MORNING REPORT

An Atypical Cause of Jaundice

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A 63-year-old woman presents to her primary care physician with a 10-day history of nausea and fatigue and a one-day history of jaundice. She reports associated mild itching, dark urine, and light colored stools. She denies any abdominal pain, diarrhea, fevers, night sweats, confusion, shortness of breath, chest pain, skin rashes, or other urinary complaints. Her initial laboratory studies show a total bilirubin of 34.6 mg/dL, direct bilirubin 25.2 mg/dL, aspartate aminotransferase (AST) 1931 U/L, alanine aminotransferase (ALT) 1147 U/L, alkaline phosphatase 131 U/L, gamma glutaminase (GGT) 49 U/L (normal range: 5-39 U/L), albumin 2.7 g/dL, INR 1.9, platelets 176 K/mm3 and creatinine of 1.1 mg/dL. The patient is admitted to the hospital for further management.

The patient's laboratories are consistent with conjugated hyperbilirubinemia, acute hepatocellular injury, and signs of liver failure (low albumin and increased INR). The most striking abnormality is the high conjugated hyperbilirubinemia. The differential diagnosis for conjugated hyperbilirubinemia can be divided into three main categories: biliary obstruction (extrahepatic cholestasis), intrahepatic cholestasis, and hepatocellular injury. Given the relatively normal alkaline phosphatase and GGT, biliary obstruction is much less likely. However, in patients with prior cholecystectomies, biliary obstruction may be associated with an early severe increase in transaminase levels before bilirubin and alkaline phosphatase trend upward. The increase of her AST and ALT levels to greater than 20 times the upper limit of normal indicates acute hepatocellular necrosis, most commonly caused by viruses (hepatitis A, B, C, D, or E), drugs (acetaminophen), toxins (alcohol), or by hepatic ischemia. Autoimmune hepatitis should be considered, especially in patients with other autoimmune diseases and in postmenopausal women. Wilson's disease should be considered not only in young adults but also in patients with AST greater than ALT associated with a disproportionate low alkaline phosphatase.

The patient's clinical history and the short time course are most consistent with an acute viral hepatitis or acute toxic injury. The patient should have a detailed history and physical exam performed to determine the etiology. Special focus should be made on medication use, exposure to sick contacts, vaccination status, risk factors for viral hepatitis, alcohol use (including binge drinking), and over-the-counter medications. For instance, supplements such as ma huang and valerian root can cause hepatic disease. On physical exam, evaluation for stigmata of chronic liver disease such as spider angiomas, palmar erythema, and caput medusa should be undertaken. Also, signs of ascites, asterixis, and encephalopathy should be assessed to further determine the severity of the liver disease.

The patient denies any recent travel or sick contacts. She also denies starting any new medications, dietary supplements, or use of acetaminophen in the past six months. The patient is married and is a retired school teacher. She does not drink alcohol and has never used illicit intravenous drugs. The patient denies blood transfusions, and she has been vaccinated for hepatitis B. Her past medical history is significant only for hyperlipidemia, for which she has taken simvastatin/ezetimibe for many years, and hypothyroidism, for which she is taking levothyroxine.

On physical exam, she is jaundiced but in no acute distress. Her mental status is normal without encephalopathy. Her abdominal exam reveals mild right upper quadrant tenderness and mild lower abdominal tenderness but no organomegaly or ascites. She has no signs of chronic liver disease or asterixis.

The physical examination confirms a more acute course of her hepatic disease. The next step should include evaluation for viral hepatitis by viral serologies, autoimmune hepatitis by obtaining antinuclear antibody (ANA) and anti-smooth muscles antibody (ASMA) titers, and evaluation for infiltrative diseases by obtaining iron profile and ceruloplasmin. We should obtain a right upper quadrant ultrasound with liver Dopplers to look for signs of biliary obstruction and to rule out portal vein thrombosis and Budd Chiari syndrome. Given the poor liver synthetic function and the very high bilirubin, her clinical condition has the potential to worsen rapidly, and she will likely need a liver biopsy. I would obtain a hepatology consult at this time to expedite her diagnosis and treatment.

