68-Year-Old Woman With Fever, Headache, Bicytopenia, and Transaminitis

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A 68-year-old woman with a history of stage III follicular non-Hodgkin lymphoma (NHL) diagnosed in 2001 (currently in remission) and recurrent diverticulitis presented to the emergency department (ED) with a 1-week history of fever, headache, neutropenia, thrombocytopenia, and rash. She resided in Peoria, Arizona, and had traveled only to Fresno, California, and Phoenix, Arizona, and had not noted any insect bites. Approximately 3 weeks previously, she began a course of ciprofloxacin and metronidazole for an episode of mild acute uncomplicated sigmoid diverticulitis seen on computed tomography (CT). On day 12 of antibiotics, the abdominal pain increased, and the treatment regimen was switched to trimethoprim-sulfamethoxazole (TMP-SMX) because of penicillin allergy. The abdominal pain improved, and she continued the TMP-SMX. A week before the current presentation, on day 7 of TMP-SMX therapy, high fevers, headache, and anorexia developed. She had no cough, shortness of breath, or abdominal or genitourinary tract symptoms. She was evaluated at an outside ED, where chest radiography and urinalysis yielded normal results, the white blood cell count (WBC) was 2.2×10^9/L, and the platelet count was 89×10^9/L (her baseline was 120×10^9/L). She was discharged from the ED and instructed to continue the TMP-SMX. The following day, she noted a nonpruritic maculopapular rash on her torso, arms, and legs, which prompted her to stop the TMP-SMX and restart the ciprofloxacin and metronidazole. On day 7 of the new course of ciprofloxacin and metronidazole, she presented to our ED with worsening headache, high fevers, and dehydration.

In the ED, her temperature was 38.3°C, pulse rate was 98 beats/min, blood pressure was 95/50 mm Hg, and oxygen saturation was 94% while the patient received 1 L/min of oxygen. She appeared uncomfortable but had no meningeal signs. She had anicteric sclera, dry oral mucosa, and no palpable lymphadenopathy. Cardiopulmonary and abdominal examinations detected no abnormalities aside from mild tachycardia. Neurologic examination revealed no focal deficits. She had a diffuse maculopapular rash on her trunk, back, abdomen, and extremities but not on the palms, soles, and oral mucosa.

Initial laboratory tests revealed the following (reference ranges provided parenthetically): hemoglobin, 13.4 g/dL (12.0-15.5 g/dL); WBC count, 0.9×10^9/L ($3.5\text{-}10.5 \times 10^9$/L); absolute neutrophil count, 0.65×10^9/L ($1.70\text{-}7.00 \times 10^9$/L); platelet count, 49×10^9/L ($150\text{-}450 \times 10^9$/L); sodium, 128 mmol/L (135-145 mmol/L); potassium, 4.1 mmol/L (3.6-5.2 mmol/L); serum bicarbonate, 20 mmol/L (22-29 mmol/L); serum urea nitrogen, 19 mg/dL (6-21 mg/dL); creatinine, 1.2 mg/dL (0.6-1.1 mg/dL); aspartate aminotransferase (AST), 181 U/L (8-43 U/L); alanine aminotransferase (ALT), 132 U/L (7-45 U/L); alkaline phosphatase, 204 U/L (55-142 U/L); total bilirubin, 0.3 mg/dL (<1.2 mg/dL); lactate, 1.10 mmol/L (0.6-2.3 mmol/L); and international normalized ratio, 1.08. A peripheral blood smear identified no morphological abnormalities. Urinalysis, chest radiography, and noncontrast CT of the head yielded normal findings.

1. Which *one* of the following diagnostic tests should be performed *next* in this patient?

a. CT of the abdomen
b. Right upper quadrant ultrasonography
c. Lumbar puncture
d. Viral hepatitis serologies
e. Bone marrow biopsy

This patient meets criteria for sepsis. She has systemic inflammatory response syndrome with temperature greater than 38.0°C, pulse rate

See end of article for correct answers to questions.

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greater than 90 beats/min, and WBC count less than 4×10^9/L and multiple potential sources of infection. Furthermore, her hypotension raises concern about evolving septic shock. Initial diagnostic testing should focus on identifying the correct source of infection to allow immediate initiation of appropriate antimicrobial therapy. The absence of abdominal symptoms and the normal findings on abdominal examination indicate that abdominal imaging such as CT is not immediately required. Similarly, assessment of hepatobiliary pathology via abdominal ultrasonography is not needed at this time. Because she appears toxic with fever and headache, it is of paramount importance to rule out life-threatening bacterial meningitis. Therefore, a lumbar puncture should be the next test performed. Viral hepatitis serologies can be performed to evaluate the abnormal liver enzymes but are not urgent. Bone marrow biopsy could be considered as part of the workup for this patient's bicytopenia, particularly in light of the history of NHL, but does not need to be performed immediately.

