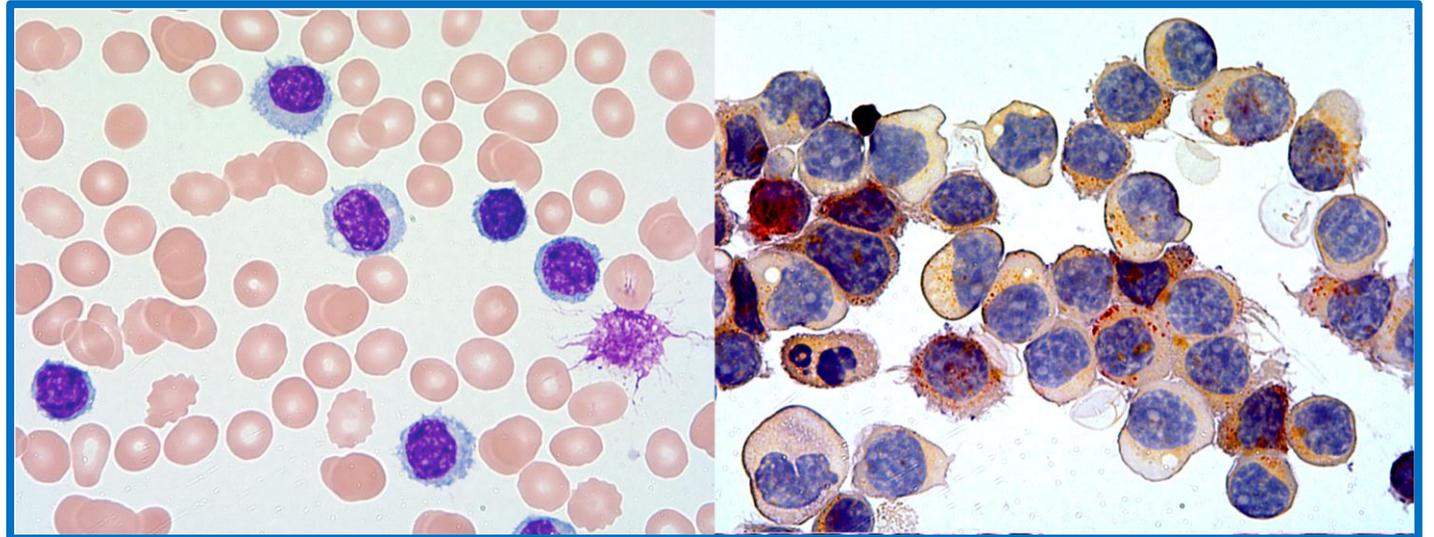
The peripheral blood smear includes several atypical lymphoid cells with oval to kidney-bean-shape nuclei, condense chromatin, and a certain amount of clear cytoplasm with visible, radiated cytoplasmic project. Included are also two small and mature forms of naive lymphocytes (A, Wright, x1000). The atypical cells (in cytopsin preparation) are stained positive for Tartrate-resistant acid phosphatase (TRAP) (B, TRAP, x1000). The bone marrow core biopsy (low to high power of views) shows a diffuse replacement of a monotonous population of mature lymphocytes with low N:C ratio, smooth nuclear contour, and abundant clear cytoplasm (fried-egg in appearance) (C and D, H&E, x200 and x600, respectively). IHC stains highlight these atypical lymphoid cells to be positive for CD20 (E, immunoperoxidase, x200) and TRAP (F, immunoperoxidase, x600).

Peripheral Blood Smear & Bone Marrow Aspirate/Biopsy (Continued)

- **What is the most likely diagnosis?**
 - A. Chronic lymphocytic leukemia
 - B. Chronic myelogenous leukemia
 - C. Acute myeloid leukemia
 - D. Hairy cell leukemia

Peripheral Blood Smear & Bone Marrow Aspirate/Biopsy (Continued)

- What is the most likely diagnosis?
 - A. Chronic lymphocytic leukemia
 - B. Chronic myelogenous leukemia
 - C. Acute myeloid leukemia
 - D. Hairy cell leukemia**



Hairy cell leukemia (HCL) is typically characterized by pancytopenia with splenomegaly. The peripheral blood review shows atypical circulating cells with hair-like cytoplasmic projections.

Peripheral Blood Smear & Bone Marrow Aspirate/Biopsy (Continued)

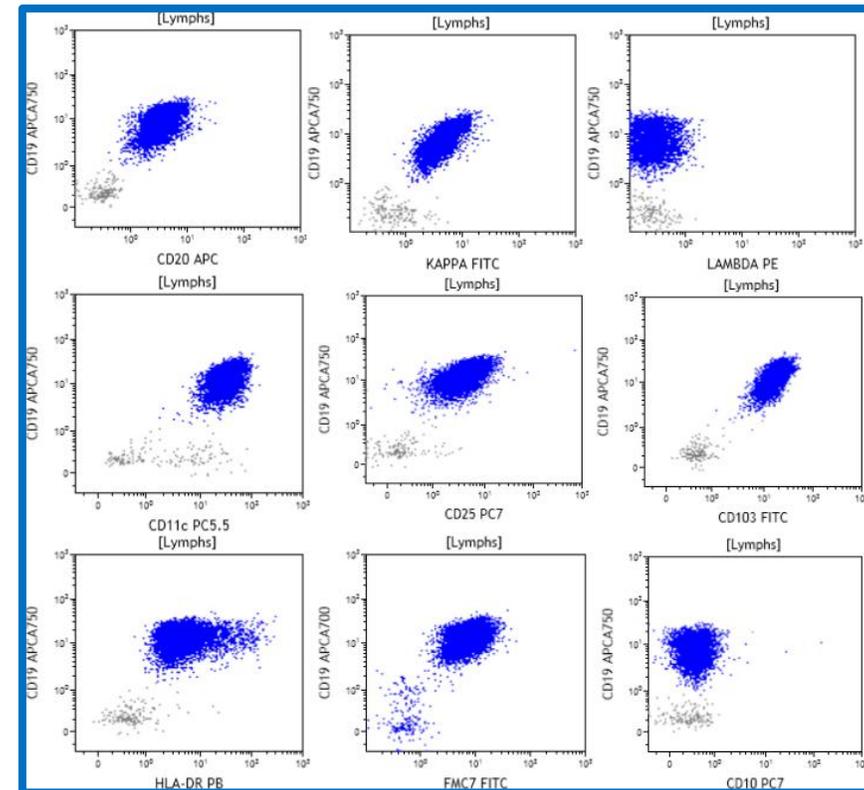
- **What is the expected flow cytometric pattern?**
 - A. CD19+, CD5+, CD23+
 - B. CD19+, CD25+, CD103+
 - C. CD19+, CD25-, CD103+
 - D. CD19-, CD25-, CD103+

Peripheral Blood Smear & Bone Marrow Aspirate/Biopsy (Continued)

○ What is the expected flow cytometric pattern?

- A. CD19+, CD5+, CD23+
- B. CD19+, CD25+, CD103+**
- C. CD19+, CD25-, CD103+
- D. CD19-, CD25-, CD103+

Typical HCL flow cytometry as shown expresses pan B-cell antigens as well as CD11c, CD25, and CD103. The hairy cell variant usually does not express CD25.



Peripheral Blood Smear & Bone Marrow Aspirate/Biopsy (Continued)

- **What is the most frequently used initial treatment?**
 - A. Cladribine
 - B. Cytarabine
 - C. Pentostatin
 - D. Interferon

Peripheral Blood Smear & Bone Marrow Aspirate/Biopsy (Continued)

- **What is the most frequently used initial treatment?**
 - A. Cladribine**
 - B. Cytarabine
 - C. Pentostatin
 - D. Interferon

Cytarabine is not used in HCL, but the other 3 are all options. Cladribine is the most commonly used, as it is easiest to administer with the least amount of side effects.

Peripheral Blood Smear & Bone Marrow Aspirate/Biopsy (Continued)

- **What is the median overall survival of this disease?**
 - A. Less than 6 months
 - B. 12 to 14 months
 - C. 2 to 5 years
 - D. Most patients are long-term survivors

Peripheral Blood Smear & Bone Marrow Aspirate/Biopsy (Continued)

- **What is the median overall survival of this disease?**
 - A. Less than 6 months
 - B. 12 to 14 months
 - C. 2 to 5 years
 - D. Most patients are long-term survivors**

The use of highly active purine analogs like cladribine and pentostatin have led to high levels of sustained remissions with even a single treatment cycle.

|| Case Presentation

- Upon suspicion of the diagnosis of HCL, the patient had flow cytometric analysis performed on bone marrow; aspirate specimen confirmed involvement of the bone marrow with CD19+, CD11c+, CD25+, CD103+ HCL. Molecular study revealed BRAF V600E mutation.
- The patient then received cladribine for one cycle and achieved complete remission.
- He presents again 5 years later with pancytopenia and is diagnosed with relapsed disease.

|| Case Presentation (Continued) ||

- **What is the best therapy to recommend?**
 - A. Repeat cladribine alone
 - B. Add a second agent (e.g., pentostatin) to cladribine
 - C. Allogeneic stem cell transplant
 - D. Clinical trial of vemurafenib

|| Case Presentation (Continued) ||

- **What is the best therapy to recommend?**
 - A. Repeat cladribine alone
 - B. Add a second agent (e.g., pentostatin) to cladribine
 - C. Allogeneic stem cell transplant
 - D. Clinical trial of vemurafenib

Unless relapse occurs very soon after the last treatment, HCL patients are likely to respond to single agent purine analog a second time. Combined purine analogs would be too toxic. Allogeneic transplant has no proven role. Clinical trial would also be an option if purine analogs were not tolerated.

|| Case Follow-Up



- The patient received cladribine and again achieved a complete remission lasting for 3.5 years.
- The patient moves away but returns after another relapse of HCL. Further treatment with purine analogs have failed and he wants treatment recommendations at this point.

|| Case Follow-Up (Continued) ||

- **What is the best therapy to recommend at this point?**
 - A. Supportive care only
 - B. Autologous stem cell transplant
 - C. Allogeneic stem cell transplant
 - D. Clinical trial of vemurafenib

|| Case Follow-Up (Continued) ||

- **What is the best therapy to recommend at this point?**
 - A. Supportive care only
 - B. Autologous stem cell transplant
 - C. Allogeneic stem cell transplant
 - D. Clinical trial of vemurafenib**

Two Phase 2 studies recently published their results on the targeting of mutant *BRAF* with vemurafenib in relapsed/refractory HCL. They found a 98% overall response rate and that most toxicities were mild (grade 1 or 2). Supportive care only would be too premature and the role of stem cell transplant in HCL is undefined.

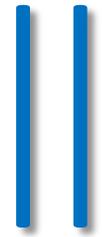
|| Case Follow-Up (Continued) ||

- The patient was initiated on a clinical trial of vemurafenib for relapsed and refractory HCL. He is tolerating the therapy and continues to respond.

Companion Case for Chapter 40

Hairy Cell Leukemia

*Justin Taylor
and
Omar Abdel-Wahab*



Clinical Case 44

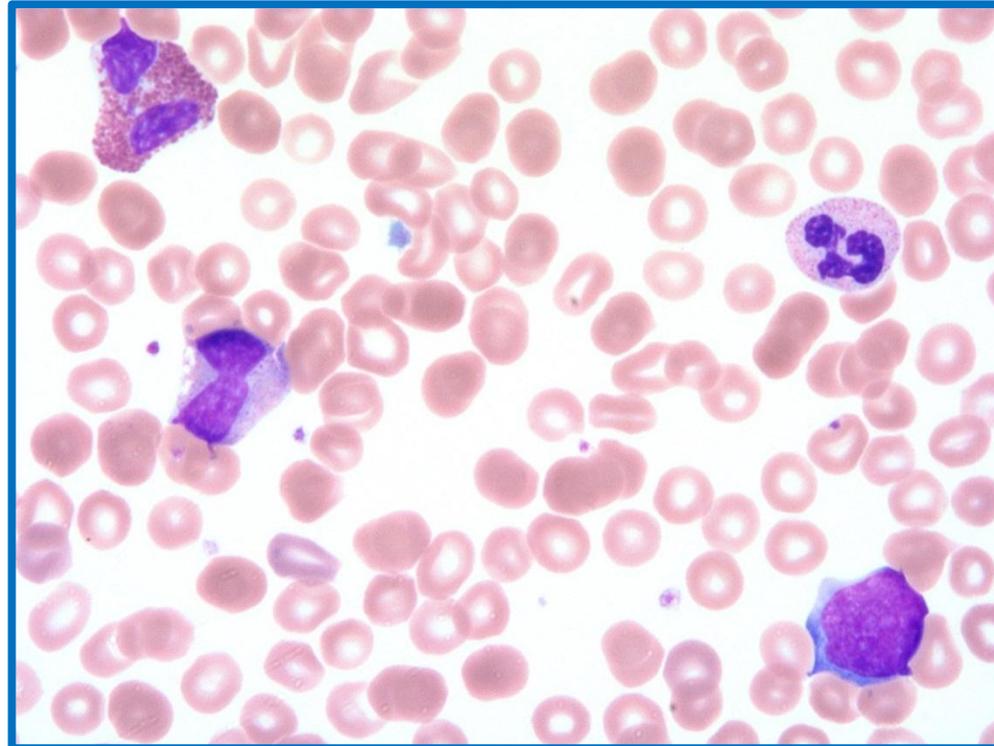


|| Case Presentation

- A 64-year-old male presents with shortness of breath and fatigue. A CBC was performed that revealed a WBC of $44.01 \times 10^9/L$ with a normal hemoglobin and platelet count. He denied any other symptoms of lymphadenopathy, fevers, chills, or weight loss. His exam reveals splenomegaly and bilateral axillary lymphadenopathy. A staging thorax computed tomography (CT) with contrast disclosed widespread adenopathy involving bilateral axillary, mediastinal, bilateral hilar and inguinal lymph nodes, as well as splenomegaly.

