CLINICAL PROBLEM-SOLVING

# A Hand-Carried Diagnosis

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*In this* Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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**A 34-year-old black woman presented to a walk-in clinic with a 3-day history of malaise. Her colleagues had noticed yellowing of her eyes over the past few days.**

Scleral icterus, which is usually apparent when total serum bilirubin levels exceed 3 mg per deciliter (51 $\mu$mol per liter), is frequently first noticed not by the patient but by others. It may result from an excess of either unconjugated bilirubin (commonly due to hemolysis or ineffective erythropoiesis) or conjugated bilirubin due to hepatocellular or cholestatic disease. In this patient, viral hepatitis is the most probable cause of jaundice and associated malaise. Biliary tract disease, alcoholic liver disease, and autoimmune hepatitis should also be considered.

**The patient said she had no fever, chills, sweats, nausea, vomiting, diarrhea, abdominal or chest pain, cough, or dyspnea. There was no history of sickle cell disease or trait or recent travel. She said that she had not eaten raw oysters or seafood. She was employed as a pharmacy technician and said that she did not have any contact with blood products. She had no history of blood transfusions, injection-drug use, or tattoos. She had had one sexual partner for the previous 2 years, and her last sexual contact occurred 6 months earlier without barrier protection; she and her partner had previously used condoms. She had taken Ortho-Novum (Ortho-McNeil), her only medication, for the previous 2 years, but she discontinued this medication 5 months earlier when she broke up with her last partner because of his infidelity. She was a nonsmoker and said that she did not use alcohol or illicit drugs.**

The patient has painless jaundice. Although it appears to be an acute process, the duration of her illness may be longer than the 3 days she has noticed scleral icterus. Intrahepatic cholestasis is a recognized complication of oral contraceptives, particularly the combination of ethinyl estradiol and norethindrone. However, the 5-month delay from the discontinuation of contraceptive use to the appearance of jaundice would be inconsistent with this diagnosis. Other hepatobiliary disorders associated with oral-contraceptive use and jaundice, albeit rare and typically related to more than 2 years of use, include hepatic-vein thrombosis, peliosis hepatis, and hepatocellular carcinoma. The incubation period for sexually transmitted hepatitis B virus infection is shorter than the 6 months since the patient's last unprotected sexual contact. Her work in a pharmacy raises the possibility of hepatic injury from surreptitious use of drugs.

**On examination, her temperature was 38.0°C, blood pressure 110/78 mm Hg, and heart rate 100 beats per minute. Skin examination revealed no rash or spider angiomas. She had scleral icterus. There was no lymphadenopathy or thyromegaly. Chest**

**and cardiac examinations were normal. On abdominal examination, she had active bowel sounds and mild tenderness on deep palpation in the right upper quadrant. On percussion, the liver measured 12 cm in length with a smooth edge. There was no splenomegaly, fluid wave, or shifting dullness. There was no caput medusae. The rectal examination revealed normal tone with light brown, guaiac-negative stool. Neurologic examination was normal, without hyperreflexia or asterixis.**

There are no signs of chronic liver disease. Fever and tachycardia are consistent with infectious hepatitis. Jaundice and these signs can also be seen with hyperthyroidism, but the examination provides no additional support for this diagnosis. Cholestatic jaundice, mediated by proinflammatory cytokines, can be observed with extrahepatic bacterial infections; occasionally, jaundice may precede, by several days, other manifestations of sepsis. Although nonspecific, her mild right-upper-quadrant tenderness could be due to gallbladder disease or an intraabdominal abscess. Viral hepatitis remains the most likely diagnosis.

**The white-cell count was 9800 per cubic millimeter. The hemoglobin level was 12.8 g per deciliter, with a normal mean corpuscular volume. The hematocrit was 36.5%, and the platelet count was 270,000 per cubic millimeter. Analysis of the peripheral-blood smear showed a normal differential count with no band forms, basophilic stippling, or schistocytes. The serum electrolyte levels were normal. The albumin level was 3.7 g per deciliter, alkaline phosphatase 800 U per liter (normal range, 53 to 128), alanine aminotransferase 100 U per liter (normal range, 10 to 35), aspartate aminotransferase 65 U per liter (normal range, 14 to 50), total serum bilirubin 4.5 mg per deciliter (76.9 μmol per liter) (normal range, 0.3 to 1.2 [5.1 to 20.5]), direct bilirubin 3.8 mg per deciliter (64.9 μmol per liter) (normal range, <0.2 [<3.4]), and γ-glutamyltransferase 1051 IU per liter (normal range, 0 to 30). Tests for hepatitis B surface antibody, hepatitis B surface antigen, hepatitis A IgM antibody, and hepatitis C antibody were ordered.**

The patient's hepatic laboratory values exhibit a cholestatic injury pattern (a ratio of serum alanine aminotransferase to alkaline phosphatase of 2 or less and an associated elevation in the serum γ-glutamyltransferase level). Despite the absence of leukocytosis and a normal differential count, given the low-grade fever and right upper-quadrant tenderness on examination, an extrahepatic process needs to be excluded by means of abdominal imaging (either an abdominal ultrasound or computed tomography). Extrahepatic cholestasis can result from a broad range of disorders besides choledocholithiasis, including intrinsic and extrinsic tumors, parasitic infections, cholangiopathy associated with the acquired immunodeficiency syndrome, and pancreatitis. Her history does not particularly support these diagnoses, although her unprotected sexual contact with her promiscuous partner warrants testing for the human immunodeficiency virus (HIV) antibody. Viral hepatitis, particularly Epstein–Barr virus infection, may occasionally present with features of cholestasis, but screening for hepatitis A, B, and particularly C (in which seroconversion can be delayed for months) is expected to have a low yield in this case.