Lumbar puncture revealed the following: colorless cerebrospinal fluid (CSF); red blood cell (RBC) count, 18.9/μL; total nucleated cells, 6.7/μL (0.0-5.0/μL); 0% neutrophils; 0% eosinophils; 21% mono/macrophages; 79% lymphocytes; 0% blasts; 0% other cells; CSF protein, 36 mg/dL (14-45 mg/dL); CSF glucose, 95 mg/dL.

2. Which *one* of the following statements is *most accurate* about the CSF findings?

a. The most likely diagnosis is acute bacterial meningitis
b. The presence of RBCs makes subarachnoid hemorrhage the most likely diagnosis
c. Fungal meningitis is likely because the patient lives in an area endemic for coccidioidomycosis
d. The slight elevation in WBCs and normal glucose level are most consistent with aseptic meningitis
e. The lymphocytes most likely represent recurrent follicular lymphoma that spread to the CSF

Acute bacterial meningitis typically presents with more than 1000 nucleated cells per microliter, a predominance of neutrophils, and elevated protein and decreased glucose levels. These findings were not seen in this CSF sample, although, notably, this patient was neutropenic and suspicion for bacterial meningitis should be maintained despite these CSF findings. Patients with subarachnoid hemorrhage typically have RBC counts in the hundreds, thousands, or even millions. In addition, this patient's CSF was clear with no evidence of xanthochromia, a reliable predictor of hemorrhage. Cerebrospinal fluid findings in fungal meningitis may be variable but most commonly include a predominance of lymphocytes, elevated protein level, and low glucose level. This patient lives in an area endemic for coccidioidomycosis, but the normal protein and glucose levels in her CSF make this diagnosis less likely. The mildly elevated WBC count and normal glucose level in this patient's CSF are consistent with aseptic meningitis, making this the most likely diagnosis. Recurrent lymphoma with leptomeningeal metastases may cause abnormal CSF findings including mild elevation in WBC count with a lymphocytic predominance, elevated protein level, and decreased glucose level. However, it is a very rare complication of follicular lymphoma, and it is much more likely that the lymphocytes in this patient's CSF are due to aseptic meningitis.

Empiric acyclovir, vancomycin, and ceftriaxone were administered intravenously until the results of CSF biochemistries and cultures were completed. Vancomycin was used instead of ampicillin for *Listeria* coverage because of the patient's penicillin allergy. Her fever resolved immediately after admission. Results of CSF cultures and herpes simplex virus polymerase chain reaction were negative, prompting discontinuation of antimicrobials. She received one dose of filgrastim, 300 μg subcutaneously, on the morning after admission, and the neutropenia resolved on day 3 of hospitalization. The liver enzyme levels continued to increase and peaked on hospital day 7 (AST, 375 U/L; ALT, 420 U/L; and alkaline phosphatase, 1019 U/L). Total bilirubin peaked at 6.8 mg/dL on hospital day 11. Coagulation test results remained normal. Computed tomography of the abdomen and pelvis revealed interval improvement in her sigmoid diverticulitis with persistent thickening of the colonic wall, no abscess or free air, no biliary duct dilatation, and no radiologic signs of acute cholecystitis. Retroperitoneal lymph nodes were

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stable compared with a study from 1 month earlier but enlarged compared with a study from 6 months previously.

3. Which *one* of the following is the *most likely* cause of acute cholestatic liver injury in this patient?

a. Sepsis due to smoldering acute diverticulitis
b. Ischemic hepatopathy from hypotension
c. TMP-SMX–induced hepatotoxicity
d. Lymphoma
e. Viral hepatitis

Abnormal results on liver function testing may occur in patients with sepsis secondary to bacterial infections such as diverticulitis as a result of cholestasis or hemolysis. In these cases, hyperbilirubinemia with bilirubin levels in the range of 2 to 10 mg/dL is typical,[1] but this patient had a normal total bilirubin level, making sepsis a less likely cause. Ischemic hepatopathy secondary to hypotension typically results in aminotransferase levels higher than those seen in this patient, whose AST and ALT peaked at under 500 U/L.[2] Trimethoprim-sulfamethoxazole–induced liver injury most commonly manifests in a cholestatic pattern,[3] and the temporal relationship between the use of TMP-SMX and the onset of this patient's symptoms is consistent with an adverse drug reaction. Our patient has a history of NHL, and recurrence of disease could potentially present with a cholestatic pattern of liver injury; however, fewer than 2% of patients with NHL have biliary tract obstruction.[4] Aside from stable retroperitoneal lymphadenopathy, no other signs of lymphoma were seen on imaging or physical examination. In patients with acute viral hepatitis, aminotransferase levels would be expected to be higher than those seen in this patient, although values similar to hers could be seen in patients with chronic viral hepatitis.[2]

