Primary Biliary Cirrhosis and Mitral Stenosis: A Rare Association

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Primary biliary cirrhosis is a rare cause of chronic liver disease in Myanmar. It usually presents with pruritus and fatigue in a middle-aged female before the appearance of jaundice. This case illustrates a woman presenting with 15 years of pruritus and 5 years of intermittent jaundice. She had no risk factors for viral hepatitis and was a non-drinker. Multiple consultations were done and treated as a chronic liver disease without probing further for the etiology. Persistently high alkaline phosphatase of biliary origin prompted us to test for anti-mitochondrial antibodies which were positive for M2 subtype. Furthermore, she was found to have clinical and echocardiographic evidence of mitral stenosis (MS). MS is usually a consequence of post-streptococcal rheumatic carditis. Molecular mimicry is the common mechanism in the pathogenesis of both conditions. Her symptoms improved after ursodeoxycholic acid treatment.

Keywords: Cirrhosis, Mitral stenosis, Primary biliary cirrhosis, Pruritus

INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic autoimmune cholestatic disease characterized by non-suppurative destruction of interlobular bile ducts eventually leading to cirrhosis and liver failure.¹² It occurs predominantly in middle-aged females and is uncommon under 25 years of age.²³ Prevalence of PBC is higher in Northern Europe and Northern America compared to Eastern Asia, Africa, and Australia.⁴

Due to the slowly progressive nature of the disease³ and lack of specific symptoms in early stages, physicians' awareness is important for arriving at the diagnosis early in the clinical course. Approximately 50-60% of patients are asymptomatic at the time of diagnosis. Fatigue and pruritus are the most common presenting symptoms, occurring in 21% and 19% of patients, respectively.²

Serologically PBC is characterized by the presence of anti-mitochondrial antibodies (AMA), which are reactive against E2 subunits of mitochondrial multienzyme complexes, the 2-oxo-acid dehydrogenase complexes comprising pyruvate dehydrogenase complex, branched chain 2-oxo-acid dehydrogenase complex, and 2-oxo-glutarate dehydrogenase complex.⁴ These specific AMA are called AMA-M2 and are detectable in up to 95% of the patients.⁶ Histologically, there is chronic non-suppurative destructive cholangitis whereby interlobular bile ducts are selectively affected. Following the stage of cholangiopathy, the affected bile ducts eventually disappear, leading to cholestatic liver failure and cirrhosis.⁷

PBC is reported to be associated with a number of other autoimmune disorders due to a shared autoimmune mechanism.⁸ In a recent study of 361 consecutive PBC patients over the period of 37 years, 61.2% was associated with at least one extrahepatic autoimmune (EHA) conditions, especially in female patients: Sjogren’s syndrome (56.1%), Raynaud’s phenomenon (29.4%), Hashimoto thyroiditis (20.4%), scleroderma and rheumatoid arthritis (9.9% each), cutaneous autoimmune diseases (8.1%), systemic lupus erythematosus and vasculitis (3.6% each), Graves’ thyroiditis (3.2%) celiac disease (1.4%), and other EHA conditions (13.1%). The association was noted to be independent of age at PBC diagnosis, AMA or antinuclear antibody (ANA) positivity, or histological stage at diagnosis.⁹

Mitrval stenosis (MS), which is mainly caused by rheumatic fever, has become rare in developed countries. In the United States, it is the most commonly seen in patients who...
have emigrated from areas where rheumatic fever is still endemic. A decline in the rate of rheumatic fever is believed to be partly due to the introduction of antibiotics. Acute rheumatic fever causes pancarditis; however, it primarily affects the endocardium, causing inflammation of the cardiac valves. Further repeated acute episodes of rheumatic fever results in chronic inflammation, and scarring leading to severe valve damage years later. Though all the cardiac valves may be involved by the rheumatic process, the mitral valve is prominently affected in virtually all cases. Thickening of mitral valve leaflets, fusion of commissures, shortening, and fusion of chordae finally result in valve stenosis. MS is two to three times more common in females than males. The patient may be entirely asymptomatic in mild cases; however, symptoms of heart failure develop with worsening stenosis.¹⁰

In this case, we report a case of PBC and MS in a middle-aged Myanmar lady. An extensive literature search failed to reveal reports of such association. We believe that autoimmune attacks of heart valves following post-streptococcal rheumatic carditis might be responsible for this association. To the best of our knowledge, this case would be the first reported case of PBC with MS from Myanmar. It highlights physicians’ awareness of PBC though it is a rare cause of chronic liver disease in the country compared to viral hepatitis and alcohol. In addition, further literature is required before we could confidently conclude the association between autoimmune etiology of these two conditions.