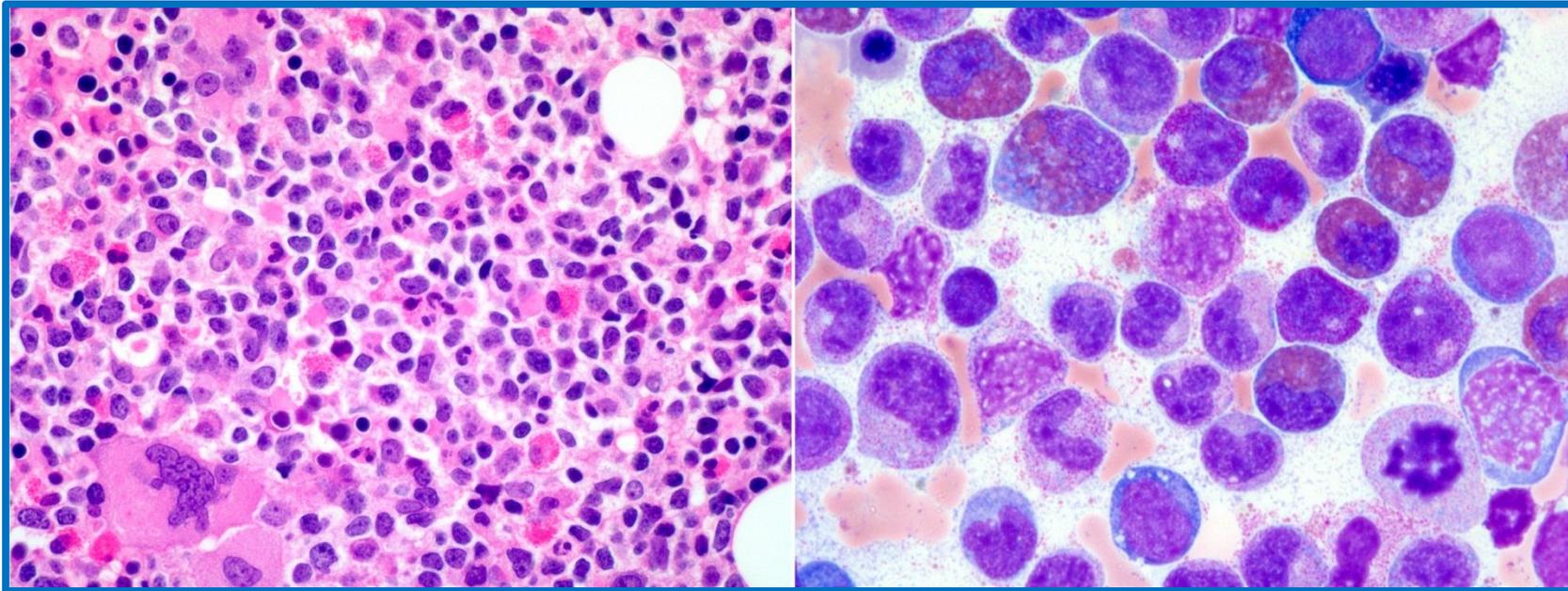
|| Case Presentation (Continued) ||

His peripheral blood smear shows circulating lymphoblasts as well as eosinophils, neutrophils, and monocytes. Giemsa. ×1000.



|| Case Presentation (Continued) ||

Subsequent analyses of the bone marrow core biopsy revealed marked hypercellularity with 40% infiltrate by lymphoblasts and a significant myeloid preponderance and increase in eosinophils. Aspirate revealed increased lymphoblasts in a background of enlarged, atypical eosinophilic precursors containing abundant, bright-red cytoplasmic granules or baso/eosinophilic primary granules and mild left-shifted myeloid cells.



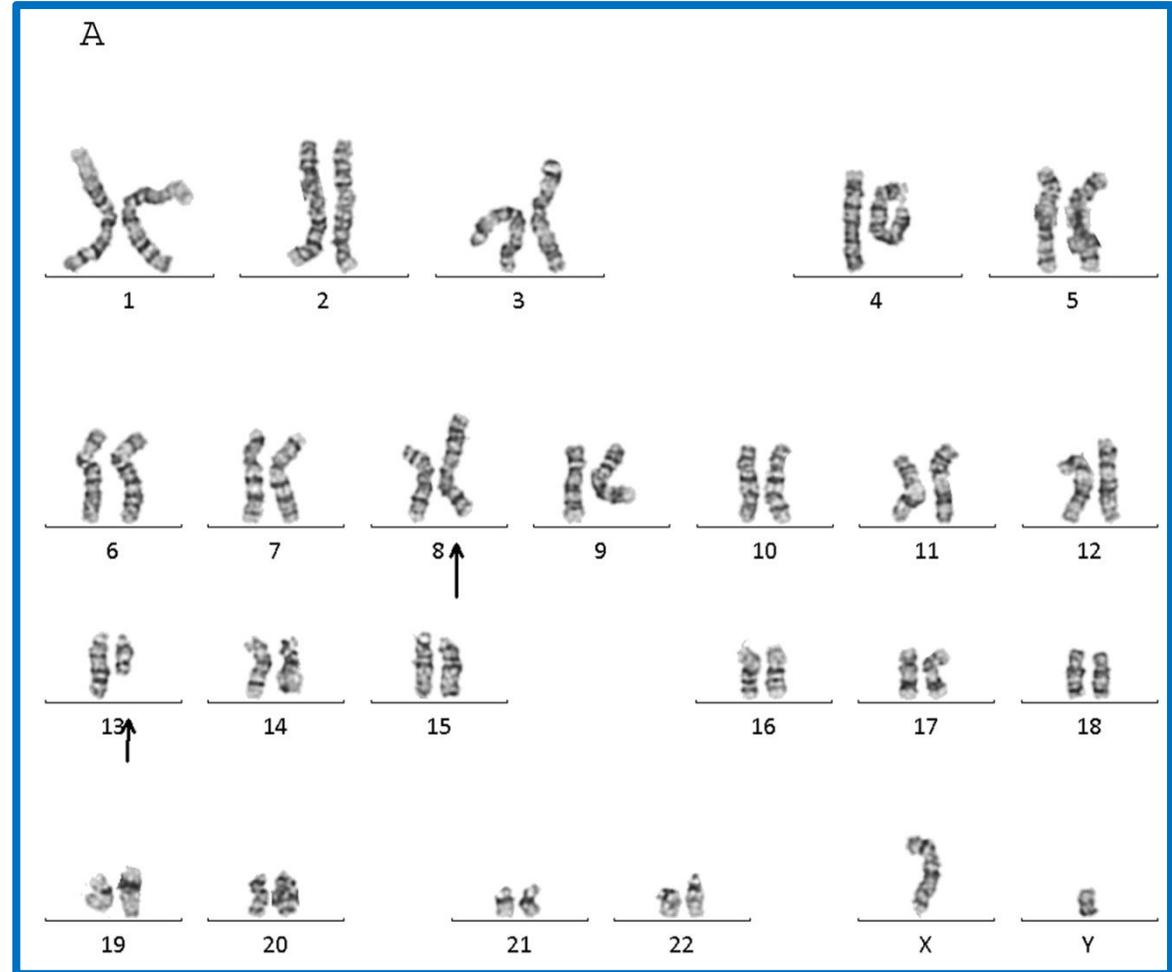
|| Flow Cytometry



- Flow cytometry showed an increased dim-CD45 population blast population that was immature B-cells (29% of total cellularity), immunophenotypically positive for CD10, CD19, TdT, CD20 (negative to dim, variable), CD34 (bimodal), CD38, and HLA-DR, with negative staining for all myeloid/monocytic markers such as CD14, CD13, CD33, or CD117.

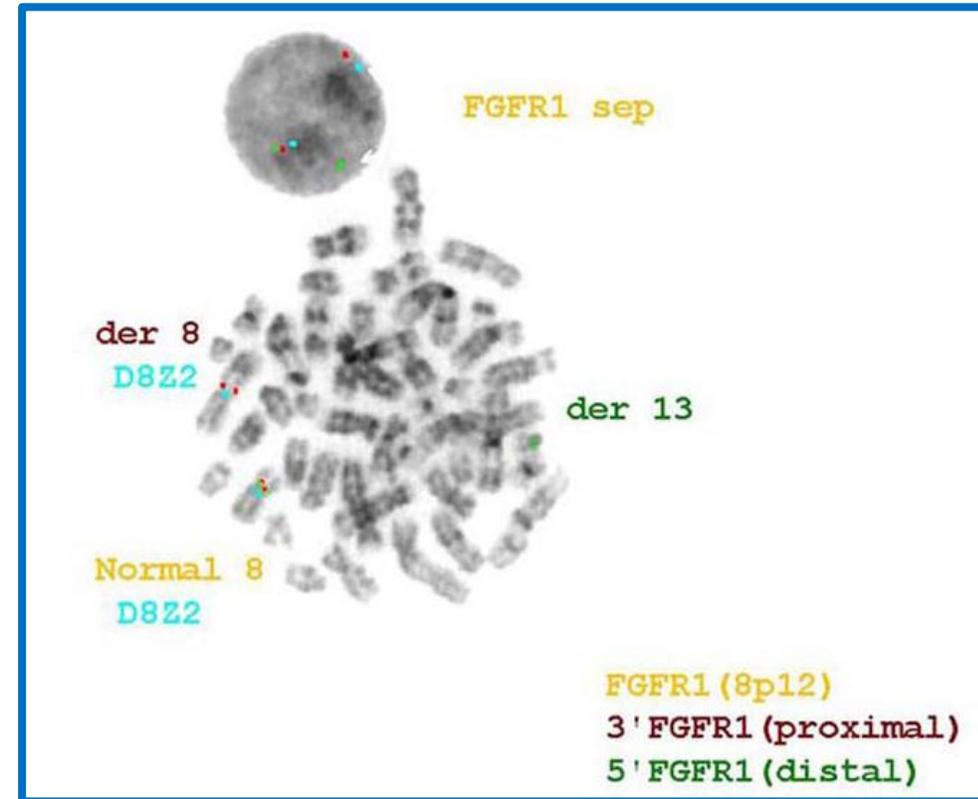
Karyotyping Analysis

- Karyotype analysis by conventional G banding of the patient's bone marrow cells showing 46,XY,t(8;13)(p11.2;q12).



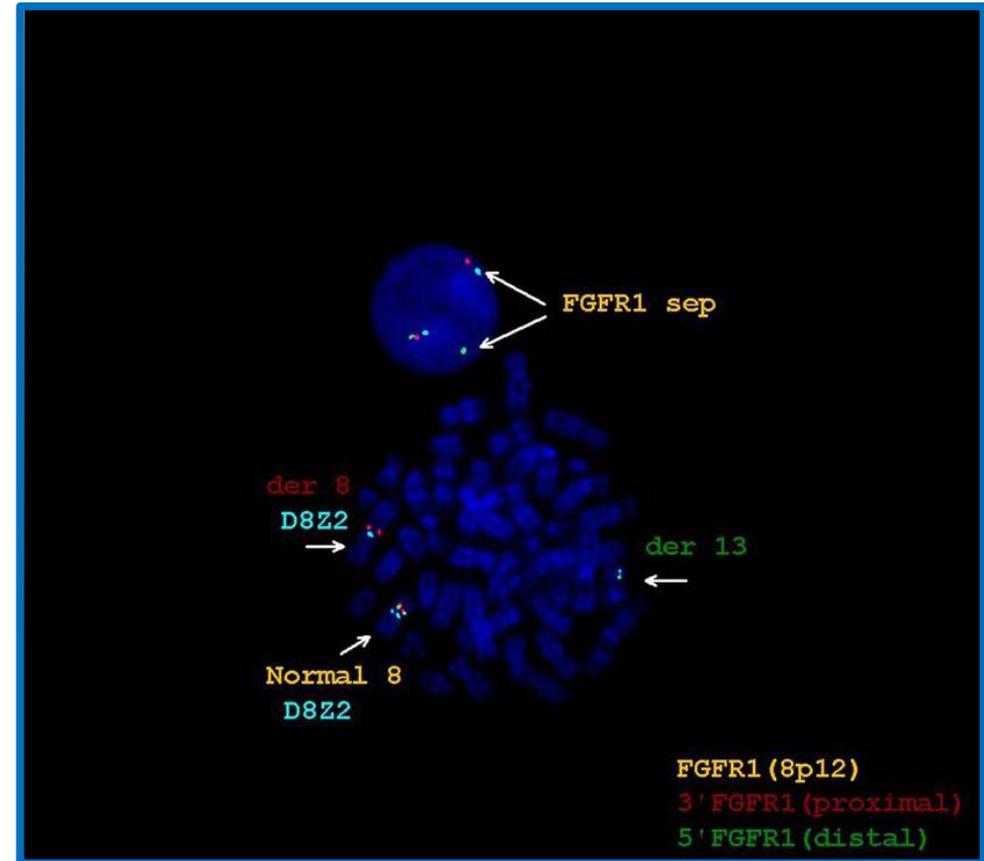
FISH Analysis

FISH analysis with an FGFR1 break-apart probe and 8 centromere probe, confirming the translocation t(8;13). The distal 5' end of FGFR1 is labeled green, the proximal 3' end of FGFR1 is labeled red, and the 8 centromere probe (8cen; D8Z2) is labeled aqua.



FISH Analysis (Continued)

In the cell in metaphase (lower portions), the proximal 3' FGFR1 (red) and 8 centromere probe (aqua) remained in the derivative chromosome 8 (upper arrow, left), while the distal 5' FGFR1 (green) was translocated to the derivative chromosome 13 (arrow, right). The normal chromosome 8 retained the red/green duet signal and the aqua signal (lower arrow, left). In the cell in interphase (upper portions), the separation of 1 red and 1 green signal and the presence of 1 red/green duet signal and 2 aqua signals represent the pattern indicating the presence of an FGFR1 rearrangement.



|| FISH Analysis (Continued) ||

- Karyotyping revealed 46,XY, t(8;13)(p11.2;q12) and FISH analysis confirmed the translocation t(8;13).
- **Which of the following is the most likely diagnosis?**
 - A. B-lymphoblastic leukemia/lymphoma associated with PDGFRB rearrangement
 - B. “Lymphocytic” variant hypereosinophilia
 - C. Chronic eosinophilic leukemia, NOS
 - D. B-lymphoblastic leukemia/lymphoma associated with FGFR1 rearrangement
 - E. B-lymphoblastic leukemia/lymphoma with secondary eosinophilia

|| FISH Analysis (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. B-lymphoblastic leukemia/lymphoma associated with PDGFRB rearrangement
 - B. “Lymphocytic” variant hypereosinophilia
 - C. Chronic eosinophilic leukemia, NOS
 - D. B-lymphoblastic leukemia/lymphoma associated with FGFR1 rearrangement**
 - E. B-lymphoblastic leukemia/lymphoma with secondary eosinophilia

The B-cell lymphoblastic lymphoma with peripheral blood and bone marrow eosinophilia and presence of the translocation $t(8;13)(p11.2;q12)$ satisfy diagnostic criteria of myeloproliferative neoplasm associated with FGFR1 rearrangement.

|| Differential Diagnosis

- FIP1L1-PDGFR α and PDGFR β -rearranged clonal eosinophilia require the presence of FIP1L1-PDGFR α or a PDGFR β fusion gene, respectively.
- Other entities share some characteristics with myeloid and lymphoid neoplasms with eosinophilia and abnormalities of FGFR1, but do not have identifiable rearrangements of FGFR1.
 - T- or B-lymphoblastic lymphoma/leukemia without FGFR1 rearrangement may exhibit a secondary/reactive eosinophilia.
 - Systemic mastocytosis requires the presence of dense infiltrates of morphologically abnormal mast cells that express CD25, elevated serum tryptase, or presence of *KITD816V*.
 - Chronic myelomonocytic leukemia requires monocytes of $>1 \times 10^9/L$ in the peripheral blood.
 - Chronic eosinophilic leukemia, NOS requires eosinophilia ($>1.5 \times 10^9/L$) along with evidence of a myeloid malignancy otherwise not classifiable.