Intrahepatic cholestatic disorders to consider if the results of abdominal imaging are nondiagnostic include primary biliary cirrhosis, although this condition is more likely in a middle-aged white woman. Another such condition to consider is primary sclerosing cholangitis. However, this condition is more likely in men. An overlap syndrome of autoimmune hepatitis in which the immune attack is directed predominantly to the bile ducts and infiltrative processes such as sarcoidosis, tuberculosis, and lymphoproliferative disorders may also be considered. Drugs such as trimethoprim–sulfamethoxazole are associated with cholestatic liver injury, but the patient's history does not provide support for this diagnosis.

**An abdominal ultrasound study showed a homogeneously enlarged liver measuring 13 cm in length. There were no gallstones, and there was no pericholecystic fluid or thickening of the gallbladder wall. The common bile duct was not dilated. The pancreatic head and spleen appeared normal. A chest radiograph revealed no abnormalities.**

The ultrasound findings are consistent with intrahepatic cholestasis, although bile-duct dilatation may not always occur in disorders associated with partial or intermittent extrahepatic obstruction. The hepatomegaly may represent an acute inflammatory, infiltrative (granulomatous or neoplastic), or congestive process. In addition to further

serologic tests (e.g., antimitochondrial antibody), the evaluation of intrahepatic cholestasis with hepatomegaly may include a liver biopsy. In the absence of biliary-duct dilatation and cholelithiasis, hospitalization is not necessary at this time, but the prothrombin time should be determined.

**The prothrombin time was normal. Antinuclear antibody and antimitochondrial antibody titers were ordered. The patient was sent home and advised to rest and increase her fluid intake while awaiting the test results. She was asked to return to the clinic for follow-up in 3 days or sooner if new symptoms or signs arose.**

The absence of liver failure with a normal neurologic examination and prothrombin time provide support for the decision to pursue outpatient evaluation of presumed intrahepatic cholestasis. In a patient with laboratory evidence of cholestasis, an antimitochondrial-antibody titer greater than 1:40 would be compatible with the diagnosis of primary biliary cirrhosis.

**The patient returned to the clinic 3 days later. She now reported a new rash, which she described as having started on her abdomen and then spread to her arms and legs. She also noted nausea without vomiting. On examination, her temperature was 37.9°C, respiratory rate 16 breaths per minute, and heart rate 98 beats per minute. Her skin was warm and moist, with diffuse erythematous, papular lesions ranging from 0.5 to 1.3 cm in diameter on the torso, arms, and palms. The aspartate aminotransferase level was 80 U per liter, alanine aminotransferase 125 U per liter, total serum bilirubin 5.5 mg per deciliter (94.0 μmol per liter), direct bilirubin 4.5 mg per deciliter (76.9 μmol per liter), alkaline phosphatase 950 U per liter, and γ-glutamyltransferase 1275 IU per liter. Tests for hepatitis B surface antibody and surface antigen, hepatitis C antibody, hepatitis A IgM antibody, antinuclear antibody, and antimitochondrial antibody were all negative.**

Although papular eruptions can occur in cholestatic disorders such as sarcoidosis and lymphoma, the rash in combination with the time since unprotected sexual contact make secondary syphilis the probable diagnosis. A rapid plasma reagin test and fluorescent treponemal antibody absorption test should be performed. Cholestatic jaundice is one of the protean manifestations of syphilis. The patient's HIV status should also be determined; persons with HIV and syphilis coinfection are reported to have more organ involvement than HIV-negative patients with syphilis.

**The rapid plasma reagin test showed a titer of 1:128; the fluorescent treponemal-antibody titer was reactive. Syphilitic hepatitis was diagnosed, and the patient was treated with two injections of 2.4 million units of penicillin G benzathine that were given 1 week apart. Her symptoms and liver-test abnormalities completely resolved within 2 weeks after the initial injection. An HIV test was negative. The rapid plasma reagin titers at 3, 6, and 9 months were 1:64, 1:16, and 1:4, respectively.**

The rash on the palms of the patient's hands narrowed the broad differential diagnosis of intrahepatic cholestatic disorders and pointed to syphilis. The clinical manifestations of syphilis resemble many other diseases. This case illustrates the clinical pearl that uncommon presentations of common diseases occur more frequently than common presentations of uncommon diseases, although there is little to suggest that syphilis should have been considered sooner.