**CASE REPORT**

A 55-year-old Myanmar lady presented with 5 years history of intermittent yellowish coloration of skin and sclera followed by 3 days of abdominal pain, especially in the epigastrium and right hypochondrium. There was no fever, chills, nausea, vomiting, or abdominal distension. Upon detailed history taking, she had been suffering from long-standing itchiness of skin on and off for the past 15 years especially at night time, worsened by hot weather and contact with clothes.

During these years, she had a pale color stool, high color urine and vague dull aching abdominal pain, along with tiredness, fatigue, and loss of appetite. She lost 7 kg over the past 5 years; however, she did not experience episodes of hematemesis, malena, abdominal distension, or impaired consciousness. She received two units of blood 4 years ago, but no history of alcohol, acupuncture, tattooing, needle sharing, or sexual promiscuity. About 10 years back, she had a rheumatic fever like illness but did not receive proper penicillin prophylaxis. There was no ingestion of herbal or alternative medicines. No similar illness was noted among other family members. She was a non-smoker and non-drinker.

**Physical examination** showed jaundice, mild hyperpigmentation of the skin, scratch marks, and moderate hepatosplenomegaly. There were no xanthelasma, clubbing, spider nevi, or ascites. Respiratory and nervous system were clinically normal. Her pulse rate was 84/min, regular, blood pressure was 110/80 mmHg. Apex beat was located at 5th intercostal space just outside the mid-clavicular line, tapping with no thrill. The first heart sound was loud, and a mid-diastolic murmur was heard at the mitral area. However, there was no evidence of pulmonary hypertension.

Her serial investigations over the past 4 years revealed rising levels of serum bilirubin, alanine transaminase, alkaline phosphatase, and gammaglutamyltranspeptidase (γGT), the most recent results being 109.8 μmol/l, 86 IU/L, 626 IU/L, and 77 IU/L, respectively. The first abdominal ultrasound 5 years ago was normal and the second scan after 1 year showed chronic hepatitis. The scan 3 years later revealed splenomegaly with portal vein diameter of 9 mm. Features of liver cirrhosis with portal hypertension became evident on her latest abdominal ultrasound, with hepatosplenomegaly, prominent caudate and left lobe enlargement, portal vein diameter of 14.4 mm and minimal ascites. Hepatosplenomegaly was also evident on computed tomography scan (Figure 1).

Hepatitis B and C serology, rheumatoid factor, ANA, and Venereal Disease Research Laboratory were all negative. Her laboratory results showed serum albumin 3.4 g/dl, globulin 3.2 g/dl, total protein 6.6 g/dl, international normalized ratio 0.96, cholesterol 3.5 mmol/l, corrected calcium 9.38 mg/dl, phosphate 4.4 mg/dl, random glucose 5.4 mmol/l and normal blood urea, and serum creatinine. There was ++ bilirubin on urinalysis. Grade III esophageal varices and portohypertensive gastropathy were noted on upper gastrointestinal endoscopy and endoscopic variceal ligation was done. Apart from normochromic normocytic anemia of 9.9 g/dl, white cells and platelets were normal. Erythrocyte sedimentation rate was 55 mm/1st h and antistreptolysin O was 160 IU/ml. Immunoglobulin assays were unavailable.

Her past history of rheumatic fever like illness and the cardiovascular findings prompted us to investigate further. Electrocardiography revealed sinus rhythm with no evidence of chamber enlargement. Chest X-ray showed mild cardiomegaly with typical mitralization of left heart border (Figure 2). An echocardiogram confirmed our clinical diagnosis showing moderate MS with a mitral valve area of 1.45 cm², left atrium diameter of 3.98 cm, and ejection fraction 57.22%. The echocardiographic evidence of mild mitral regurgitation, mild aortic regurgitation, and mild
tricuspid regurgitation was also noted. There were no features of pulmonary hypertension.

She had a number of consultations in the past and was treated symptomatically without significant improvement. In light of the long history of pruritus, intermittent jaundice and cholestatic picture on investigations, we tested for AMA though cases of PBC were rare in our clinical setting. The result was positive (more than 200 units) for M2 subtype. Liver biopsy was not performed as the patient did not agree for it. Thus, our patient was having both PBC and MS. Ursodeoxycholic acid (UDCA) 250 mg three times daily was given along with propanolol to reduce portal pressure. She was also referred to a cardiologist for further assessment of MS. Her symptoms, especially itchiness, improved after UDCA treatment on subsequent follow-ups.