|| Differential Diagnosis (Continued) ||

- **In cases of B- or T-lymphoblastic lymphoma/leukemia or other hematologic malignancy with eosinophilia, what test can evaluate for PDGFRA rearrangement?**
 - A. FISH using a probe for the *CHIC2* gene
 - B. Cytogenetics by karyotype
 - C. RT-PCR targeting the 3' region of *PDGFRA*
 - D. Both A and C

|| Differential Diagnosis (Continued) ||

- **What test can be done to evaluate for PDGFRA rearrangement?**
 - A. FISH for 4q12 deletion
 - B. Cytogenetics by karyotype
 - C. RT-PCR targeting the 3' region of PDGFRA
 - D. Both A and C**

The 800 kb deletion leading to FIP1L1-PDGFRA fusion is not detectable by karyotype, but can be assessed for by FISH for 4q12 deletion (includes the *CHIC2* gene) or RT-PCR. FISH with a break-apart probe that encompasses FIP1L1 and PDGFRA can also be used.

|| Differential Diagnosis (Continued) ||

- **What test should be used to evaluate for FGFR1 and PDGFRB rearrangement in cases of clonal eosinophilia after negative FIP1L1-PDGFRB screening?**
 - A. FISH for FGFR1 rearrangement
 - B. RT-PCR for *ETV6-PDGFRB* fusion gene
 - C. FISH for PDGFRB rearrangement
 - D. Cytogenetics by karyotype
 - E. All of the above

|| Differential Diagnosis (Continued) ||

- **What test should be used to evaluate for FGFR1 and PDGFRB rearrangements in cases of clonal eosinophilia after negative FIP1L1-PDGFRB screening?**
 - A. FISH for FGFR1 rearrangement
 - B. RT-PCR for *ETV6-PDGFRB* fusion gene
 - C. FISH for PDGFRB rearrangement
 - D. Cytogenetics by karyotype**
 - E. All of the above

Karyotype should be done to look for 5q33 and 8p11.2 translocations, which would suggest PDGFRB or FGFR1-rearranged disease, respectively. FISH or RT-PCR is used to confirm the respective involvement of PDGFRB or FGFR1.

|| Differential Diagnosis (Continued) ||

- **What is the most common fusion gene identified in FGFR1-associated myeloid and lymphoid neoplasms?**
 - A. *CEP110-FGFR1*
 - B. *FGFR1OP1-FGFR1*
 - C. *BCR-FGFR1*
 - D. *ZNF198-FGFR1*
 - E. *TRIM24-FGFR1*

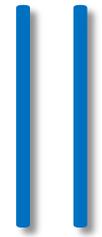
|| Differential Diagnosis (Continued) ||

- **What is the most common fusion gene identified in FGFR1-associated myeloid and lymphoid neoplasms?**
 - A. *CEP110-FGFR1*
 - B. *FGFR1OP1-FGFR1*
 - C. *BCR-FGFR1*
 - D. *ZNF198-FGFR1***
 - E. *TRIM24-FGFR1*

The *ZNF198-FGFR1* fusion gene resulting from the translocation t(8;13)(p11;q12) is present in approximately 50% of cases of myeloid/lymphoid neoplasms with FGFR1 rearrangement.

Companion Case for Chapter 8
PDGFRA/PDGFRB/FGFR1 Myeloid
Neoplasms

*Joseph Clara
and
Eric Padron*



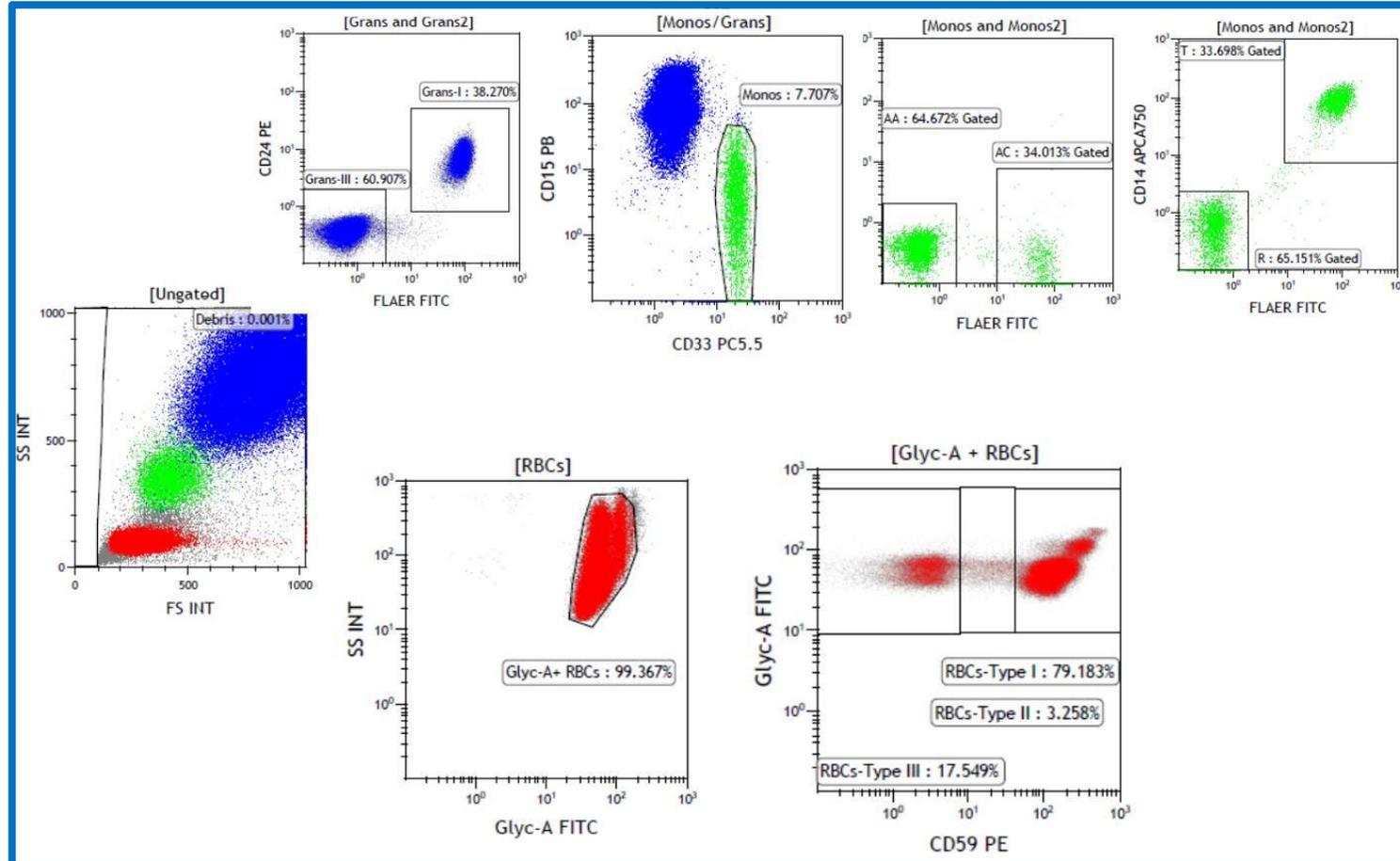
Clinical Case 45



|| Case Presentation

- A 30-year-old female with no significant PMH presents with severe fatigue and jaundice.
- She presented to the hospital and had a CBC performed that revealed a WBC of $12 \times 10^9/L$ with normal differential, hemoglobin of 6.7 g/dL, and platelets of $10^9/k\mu L$.
- Haptoglobin was $<8\text{mg/dL}$ and LDH of 2532 U/L. DAT was negative. She denied any other symptoms; no lymphadenopathy, fevers, chills, or weight loss.
- Her exam revealed scleral icterus and hepatosplenomegaly.
- Bone marrow aspirate and biopsy revealed a normocellular marrow with minimal erythroid dysplasia.

Flow Cytometry Findings



|| Flow Cytometry

- The flow cytometry revealed a distinct CD59 deficient red blood cell population, CD14 deficient monocyte population, and a distinct CD24 deficient and CD15 (+) neutrophil population.
- **Which of the following is the most likely diagnosis?**
 - A. Myelodysplastic syndrome
 - B. Acute myeloid leukemia
 - C. Primary myelofibrosis
 - D. Paroxymal nocturnal hemoglobinuria
 - E. Acute immune hemolytic anemia

|| Flow Cytometry (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Myelodysplastic syndrome
 - B. Acute myeloid leukemia
 - C. Primary myelofibrosis
 - D. Paroxymal nocturnal hemoglobinuria**
 - E. Acute immune hemolytic anemia
- Flow cytometry is characteristic of PNH as clones have been demonstrated in two distinct cell lineages.
- Patient does not have AIHA as her DAT is negative.
- Bone marrow studies are not consistent with MDS, AML, or myelofibrosis.

|| Prognosis



- **Which of the following confers poor prognosis for this patient?**
 - A. Thrombocytopenia at diagnosis
 - B. Absence of smooth muscle dystonia
 - C. PNH clone of monocyte lineage
 - D. Age <55 years at diagnosis
 - E. None of the above

|| Prognosis (Continued) ||

- **Which of the following confers poor prognosis for this patient?**
 - A. Thrombocytopenia at diagnosis**
 - B. Absence of smooth muscle dystonia
 - C. PNH clone of monocyte lineage
 - D. Age <55 years at diagnosis
 - E. None of the above
- This patient has thrombocytopenia at diagnosis, which has been shown to be a poor prognostic factor.
- Absence of smooth muscle dystonia and PNH clone of monocytic lineage have not been shown to be associated with prognosis.
- Age >55 years at diagnosis confers poor prognosis, not <55 years.
- Thrombosis (not listed) is also a poor prognostic factor. Additionally, it is the most common cause of mortality in PNH patients.

|| Diagnosis

- **What is the genetic aberration in paroxysmal nocturnal hemoglobinuria?**
 - A. TP53
 - B. JAK2 V617F
 - C. Monosomy 7
 - D. CALR
 - E. PIG-A

|| Diagnosis (Continued) ||

- **What is the genetic aberration in paroxysmal nocturnal hemoglobinuria?**
 - A. TP53
 - B. JAK2 V617F
 - C. Monosomy 7
 - D. CALR
 - E. PIG-A**
- Paroxysmal nocturnal hemoglobinuria is an acquired clonal disorder as a result of PIG-A mutation. PIG-A encodes for an enzyme essential in the biosynthesis of glycosylphosphatidylinositol (GPI), which is responsible for attachment of different proteins to the cell surface.

|| Treatment



- **What is an indication for allogeneic hematopoietic stem cell transplant referral?**
 - A. Catastrophic venous thromboembolism
 - B. Worsening transfusion requirements
 - C. Evolution to MDS
 - D. Debilitating pain from smooth muscle dystonia
 - E. All of the above

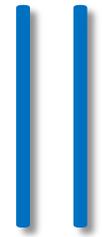
|| Treatment (Continued) ||

- **What is an indication for allogeneic hematopoietic stem cell transplant referral?**
 - A. Catastrophic venous thromboembolism
 - B. Worsening transfusion requirements
 - C. Evolution to MDS**
 - D. Debilitating pain from smooth muscle dystonia
 - E. All of the above
- In cases with evolution to MDS or leukemia, patients are eligible for allogeneic hematopoietic stem cell transplant.
- Another indication would be lack of response to eculizumab.

Companion Case for Chapter 11

Paroxysmal Nocturnal Hemoglobinuria

*Hilda Ding
and
Michael Jaglal*



Clinical Case 46



|| Case Presentation

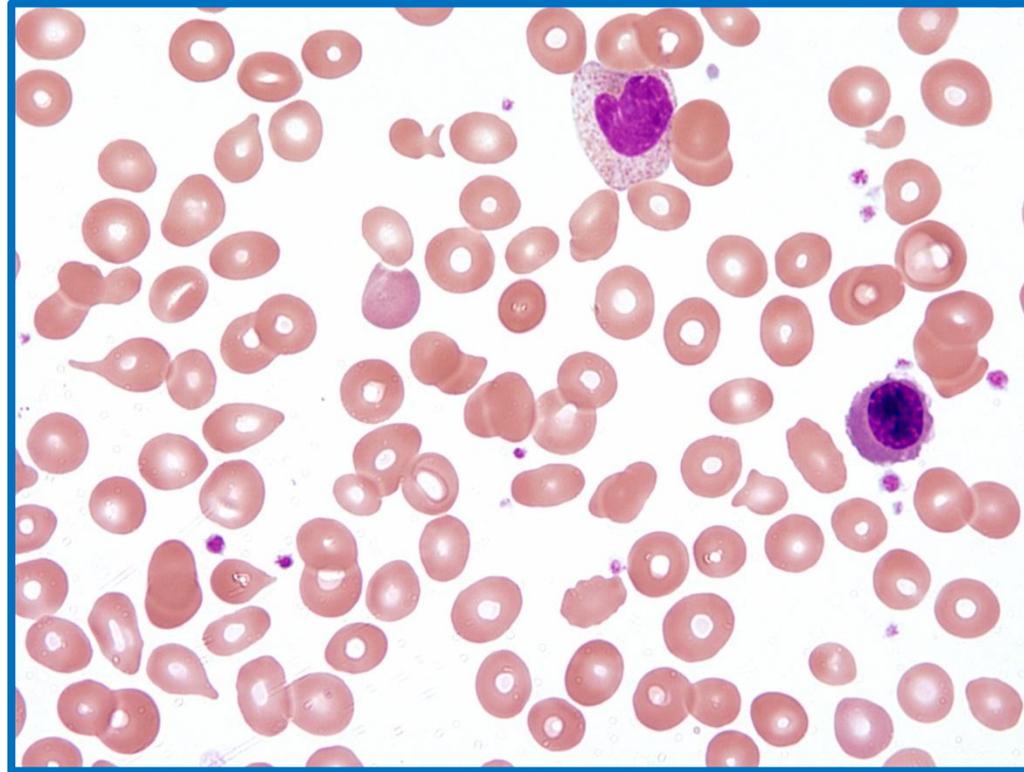
- A 61-year-old female with a history of hypothyroidism presents as a referral from her primary care physician after being found to have a persistent, new leukocytosis (21,000/microliter) in conjunction with mild anemia (9.8 g/dL) and thrombocytopenia (110,000/microliter).
- Symptomatically, the patient has had mild fatigue over the past 2 to 3 months with occasional low-grade fevers and an unintentional weight loss of 10 pounds over the past 6 months.
- Physical exam revealed palpable spleen 6 cm below the left costal margin.
- She undergoes a bone marrow aspiration and biopsy. The results are shown in the next slides.

|| Case Presentation (Continued) ||

The peripheral blood smear reveals a left-shifted leukocytosis with the presence of immature myeloid cells, nucleated erythroid precursors, along with tear-drop-shaped red blood cells.

