84-Year-Old Man With Night Sweats, Weight Loss, and Diarrhea

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An 84-year-old man with a history of coronary artery disease, hypertension, hyperlipidemia, ischemic stroke, and gastroesophageal reflux disease presented to the outpatient gastroenterology clinic with a 3-month history of night sweats, generalized weakness, nausea, vomiting, nonbloody postprandial diarrhea, and an 18-kg weight loss. He also reported a recent rash and daily morning stiffness in his fingers and knees lasting up to about 30 minutes. He denied alcohol or intravenous drug abuse. Previously, he had been taking several medications, but all had been recently discontinued because of the persistent diarrhea.

On examination, the patient had normal vital signs. He appeared cachectic, with a distended abdomen with flank dullness but no pain on palpation. The joints of his fingers and knees were tender to palpation, and soft tissue swelling was evident. No other abnormalities were found on examination of the head, ears, eyes, nose and throat, skin, and lymphatic, cardiac, respiratory, and thyroid systems. A computed tomographic (CT) scan of the abdomen and pelvis obtained 1 month previously at another institution revealed abdominal and pelvic ascites and mildly prominent aortocaval and periportal lymph nodes. A positron emission tomographic/CT scan also obtained at another facility did not suggest malignancy.

Laboratory studies yielded the following results (reference ranges provided parenthetically): hemoglobin, 12.9 g/dL (13.5-17.5 g/dL); leukocytes, 2.1×10^9/L ($3.5\text{-}10.5\times10^9$/L); neutrophils, 0.7×10^9/L ($1.7\text{-}7.0\times10^9$/L); lymphocytes, 0.8×10^9/L ($0.9\text{-}2.9\times10^9$/L); monocytes, 0.2×10^9/L ($0.3\text{-}0.9\times10^9$/L); eosinophils, 0.4×10^9/L ($0.05\text{-}0.50\times10^9$/L); platelet count, 61×10^9/L ($150\text{-}450\times10^9$/L); creatinine, 1.1 mg/dL (0.8-1.3 mg/dL); lactate dehydrogenase, 148 U/L (122-222 U/L); aspartate aminotransferase, 32 U/L (8-48 U/L); alanine aminotransferase, 23 U/L (7-55 U/L); total bilirubin, 0.4 mg/dL (0.1-1.0 mg/dL); alkaline phosphatase, 93 U/L (45-115 U/L); erythrocyte sedimentation rate, 86 mm/h (0-22 mm/h); C-reactive protein, 16.6 mg/L (≤8.0 mg/L); and thyrotropin, 2.4 mIU/L (0.3-5.0 mIU/L). A peripheral blood smear revealed rouleaux formation. No abnormalities were detected on stool studies.

1. **Which *one* of the following diagnostic tests should be performed *first* in this patient?**
   a. Esophagogastroduodenoscopy with small bowel aspiration biopsy
   b. Right upper quadrant ultrasonography
   c. Diagnostic paracentesis
   d. Transthoracic echocardiography
   e. Bone marrow biopsy

This patient presented with a constellation of gastrointestinal symptoms, clinical evidence of ascites, and laboratory values notable for pancytopenia and elevation of inflammatory markers. Although it may help with evaluation of the patient's diarrhea, esophagogastroduodenoscopy with small bowel aspiration biopsy would not give any information about the etiology of the ascites. Ascites is most frequently due to portal hypertension secondary to end-stage liver disease. Right upper quadrant ultrasonography may be helpful in detecting any hepatic and biliary abnormalities. However, in this case, there was no clinical or laboratory suspicion of decompensated cirrhosis, and thus, right upper quadrant ultrasonography should not be the first test. Evaluation of ascitic fluid can quickly establish a general diagnosis, so diagnostic paracentesis should be performed first. Cardiac failure may lead to the formation of ascites, but with no cardiac symptoms and normal findings on cardiac examination, transthoracic echocardiography would not be the best first test in this patient. Finally, with pancytopenia and evidence of lymphadenopathy on outside imaging, a bone marrow biopsy may be

See end of article for correct answers to questions.