**DISCUSSION**

PBC is a slowly progressive cholestatic chronic liver disease that eventually results in advanced fibrosis, cirrhosis, and liver failure over a period of 10-20 years without treatment. It predominantly affects middle-aged females usually presenting between 5th and 7th decades. The first case of PBC was reported in 1851 as prolonged obstructive jaundice with patent bile ducts. PBC has a female preponderance with female to male ratio reported from 8:1 to 10:1.

Multiple genetic factors with superimposed environmental triggers are attributed in the pathogenesis of PBC. Genetic predisposition is evidenced by approximately 100 times higher prevalence in first-degree relatives than in the general population. Human leukocyte antigen (HLA) DR3, DR8, and DR4 are more frequent in white populations whereas DR2 and DR8 haplotypes are common in Japanese patients. HLA DR8 and DQ2 were reported in Chinese patients, in contrast to a study from Brunei where HLA Class I alleles specifically B7, Cw7, and Cw12 are more significant associated with PBC. Due to resource limitations, we could not perform genetic study of our patient.

The common symptoms of PBC are fatigue and pruritus. Skin hyperpigmentation, hepatosplenomegaly, xanthelasmas, and scratch marks can be seen on physical examination. Jaundice is usually a late feature but was reported in 20% of patients with early disease. The patients in advanced stages present with complications of liver cirrhosis such as ascites, encephalopathy, and variceal bleeding. In 20-60%, individuals are totally asymptomatic.

PBC is diagnosed by clinical features, a persistent cholestatic picture with a preferential elevation of serum alkaline phosphatase and γGT activities of more than 6 months and presence of AMA with M2 specificity. The liver biopsy is useful for staging although its role in diagnosis is uncertain. However, histology is essential for the diagnosis of PBC in AMA-negative patients with cholestatic liver disease. Our patient had typical features of PBC with a long history of pruritus, intermittent jaundice as well as elevated alkaline phosphatase with normal biliary system on ultrasound, positive AMA M2 subtype, and esophageal varices on endoscopy. However, she was diagnosed only after 15 years of pruritus and 5 years of jaundice despite considerable consultations which was mainly due to the paucity of PBC cases in the country and limitations in diagnostic tools.

In recent years, rates of PBC was reported to be increasing; the incidence and prevalence rates ranging from 0.33-5.8 per 100,000 inhabitants/year and 1.91-40.2 per 100,000 inhabitants, respectively. This rising trend was attributed to increasing disease awareness, better detection, availability of effective therapy, digitalized patient registration, and more rigorous epidemiological studies. However, these reasons are appropriate only for the period between 1969 and 1999. From 2000 to 2008, the rising incidence
and prevalence was an actual increase in PBC occurrence, rather than increase in detection and reporting or improved survival. PBC is less common and less reported in Asia than in the Western countries with little or no data available on the rates in the Asia Pacific region.\textsuperscript{14}

MS results mainly as a consequence of chronic inflammation following acute episodes of rheumatic fever. The molecular mimicry between M protein and Group A carbohydrate of beta-hemolytic streptococcus and cardiac myosin leads to the autoimmune attack of all three layers of the heart. Evidence suggests that antibody against Group A carbohydrate reacts with valve endothelium promoting inflammation, T-cell activation, leading to eventual fibrosis, and scarring.\textsuperscript{18,19} Mitral valve is the most commonly affected either alone or in combination with aortic and tricuspid valves with variable amounts of lymphocytic infiltration on histology.\textsuperscript{20} Similarly, molecular mimicry is the most widely proposed mechanism for the initiation of autoimmunity in PBC, which also has predominant lymphocytic infiltration of intrahepatic bile ducts.\textsuperscript{2} This shared pathogenesis between PBC and MS might explain the finding of our patient.

**CONCLUSION**

PBC was reported to be associated with various immune conditions such as rheumatoid arthritis, Sjogren’s syndrome, Graves’ disease, diabetes mellitus, and autoimmune pancreatitis. However, we could not identify a report on PBC with MS to date, and our case might possibly represent the first patient with PBC and MS. However, further reports and literature is essential for a more accurate explanation of the association.

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**REFERENCES**


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