MAYO CLINIC

76-Year-Old Man With Abdominal Pain, Fever, and Maculopapular Rash

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See end of article for correct answers to questions.

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A 76-year-old man with a history of vasovagal syncope and diverticulitis presented to his local urgent care center with abdominal pain, fever, and maculopapular rash of 1 day's duration after receiving the influenza vaccine. Before this illness, he was in his usual state of health. Initially, an acute viral illness was believed to be the cause. His medical team recommended symptomatic treatment.

Four days later, he returned to his primary care physician because of fever as high as 38°C, tachycardia, nausea, decreased appetite, and abdominal pain. History taken at that time revealed travel to Central America 2 weeks before his presentation. Laboratory evaluation revealed the following (reference ranges provided parenthetically): white blood cell count (WBC), 29.5 × 10^9/L (3.5-10.5 × 10^9/L) with elevated neutrophil and eosinophil counts; alkaline phosphatase, 262 U/L (45-115 U/L); aspartate aminotransferase, 35 U/L (8-48 U/L); alanine aminotransferase, 132 U/L (7-55 U/L); bilirubin, 6.9 mg/dL (≤1.2 mg/dL) (predominantly direct); international normalized ratio (INR), 1.7 (0.8-1.2); ammonia, 68 μmol/L (≤30 μmol/L); and C-reactive protein, 50.4 mg/L (≤8.0 mg/L). The patient was hospitalized, and ampicillin-sulbactam was initiated. Results of abdominal ultrasonography were inconclusive for biliary obstruction. Subsequent magnetic resonance cholangiopancreatography revealed no evidence of extrahepatic biliary obstruction.

The patient continued to have abdominal pain, nausea, and jaundice of unknown etiology. Given concern for a drug reaction, his antibiotics were changed to ciprofloxacin, metronidazole, and doxycycline. With his recent travel history, serologic evaluation for *Ehrlichia*, viral hepatitis, cytomegalovirus, *Babesia*, Lyme disease, and malaria was performed but returned negative results.

1. Which *one* of the following is the *most likely* cause of this patient's jaundice?

a. Chagas disease
b. Ampicillin-sulbactam
c. Hemolysis
d. Infiltrative disease
e. Extrahepatic biliary obstruction

Test results were negative for common Central American infections that cause cholestatic liver injury, and involvement of the biliary tree is rare in Chagas disease, especially in the acute phase.[1] Symptoms had begun before antibiotic therapy, excluding ampicillin-sulbactam as the likely cause. Hemolysis can cause jaundice, but elevation is usually seen in the indirect (unconjugated) bilirubin, and this patient had direct (conjugated) bilirubin elevation. Since Chagas disease does not typically cause cholestasis, antibiotics were initiated after the jaundice, the bilirubin is conjugated, and MRCP was negative, infiltrative disease would be the most likely cause of this patient's symptoms in this case. Finally, ultrasonography and magnetic resonance cholangiopancreatography ruled out extrahepatic biliary ductal obstruction.

Infiltrative diseases to consider as an etiology for intrahepatic cholestasis are amyloidosis, sarcoidosis, lymphoma, primary malignant tumor of the liver, or metastatic disease.[2] In this case, without a clear lesion seen on magnetic resonance imaging or ultrasonography, a diffuse process is more likely. With no evidence of biliary obstruction, other causes of elevated liver test results could include primary biliary cirrhosis, systemic inflammation, or drug effect.[2] When a patient presents with elevated liver test results, no clear etiology, and evidence of severe hepatic synthetic dysfunction (elevated INR [>1.5]), the practitioner must consider the possibility of acute liver failure. Such patients should be referred to a liver transplant center.

