A 44-Year-Old Woman With Jaundice and Abdominal Pain

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INTRODUCTION

Primary biliary cirrhosis (PBC) is an autoimmune disease of the liver. It is characterized by a T-cell-mediated attack of the small, intrahepatic bile ducts. The exact etiology is unknown, but it is thought to be a result of a combination of genetic predisposition and environmental factors. The vast majority of patients affected by PBC are women. The natural history of the disease varies by patient, but it is generally thought to be a chronic, progressive disease that carries a high mortality rate if not treated definitively with liver transplantation. The diagnosis of PBC is made with the combination of clinical findings and laboratory data, including antimitochondrial antibodies. The diagnosis can also be further confirmed with a liver biopsy. We present a case of a woman who presented with abdominal pain, jaundice, and significant weight loss and was diagnosed with PBC based on autoantibody testing and liver biopsy. We also present a review of the epidemiology, etiology, clinical findings, diagnosis, and treatment options for PBC.

CASE PRESENTATION

A 44-year-old woman with a past medical history of cholelithiasis, status-post cholecystectomy three years prior, presented to her primary care physician complaining of progressively worsening right-sided abdominal pain of two months duration. She described the pain as “heavy,” located throughout the right side of her abdomen, 5/10 in intensity, and progressively worsening throughout the day. She reported that the pain was exacerbated by lying on her right side. She did admit to occasional radiation to her back and flank on the right side. The pain was not associated with eating. She also denied any nausea, vomiting, diarrhea, melena, hematochezia, dysphagia, decreased appetite, or pruritus. Review of systems was otherwise positive for a 35-pound, unintentional weight loss over the prior three months. After her primary care physician noted abnormalities in her routine lab work, the patient was told to present to the emergency department for further workup.

Vital signs at the time of presentation were only notable for a pulse of 100 beats per minute and a temperature of 99.0 degrees Fahrenheit. Head and neck examination revealed sublingual icterus, as well as scleral icterus bilaterally. Abdominal examination revealed mild tenderness to palpation in the epigastric region, as well as the right upper quadrant without rebound or guarding. A Murphy’s sign was absent. The liver edge was palpated at 12 cm below the right costal margin, and the spleen was palpated at 3 cm below the left costal margin. Spider angiomata were noted in two spots on the right forearm, one spot on the left lower leg, and one spot on the back. Palmar erythema was noted as well.

Initial laboratory workup revealed an elevated total bilirubin of 4.7 mg/dl (<1.3 mg/dl), alkaline phosphatase of 795 U/L (20-120 U/L), GGT of 1,199 U/L (<55 U/L), AST of 318 U/L (<46 U/L), and ALT of 289 U/L (<46 U/L). Erythrocyte sedimentation rate was mildly increased at 22 mm/hr (0-20 mm/hr). Total cholesterol was 554 mg/dl (<200 mg/dl), triglyceride level was 923 mg/dl (<150 mg/dl), and LDL level was 344 mg/dl (<130 mg/dl). An acute hepatitis panel was performed and was negative. An ammonia level was elevated at 72 Umol/L (9-35 Umol/L). Urine drug screen and salicylate levels were not abnormal.

Imaging at the time of admission included a right upper quadrant ultrasound that revealed an enlarged liver at approximately 25 cm in sagittal dimension with no focal hepatic abnormality, an enlarged spleen at approximately 15.7 cm in sagittal dimension, normal flow in the portal vein, and an enlarged 2.3 cm lymph node near the porta hepatitis. The gallbladder was surgically absent. The common bile duct was noted to be normal, and no masses or free fluid were appreciated. Computed tomography of the abdomen on the day of admission confirmed the findings of the abdominal ultrasound (Figures 1, 2). A routine chest radiograph revealed no acute cardiopulmonary process.

A rheumatologic workup was pursued. While anti-
nuclear antibody levels were negative, the anti-mitochondrial antibody level was elevated at 26.5 units (<20 units). C-ANCA, P-ANCA, alpha-1-antitrypsin level, transferrin, ceruloplasmin, and AFP were all normal. An outpatient liver biopsy was performed to further confirm the suspected diagnosis of PBC. The results revealed severe portal lymphocytic and granulomatous inflammation with small interlobular duct ductopenia/destruction and extensive periportal necroinflammatory changes, consistent with early-stage primary biliary cirrhosis (Figures 3, 4).