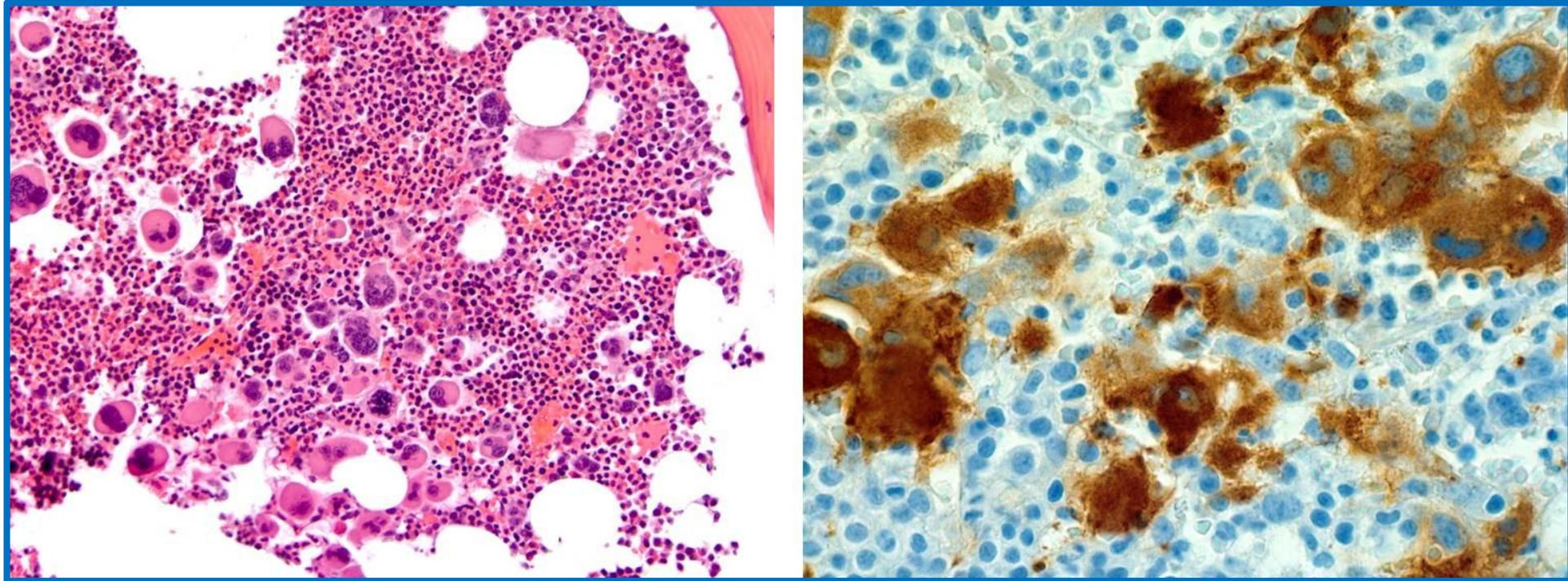
The bone marrow core biopsy shows atypical megakaryocyte hyperplasia with bizarre, cytologically atypical nuclei, with occasional cluster formation. A reticulin stain reveals evidence of moderate fibrosis.

Peripheral Blood Smear



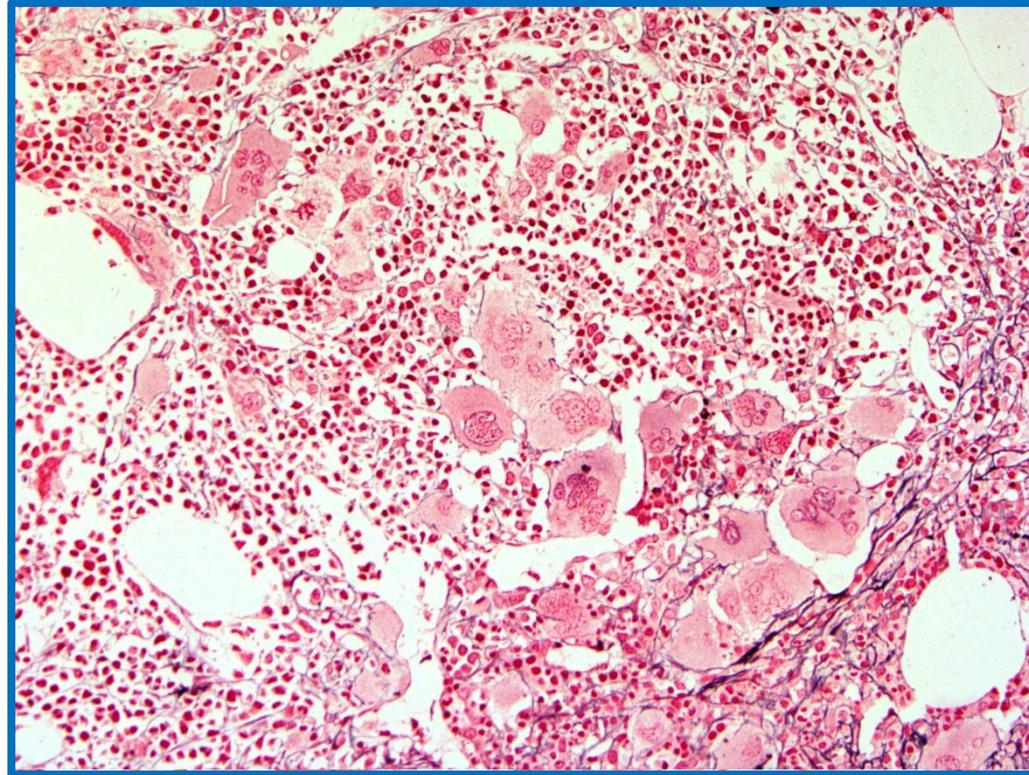
The peripheral blood film shows circulating myeloid and erythroid precursors, namely leukoerythroblastosis, as well as many tear-drop cells (Wright stain, x1000).

|| Bone Marrow Biopsy



The H&E section of bone marrow core biopsy shows hypercellularity associated with markedly atypical megakaryocytic hyperplasia and myeloid predominance. Megakaryocytes are hyperlobated, hyperchromatic, or display disjointed nuclei. Occasional small megakaryocytes are also noted (left, x200). CD61 stain highlights megakaryocytes in clusters including predominantly hyperlobated forms (right, immunoperoxidase x600).

|| Bone Marrow Biopsy (Continued) ||



Reticulin stains show only focally increased reticulin fibers (0 to 1+ out of 3+) (reticulin, x200).

|| Molecular Testing

- Molecular testing revealed *JAK2 V617F* mutation with a mutant allele frequency of 62%. Next generation sequencing demonstrated an *ASXL1* mutation with mutant allele frequency of 43%.
- **What is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia
 - B. Primary myelofibrosis
 - C. Essential thrombocythemia
 - D. Polycythemia vera
 - E. Chronic myelomonocytic leukemia

|| Molecular Testing (Continued) ||

- **What is the most likely diagnosis?**
 - A. Chronic myelogenous leukemia
 - B. Primary myelofibrosis**
 - C. Essential thrombocythemia
 - D. Polycythemia vera
 - E. Chronic myelomonocytic leukemia

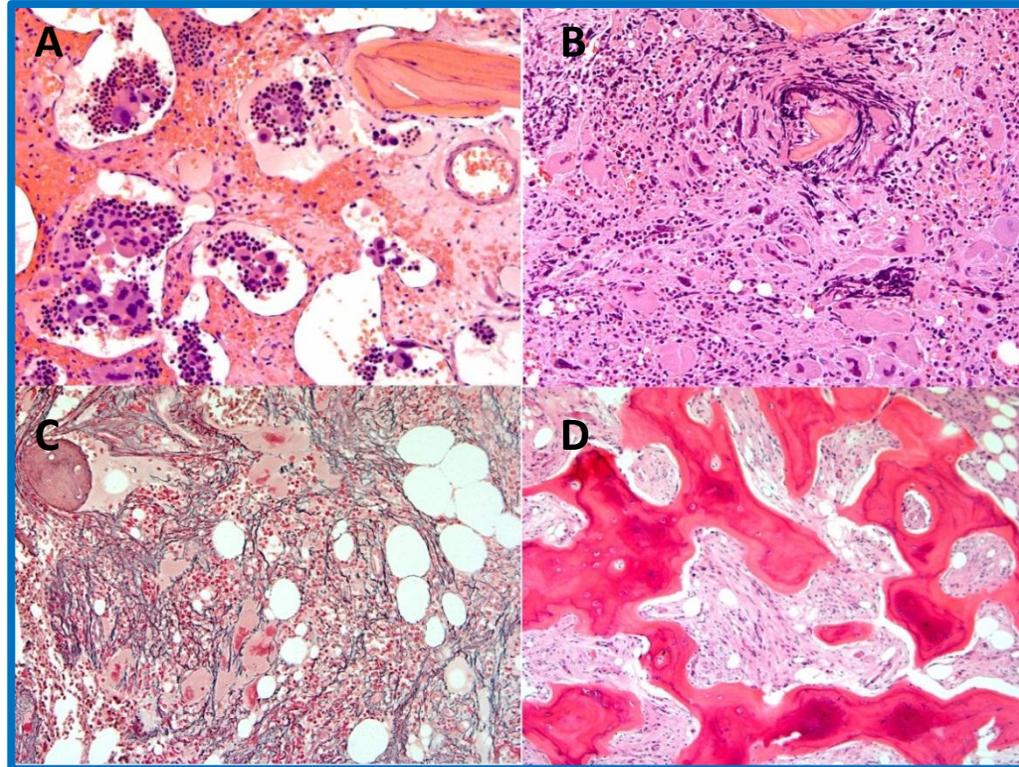
Primary myelofibrosis is a *BCR-ABL1*-negative myeloproliferative neoplasm (MPN) that is often accompanied by splenomegaly, constitutional symptoms, and cytopenias. *JAK2* mutations are often seen. Megakaryocytes in CML are characteristically termed “dwarf megakaryocytes” due to their atypically small size as opposed to the enlarged, bizarre megakaryocytes seen in PMF. ET megakaryocytes are hyperlobated and resemble a “stag-horn.” The overall findings are not compatible with CMML as this patient has no evidence of a persistent absolute monocytosis or myelodysplasia.

|| Case Presentation



- A 34-year-old otherwise healthy young man presents with constitutional symptoms. He is noted to have peripheral blasts of 2%, WBC of 30 k/ μ L, and anemia of 7.2 g/dL. He undergoes a bone marrow aspiration and biopsy and the results are consistent with the fibrotic phase of PMF.

|| Fibrotic Phase of PMF ||



The bone marrow core biopsy shows significantly dilated sinusoidal spaces containing trilineage hematopoietic elements, called intrasinusoidal hematopoiesis (A, H&E, x200), which is seen in conjunction with syncytial clustering, spindly megakaryocytes (B, H&E, x200) in the fibrotic stage of PMF. The patient also has severe reticulin fibrosis (3+) (C, reticulin stain, x200) and osterosclerosis (D, H&E, x100), which are also characteristic findings in the fibrotic phase PMF.

|| Fibrotic Phase of PMF (Continued) ||

- **What would be the most reasonable treatment recommendation?**
 - A. Ruxolitinib
 - B. Hydroxyurea
 - C. Erythropoietin
 - D. Allogeneic hematopoietic cell transplant
 - E. Thalidomide/Prednisone

|| Fibrotic Phase of PMF (Continued) ||

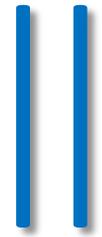
- **What would be the most reasonable treatment recommendation?**
 - A. Ruxolitinib
 - B. Hydroxyurea
 - C. Erythropoietin
 - D. Allogeneic hematopoietic cell transplant**
 - E. Thalidomide/Prednisone

Allogeneic hematopoietic cell transplant is the only curative treatment in primary myelofibrosis. Referral is made at initial diagnosis in patients who have high-risk disease and are potential transplant candidates. Patient is high risk by DIPSS (5 points, see Chapter 4).

Companion Case for Chapter 4

Primary Myelofibrosis

*Andrew Kuykendall
and
Kenneth Zuckerman*



Clinical Case 47



|| Case Presentation

A 56-year-old male with PMH of hypertension presents with fever of 10 days (Tmax 39.8°C), progressive fatigue, weight loss, and bruising.

He presented to the hospital and a CBC revealed a WBC of 2.6 k/ μ L with ANC 500 cells/ μ L, hemoglobin of 9.5 g/dL with MCV of 85 fL, and platelets of 32 k/ μ L.

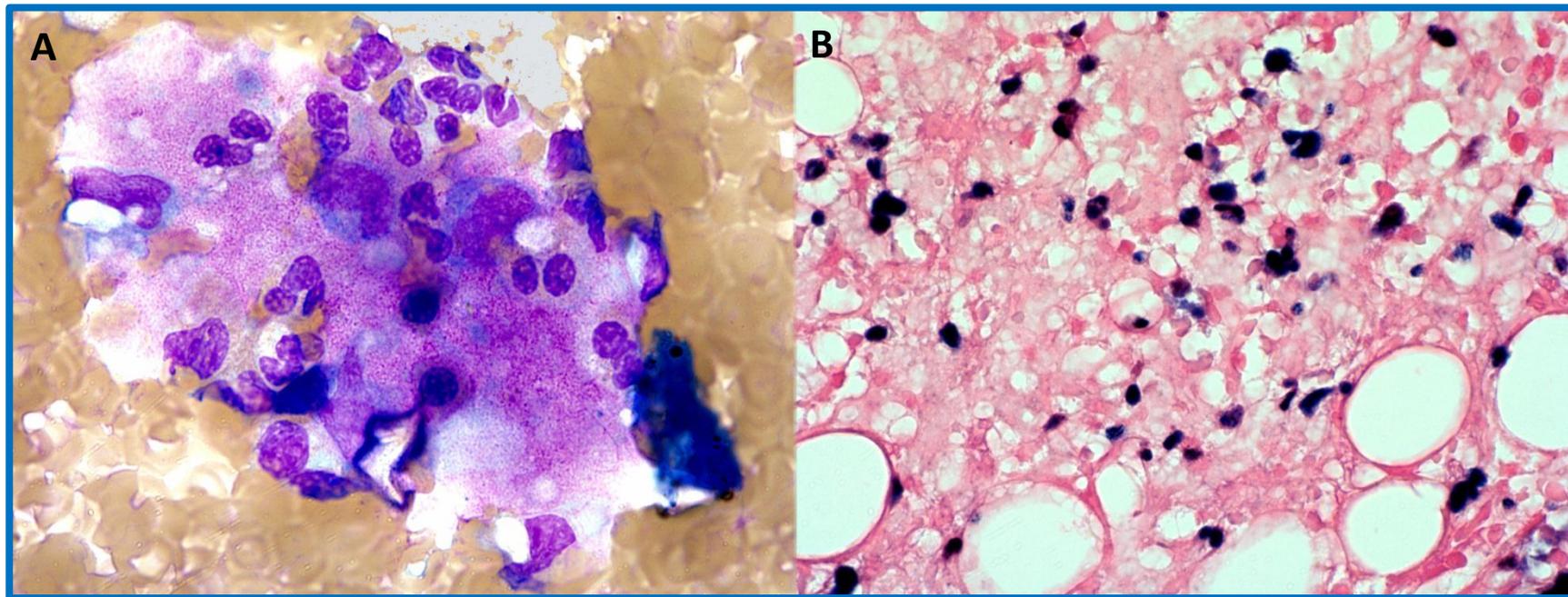
Vital signs revealed T 40.0°C, HR 102 beats/min, BP 135/98 mmHg, RR 18/min, SaO₂ 97% on room air.