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At this point, the patient was transferred to Mayo Clinic for further evaluation. On arrival, he was oriented to person, place, and time but very somnolent. His temperature was 36.9°C, heart rate was 108 beats/min, blood pressure was 138/75 mm Hg, and respiratory rate was 24 breaths/min. Physical examination revealed a maculopapular rash on his face, neck, back, and abdomen. Laboratory tests revealed the following: hemoglobin, 12.9 g/dL (13.5-17.5 g/dL); WBC, 37.9 × 10^9/L (11% eosinophils); platelet count, 88 × 10^9/L (150-450 × 10^9/L); INR, 1.9; alkaline phosphatase, 149 U/L; aspartate aminotransferase, 29 U/L; alanine aminotransferase, 70 U/L; total bilirubin, 11.6 mg/dL; direct bilirubin, 9.7 mg/dL (0.0-0.3 mg/dL); ferritin, 1217 μg/L (24-336 μg/L); and lactate dehydrogenase (LDH), 517 U/L (122-222 U/L). Serum protein electrophoresis was negative for monoclonal protein, and the tryptase level was normal. Computed tomographic (CT) angiography of the chest, performed to exclude pulmonary embolism, revealed lymphadenopathy of the chest and upper abdomen and splenomegaly. No pulmonary embolism was identified. Transthoracic echocardiography revealed a left ventricular ejection fraction of 47% with posterior and apical regional wall motion abnormalities.

2. Eosinophilia can be associated with many disease processes, but it would be *unexpected* in which *one* of the following diagnoses?

a. T-cell lymphoma
b. DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome
c. Eosinophilic granulomatosis with polyangiitis
d. Parasitic infection
e. Adult Still disease

There are many causes of secondary hypereosinophilia, including malignant neoplasms, drug reactions like DRESS syndrome, parasitic infections, and autoimmune disorders like eosinophilic granulomatosis with polyangiitis.[3] These processes must be excluded before evaluating a person for a primary hypereosinophilic syndrome or a clonal eosinophilia.[4] Adult Still disease can present with symptoms similar to this patient's, but eosinophilia is not a typical finding in adult Still disease,[3] making it the least likely cause.

Given the complexity of this case, additional consultations were requested. Colleagues from the infectious disease service recommended extensive work-up, which yielded negative findings. The dermatology service was consulted and performed a skin biopsy of the maculopapular rash. Pathologic examination of the specimen revealed neutrophilic dermatosis. Given the rash, hypereosinophilia, and negative results on infectious disease evaluation, prednisone was initiated and titrated to a dose of 100 mg/d. The patient's cholestasis and eosinophilia initially improved with the prednisone.

3. Which *one* of the following is the *most likely* cause of this patient's neutrophilic dermatosis?

a. Pyoderma gangrenosum
b. SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome
c. Sweet syndrome
d. Behçet disease (Silk Road disease)
e. Rheumatoid neutrophilic dermatosis

All of the listed diagnoses have biopsy findings consistent with a neutrophilic dermatosis.[5-7] The clinical scenario helps narrow the differential diagnosis. Pyoderma gangrenosum is a neutrophilic dermatosis with slowly expanding ulcerated plaques.[5] Our patient did not have these physical findings. SAPHO syndrome is a disease with components of synovitis, acne, pustulosis, hyperostosis, and osteitis.[6] Neutrophilic pseudoabscesses are common with SAPHO syndrome,[6] but this patient had no other features of this syndrome. Sweet syndrome is the most likely cause of this patient's neutrophilic dermatosis because it involves an acute widespread rash and fever. It is associated with an underlying systemic disease in 35% of cases, often a hematologic malignancy.[5] Patients with Behçet disease (Silk Road disease) can have a widespread neutrophilic rash, but it is usually accompanied by oral, ocular, and/or genital lesions.[7] Rheumatoid neutrophilic dermatosis is seen in patients with advanced rheumatoid arthritis.[5]

Given the association between Sweet syndrome and hematologic malignancy, hematologic evaluation was performed. Positron emission tomography–CT revealed diffuse fludeoxyglucose F 18 uptake in the patient's lymph nodes, spleen, and bone marrow.

Flow cytometry on peripheral blood identified a CD4-positive T-cell population suggestive of a reactive T-cell expansion or a clonal T-cell population. Results of subsequent T-cell gene rearrangement studies were equivocal. Bone marrow biopsy revealed hypercellular marrow with marked eosinophilia and eosinophilic precursor cells but, unfortunately, provided no definitive diagnosis. However, these findings, in association with the increased LDH level, diffuse lymphadenopathy, and negative results on infectious disease work-up, were concerning for lymphoma.