**DISCUSSION**

Primary biliary cirrhosis (PBC) is a progressive autoimmune disease that primarily affects women. Of the estimated 9,232 cases of PBC in the United States in 1996, 88.7% occurred in females.\(^4\) Autoimmune-mediated destruction of intrahepatic bile ducts eventually leads to bile flow obstruction, hepatic fibrosis, cirrhosis, and eventual liver failure. The exact etiology continues to be a subject of investigation, but it is described by Gershwin and Mackay to be a combination of genetic predisposition and underlying environmental factors.\(^5\) Selmi et al. also suggest a genetic component by showing that the concordance of PBC in monozygotic twins is about 63%.\(^1\) Based on a systematic review of epidemiologic studies published by Boonstra et al. in the *Journal of Hepatology* in 2012, worldwide incidence rates of PBC range from 0.33-5.8 per 100,000 and prevalence rates range from 1.91-40.2 per 100,000.\(^6\)

Due to improved awareness and diagnosis earlier in the clinical course, 50-60% of patients are asymptomatic at the time of diagnosis.\(^7\) The most common symptoms seen in PBC are fatigue and pruritus.\(^8\) Pruritus is estimated to occur in 25%-75% of patients with PBC. It can often precede the actual diagnosis by several years, highlighting the need to consider PBC in any patient with pruritus that is not associated with a rash.\(^9\) The

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**Figure 1:** Axial contrast-enhanced CT demonstrates hepatosplenomegaly with an enlarged perportal lymph node (arrow), which measures greater than one centimeter in maximal short axis diameter.

**Figure 2:** Coronal contrast-enhanced images show hepatosplenomegaly with the liver and spleen measuring 28 and 23 centimeters in maximal craniocaudal dimensions, respectively.
pruritis in PBC is thought to be directly related to cholestasis, decreased bile excretion, and subsequent accumulation of bile in the plasma and tissues. Fatigue is the most consistent symptom of PBC, occurring in about 70%-80% of patients. The exact etiology is still unknown, but peripheral muscle fatigability and autonomic dysfunction as mechanisms have been proposed. Less common symptoms may include Sicca Syndrome (dry eyes and mouth), cutaneous calcinosis, Raynaud’s phenomenon, and dysphagia, as PBC can be associated with other autoimmune diseases such as Sjogren’s syndrome and scleroderma. The physical exam is often normal in the asymptomatic patient. Skin hyperpigmentation due to melanin deposition may be seen earlier in the course, while jaundice is a late manifestation. Hepatomegaly is found in about 70% of patients, and splenomegaly may develop as the disease progresses.

The diagnosis of PBC should always be considered in the setting of cholestasis after the exclusion of other liver diseases. Most patients have a significantly elevated alkaline phosphatase with milder elevations in the aminotransferases. The degree of alkaline phosphatase elevations generally correlates with the severity of ductopenia and inflammation. As the disease progresses, a rise in serum bilirubin, along with a decrease in serum albumin and platelets, may signal the development of cirrhosis and portal hypertension. Serum cholesterol levels are often markedly elevated as well.

While anti-nuclear antibody (ANA) is only positive in approximately 70% of patients with PBC, anti-mitochondrial antibody (AMA) is found in nearly 95% of cases. As in this case, primary biliary cirrhosis will often manifest with nonspecific findings on ultrasonography and CT. Common imaging findings include signs of portal hypertension, including splenomegaly, ascites, and varices. Hepatomegaly is also often present, particularly in earlier phases of the disease. Enlarged upper abdominal lymph nodes, which can enhance, are also a common finding. MRI can have improved specificity, particularly in later stages of the disease, manifesting a periporal halo sign. This sign is characterized by low T1 and T2 signal intensity in a periporal distribution without mass effect. The sign reflects periporal parenchymal loss adjacent to regenerative nodule formation. Aside from diagnostic utility, cross sectional imaging can also be used for screening for hepatocellular carcinoma, as these patients carry an increased risk (~5%).