His exam reveals bruising of bilateral lower extremities, diffuse lymphadenopathy, hepatosplenomegaly with a palpable liver 4 cm and spleen 2 cm below the costal margin.

A bone marrow biopsy was performed, and the histologic findings are presented on the next slide.

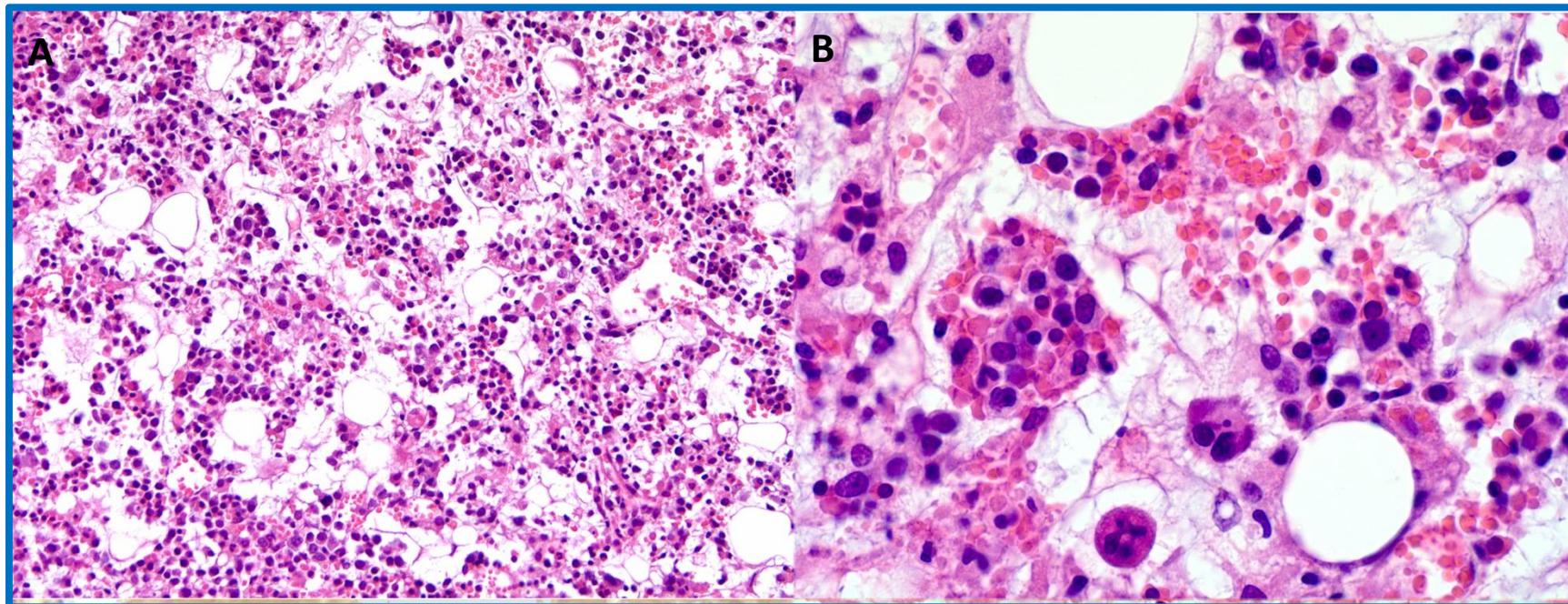
|| Bone Marrow Aspirate ||

- The bone marrow aspirate showed numerous giant histocytes distended with various hematopoietic elements (A, Wright-Giensa, x1000 total magnification). A Prussian blue stain showed iron deposits obscuring the nucleus (B, Prussian blue, x1000).



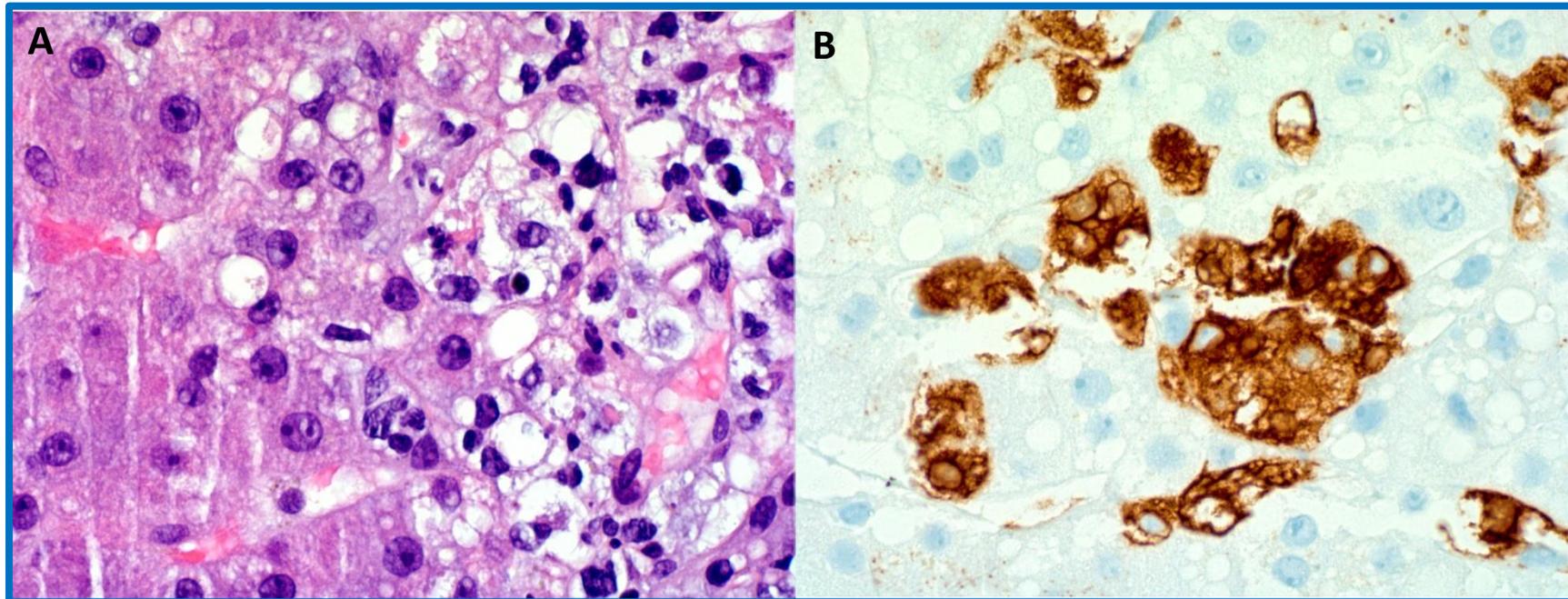
|| Bone Marrow Core

- The sections of bone marrow core biopsy demonstrated numerous enlarged histiocytes with hemophagocytosis (engulfing nRBCs, lymphocytes, myeloid precursors, and platelets into the cytoplasm) that resulted in reduced normal hematopoiesis and profound peripheral cytopenia (A and B, H&E, x200 and x600, respectively).



|| Liver Biopsy

- A liver biopsy demonstrated an aggregate of histocytes with the same phenomenon (A, H&E, x600) highlighted by the histiocytic marker CD68 (B, Immunoperoxidase, x600).



|| Additional Workup

- Additional laboratory workup revealed:

AST 1276 U/L, ALT 2541 U/L, ferritin 2310 ng/mL, d-dimer 1560 ng/mL, fibrinogen 95 mg/dL, PT 12.6 sec, PTT 34 sec, fasting triglycerides 4.1 mmol/L, EBV EA-IgG negative, EBV VCA IgM negative, EBV NA-IgG positive, EBV VCA IgG positive, elevated sIL-2R. A lymph node biopsy revealed a T-cell lymphoproliferative disorder.

- **Which of the following is the most likely diagnosis?**
 - A. Active EBV infection
 - B. Hemophagocytic lymphohistiocytosis
 - C. Sepsis/SIRS
 - D. Disseminated intravascular coagulation

|| Diagnosis



- **Which of the following is the most likely diagnosis?**
 - A. Active EBV infection
 - B. Hemophagocytic lymphohistiocytosis**
 - C. Sepsis/SIRS
 - D. Disseminated intravascular coagulation
- This patient presents with pancytopenia and meets multiple laboratory criteria for the diagnosis of HLH. The bone marrow and liver biopsies show characteristic histopathologic features indicative of HLH. The underlying etiology is likely the newly diagnosed T-cell lymphoproliferative disorder.
- The EBV panel is reflective of previous exposure, not active infection. The patient's vital signs are also not consistent with sepsis/SIRS. Normal PT and PTT, clinical and histologic features are not compatible with DIC.

|| Diagnosis (Continued) ||

- **Which of the following are causes of acquired HLH?**
 - A. Infection
 - B. Malignancy
 - C. Autoimmunity
 - D. Posthematopoietic stem cell transplantation
 - E. All of the above

|| Diagnosis (Continued) ||

- **Which of the following are causes of acquired HLH?**

- A. Infection
- B. Malignancy
- C. Autoimmunity
- D. Posthematopoietic stem cell transplantation
- E. All of the above**

- All of the above are known triggers of aHLH with infection, malignancy, and autoimmunity more common than in the post-HSCT setting.
- EBV, HIV, and CMV are common viral triggers. *Mycobacterium tuberculosis* and *rickettsia spp.* are reported as the most common bacterial etiologies, while *leishmania* was the most common parasitic infection, and *histoplasma* the most common fungal cause.

|| Treatment



- **Therapy for HLH is aimed to target which of the following?**
 - A. B-lymphocytes
 - B. Natural killer cells
 - C. Neutrophils
 - D. Augment the function of cytokines

|| Treatment (Continued) ||

- **Therapy for HLH is aimed to target which of the following?**
 - A. B-lymphocytes
 - B. Natural killer cells**
 - C. Neutrophils
 - D. Augment the function of cytokines

Therapy is targeted to cytotoxic T-lymphocytes, natural killer cells, macrophages, and the suppression of cytokines, which all seek to ameliorate the excessive activation of immune cells.

|| Treatment (Continued) ||

- **Which of the below confers worse prognosis for this patient?**
 - A. Splenomegaly on presentation
 - B. Male gender
 - C. Fever more than 3 days
 - D. Platelet count of less than 40 k/ μ L
 - E. All of the above

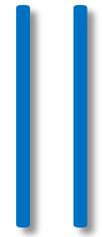
|| Prognosis

- **Which of the below confers worse prognosis for this patient?**
 - A. Splenomegaly on presentation
 - B. Male gender
 - C. Fever more than 3 days
 - D. Platelet count of less than 40 k/ μ L
 - E. All of the above**
- Increasing age, male gender, thrombocytopenia (<40 k/ μ L), presentation with splenomegaly, active EBV infection, DIC, fever not subsiding within 3 days of diagnosis, ferritin >50,000 ng/mL, hypoalbuminemia, and lack of etoposide during management have all been reported to be associated with worse prognosis.
- Malignancy-associated HLH has been shown to have worse clinical outcomes.

Companion Case for Chapter 49

Hemophagocytic Lymphohistiocytosis

*Hilda Ding
and
Lubomir Sokol*



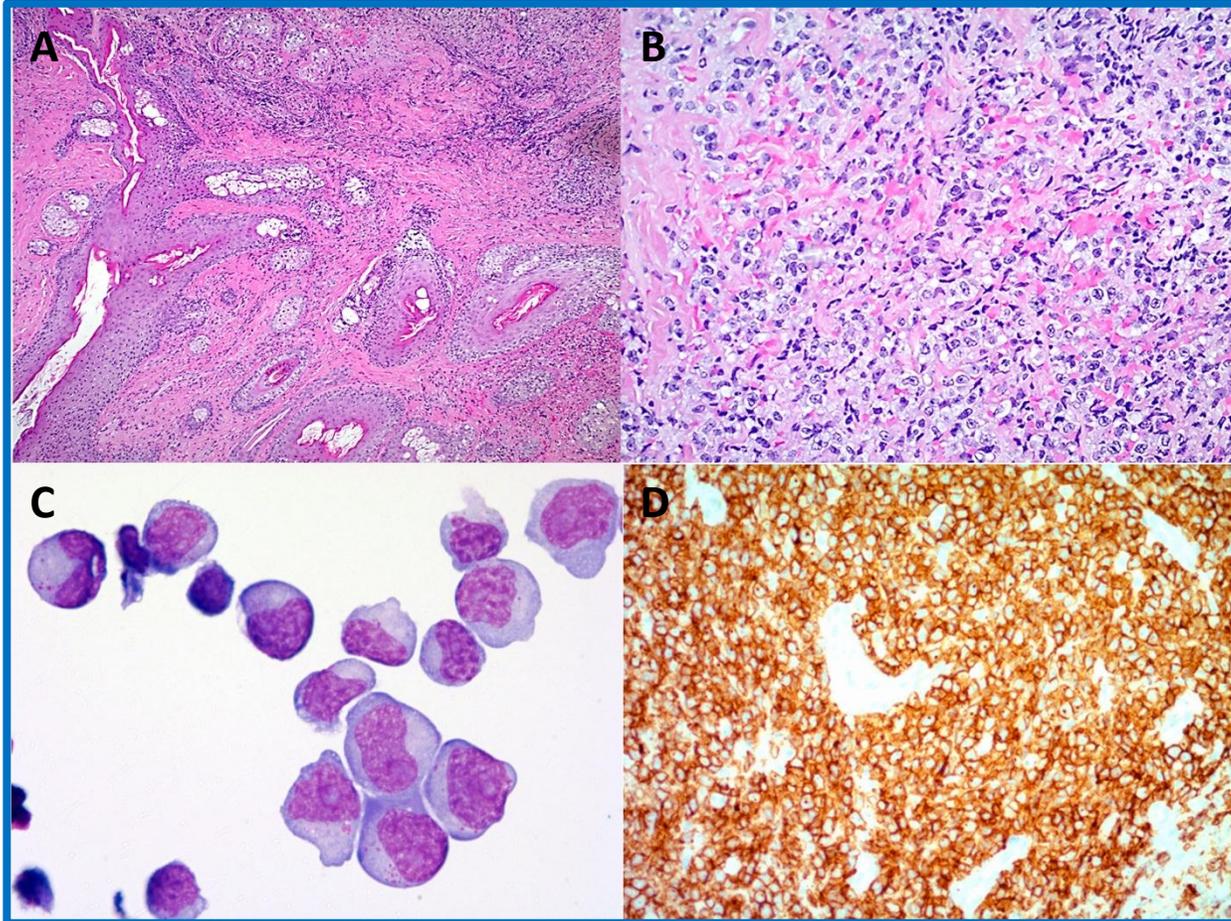
Clinical Case 48



|| Case Presentation

- A 50-year-old male with no significant PMH presents with a “pimple” like lesion on his left ear lobe that has been increasing in size and causing swelling of his ear. He also endorses weight loss of 20 pounds over 3 months. A CBC revealed a WBC of 7.9, Hgb of 13.5, and platelets of 387. His exam reveals edema of the left side of the face, and large eschar behind the left ear and inside the ear canal, and enlarged cervical lymph nodes. PET/CT showed extensive areas of soft tissue swelling and hypermetabolism throughout the left side of the head, face, and neck. There were enlarged level II cervical lymph nodes. There was normal metabolism in the chest, abdomen, and pelvis with no adenopathy. However, there were numerous sites of hypodense areas in the musculature throughout the chest, abdomen, pelvis, and proximal thighs that were associated with glucose hypermetabolism.