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warranted. However, it should not be the first test performed.

The patient underwent diagnostic paracentesis with removal of 2.23 L of straw-colored fluid. Analysis of the ascitic fluid revealed the following: total protein, 4.0 g/dL; albumin, 1.04 g/dL; total nucleated cells, 414/μL; neutrophils, 24.0%, amylase 8 U/L. The patient's serum albumin level was 2.0 g/dL (3.4-4.7 g/dL), and his serum total protein level was 7.3 g/dL (6.3-7.9 g/dL). Cytologic testing was negative for malignancy.

2. Which *one* of the following is the *most likely* etiology of the ascites in this patient?

a. Liver cirrhosis
b. Myxedema
c. Pancreatitis
d. Heart failure
e. Peritoneal serositis

The serum-ascites albumin gradient (SAAG) determines whether ascites is exudative or transudative. The SAAG is calculated by subtracting the ascitic fluid albumin concentration from the serum albumin concentration. In most cases, a SAAG value of 1.1 g/dL or higher confirms with more than 95% accuracy the clinical suspicion of portal hypertension–related ascites from conditions such as liver cirrhosis and heart failure. However, the total protein concentration in cirrhosis-related portal hypertension is usually less than 2.5 g/dL, whereas that for heart failure is more than 2.5 g/dL.[1] There are other diseases in which the SAAG value is 1.1 g/dL or less, including malignancies causing peritoneal carcinomatosis, conditions causing peritoneal serositis such as systemic lupus erythematosus (SLE), tuberculous peritonitis, pancreatitis, hypothyroidism causing myxedema, and nephrotic syndrome. These conditions are usually associated with increased ascitic fluid total protein levels higher than 2.5 g/dL, although it is usually less than 2.5 g/dL in myxedema and nephrotic syndrome.

Our patient underwent repeated CT of the abdomen and pelvis, which revealed mural thickening and enhancement of the entire colon but no abnormalities of the liver or pancreas. A CT scan of the chest yielded normal findings. Colonoscopy with random biopsies was unrevealing. Findings on a QuantiFERON test for tuberculosis and a bone marrow biopsy were also normal. The patient's calculated SAAG value was 0.96 g/dL, and his ascitic total fluid protein level was 4.0 g/dL, which made liver cirrhosis or heart failure unlikely etiologies of his ascites. Myxedema and pancreatitis were unlikely given his normal thyroid function test results, the absence of abdominal pain, and no evidence of pancreatic inflammation on abdominal CT.

In this patient, notable elevation in the erythrocyte sedimentation rate and C-reactive protein level, low SAAG value with normal ascitic protein level, CT findings of colonic mural thickening, and an essentially negative work-up for malignancy made peritoneal serositis most likely.

3. In view of the high suspicion for serositis, which *one* of the following would be the *best* diagnostic test to order next?

a. Metaraminol provocative test
b. Measurement of serum angiotensin-converting enzyme level
c. Anti-*Saccharomyces cerevisiae* antibody (ASCA) test
d. Antinuclear antibody (ANA) test
e. Measurement of serum amylase level

Serositis, which is the inflammation of serous membranes, can be a manifestation of several diseases, including familial Mediterranean fever (FMF), inflammatory bowel disease, pancreatitis, and SLE. The metaraminol provocative test has high sensitivity and specificity for the diagnosis of FMF, which usually presents in childhood in individuals with Mediterranean ethnic backgrounds.[2] In addition, the most common presentation of FMF is recurrent abdominal pain secondary to serosal peritonitis. Our patient did not fit this clinical profile. Measurement of the serum angiotensin-converting enzyme level would be a reasonable test to check for sarcoidosis given the multisystemic nature of the disease. However, the lack of pulmonary findings and the normal results on small bowel and colon biopsies in our patient make sarcoidosis less likely. The ASCA test may be ordered for further evaluation of inflammatory bowel disease, especially to distinguish ulcerative colitis and Crohn disease, but the