Further workup demonstrates negative serologies for hepatitis A, B, and C and Epstein-Barr virus. She has a negative cytomegalovirus PCR. She has an ANA less than 1:40, ASMA less than 1:40, anti-mitochondrial antibody titer less than 1:40, and normal alpha-1-antitrypsin and ceruloplasmin levels. Her ferritin level is 2181

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ng/mL, which is compatible with acute inflammation. The gamma globulin fraction on serum protein electrophoresis is elevated. Right upper quadrant ultrasound shows normal echogenic liver, normal bile ducts, no ascites, and patent portal vein with evidence of portal hypertension. The hepatology service recommends a liver biopsy, which shows mixed portal inflammation and the presence of damaged bile ducts. An atypical antineutrophil cytoplasmic antibodies (atypical p-ANCA) screen is done, which returns positive. The patient is started on budesonide, 3 mg orally three times a day, for presumptive autoimmune hepatitis.

Autoimmune hepatitis is divided in two types based on the associated autoantibodies. Type 1 or "classic autoimmune hepatitis" is usually associated with positive ANA and ASMA. Type 2 on the other hand is less common and usually associated with antibodies to liver/kidney microsomes (ALKM-1). There has been one other case report of a patient with type 1 autoimmune hepatitis with negative ANA and ASMA but positive atypical p-ANCA (as in our patient). Atypical p-ANCA are antibodies that have an atypical staining pattern on immunofluorescence directed against a myeloid 50-kd nuclear envelope protein. These antibodies are nonspecific and can be seen also in primary sclerosing cholangitis and in inflammatory bowel disease. In one study, 81% of patients with autoimmune hepatitis had atypical p-ANCA.

The patient's liver biopsy pattern includes dense mononuclear infiltrates consisting of lymphocytes and plasma cells, characteristic autoantibodies, and increased gamma globulin. These findings are most consistent with autoimmune hepatitis. Establishing the diagnosis can be challenging sometimes. A scoring system using a simplified revision of the International Autoimmune Hepatitis Group criteria can be used to help make the diagnosis. This scoring system takes into consideration autoantibodies, IgG level, liver histology, and absence of viral hepatitis to predict the probability of autoimmune hepatitis.

The patient initially feels better, but she continues to have persistent hyperbilirubinemia. A few days later, she develops worsening renal function and fatigue. Her budesonide is changed to prednisolone, but soon she becomes encephalopathic and is transferred to the ICU. Liver transplant evaluation is initiated. Blood and urine cultures are obtained. Her blood culture grows *Enterobacter cloacae* and urine culture grows *Klebsiella pneumoniae*. No ascites is detected on repeat ultrasound. In the ICU, she receives intravenous fluids, broad-spectrum antibiotics, rifaximin, and lactulose. Her renal function, total bilirubin, and mental status continue to deteriorate. She undergoes liver transplant a week later after treatment of her infection is complete.

Autoimmune hepatitis can present with a wide spectrum of severity. Poor prognostic indicators include severe hepatic inflammation on presentation, inability to achieve remission, or the development of multiple relapses. Treatment with steroids may improve quality of life, prolong survival, and delay the need for transplantation. Azathioprine has been used as a steroid sparing agent. Remission is generally not seen before 12 months, but 90% of patients will have improvement in aminotransferases, bilirubin, and gamma globulin within two weeks. Histological improvement usually takes three to eight months.

Take Home Points

1. Autoimmune hepatitis should be in the differential diagnosis for patients with elevated transaminases and hyperbilirubinemia, especially when other autoimmune diseases are present.
2. Conventional autoantibodies, such as ANA and ASMA, are typically elevated in type 1 autoimmune hepatitis; on occasion, atypical p-ANCA may be the only marker of autoimmune hepatitis.
3. The severity of autoimmune hepatitis ranges from asymptomatic presentation to fulminant hepatic failure.

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