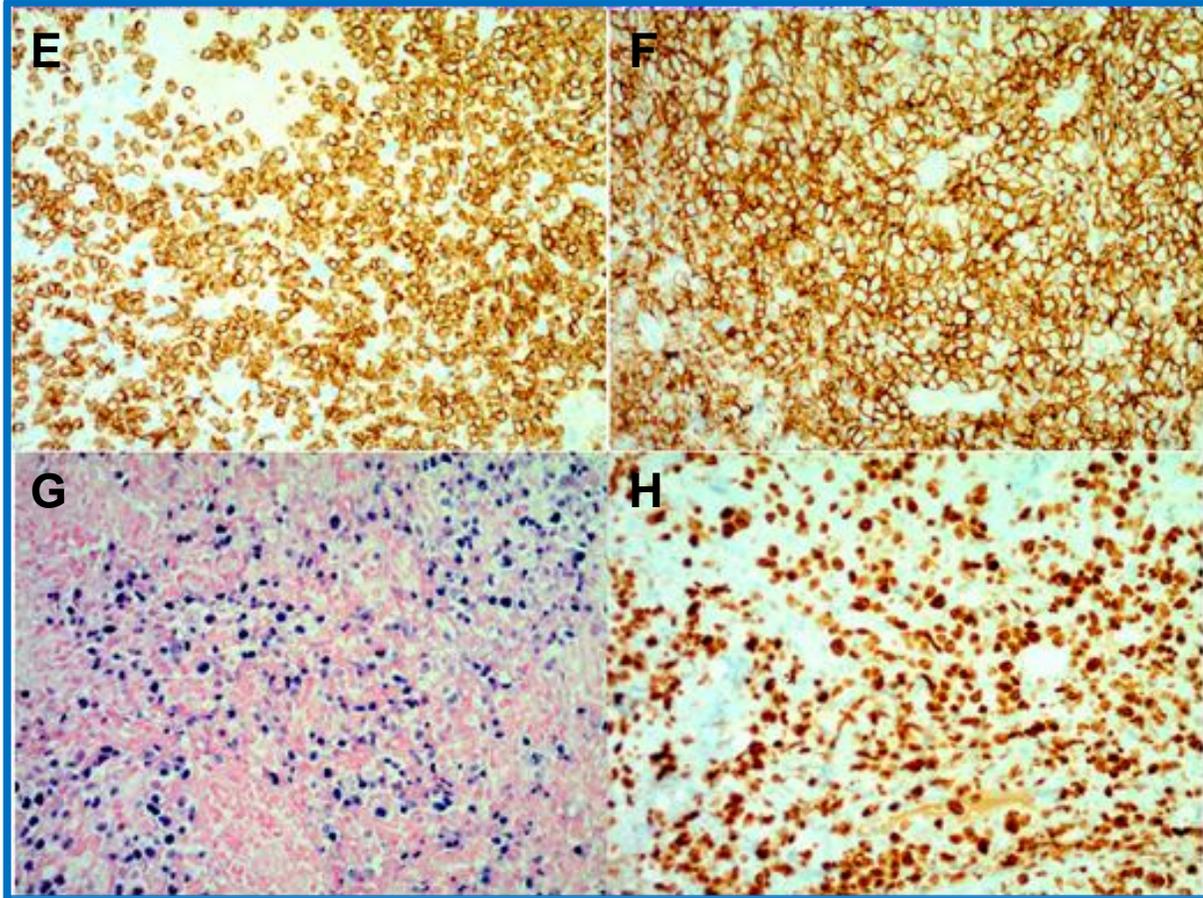
Case Presentation (Continued)



Left ear cartilage biopsy:

The H&E sections showed a low power view of intact squamous mucosa with submucosal atypical cell infiltrate (A, H&E, x40). The atypical cells were medium to large in size with disperse to vesicular chromatin, irregular nuclear border, and a certain amount of clear cytoplasm associated with hyaline fibrotic bands (B, H&E, x100). Touch imprint demonstrated large atypical lymphoid cells with irregular nuclei, prominent nucleoli, and cytoplasmic reddish granules (C, Wright-Giemsa, x1000). Immunohistochemical stain was positive for CD2 (D, immunoperoxidase, x200).

Case Presentation (Continued)



- Immunohistochemical stains also revealed these atypical cells to be positive for cytoplasmic CD3 ϵ and CD56 (E and F, respectively; x200) as well as in situ hybridization showed the neoplastic NK cells positive for EBV (G, ISH, x200). The proliferation index by Ki-67 was high, up to 80% to 90% (H, x200). Atypical cells were also positive for CD2, TIA1, granzyme B1 and negative for CD4, CD5, CD8, TCR δ , and TCR β F1 (not shown).

Flow Cytometry of the Left Ear Biopsy

- The flow cytometry revealed: CD45 (+), CD3(cytoplasmic) (+), CD2 (+), CD56 (+) and CD30 (+, weak/partial), CD4 (-), CD8 (-), CD7 (-), CD5 (-), CD10 (-), CD20 (-). Ki-67 index was 80% to 90%. In addition, EBV was positive by EBER. T-cell receptor gene rearrangement studies were negative.
- **Which of the following is the most likely diagnosis?**
 - A. Primary cutaneous $\gamma\delta$ TCL
 - B. Peripheral T-cell lymphoma, not otherwise specified
 - C. Lymphomatoid granulomatosis
 - D. Extranodal NK/T-cell lymphoma, nasal type
 - E. Monomorphic enteropathy-associated T-cell lymphoma

Flow Cytometry of the Left Ear Biopsy (Continued)

- **Which of the following is the most likely diagnosis?**
 - A. Primary cutaneous $\gamma\delta$ T-cell lymphoma
 - B. Peripheral T-cell lymphoma, not otherwise specified
 - C. Lymphomatoid granulomatosis
 - D. Extranodal NK/T-cell lymphoma, nasal type**
 - E. Monomorphic enteropathy-associated T-cell lymphoma
- The phenotype (CD56[+], cytoplasmic CD3[+], EBV[+] by EBER) and germline configuration of the T-cell receptor are characteristic of ENKTL.

|| Differential Diagnosis

- Primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) presents with skin lesions that are positive for CD56 and cytotoxic markers.
- Lymphomatous granulomatosis (LYG) can present with dermal papules or subcutaneous nodules with an angiocentric and angiodestructive infiltrate of CD4+ T-cells.
- In LYG, EBV-positive B-cells are admixed with a prominent background of CD3+ T-cells.
- Enteropathy-associated T-cell lymphoma (EATL) may spread to the skin, and a monomorphic variant expresses CD56, and can be EBV positive.

|| Differential Diagnosis (Continued) ||

- **What is one of the diagnostic features of primary cutaneous $\gamma\delta$ TCL that distinguishes it from ENKTL?**
 - A. Cytotoxic protein expression
 - B. CD56-
 - C. EBV-
 - D. CD3+
 - E. CD2+

|| Differential Diagnosis (Continued) ||

- **What is one of the diagnostic features of primary cutaneous $\gamma\delta$ TCL that distinguishes it from ENKTL?**
 - A. Cytotoxic protein expression
 - B. CD56-
 - C. EBV-**
 - D. CD3+
 - E. CD2+
- PCGD-TCL expresses CD56 and cytotoxic proteins, but is negative for EBV. The cells are also strongly positive for TCR δ .

|| Differential Diagnosis (Continued) ||

- **EBV positivity is seen in cells of which lineage in lymphomatous granulomatosis, which help differentiate it from ENKTL?**
 - A. B cell
 - B. T cell
 - C. NK cell
 - D. Plasmacytoid dendritic cell

|| Differential Diagnosis (Continued) ||

- **EBV positivity is seen in cells of which lineage in lymphomatoid granulomatosis, which help differentiate it from ENKTL?**
 - A. B cell
 - B. T cell
 - C. NK cell
 - D. Plasmacytoid dendritic cell
- Although a marked T-cell infiltrate is seen in LYG, the EBV-positive cells are actually of B-cell origin.

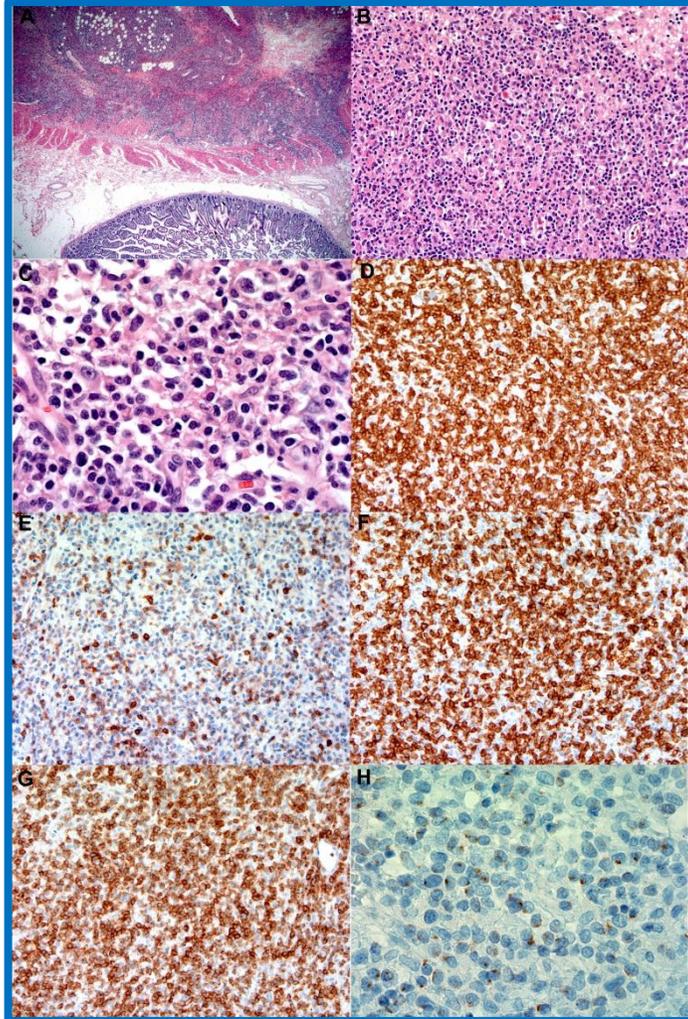
|| Differential Diagnosis (Continued) ||

- **ENKTL typically lacks the expression of which surface marker, which helps distinguish it from monomorphic enteropathy-associated T-cell lymphoma?**
 - A. CD4
 - B. CD8
 - C. Surface CD3
 - D. CD56
 - E. CD5

|| Differential Diagnosis (Continued) ||

- **ENKTL typically lacks the expression of which surface marker, which helps distinguish it from monomorphic enteropathy-associated T-cell lymphoma?**
 - A. CD4
 - B. CD8**
 - C. Surface CD3
 - D. CD56
 - E. CD5
- Monomorphic EATL expresses CD56 and can be EBV positive, but expresses CD8 (>80%) whereas ENKTL is CD8-.

|| Differential Diagnosis (Continued) ||



- **Monomorphic EATL:** The section of small bowel shows intact mucosa surface with diffuse atypical lymphoid infiltrate throughout the whole thickness of the bowel wall but devoid of mucosa (A, H&E, x40). Atypical cells consist of medium-sized lymphoid cells with dispersed to vesicular chromatin, irregular nuclear border, and an abundant eosinophilic cytoplasm associated with few immunoblasts, increased vasculatures, and histiocytes in the background (B and C, H&E, x200 and x600, respectively). A battery of immunohistochemical staining highlights the neoplastic lymphoid cells are CD3+, CD5 (-), CD8 (+), CD56 (+) and TIA (+) (D through H, immunoperoxidase, x200, respectively)

|| Differential Diagnosis (Continued) ||

- **What is the diagnostic classification of apparent ENKTL cases that are EBV+ but negative for CD56 and cytotoxic molecules?**
 - A. Angioimmunoblastic T-cell lymphoma
 - B. Aggressive NK-cell leukemia
 - C. Peripheral T-cell lymphoma, not otherwise specified
 - D. Primary cutaneous $\gamma\delta$ T-cell lymphoma
 - E. Subcutaneous panniculitis-like T-cell lymphoma

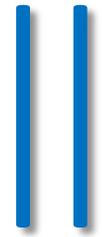
|| Differential Diagnosis (Continued) ||

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 - B. Aggressive NK-cell leukemia
 - C. Peripheral T-cell lymphoma, not otherwise specified**
 - D. Primary cutaneous $\gamma\delta$ T-cell lymphoma
 - E. Subcutaneous panniculitis-like T-cell lymphoma
- If CD56 is negative, both cytotoxic molecules and EBER should be positive for the diagnosis of ENKTL. Otherwise, it is classified as PTCL-NOS.

