Peripheral T-Cell Non-Hodgkin Lymphoma

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QUESTIONS

1. A 35-year-old man presents with a 3-week history of cough. Two weeks ago he completed a 5-day course of azithromycin without improvement in his symptoms. A subsequent chest radiograph showed a widened mediastinum consistent with mediastinal lymphadenopathy. A chest computed tomography (CT) scan confirmed the presence of an 8-cm mediastinal mass. The patient underwent a mediastinoscopy and biopsy, pathology from which revealed a population of lymphocytes that were negative for CD10, CD19, CD20, TdT, Pax 5, and CD15 but were positive for CD30. Which of the following is the most important immunohistochemical test to help establish the diagnosis?
   A. Cyclin D1
   B. Anaplastic lymphoma kinase (ALK)
   C. Periodic acid-Schiff stain
   D. Epstein-Barr virus (EBV) early RNA (EBER)

2. A 46-year-old Caucasian woman with a 10-year history of osteoarthritis is referred to a hematologist for evaluation of neutropenia. She has been managed with nonsteroidal anti-inflammatory drugs (NSAID) as needed. A recent complete blood count (CBC) at her primary care physician’s office demonstrated a normal total white blood cell count but a neutrophil count of 310 cells/µL. Repeat CBC at the hematologist’s office confirms this finding. Her hemoglobin, hematocrit, and platelet count are normal. Her exam is notable for a spleen palpable 2 finger breadths below the left costal margin, but there is no palpable adenopathy. Her past medical history is notable for an episode of bronchitis 1 year ago but no other significant illnesses. She has lived her entire life in the northeastern United States. Which of the following is the most likely diagnosis?
   A. Adult T-cell leukemia/lymphoma, smoldering type (ATLL)
   B. NSAID-induced granulocytopenia
   C. T-cell prolymphocytic leukemia (T-PLL)
   D. T-cell large granular lymphocytic leukemia (T-LGL)
   E. Lyme disease

3. A 52-year-old man is referred to a hematologist for management of lymphocytosis. He presented to his primary care physician complaining of fevers, night sweats, and hepatosplenomegaly and was found to have a white blood cell count of 86,000 cells/µL with 92% lymphocytes on differential. His hemoglobin is low at 9.4 g/dL and his platelet count is low at 89,000/µL. Flow cytometry from the peripheral blood reveals a population of cells positive for CD2, CD3, CD4, CD5, and CD 7 and negative for CD8 and CD20. Cytogenetic analysis reveals inversion 14. His serum calcium and creatinine levels are normal. He has an elevated lactate dehydrogenase (LDH) as well as elevated aspartate aminotransferase and alanine aminotransferase. There is no palpable adenopathy. His past medical history is notable for irritable bowel syndrome, hypertension, and diabetes. What is the most likely diagnosis?
   A. Hepatosplenic T-cell lymphoma
   B. B-cell prolymphocytic leukemia with loss of CD20 expression
   C. Enteropathy associated T-cell lymphoma (EATL)
   D. T-cell prolymphocytic leukemia (T-PLL)
   E. Adult T-cell leukemia/lymphoma (ATLL)

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4. A 68-year-old man presents with acute onset of fevers, rash, and diffuse lymphadenopathy. A biopsy of a cervical lymph node is consistent with angioimmunoblastic T-cell lymphoma. A bone marrow biopsy shows 20% involvement with lymphoma, increased red blood cell precursors, and normal numbers of megakaryocytes. Iron stores are adequate. He is started on cyclosporine. Two days after initiating cyclosporine, his hemoglobin decreases from 12 g/dL to 9 g/dL and his total bilirubin increases from 0.8 g/dL to 2.4 g/dL. His creatinine is unchanged and his platelets remain normal. He is mentating normally. He reports no melena or hematochezia. What is the most likely cause of his progressive anemia?
A. Autoimmune hemolysis
B. Cyclosporine-induced hemolytic-uremic syndrome
C. Marrow infiltration from angioimmunoblastic T-cell lymphoma
D. Gastrointestinal bleeding secondary to gastrointestinal involvement with lymphoma

5. A 36-year-old man was diagnosed with localized NK/T-cell lymphoma, nasal type after presenting with ulceration of the hard palate with subsequent erosion into the sinonasal cavity. A CT scan of the chest, abdomen, and pelvis shows no evidence of disease outside of the sinonasal cavity. A bone marrow biopsy shows no evidence of involvement with lymphoma. The patient has pain at the site of ulceration but is otherwise asymptomatic. Which of the following is the most important first step in management?
A. Surgical correction of his palatal defect to prevent infection during subsequent chemotherapy
B. Radiotherapy for local disease control
C. Combination chemotherapy to prevent dissemination of disease
D. Intrathecal chemotherapy

