Case Report

Primary Biliary Cholangitis as the Initial Manifestation of Systemic Lupus Erythematosus: A Case Report

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex autoimmune disease affecting multiple organs, commonly seen in women of childbearing age. Its incidence varies globally, ranging from 1 to 10 cases per 100,000 person-years. Liver involvement in SLE is relatively rare, occurring in 3-9% of cases. Primary biliary cholangitis (PBC), a chronic autoimmune liver disease, leads to bile duct destruction, cholestasis, and, if untreated, liver cirrhosis. The global prevalence of PBC is 14.6 per 100,000 persons, with lower rates observed in the Asia-Pacific region. PBC can coexist with SLE, though rare, with a reported prevalence of 0.27% among SLE inpatients. PBC often precedes SLE diagnosis in patients with both conditions and is associated with more severe disease manifestations and complications.

A 20-year-old woman presented with jaundice, abdominal pain, and fever, alongside a history of acute cholestatic liver failure and kidney injury. Investigations revealed liver cirrhosis, confirmed PBC through antibody testing, and severe SLE. Treatment included steroids, hydroxychloroquine, ursodeoxycholic acid (UDCA), and supportive therapies, resulting in significant clinical improvement.

Clinicians should consider the possibility of overlapping autoimmune diseases such as PBC and SLE, especially in young women presenting with cholestasis and systemic symptoms.

Keywords: Primary biliary cholangitis, Autoimmune hepatitis, Systemic lupus erythematosus, Cholestasis, Intrahepatic cholestasis

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INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by the progressive destruction of the bile ducts, leading to cholestasis and potentially liver cirrhosis if untreated. The global incidence and prevalence of PBC are estimated at 1.76 and 14.60 per 100,000 persons, respectively. These rates vary significantly by region, with North America exhibiting the highest incidence and prevalence (2.75 and 21.81 per 100,000 persons), followed by Europe (1.86 and 14.59 per 100,000 persons), and the lowest rates observed in the Asia-Pacific region (0.84 and 9.82 per 100,000 persons) (1). The disease is primarily observed in middle-aged women, and its etiology is linked to genetic, environmental, and immunological factors. The hallmark of PBC is the presence of antimitochondrial antibodies (AMA), which are detected in 90-95% of cases, along with elevated levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), indicating bile duct damage (1).If left untreated, PBC may lead to liver failure and other complications, such as hepatocellular carcinoma and esophagogastric varices. Systemic lupus erythematosus (SLE), on the other hand, is a multisystemic autoimmune disease that predominantly affects young women. SLE is marked by antinuclear antibodies (ANA) and a wide array of clinical manifestations, ranging from mild cutaneous involvement to severe organ damage affecting the kidneys, heart, and central nervous system. While SLE typically presents with a combination of systemic symptoms such as fatigue, arthralgia, and skin rashes, it can also involve the liver, though hepatic manifestations are less common (2). The overlap of PBC and SLE is rare, but emerging evidence suggests that autoimmune diseases frequently coexist, making PBC a potential initial manifestation of SLE in certain patients.In this case report, we describe a patient with PBC who was later diagnosed with SLE, highlighting the diagnostic challenges and clinical implications of this unusual overlap syndrome. Early recognition of PBC in patients with SLE is crucial, as liver involvement can significantly influence disease prognosis and treatment strategies. This report highlights the importance of considering overlapping autoimmune diseases in patients with atypical presentations. Early recognition and treatment of PBC and SLE are critical to preventing disease progression and managing potential complications. The coexistence of these two diseases presents a complex clinical challenge but offers valuable insight into the interplay between autoimmune liver diseases and systemic conditions like SLE.

CASE REPORT

A 20-year-old woman was admitted to Adam Malik Hospital due to jaundice, recurrent right upper quadrant pain, and fever 2 weeks before admission. She also experienced nausea and vomiting, anorexia, increased abdominal girth, generalized weakness, which caused immobilization, bilateral lower extremity edema, and foamy, tea-colored urine. She had a history of acute cholestatic liver failure, seizure, and acute kidney injury and was admitted to intensive care one month before admission. She denied consuming any anti-seizure drugs, and the seizure had not been repeated. She denied consuming any medication after her previous hospital admission.

On examination, she was moderately ill, compos mentis, with stable vital signs. Her visual analog scale for abdominal pain was 4-5 out of 10. She had anemic conjunctivae and icteric sclera (Figure 1). Her abdominal examination revealed right hypochondriac pain and shifting dullness, with a typical bowel sound. She had bilateral non-pitting lower extremity edema. Her skin was jaundiced, and rashes on her trunk were present (Figure 2). Other physical and neurological examinations were unremarkable.