Companion Case for Chapter 45

Extranodal Natural Killer/T-Cell Lymphoma

*Joseph Clara
and
Lubomir Sokol*



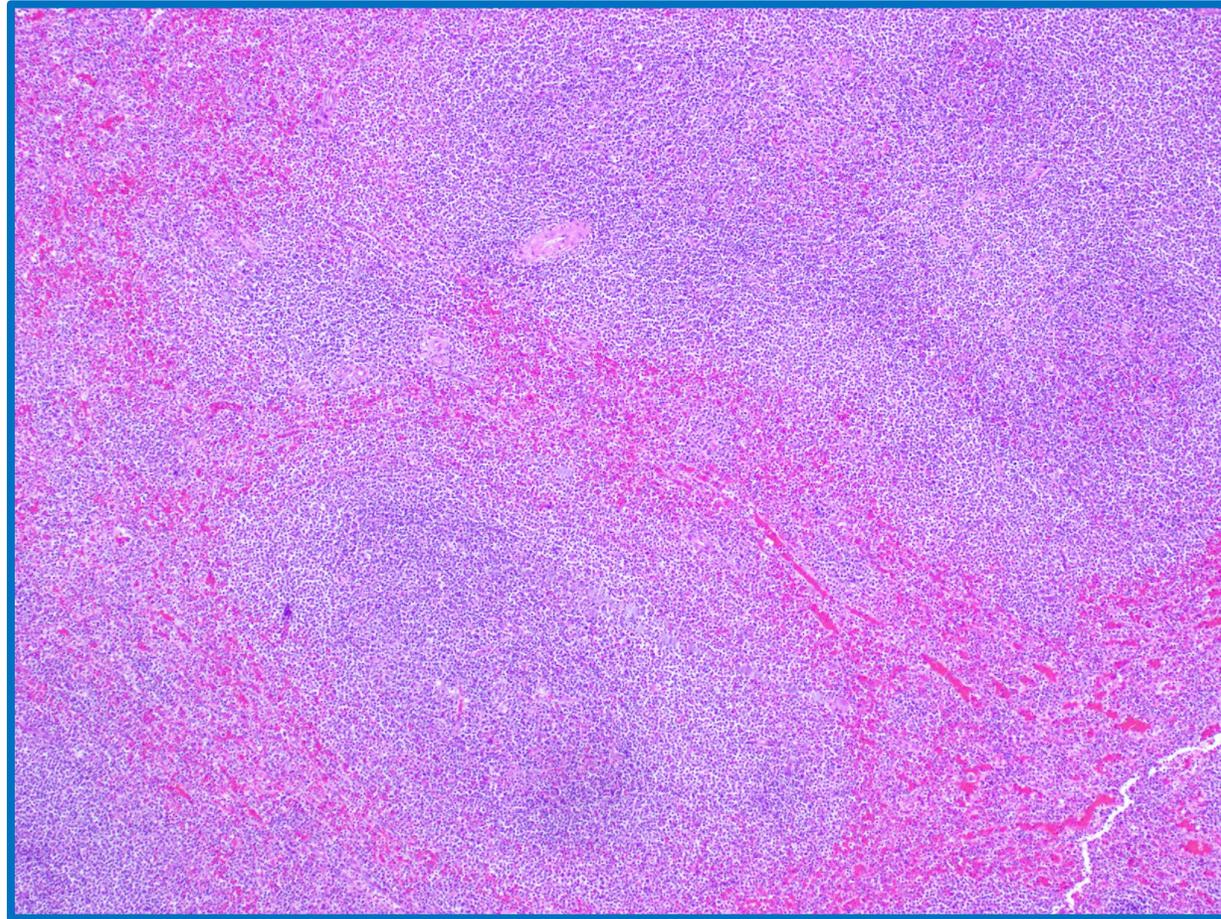
Clinical Case 49



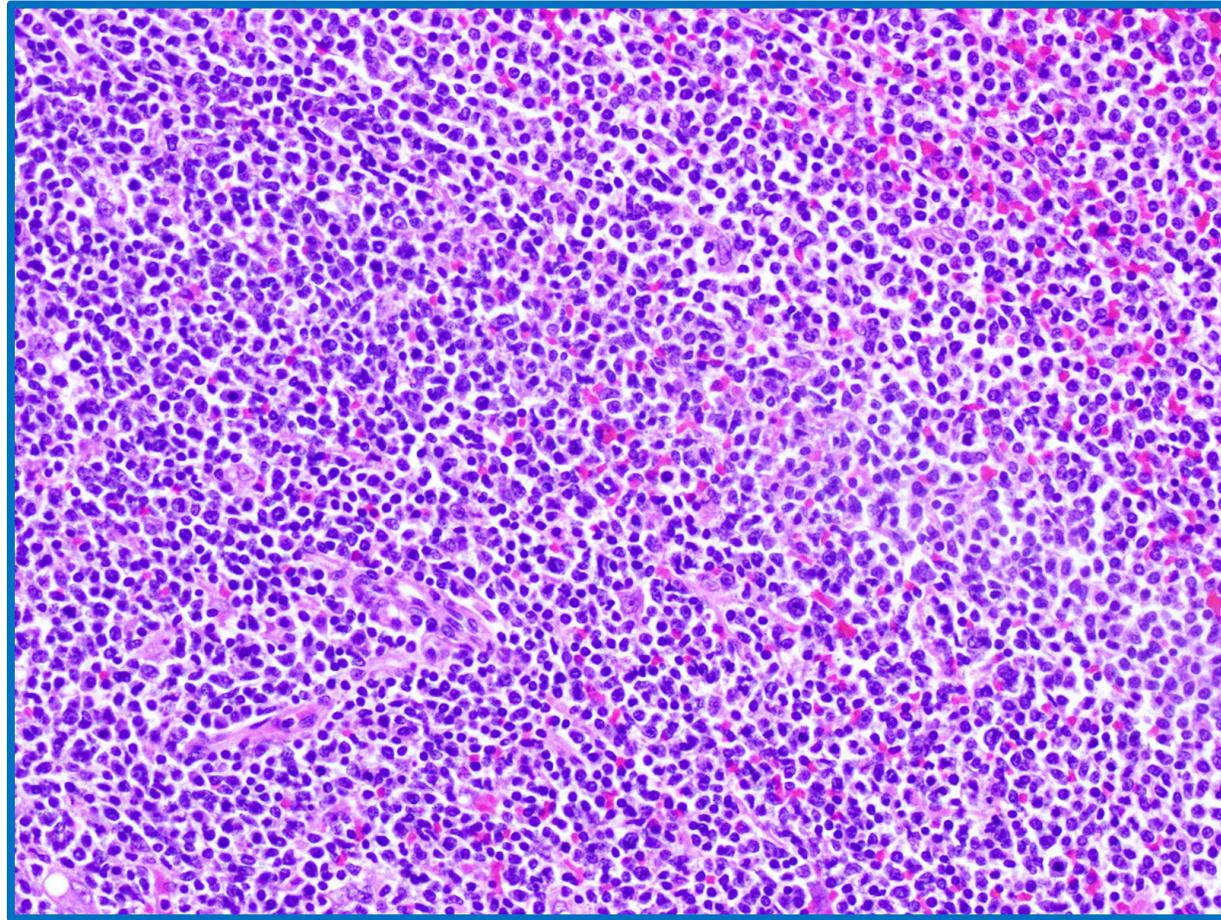
|| Case Presentation

- A 63-year-old male with PMH of Parkinson's disease presents with fatigue, abdominal discomfort, and early satiety. A CBC revealed a WBC of 6.3 k/ μ L with 82% lymphocytes, hemoglobin of 8.4 g/dL, and platelet count of 144 k/ μ L. The reticulocytes and LDH were high, and the haptoglobin was low. He did not have lymphadenopathy, fevers or chills, but had lost weight. His exam reveals splenomegaly with a palpable spleen 5 cm below the costal margin.

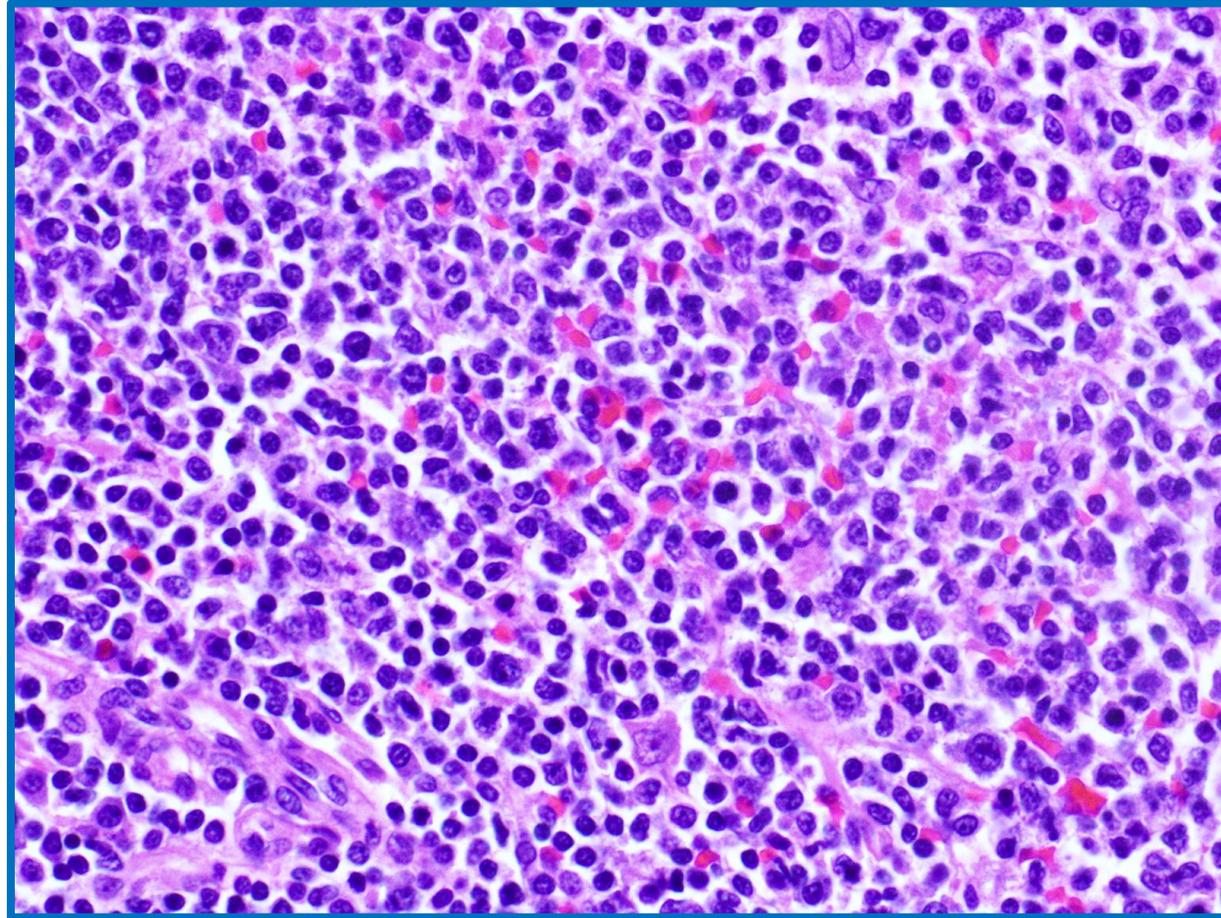
|| Splenic Biopsy



|| Splenic Biopsy (Continued) ||



|| Splenic Biopsy (Continued) ||



|| Splenic Biopsy (Continued) ||

A splenic biopsy shows marked expansion of the white pulp by an atypical lymphoid infiltrate composed of small- to medium-sized lymphocytes with condensed chromatin, indistinct nucleoli, and variable amounts of pale cytoplasm. Mitotic figures are rare.

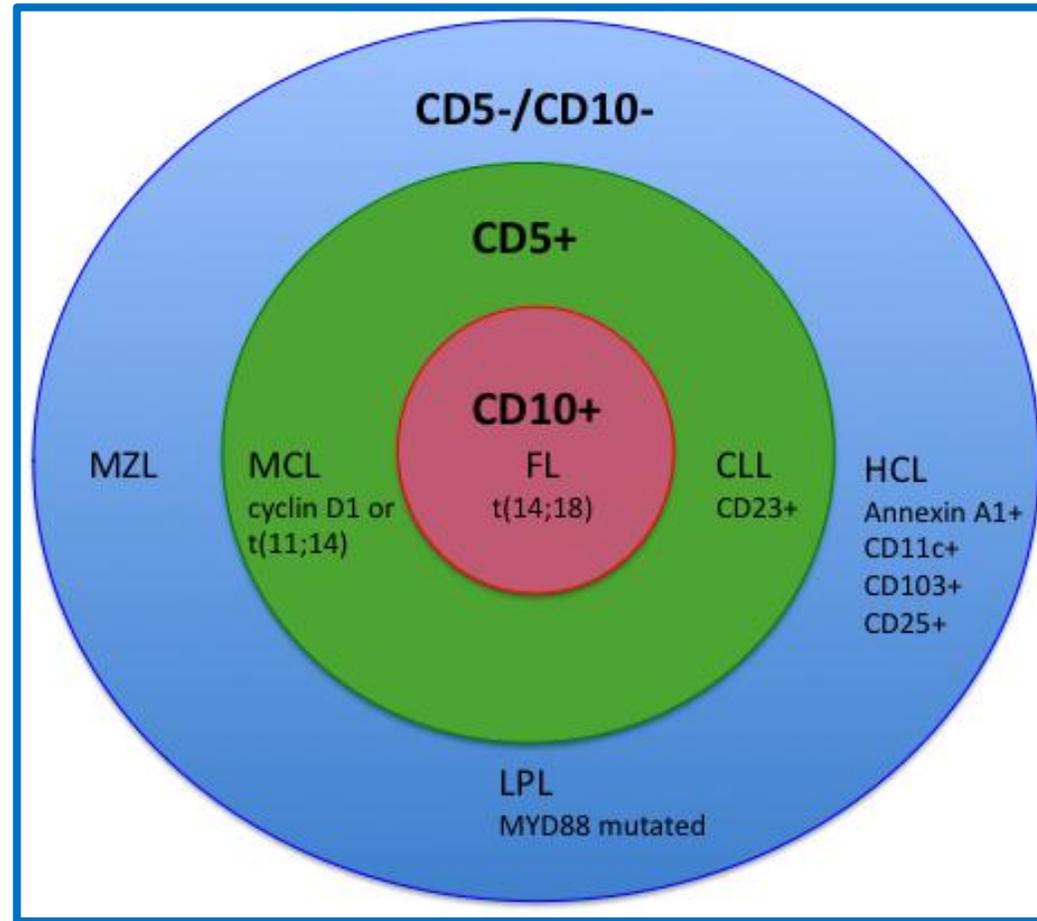
|| Flow Cytometry

- Flow cytometry revealed: CD20(+), CD10(-), CD5(-), CD23(-), CD103(-), moderate surface lambda light chain (+), surface kappa light chain(-).
- **Which of the following is the most likely diagnosis?**
 - A. Mantle cell lymphoma
 - B. Small lymphocytic lymphoma
 - C. Hairy cell leukemia
 - D. Follicular lymphoma
 - E. Splenic marginal zone lymphoma

|| Flow Cytometry (Continued) ||

- **Which of the following is the most likely diagnosis?**
 - A. Mantle cell lymphoma
 - B. Small lymphocytic lymphoma
 - C. Hairy cell leukemia
 - D. Follicular lymphoma
 - E. Splenic marginal zone lymphoma**
- The histologic and phenotypic findings (CD5-, CD10-, CD23-) are compatible with splenic marginal zone lymphoma. The vast majority of cases of mantle cell lymphoma express CD5, and lack CD10 and CD23. Nearly all are cyclin D1 (BCL-1) positive with the characteristic translocation $t(11;14)(q13;q32)IgH-CCND1$ by FISH analysis. CLL/SLL typically expresses CD5, CD23, dim CD20, but is negative for CD10. Hairy cell leukemia, in addition to characteristic morphologic findings, will express CD11c, CD25, and CD103. It has been shown that the majority of cases of HCL are associated with the *BRAF* V600E mutation. Follicular lymphoma derives from germinal center B-cells, and thus, CD10 is typically positive, while CD5 should be negative. See next slide for figure highlighting differences by immunophenotype.