ANSWERS

1. The correct answer is (B), ALK. In a young man with a mediastinal mass, the primary differential diagnosis would be Hodgkin lymphoma, mediastinal diffuse large B-cell lymphoma, T-cell anaplastic large cell lymphoma (ALCL), T-cell lymphoblastic leukemia/lymphoma, thymoma, and a germ cell tumor. A germ cell tumor is ruled out by the presence of a lymphocytic infiltrate. The process is TdT-negative, which essentially rules out lymphoblastic lymphoma. Mediastinal diffuse large B-cell lymphoma is CD20-positive and therefore unlikely in this case. Thus, the primary differential diagnosis is between Hodgkin lymphoma and ALCL. Both can present as a bulky mediastinal mass in a young man. Hodgkin lymphoma is often CD15-positive, and almost all cases will be positive for the B-cell marker Pax 5. The fact that both of these tests were negative should make the clinician suspicious of ALCL. Most cases of ALCL in young patients will have the t(2;5) translocation or variant translocations and will express the ALK protein; therefore, this would be the most important test to perform in this case. Both Hodgkin lymphoma and T-cell lymphomas can be EBV-positive, so EBER would not help narrow the differential diagnosis. Cyclin D1 is a marker for mantle cell lymphoma, which would not be high in the differential in a young man. Periodic acid-Schiff stain demonstrates glycogen and related mucopolysaccharides and is typically positive in lymphoblastic lymphoma. However, the fact that this process was negative for CD10 and TdT essentially rules out lymphoblastic lymphoma. Establishing the correct diagnosis is critical since all of the entities in the differential diagnosis in this case are potentially curable but are treated very differently.

2. The correct answer is (D), T-LGL. Isolated neutropenia with mild splenomegaly in an otherwise asymptomatic patient is a classic presentation of T-LGL. Many cases are associated with rheumatoid arthritis, which should be considered in this patient with a long-standing history of what previously has been diagnosed as osteoarthritis. NSAIDs can cause granulocytopenia, but this would not account for the enlarged spleen. TPLL can cause splenomegaly but is generally an aggressive disease, and the patient should have lymphocytosis rather than a normal total white blood cell count and isolated neutropenia. Also, most patients with TPLL will have fevers, fatigue, or weight loss. Smoldering ATLL would not typically present with isolated neutropenia. Also, this disease is associated with HTLV-1, a retrovirus common in parts of the Caribbean, Africa, and South America but not the northeastern United States. Lyme disease is endemic to the northeastern United States but does not cause splenomegaly or neutropenia.

3. The correct answer is (D), T-PLL. T-PLL often presents with the acute onset of systemic symptoms such as fever, fatigue, and night sweats. Patients
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will have a lymphocytosis and will often be anemic and thrombocytopenic. Hepatosplenomegaly is common, but lymphadenopathy is less prominent. The neoplastic cells are usually positive for CD2, CD3, CD4, CD5, and CD7 and negative for CD8 and B-cell markers. Inversion 14 is the most common cytogenetic abnormality. The patient’s history of irritable bowel syndrome suggests the possibility of undiagnosed sprue and subsequent EATL, but EATL does not typically cause profound lymphocytosis or hepatosplenomegaly. Hepatosplenic T-cell lymphoma can cause hepatosplenomegaly, abnormal liver function tests, anemia, and thrombocytopenia but does not typically cause such a marked lymphocytosis. Also, hepatosplenic T-cell lymphoma is usually CD4- and CD8-negative and is associated with isochromosome 7. ATLL, especially the leukemic phase, could present in a similar manner to this patient’s presentation, but leukemic ATLL is often associated with hypercalcemia and is not classically associated with inversion 14, making ATLL less likely. B-cell prolymphocytic leukemia with aberrant loss of CD20 is unlikely in a patient never before treated with an anti-CD20 monoclonal antibody and is ruled out in this case by the coexpression of multiple T-cell markers (CD2, CD3, CD4, and CD7).

4. The correct answer is (A), autoimmune hemolysis. Angioimmunoblastic T-cell lymphoma (AILT) is associated with a variety of autoimmune phenomena, including autoimmune hemolysis, arthritis, and hypothyroidism. The acute onset of anemia with hyperbilirubinemia supports this diagnosis. Marrow infiltration is a common cause of anemia in lymphoma patients. However, in this case there was only 20% marrow involvement and, more importantly, red blood cell precursors were increased in the marrow, suggesting adequate production in the setting of peripheral red blood cell destruction or loss. Cyclosporine can induce hemolytic-uremic syndrome (HUS), but a normal platelet count and normal creatinine make this a less likely cause of anemia in this circumstance. Review of the peripheral smear for schistocytes would be an important procedure to definitively rule out HUS. Although certain T-cell lymphomas—such as enteropathy-associated T-cell lymphoma—commonly involve the gastrointestinal tract, this is less common with AILT. Also, gastrointestinal bleeding would not explain the rising bilirubin and is less likely given the lack of reported melena or hematochezia.

5. The correct answer is (B), radiotherapy for local disease control. In general, surgery does not play a role in the management of NK/T cell lymphoma and would not be the optimal first step in management in this case even with a profound defect in the hard palate. Although involvement of the sinuses can be a risk factor for central nervous system dissemination with aggressive lymphomas, intrathecal chemotherapy also would not be the initial management in this case since the disease is localized and there are no neurologic symptoms. The utility of combination chemotherapy in localized NK/T cell lymphoma, nasal type is an area of debate. Most studies suggest, however, that treatment outcomes are best in localized disease if radiotherapy is administered first, prior to administration of chemotherapy.