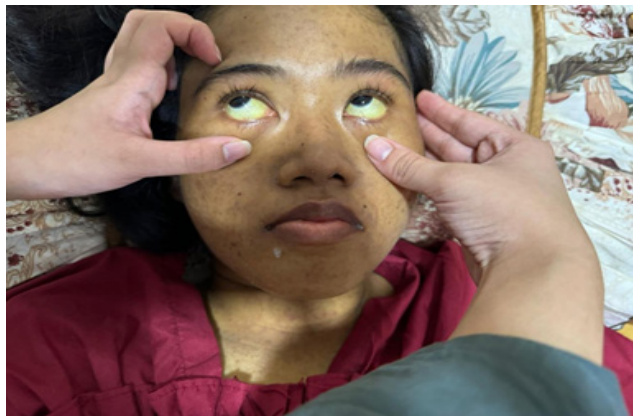

Figure 1. Icteric Sclera (Written informed consent was obtained from the patient for publication of this clinical image.)

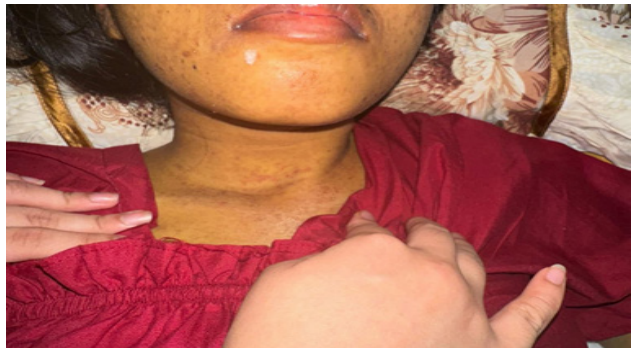

Figure 2. Jaundice Skin (Written informed consent was obtained from the patient for publication of this clinical image.)

Initial laboratory examination revealed normocytic anemia (Hb 8.0 g/dL, MCV 82 fL, MCH 28.6 pg) and thrombocytopenia (68.000/uL), increased serum aspartate transaminase (AST) with a normal alanine transaminase (ALT), increased ALP (831 U/L) and gamma GT (657 U/L), increased total bilirubin (direct predominance) (total 9.17 mg/dL, direct 7.68 mg/dL), hypoalbuminemia (1.5 g/dL), increased INR (2.6 s) and prothrombin time (35.3 s), increased CA 19-9 (265 U/mL) and AFP level (11 ng/mL), increased urea (128 mg/dL) and creatinine (2.64 mg/dL), and a non-reactive viral hepatitis marker (anti HCV, HbsAg, and anti HAV). Her urinalysis showed proteinuria (+1) and bacteriuria (+145). The fecal occult blood test was positive. She later underwent an abdominal computed tomography (CT) scan with a contrast agent, which revealed liver cirrhosis, splenomegaly, cholecystitis, diffuse colitis involving the whole colon, ascites, bilateral inguinal lymphadenopathy, and left pleural effusion with pleuritis. She underwent a gastroscopy, which revealed esophagitis and diffuse gastritis. During hospitalization, additional history-taking revealed she had been experiencing hair loss and polyarthritis. ANA and 24-hour protein urine tests were done, and both were elevated. Antinuclear antibody (ANA) profile, perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), antimitochondrial antibody (AMA), and antismooth muscle antibody (ASMA) tests revealed positive antibodies for antimitochondrial antibody type M2 (AMA-M2), ribonucleoprotein/Smith (RNP/Sm), Smith (Sm) antibody, Sjögren's syndrome-related antigen A (SSA), Ro-52 antibody, and Sjögren's syndrome-related antigen B (SSB), Histones, and Ribosomal Protein.

She was diagnosed with PBC, liver cirrhosis, Child-Pugh class C, severe SLE, acute kidney injury stage III, hypoalbuminemia, anemia, and thrombocytopenia due to chronic liver disease. She was treated with pulse dose steroids, hydroxychloroquine, ursodeoxycholic acid (UDCA), diuretics, propranolol, and albumin transfusion. After 6 days, she was allowed to undergo outpatient treatment. Ursodeoxycholic acid (UDCA), propranolol, spironolactone, furosemide, steroid, and hydroxychloroquine were continued. She showed remarkable improvement in clinical and laboratory parameters during the follow-up visit. An magnetic resonance cholangiopancreatography (MRCP) evaluation was done during the outpatient visit and revealed liver cirrhosis without any abnormality on the biliary system.