Ultrasonography of the liver revealed normal echogenicity, no intrahepatic or extrahepatic biliary dilatation, and normal Doppler flow patterns. Viral hepatitis serologies including hepatitis B core antibody, hepatitis B surface antigen, hepatitis C virus, and hepatitis A virus IgM yielded negative results. Work-up for other autoimmune liver diseases, including antinuclear antibody, antimitochondrial antibody, and anti–smooth muscle antibody tests, was negative. Serologies and serum polymerase chain reaction for Epstein-Barr virus and cytomegalovirus indicated past infection without active viremia. Results of Q fever, *Strongyloides*, *Schistosoma*, toxoplasmosis, *Bartonella*, and coccidioidomycosis serologies were negative, as were human immunodeficiency virus and *Mycobacterium tuberculosis* by QuantiFERON. Flexible sigmoidoscopy revealed mild erythema in the sigmoid colon limited to the area 15 cm to 25 cm from the anal verge, which was identified histologically as nonspecific mild focal active colitis.

Ultrasonography-guided liver biopsy was performed. Pathologic examination of the specimen suggested acute hepatitis with a cholestatic pattern consistent with drug-induced liver injury, in this case most likely due to TMP-SMX.

4. Which *one* of the following statements is *most appropriate* for counseling this patient with TMP-SMX–induced cholestatic liver injury?

a. The majority of cases are self-limited and resolve with discontinuation of TMP-SMX
b. There is a 50% chance that "vanishing duct syndrome" will develop
c. Liver transplant evaluation should be initiated as an inpatient because there is a high likelihood of progression to fulminant liver failure
d. Ursodeoxycholic acid, 300 mg orally twice a day, should be prescribed because it has been proven effective for TMP-SMX–induced cholestasis
e. TMP-SMX desensitization may be appropriate in the future

Most cases of TMP-SMX–induced liver injury resolve when the medication is discontinued and do not cause permanent liver damage. Ductopenia or "vanishing duct syndrome" is very rare in TMP-SMX–induced hepatotoxicity, reported in only a handful of patients.[5] Although fulminant liver failure has been reported secondary to TMP-SMX,[6] it is rare, and most patients recover without need for liver transplant. The effectiveness of treating patients with drug-induced cholestatic liver injury with ursodeoxycholic acid or corticosteroids remains unclear; it appears that treatment with ursodeoxycholic acid may improve symptoms of cholestasis but does not accelerate recovery.[7] Patients with

severe adverse reactions to TMP-SMX should avoid both components of the medication in the future and should not attempt rechallenging or desensitization because of the potential for severe systemic toxicity.[7] This patient will most likely recover normal liver function once the medication is discontinued and is unlikely to experience progression to fulminant liver failure requiring transplant.

5. Which *one* of the following adverse effects (AEs) of TMP-SMX is the *most common*?

a. Aseptic meningitis
b. Hepatotoxicity
c. Hyperkalemia
d. Rash
e. Neutropenia

Aseptic meningitis is a rare presentation of drug-induced hypersensitivity that may be caused by exposure to TMP-SMX.[8] Symptoms may progress from fever and headache to confusion and coma if the medication is not discontinued. This reaction is immune mediated; the exact mechanism remains unclear, but it is likely not IgE mediated.[8] Hepatotoxicity is a recognized complication of treatment with sulfonamides such as TMP-SMX.[9] Incidence rates are typically less than 10%, although this incidence varies somewhat by ethnicity, and rates in some populations may be as high as 16%.[3] Hyperkalemia may be observed with TMP-SMX treatment because trimethoprim acts as a potassium-sparing diuretic by blocking amiloride-sensitive sodium channels in the collecting duct; this complication is more common at higher doses but may occur at low doses as well and is accelerated by impaired renal function.[10] Skin reactions are the most common AE in patients treated with sulfonamide drugs such as TMP-SMX and may take a wide range of forms, including the maculopapular rash experienced by this patient on the torso, arms, and legs.[9] Hematologic effects from TMP-SMX including neutropenia have been reported but they are rare.[9] This patient experienced aseptic meningitis, hepatotoxicity with a cholestatic pattern, maculopapular rash, and neutropenia as well as thrombocytopenia.