4. In view of the abnormal bone marrow biopsy findings but no clear etiology, which *one* of the following is the *best* next step in determining this patient's diagnosis?

a. Lymph node biopsy
b. Repeated bone marrow biopsy
c. Flow cytometry of peripheral blood
d. Repeated infectious serologies because time has passed
e. Empirical chemotherapy

Positron emission tomography–CT findings of diffuse bone marrow, lymph node, and splenic avidity keeps hematologic malignancy high on the differential diagnosis. Tissue confirmation is needed. The best next step is lymph node biopsy. Repeating the bone marrow biopsy or flow cytometry would be unlikely to yield new data. If an infectious process was involved, it should have been apparent during the previous extensive testing. Empirical chemotherapy would not be appropriate without a diagnosis. Another option would be liver biopsy, given the likely liver infiltrate. Pathologic examination of a lymph node biopsy specimen provided the diagnosis of angioimmunoblastic T-cell lymphoma.

Unfortunately, at this point in the clinical course, the patient's condition deteriorated, with development of hypoxic respiratory failure and atrial fibrillation with rapid ventricular response. He required intubation. The hematology service recommended initiation of methylprednisolone, 1000 mg/d, and the patient was transferred to their service. With corticosteroids, his condition improved and he was able to be extubated. After long discussions with the patient and his family, the decision was made to start gemcitabine chemotherapy. He was not a candidate for first-line anthracycline-based chemotherapy given his very poor performance status and cholestatic liver failure.

5. Which *one* of the following pairs of factors places this patient with T-cell lymphoma at high risk (>5%) for tumor lysis syndrome (TLS)?

a. LDH level more than 2 times the upper limit of normal and bulky disease
b. Gemcitabine-based therapy and thrombocytopenia
c. Bulky disease and thrombocytopenia
d. *JAK2* mutation and WBC greater than 25×10^9/L
e. LDH level greater than 2 times the upper limit of normal and WBC greater than 25×10^9/L

Adult T-cell lymphoma is considered an intermediate risk factor for TLS unless the LDH level is greater than 2 times the upper limit of normal and the patient has bulky disease.[8] The chemotherapy regimen, platelet count, presence of *JAK2* mutation, and WBC are not components of the TLS risk stratification for peripheral T-cell lymphomas. Prophylactic rasburicase and hydration are recommended when a patient is at high risk for TLS.[8,9]

The patient's disease course concluded with development of disseminated intravascular coagulation and TLS. Chemotherapy was discontinued because of limited response and complications related to therapy. He was discharged from the hospital with hospice support and died 3 days after dismissal.

DISCUSSION

Angioimmunoblastic T-cell lymphoma represents 18.5% of peripheral T-cell lymphoma diagnoses.[10,11] It often presents with fevers, night sweats, and hepatosplenomegaly, and 82% of patients have nodal and extranodal disease at the time of diagnosis.[10] The median age at diagnosis is 65 years, and there is a slight male predominance.[10] Current recommendations support cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone for young, physically fit patients[12,13] and cyclophosphamide, doxorubicin, vincristine, and prednisone as the standard for all others.[13]

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The 5-year survival after anthracycline-based chemotherapy is 26% for all peripheral T-cell lymphomas[10] and 32% for angioimmunoblastic T-cell lymphomas.[11] Our patient was older, had poor performance status, and cholestatic liver failure, making treatment difficult. Cyclophosphamide requires hepatic conversion,[14] and vinca alkaloids and anthracyclines are contraindicated in patients with cholestatic liver failure.[15] We chose gemcitabine because data has suggested it as an alternative therapy in patients with severe liver dysfunction.[15]

Lymphoma should always be considered in patients with cholestasis but no obvious biliary obstruction. Lymphoma can affect liver chemistries in several ways. Murakami and Shimizu[16] reviewed 5 major ways lymphoma causes abnormal liver chemistries: (1) intrahepatic cholestasis from infiltrative disease, (2) extrahepatic cholestasis due to bulky lymph node disease can obstruct biliary flow, (3) liver ischemia and liver failure from compression of extrahepatic or intrahepatic circulation, (4) viral infections such as cytomegalovirus, Epstein-Barr virus, and herpes simplex virus are more common in immunosuppressed patients with lymphoma, and (5) hemophagocytic syndrome can cause elevated liver test results in patients with aggressive lymphomas. The manifestations of hepatic involvement in hemophagocytic syndrome can include hepatomegaly, cholestasis, hepatitis, or fulminant liver failure.[16]

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CORRECT ANSWERS: 1. d. 2. e. 3. c. 4. a. 5. a