DISCUSSION

PBC is a chronic autoimmune condition characterized by periportal inflammation and ductal necrosis, which can result in a reduction in the number of ducts (ductopenia). The diagnosis of PBC should contain at least two criteria: 1. Biochemical evidence of cholestasis (increased ALP/GGT) and exclusion of extrahepatic cholestasis by imaging examination; 2. The presence of AMA/AMA-M2 or other PBC-specific autoantibodies (anti-sp100/anti-gp210); and 3. Histological evidence of non-suppurative destructive cholangitis and destruction of the interlobar bile ducts (3). Our patient fulfilled the 1st and 2nd criteria for PBC. Histological examination was not done.

As in another autoimmune disease, female predominance also occurs in PBC, possibly due to hormonal (particularly estrogen) and genetic factors. Unlike in this case, which involves a 20-year-old female patient, PBC usually occurs in middle-aged women. Estrogen modulates immune responses, which influences the activity and regulation of immune cells. This could potentially lead to a loss of tolerance and increased autoimmunity in women. The presence of estrogen receptors, particularly estrogen receptor alpha (ERα), has been linked to the immune response differences observed in PBC. Estrogen also affects bile acids and cholangiocytes. It stimulates the cholangiocytes to secrete exosomes containing the long noncoding RNA (lncRNA) H19, thereby exacerbating cholestatic liver injury, a characteristic of PBC (4).

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by periportal inflammation, hypergammaglobulinemia, circulating autoantibodies, and liver necrosis. It predominantly affects young women. AIH diagnosis should fulfill at least two criteria: 1. ALT levels over five times the upper limit normal (ULN) value; 2. Serum IgG levels over two times ULN or positive ASMA test; 3. Liver biopsy showing moderate/severe periportal/periseptal lymphocytic piecemeal necrosis or liver biopsy showing interface hepatitis – atypical findings of AIH. PBC and AIH often occur concomitantly, known as PBC/AIH overlap syndrome. It occurs when a patient fulfills at least two criteria for both AIH and PBC. Patients with PBC/AIH overlap syndrome may experience a more rapid progression to cirrhosis and liver failure, which is associated with a more severe clinical outcome compared with those with PBC alone (5). Our patient fulfilled two criteria for PBC and only one criterion for AIH. In this case, the overlap of PBC and AIH did not occur.

If untreated, PBC leads to cholestasis and cirrhosis. The clinical manifestations of PBC vary among patients, ranging from asymptomatic to severe symptoms. Patients with PBC often experience debilitating fatigue, mild to severe itching that worsens at night, jaundice, and hepatosplenomegaly. Cholestasis disrupts lipid metabolism, resulting in the accumulation of cholesterol deposits on the skin and tendons, which manifest as xanthelasma or xanthoma. Patients with

PBC are at increased risk for bone density loss due to malabsorption of fat-soluble vitamins, leading to conditions such as osteoporosis and osteopenia. Other symptoms may be experienced, such as abdominal pain, dry eyes, and dry mouth (sicca syndrome), and other autoimmune-related symptoms. The progression of symptoms often correlates with the stage of liver disease, and early diagnosis and treatment are crucial to managing the condition and improving patient outcomes (6). Our patients experienced abdominal pain and generalized weakness. She experienced symptoms due to decompensated liver cirrhosis, such as jaundice and ascites. Other manifestations were related to other autoimmune conditions, such as the theory that PBC often co-occurs with another autoimmune disease.

The presence of positive antibodies in PBC is a critical aspect of its diagnosis and management. Antimitochondrial antibodies (AMA) are a hallmark in most cases (90-95%). These antimitochondrial antibodies target the mitochondrial membranes of biliary epithelial cells, leading to progressive non-suppurative biliary cholangitis (7). AMA-M2, a subtype of AMA, is more specific to PBC and is considered a pivotal biomarker for its diagnosis. AMA-M2 is detected in most patients with PBC and is less frequently found in other conditions, such as drug-induced liver injury, viral hepatitis (B, C, and E), alcoholic liver disease, non-alcoholic fatty liver, and primary hepatic carcinoma (8). Another variant of PBC, which lacks AMA antibodies and shares similar clinical, biochemical, and histopathological aspects, is known as AMA-neg PBC. AMA-neg PBC may possess other PBC-specific antibodies, including anti-glycoprotein 210 (anti-gp210), anti-sp100, anti-kelch-like-12, and anti-hexokinase-1 antibodies. The presence of PBC-specific antibodies avoids the need for liver biopsy. Our patients had a negative AMA but a borderline AMA-M2. Her ANA levels were elevated, and her other positive autoantibodies were RNP/Sm, Sm, SSA, Ro-52, SSB, Histones, and Ribosomal Protein.