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ASCA test has poor predictive value as a standalone test.[3] Crohn disease does cause serositis, but this diagnosis is less likely as an initial presentation in an 84-year-old man with normal endoscopic examination findings and negative biopsy results. In this patient with joint pain and morning stiffness, a recent facial rash, multiple systemic symptoms, pancytopenia, and serositis, we proceeded with an evaluation for SLE. Measurement of ANAs is the best test to perform at this time to evaluate for SLE. Measurement of the serum amylase level would not be the best test because of the low suspicion for pancreatitis.

The patient's ANA test was moderately positive at 5.1 U (positive, ≥3.0 U). IgG β2-glycoprotein 1 (antiphospholipid) antibody results were markedly positive at 35.8 U/mL (positive, ≥15 U/mL), and complement levels including total complement, C3, and C4 were very low. Double-stranded DNA antibodies and Smith antibodies were absent. With morning stiffness and synovitis in several joints, evidence of peritoneal serositis, lymphopenia, thrombocytopenia, and positive ANA and antiphospholipid antibody results, the patient met at least 4 of the 17 Systemic Lupus International Collaborating Clinics criteria required to diagnose SLE.[4] The diagnosis was based on at least 2 clinical criteria (joint disease, lymphopenia/thrombocytopenia, peritoneal serositis) and 2 immunologic criteria (a positive ANA titer, positive antiphospholipid antibodies, and low complement levels).

4. Which *one* of the following treatments should be initiated at this time?

a. Methotrexate
b. Methylprednisolone
c. Azathioprine
d. Mycophenolate
e. Infliximab

Several common drugs are used in the treatment of SLE. They include nonsteroidal anti-inflammatory drugs, antimalarials (primarily hydroxychloroquine), corticosteroids, and immunosuppressive agents including leflunomide, methotrexate, azathioprine, mycophenolate, and belimumab.[5] Similar to other immunosuppressive agents, methotrexate is used in the treatment of SLE when there is extensive organ involvement and an inadequate response to corticosteroids. It is also effective for inflammatory arthritis, a common manifestation in lupus. Although it would benefit this patient's arthritis, it is not the preferred initial treatment. In this patient who presented with an acute flare of SLE, the preferred initial treatment is methylprednisolone because corticosteroids produce rapid clinical improvement. Two slower-acting but steroid-sparing agents for the treatment of SLE are azathioprine, which is an immunosuppressive antimetabolite, and mycophenolate, a powerful inhibitor of lymphocyte proliferation. These agents are generally initiated with high-dose corticosteroids and require several weeks to reach effectiveness. They are not appropriate as initial monotherapy for a patient with active SLE. Infliximab, a chimeric IgG1κ monoclonal antibody and high-affinity antagonist of tumor necrosis factor receptors, has not been studied in the treatment of SLE. However, tumor necrosis factor inhibitors are generally not used in the treatment of lupus because of their potential to exacerbate and/or cause drug-induced lupus.

The patient was initially treated with two 500-mg doses of intravenous methylprednisolone. He was then transitioned to daily oral prednisone at 60 mg with plans to gradually taper off over a 3-month period. Along with the corticosteroids, hydroxychloroquine and mycophenolate were administered as steroid-sparing agents. Both drugs were used to help maintain control of disease activity and to prevent clinical relapse.[5]

5. Which *one* of the following is recommended while the patient is receiving long-term systemic corticosteroid therapy?

a. Monthly complete blood cell count
b. Monthly liver enzyme measurement
c. Calcium and vitamin D replacement
d. Monthly eye examination
e. Sucralfate