|| Flow Cytometry (Continued) ||



|| Differential Diagnosis

- **An important differential diagnosis of MZL is lymphoplasmacytic lymphoma (LPL) as they share a common immunophenotype. Mutation of which gene is associated with the majority of cases of LPL and is negative in MZL?**
 - A. *TP53*
 - B. *NOTCH1*
 - C. *ATM*
 - D. *MYD88*
 - E. *SF3B1*

|| Differential Diagnosis (Continued) ||

- **An important differential diagnosis of MZL is lymphoplasmacytic lymphoma (LPL) as they share a common immunophenotype. Mutation of which gene is associated with the majority of cases of LPL and is negative in MZL?**
 - A. *TP53*
 - B. *NOTCH1*
 - C. *ATM*
 - D. *MYD88***
 - E. *SF3B1*

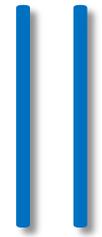
|| Differential Diagnosis (Continued) ||

- LPL is also CD5 and CD10 negative as in MZL; the *MYD88* mutation helps to diagnose LPL as it is present in 91% of cases and very rare in MZL (*NEJM* 2012, 367:826-33).
- HCL is also CD5 and CD10 negative; Annexin A1, CD11c, CD25, and CD103 coexpression suggests HCL.

Companion Case for Chapter 41

Marginal Zone Lymphoma

*Nishan Tchekmedyian,
Danny Nguyen,
and
Celeste Bello*



Clinical Case 50



|| Case Presentation

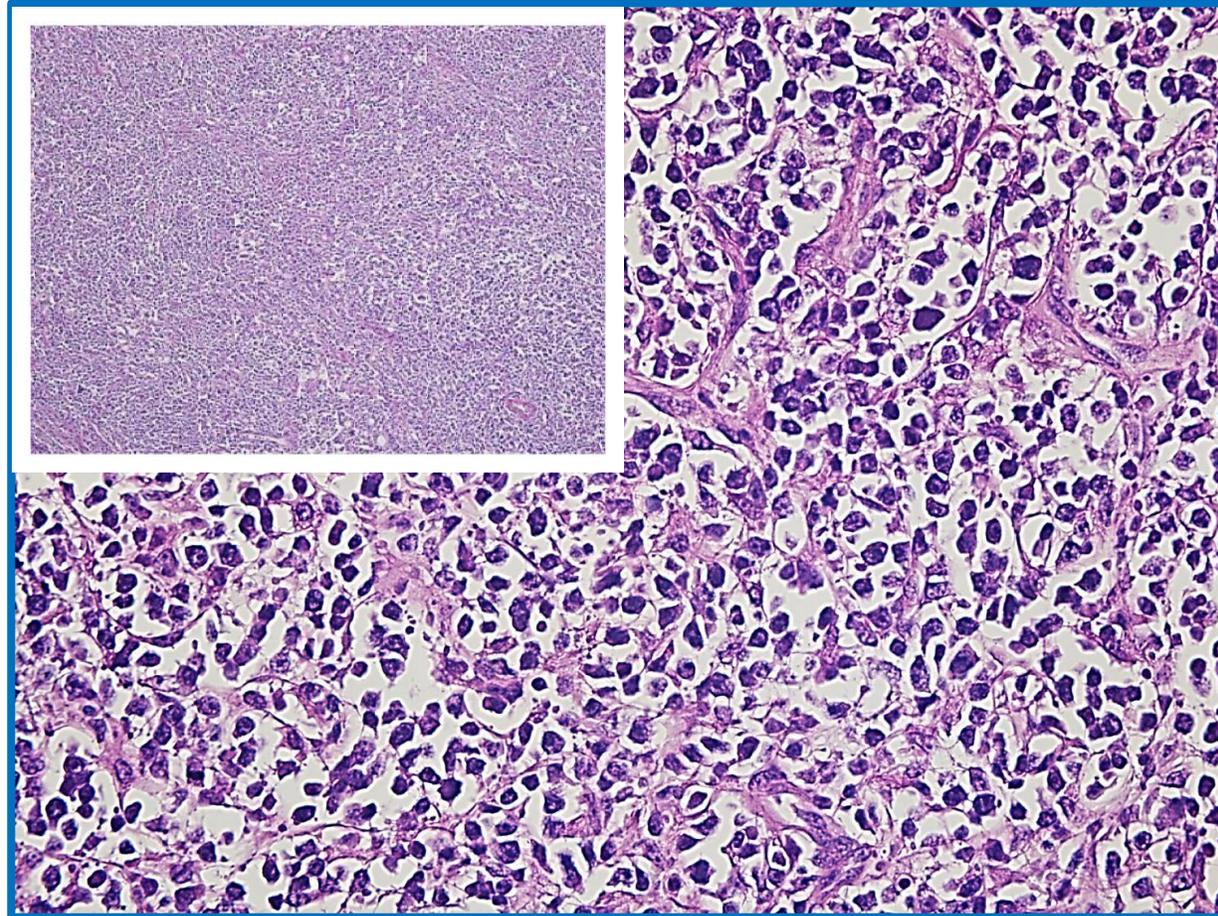


A 45-year-old man presents with a progressively increasing left thigh mass for the past 6 weeks. He complains of night sweats, chills, reduced appetite, and weight loss. He has otherwise been healthy prior to this episode and works in construction. On physical exam, he had a palpable, hard, fixed erythematous 10 x 13 cm left thigh mass. No palpable lymph nodes or hepatosplenomegaly were noted.

CBC: WBC 7.85 k/uL (neutrophils: 56%, lymphocytes: 37%, monocytes: 5%, eosinophils: 2%), Hgb 11.7 g/dL, MCV 84.1 fL, RDW 15.2%, platelets 178 k/ μ L

LDH: 678 U/L

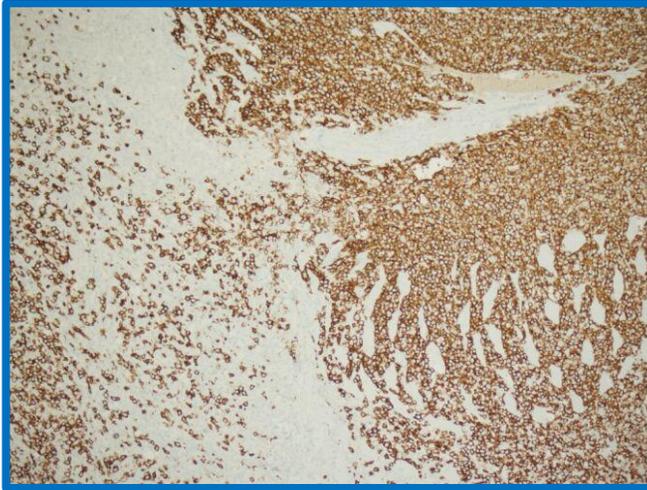
|| Biopsy of the Mass



|| Immunohistochemistry



BCL2



CD20



CD45

|| Pathology

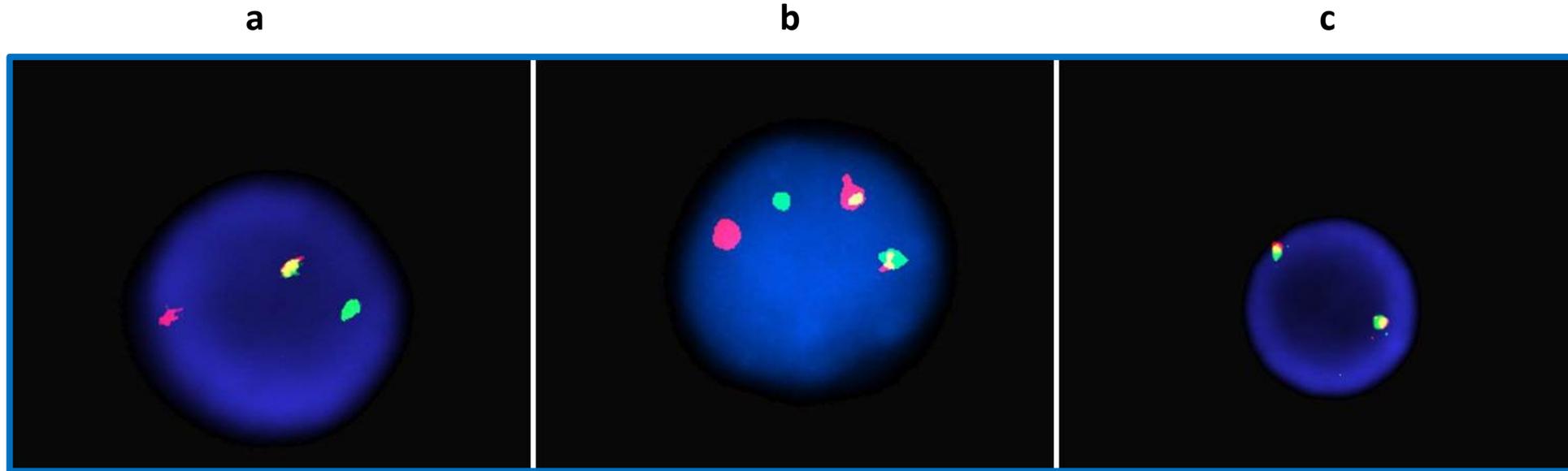


Diffuse atypical lymphoid proliferation with extensive intramuscular infiltration. Cytologically, these atypical cells are medium to large in size, and most with centrally-located nucleoli. Frequent mitoses are seen. A proliferative index by Ki-67 shows 80% positivity. These atypical cells are diffusely positive for CD45, CD20, c-MYC, BCL2 and MUM-1. CD3 and CD57 IHC stains background small T cells.

Pathologic diagnosis of diffuse large B-cell lymphoma.

FISH showed a rearrangement of *MYC/8q24* and *BCL2*.

|| Positive *MYC/BCL2* FISH (Negative *BCL6*) ||



- a). FISH test using c-MYC break apart probe. One isolated red, one isolated green, and one fusion indicate presence of c-MYC gene rearrangement.
- b). One red (*BCL2*), one green (*IgH*), two fusion signals indicate presence of t(14;18)(q32;q21) translocation or *BCL2* gene rearrangement.
- c). FISH test using *BCL6* break apart probe, two fusion signals indicate no *BCL6* gene rearrangement.

|| Question:



- **Which of the following are required to make the diagnosis of “double hit” lymphoma?**
 - A. >70% cells staining c-MYC and BCL2 by immunohistochemistry
 - B. Presence of MYC and BCL2 rearrangement by FISH
 - C. Gene expression profiling
 - D. Presence of BCL2 and BCL6 rearrangement by FISH

|| Question: (Continued) ||

- **Which of the following are required to make the diagnosis of “double hit” lymphoma?**
 - A. >70% cells staining c-MYC and BCL2 by immunohistochemistry
 - B. Presence of MYC and BCL2 rearrangement by FISH**
 - C. Gene expression profiling
 - D. Presence of BCL2 and BCL6 rearrangement by FISH
- The diagnosis of “double-hit” lymphoma is defined by the presence of *MYC* and *BCL2* rearrangement by FISH analysis, and *not* by IHC staining. Less commonly, patients may have rearrangement of *MYC* and *BCL6*.
- Lymphomas with positive c-MYC and BCL2 stain by IHC are known as “double expressors.” It also confers a poor prognosis, but there is little overlap between double expressors and double-hit lymphoma.

|| Question: (Continued) ||

- **What is the most common cell of origin as seen by gene expression profiling?**
 - A. Germinal center B-cell (GCB)
 - B. Activated B-cell (ABC)
 - C. Pro-B cell
 - D. Could be A or B

|| Question: (Continued) ||

- **What is the most common cell of origin as seen by gene expression profiling?**
 - A. Germinal center B-cell (GCB)**
 - B. Activated B-cell (ABC)
 - C. Pro-B cell
 - D. Could be A or B

Gene expression profiling studies have shown that more than 90% of “double-hit” lymphomas are of germinal center origin (GCB type).

|| Question: (Continued) ||

- **What is the current first-line treatment for “double-hit” lymphoma?**
 - A. R-CHOP
 - B. Dose adjusted R-EPOCH
 - C. R-HyperCVAD
 - D. Unclear, consider all of the above regimens

|| Question: (Continued) ||

- **What is the current first-line treatment for “double-hit” lymphoma?**
 - A. R-CHOP
 - B. Dose adjusted R-EPOCH
 - C. R-HyperCVAD
 - D. Unclear, consider all of the above regimens**
- Although retrospective studies have shown R-CHOP is a suboptimal regimen, more aggressive regimens have not shown an overall survival advantage over R-CHOP despite showing higher response rates and EFS.
- We are awaiting results from NCT00118209 to assess the optimal treatment regimen. Current guidelines still consider R-CHOP as standard of care although more intensive regimens are frequently utilized.

Supplemental Readings

1. Johnson NA, Slack GW, Savage KJ, et. al. Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. *J Clin Oncol*, 2012; 30(28), 3452-3459.
2. Green TM, Young KH, Visco C, et. al. Immunohistochemical Double-Hit Score Is a Strong Predictor of Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. *J Clin Oncol*, 2012; 30(28), 3460-3467.
3. Valera A, Lopez-Guillermo A, Cardesa-Salzman T, et. al. MYC Protein Expression and Genetic Alterations Have Prognostic Impact In Patients With Diffuse Large B-Cell Lymphoma Treated With Immunochemotherapy. *Haematologica*, 2013; 98(10), 1554-1562.
4. Cook JR, Goldman B, Tubbs RR, et. al. Clinical Significance of MYC Expression and/or “High-Grade” Morphology in Non-Burkitt, Diffuse Aggressive B-cell Lymphomas: A SWOG S9704 Correlative Study. *Am J Surg Pathol*, 2014; 38(4), 494-501.

Companion Case for Chapter 33

Double Hit Lymphoma

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