Our patient later met the criteria for severe SLE (ANA 54.71, ACR/EULAR 2017 total score: 17) and was treated with steroids and immunosuppressant drugs for the condition. ANA is present in many patients with PBC, especially the AMA-neg PBC variant. The prevalence of positive ANA tests in patients with PBC varies across studies (20-50%). The multiple nuclear dots and rim-like/membranous patterns are the most specific ANA patterns associated with PBC, often linked to anti-sp100 and anti-gp210 antibodies (9). Unfortunately, the ANA-IF test to evaluate the ANA pattern was not done in this patient. A positive ANA test may indicate a more complex autoimmune profile. ANAs in PBC may target nuclear components of liver cells, leading to cellular damage and apoptosis. This process exacerbates the inflammatory response, further damaging the bile ducts and contributing to the progression of liver fibrosis and cirrhosis (10).

Our patient had elevated CA19-9 and AFP levels. CA 19-9 is primarily a tumor marker for pancreatic and biliary tract cancers. However, its specificity is limited due to elevations in benign conditions such as cholestasis, cirrhosis, and hepatitis (11). In the context of biliary pathology, CA 19-9 levels can be significantly elevated in cases of obstructive jaundice, which is often seen in PBC. This elevation is due to impaired hepatic clearance and epithelial cells' inflammatory hypersecretion of CA 19-9 (12). The overlap in CA 19-9 levels between benign and malignant conditions necessitates careful interpretation. CA 19-9 role in benign conditions like PBC is more complex. Imaging studies and other diagnostic modalities should be used with CA 19-9 measurements to confirm the presence or absence of malignancy (11,13). In our case, we found no biliary or pancreatic structural abnormalities on the abdominal CT scan with contrast.

Various factors, including lipid metabolism, treatment response, and complications such as esophagogastric varices, influence the prognosis of PBC. Hypercholesterolemia resulting from a lipid metabolism disorder is a significant factor in the prognosis of PBC. Patients with baseline total cholesterol (TC) levels above 200 mg/dL are at a higher risk of poor liver-related outcomes (14).

The development of esophagogastric varices (EGV) significantly affects prognosis. EGV is a common complication in PBC, which occurs in 76.2% of patients with PBC in the previous cohort study. The study also showed that 31.2% of patients presented with EGV bleeding at the initial diagnosis. The size of EGV influences the prognosis of PBC. The 5-year cumulative liver transplant (LT)-free survival rates were lower in those with large-sized esophageal varices (75.7%) and best in those without EGV (88.2%) (15). Therefore, a profile lipid test and endoscopic evaluation should be performed to assess prognosis in patients with PBC. Our patient underwent gastroscopy, and no EGV was found.

Ursodeoxycholic acid (UDCA) is the primary treatment for PBC, administered at a dosage of 13-15mg/kg/day. UDCA is a bile acid that helps to improve liver function and slow the progression of the disease by reducing liver inflammation and damage. UDCA works by altering the bile acid pool, reducing the concentration of toxic bile acids, and improving bile flow, alleviating cholestasis. The response to UDCA is crucial as it predicts the long-term prognosis for patients with PBC. The recommended period for assessing the response to UDCA is between 6 to 12 months after the initiation of treatment. During this period,

clinicians should monitor liver function tests, particularly alkaline phosphatase levels, as a marker of treatment efficacy. A favourable response to UDCA is typically indicated by a significant reduction in alkaline phosphatase levels, which correlates with improved liver function and a better prognosis. For patients with an inadequate response to UDCA, second-line treatments such as obeticholic acid and fibrates are recommended. The evaluation of treatment response is crucial for predicting long-term outcomes (16). Our patient was given 750 mg of UDCA daily. After 3 weeks of treatment, she showed remarkable clinical improvement. This case highlights the unusual presentation of PBC as the initial manifestation of SLE. Other causes of jaundice need to be considered, as it is not always the primary complaint of stones or cirrhosis. The early recognition of overlapping autoimmune conditions is crucial for timely and appropriate management. A comprehensive diagnostic evaluation, including antibody testing, is essential to differentiate between PBC and other liver diseases. The patient's favorable response to treatment underscores the importance of a multidisciplinary approach and personalized care in managing complex autoimmune disorders.

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