Systemic corticosteroids have been associated with adverse effects in patients receiving high doses or prolonged courses. Multiple organ systems can be affected, including the endocrine (diabetes mellitus, hypothalamic-pituitary-adrenal insufficiency), cardiovascular (hypertension), gastrointestinal (gastritis),

musculoskeletal (osteoporosis), and immune (heightened risk of infections, opportunistic infections) systems.[6] Corticosteroids are known to induce neutrophil-predominant leukocytosis. However, long-term complete blood cell count monitoring is not required. Corticosteroids can also affect the gastrointestinal system, most commonly causing gastritis and peptic ulcer disease, and can result in liver abnormalities including steatohepatitis, which when severe, can cause liver enzyme elevation. Because this is a rare event, patients receiving corticosteroids do not typically undergo routine liver enzyme measurements. One of the more serious corticosteroid-induced adverse effects is osteoporosis. Corticosteroids induce a negative calcium balance by decreasing intestinal calcium absorption and increasing urinary calcium excretion. Calcium supplementation can therefore reduce bone loss in patients receiving long-term corticosteroid therapy. It is recommended that these patients maintain a total calcium intake of 1200 mg/d and vitamin D intake of 800 IU/d through diet and/or supplements.[7] The risk of both cataracts and glaucoma is increased in patients taking systemic corticosteroids. Ocular toxicity can also be seen with the use of hydroxychloroquine, another medication used for the treatment of lupus. Patients receiving a prolonged course of these medications should be examined periodically by an ophthalmologist. However, a monthly eye examination is not required.[6] Patients taking corticosteroids can receive gastrointestinal prophylaxis with proton pump inhibitors if they are also taking nonsteroidal anti-inflammatory drugs, which increase the risk of gastrointestinal adverse effects by 4-fold.[8] However, sucralfate is not typically given for this purpose.

Calcium carbonate, 500 mg 3 times a day, was administered on initiation of corticosteroid therapy. The patient's 25-hydroxyvitamin D level was low at 12 ng/mL (25-80 ng/mL). Thus, he was given a loading dose of cholecalciferol (vitamin D_3), 50,000 U/d for a total of 5 days, and was prescribed 50,000 U once weekly for 6 weeks.

Four months after hospital discharge, the patient reported feeling better. He was eating regularly, had gained weight, and his abdominal distention and diarrhea had improved.

DISCUSSION

Systemic lupus erythematosus is an autoimmune disorder with clinical manifestations that can affect any organ or system.[9] The diagnosis of SLE requires at least 4 of the 17 Systemic Lupus International Collaborating Clinics criteria or 4 of the 11 American College of Rheumatology criteria for the classification of SLE. Systemic lupus erythematosus can have serosal involvement of the pleura, pericardium, and peritoneum.[4] Inflammation of the pleural and pericardial serous membranes is relatively common and one of the several manifestations of the disease. Serositis or inflammation of serous membranes involving the pericardium, pleura, and peritoneum can cause pain, fluid accumulation, adherence, and even fibrosis.[4]

Most cases of peritoneal serositis with ascites, known as lupus peritonitis, are undiagnosed. In a postmortem study, 60% to 70% of patients with SLE had peritonitis, although it had been clinically diagnosed in only approximately 10%.[10] In fact, late diagnosis of SLE is more commonly accompanied by serositis.[10] The key to diagnosis is clinical suspicion and the use of diagnostic paracentesis. Ascites in SLE occurs as result of peritoneal inflammation and usually results in an exudative fluid.[1] It should be considered a diagnosis of exclusion, and a comprehensive work-up should be undertaken to rule out the most common causes of exudative ascites such as peritoneal carcinomatosis, tuberculous peritonitis, nephrotic syndrome, and severe malnutrition.[1]

The prognosis of patients with lupus peritonitis is usually good if treatment is initiated promptly. Given that the major component of the disease is inflammation, therapies are based on anti-inflammatory drugs, most commonly corticosteroids that are later transitioned to corticosteroid-sparing agents.[4] Although serositis related to lupus usually responds to corticosteroids, refractory cases of fluid accumulation in the serosal cavity have been reported. In these cases, immunomodulators or immunosuppressors and even surgical procedures such as pleurodesis may be required.[4,11]

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