DISCUSSION

When patients present with a constellation of signs and symptoms including fever, headache, rash, hypotension, cytopenias, and abnormal liver enzyme levels, clinicians are obligated to rule out infection. In most cases, that assumption will be correct, so much so that premature closure and confirmation bias may lead clinicians to an incorrect diagnosis. Maintaining a broad differential diagnosis throughout the evaluation and management of these patients is essential to ensure that alternative etiologies are not overlooked. This case illustrates a classic noninfectious cause of fever, rash, cytopenia, and cholestasis—TMP-SMX toxicity.

Clinicians have used TMP-SMX for over 40 years as a cost-effective treatment for various common infections including urinary tract infections, respiratory tract infections, and skin infections. Trimethoprim-sulfamethoxazole inhibits bacterial synthesis of tetrahydrofolic acid, the physiologically active form of folic acid, thereby inhibiting bacterial DNA synthesis. It should be noted that a 50,000-times higher concentration of TMP would be required to inhibit the human form of dihydrofolate reductase, so it is a generally safe medication with a well-defined AE profile in immunocompetent patients.[11] These AEs include type A reactions, which are pharmacologically predictable and include gastrointestinal tract upset, hyperkalemia, and dose-related myelosuppression, and type B reactions, which are idiosyncratic and include severe liver failure, early-onset myelosuppression, and Stevens-Johnson syndrome.

Gastrointestinal tract (3%-8%) and cutaneous (3%-4%) AEs are most common and are attributed to the sulfonamide portion of the medication. These AEs tend to be mild and dose related and often do not necessitate discontinuation of the drug. The most commonly encountered gastrointestinal tract symptoms are nausea, vomiting, and anorexia. Multiple skin manifestations have been described including a maculopapular rash, as seen in this patient, urticaria, diffuse erythema, morbilliform lesions, erythema multiforme, purpura, or photosensitivity. Trimethoprim-sulfamethoxazole should be discontinued at the first sign of rash. Severe skin reactions like Stevens-Johnson syndrome and toxic epidermal necrolysis are rare, although they occur more commonly with sulfonamides than they do with other classes of antibiotics. Sulfonamides have been associated with forms of anemia, granulocytopenia, agranulocytosis, and thrombocytopenia. However, cytopenias are

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generally considered to be a rare AE of TMP-SMX.[9]

The trimethoprim portion of TMP-SMX is known to decrease the tubular secretion of creatinine, thus causing a mild, approximately 10% elevation in serum creatinine. It also decreases potassium excretion by altering the transepithelial voltage in the distal renal tubule resulting in hyperkalemia, especially in older patients or those with baseline renal dysfunction. Sudden death has been reported in older patients taking TMP-SMX and spironolactone, presumably due to hyperkalemia.[9]

Trimethoprim-sulfamethoxazole—induced hepatotoxicity may arise from a hypersensitivity reaction associated with glutathione metabolism or from metabolite-related toxicity. Sulfamethoxazole is metabolized in the liver via cytochrome P450 subtype 2C9 to hydroxylamine, which is hepatotoxic. The resulting liver injury may follow a hepatocellular pattern or, more commonly, a cholestatic pattern as seen in this patient.[3]

Drug-induced aseptic meningitis is an important entity to consider in patients like ours. A recent review[12] confirmed that the commonly implicated drugs are nonsteroidal anti-inflammatory drugs, antibiotics (most commonly trimethoprim), immunosuppressants and immunomodulators, and antiepileptics. Previous exposure to the drug was seen in 26% to 35% of patients. These reactions are mostly likely related to a hypersensitivity response, although mechanisms have not been fully elucidated. Drug-induced aseptic meningitis is typically a diagnosis of exclusion.

This patient's initial presentation was concerning for infection, but negative findings on infectious disease work-up and broader consideration of symptoms pointed to a pattern that was consistent with drug toxicity secondary to TMP-SMX. The temporal relationship between the initiation of TMP-SMX and the onset of the patient's most severe symptoms was especially important in making this diagnosis, which highlights the importance of obtaining a thorough history to elucidate a detailed timeline of events. Invasive diagnostic testing including liver biopsy was ultimately required to confirm this patient's diagnosis. Because TMP-SMX is a medication commonly used by clinicians in both the inpatient and outpatient settings, awareness of its AE profile, including both common and uncommon effects, is essential for early recognition of patients with drug toxicity so the medication can be discontinued promptly.

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