The classic findings on liver biopsy of patients with PBC is asymmetric destruction of the bile ducts within the portal triads. Patients are further classified into stages (i.e., stage one through four) based on the degree of destruction and the number of bile ducts involved. Stage 1 is inflammation localized to the portal triads, while stage 4 represents end-stage liver disease. In 2009, The American Association for the Study of Liver Diseases (AASLD) published recommendations for the diagnosis of PBC. The diagnosis can be made if any two of the following three criteria are met:

- Biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation
- Presence of AMA

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• Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts

The only FDA-approved therapy for PBC is ursodeoxycholic acid (UDCA). Several studies have supported the usefulness of UDCA in slowing the progression of liver failure and improving mortality rates. UDCA is indicated for any patient with PBC and abnormal liver chemistries, regardless of stage. Appropriate dosing of UDCA is paramount, as studies have shown superior results with a dose of 13-15 mg/kg/day when compared to either a lower or higher dose. Some of the other medications that have been tested as a single agent in the treatment of PBC include chlorambucil, penicillamine, cyclosporine, corticosteroids, azathioprine, mycophenolate mofetil, thalidomide, methotrexate, malotilate, and colchicine. None of the above-mentioned medications have been shown to be of benefit, either as single-agent treatments or in combination with UDCA. Treatment of the major symptoms of PBC, including fatigue and pruritis, is also often a focus of management. At this time, there is no recommended therapy for fatigue in PBC. The selective serotonin reuptake inhibitor, fluoxetine, has not shown any improvement of fatigue in the setting of PBC, while modafinil, a medication used for excessive daytime sleepiness, has shown some benefit. Pruritis in PBC is not generally relieved by UDCA. The AASLD recommends that bile acid sequestrants be used as a first-line treatment for pruritis, followed by rifampicin, oral opiate antagonists, or sertraline for refractory cases. Outcomes for liver transplantation in patients with PBC are generally more favorable than transplants for other indications. Transplantation also improves fatigue, pruritis, and bone disease in PBC. Timing of transplantation is key and can be better determined by using one of several prognostic formulas. One of the most widely used, the Mayo model, takes into account several factors, including serum bilirubin level, serum albumin level, age, prothrombin time, and presence or absence of peripheral edema. In combination with the Mayo model, the Model for End-Stage Liver Disease (MELD) is also used to guide timing of liver transplantation. Up to 20%-25% of patients who undergo transplantation for PBC will have recurrent disease in 10 years; however, cyclosporine-based immunosuppression appears to reduce recurrence risk.

In conclusion, PBC is a progressive, autoimmune disease of the liver seen primarily in women. It is diagnosed based on a combination of clinical findings and laboratory data, with elevation of alkaline phosphatase and the presence of AMA being the hallmarks. The most consistent symptoms of PBC are fatigue and pruritis. Skin hyperpigmentation due to melanin deposition may also be seen early in the course, while jaundice is a late presentation. Per the AASLD practice guidelines, the diagnosis is largely based on biochemical evidence of cholestasis, presence of AMA, and liver biopsy. The only FDA-approved medication for treatment of PBC is UDCA, which has been shown to improve survival. Liver transplantation is a definitive treatment with overall favorable outcomes. PBC should be suspected in any patient with unexplained cholestasis or pruritis. Timely diagnosis and early referral to a specialist is imperative for these patients.

REFERENCES

Dr. Guillory is a Chief Resident of the Internal Medicine Program in the Department of Medicine at Louisiana State University Health Sciences Center in New Orleans. Dr. Jordan is a second-year Resident in Internal Medicine in the Department of Medicine at LSUHSC-New Orleans. Dr. Spieler is an Assistant Professor in the Department of Radiology at LSUHSC-New Orleans. Dr. Safley is a Chief Resident of the Department of Pathology at LSUHSC-New Orleans. Dr. Hutchings is an Assistant Professor in the Department of Gastroenterology at LSUHSC-New Orleans. Dr. Saketkoo is an Assistant Professor in the Department of Rheumatology; Scleroderma and Sarcoidosis Patient Care and Research Center Director; and Associate Director of the Rheumatology Fellowship at LSUHSC-New Orleans. Dr. Lopez is the Richard Vial Professor and Vice Chair for Education in the Department of Medicine at LSUHSC-New Orleans.