## COMMENTARY

Syphilitic hepatitis is a rare complication of primary and secondary syphilis. The majority of the cases reported in the past few decades have involved findings similar to those in our patient, with cholestatic jaundice, hepatomegaly, and elevations in alkaline phosphatase levels that are much greater than the elevations in aminotransferase or bilirubin levels.[1] Since syphilis is known as "the great imitator," and syphilitic hepatitis is rare, it is not surprising that the diagnosis of cholestatic jaundice due to *Treponema pallidum* infection was delayed.

The time from inoculation with *T. pallidum* to the presentation of primary syphilis with a chancre is inversely proportional to the inoculation dose and is typically 10 to 90 days. It is not uncommon for women to present with secondary syphilis, since chancres are painless, may reside unseen in the vagina, and typically resolve spontaneously within 3 to 6 weeks. The usual time from inoculation to the appearance of manifestation of secondary syphilis is 60 to 180 days.[2]

Our patient's presentation with secondary syphilis 6 months after her last unprotected sexual encounter is on the later side but within this period.

The overall rate of primary and secondary syphilis — the most infectious stages — steadily decreased from a high in the early 1990s to a nadir in 2000, but this rate has since increased again. These patterns, however, are driven by rates among whites (0.5 case per 100,000 persons in 2000, increasing to 1.6 cases per 100,000 in 2004). In contrast, the rate among blacks has fallen since 2000, but remains substantially higher than that among whites (9.0 cases per 100,000 persons in 2004).[3] The greatest overall increase in syphilis rates since 2000 has occurred among men who have sex with men (accounting for 70% of the patients with syphilis in 2004), many of whom are HIV-positive. Yet this case reminds us that heterosexual transmission still occurs, and immunocompetent patients are also at risk.

Syphilis in HIV-infected patients with clinically significant immunosuppression is reported to be associated with more protracted constitutional symptoms, greater organ involvement, and more rapid progression to neurologic involvement (e.g., meningitis or optic neuritis) than is syphilis in HIV-negative patients.[4,5] The discussant appropriately highlighted the need for HIV testing in our patient. This testing is relevant not only because HIV is a common coinfection, but also because the presence of HIV infection would warrant an evaluation for neurosyphilis by means of a lumbar puncture, whereas such an evaluation would not be necessary in the absence of HIV infection.[1,4,5]

*T. pallidum* remains sensitive to penicillin, with no resistance reported.[6] Long-acting penicillin preparations are still used because of the slow dividing times of *T. pallidum* in vivo; on average, the number of *T. pallidum* organisms doubles once per day.[7] Although data are lacking from clinical trials to guide the optimal regimen, according to case reports, the standard treatment of primary and secondary syphilitic hepatitis has typically been 2.4 million units of penicillin G benzathine given intramuscularly weekly for 1 to 3 weeks.[8-10] A single, intramuscular injection of penicillin G benzathine at a dose of 2.4 million units provides low but persistent serum levels of penicillin, lasting up to 30 days, and is the standard treatment for primary, secondary, and early latent syphilis.[6,11]

The response of syphilitic hepatitis to treatment is rapid, with resolution of the biochemical findings and clinical features within 2 to 3 weeks after the start of treatment.[10,11] The assessment of the ultimate success of therapy for primary or secondary syphilis should be based on serial monitoring of Venereal Disease Research Laboratory test results or rapid plasma reagin titers. Successfully treated patients will have a decline in titer within 6 months after initiating therapy that is four times greater than that among patients who have not been successfully treated.[10] Our patient's rapid response and falling rapid plasma reagin titers are consistent with successful treatment.

Our patient did not have the Jarisch–Herxheimer reaction, which is characterized by the acute onset of fever, rash, myalgia, headache, and hypotension. Since *T. pallidum* lacks endotoxin, this reaction is now believed to result from the release of large amounts of treponemal lipoproteins that stimulate the production of inflammatory mediators.[12,13] Given her high titers, suggesting a large treponemal load, she was at risk for this reaction. In addition to antibiotic therapy, partner notification and contact tracing are essential elements of appropriate follow-up and disease containment.

A critical part of the initial evaluation of patients with jaundice is determining whether hospital admission is warranted. Both the team caring for the patient and our discussant were comfortable with outpatient evaluation, since the patient was considered to be reliable (and proved to be so), and there was no evidence of severe dehydration or liver failure (including no evidence of encephalopathy and a normal prothrombin time). In addition, without ultrasound evidence of bile-duct dilatation and in the absence of toxic effects in the patient's appearance, the likelihood of acute ascending cholangitis was low. However, as the discussant noted, despite the absence of common-duct dilatation on ultrasonography, there is still a 10% chance of extrahepatic obstruction from choledocholithiasis.[14]

The key to the diagnosis in our patient was the palmar rash. Despite the known link between secondary syphilis and cholestatic jaundice, both the team and the discussant omitted syphilis from their initial differential diagnosis. This case illustrates the importance of pattern recognition in making diagnoses.

Watchful waiting can be a powerful tool when evaluating outpatients with a stable condition.

Patience in our case averted an unnecessary, costly, and potentially hazardous liver biopsy or endoscopic retrograde cholangiopancreaticography. Furthermore, it permitted the disease to unfold and led the patient to literally deliver a hand-carried diagnosis to her physicians.

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