Case Report

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# Antimitochondrial antibody-negative primary biliary cirrhosis with secondary Sjogren syndrome: a case report

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**Introduction and importance:** Primary biliary cholangitis (PBC) is a rare immune-mediated liver disease characterized by the destruction of intrahepatic bile ducts and a positive antimitochondrial antibody (AMA), which is considered a serological hallmark for the diagnosis. Rarely, AMA can be absent/nondetectable in a few cases and is referred to as 'AMA-negative'.

**Case presentation:** The authors present such an uncommon case of AMA-negative PBC in a 39-year-female with Sjogren's syndrome who presented with fatigue, pruritus, and dry eyes.

**Clinical discussion:** Previously published studies state that approximately only about 5% of patients with PBC are 'AMA-negative'. For patients negative for AMA, the diagnosis has to be based on typical pathological features of this disease. Once a diagnosis of PBC is established, regardless of whether it is positive or negative for AMAs, ursodeoxycholic acid is a widely accepted treatment.

**Conclusion:** The presence/absence of AMAs is associated with similar clinical, biochemical, and histopathological characteristics in PBC. The identification of AMAs alone should not impact the diagnosis or treatment of PBC.

**Keywords:** AMA-negative, antimitochondrial antibody, primary biliary cirrhosis, Sjogren's syndrome

## Introduction

Primary biliary cholangitis (PBC) is an immune-mediated liver condition that affects 14.6 per 100 000 people worldwide and is defined by the presence of antimitochondrial antibodies (AMA) and the destruction of small-sized to medium-sized intrahepatic bile ducts[1,2]. In addition, PBC is less common in Asian populations affecting 9.82 per 100 000 persons[3]. PBC, formerly known as primary biliary cirrhosis, is a chronic, progressing liver condition that, if left untreated, can lead to end-stage liver disease. Historically, untreated patients with PBC had an average survival of 9–10 years compared to the 10-year survival of 80% of patients receiving UDCA treatment[4]. Patients presenting with clinical signs and a biochemical pattern of cholestasis can be diagnosed with PBC using the serological marker 'AMA'. Only about 5% of PBC patients, lack detectable AMA and are referred to as 'AMA negative' patients[5].

### HIGHLIGHTS

- Antimitochondrial antibody (AMA) is a serological hallmark in primary biliary cholangitis (PBC).
- Only 5% of PBC patients lack detectable AMA and are referred to as 'AMA negative' patients.
- AMA-negative PBC shares similar clinical, biochemical, and histopathological characteristics with AMA-positive PBC.

Sjögren's syndrome (SS) is a chronic systemic autoimmune disorder characterized by lymphoplasmacytic infiltrates of the exocrine glands, which results primarily in xerostomia and xerophthalmia but may also cause extra glandular manifestations[6]. The total incidence was estimated as 0.043% in a recent meta-analysis, albeit prevalence varied across different geographic areas. In general, women are affected more often than men, with a female-to-male ratio of roughly 10:1[7]. It can be divided into two categories: primary and secondary SS, depending on whether an underlying autoimmune disorder is present. Secondary SS presents as an entity associated with another autoimmune condition that can at times be associated with PBC[8].

Here, we report a case of AMA-negative PBC in a patient with coexisting SS.

## Case presentation

A 39-year-old female with recently diagnosed dyslipidemia presented to our center with clinically significant weight loss over one

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year, yellowish discoloration of the eyes for 3 months, which was associated with pruritus and easy fatigability but without a clay-colored stool, and abdominal pain.

She also had a history of small joint pain, predominantly proximal interphalangeal joint pain, and hair fall but the history of photosensitive rashes and sicca symptoms were absent.

Upon examination, she was icteric and her liver and spleen were palpable. The rest of the general and systemic physical examination including vitals were unremarkable.

Laboratory investigations revealed a cholestatic pattern of liver injury (Table 1). An abdominal US study showed hepatosplenomegaly and magnetic resonance cholangiopancreatography suggested a normal biliary tree except for a focal indentation at the common hepatic duct after the confluence of ducts. Autoimmune workup revealed negative AMA and anti-smooth muscle antibody by immunofluorescence method, negative anti-LKM, normal serum IgG, and ceruloplasmin but positive anti-neutrophil antibody (ANA) by immunofluorescence. A liver biopsy revealed lymphoplasmacytic infiltration of portal tracts with ill-formed granuloma suggesting primary biliary cirrhosis. Biopsy further revealed portal to portal and portal to central fibrosis along with areas of parenchymal destruction (Fig. 1). ENA (extractable nuclear antigen) profiling was positive for Anti-Ro-52 (Table 2). The Schirmer test came positive and a minor salivary glands biopsy confirmed lymphocytic infiltration of salivary glands. C3, C4, and dsDNA were negative and lupus was ruled out.

With a diagnosis of primary biliary cirrhosis and secondary SS, she was managed with ursodeoxycholic acid 600 mg/day with a short course of prednisolone along with other supportive therapies for sicca symptoms.

She is under regular follow-up at our center and her liver enzymes are gradually improving over 6 months of follow-up.

**Table 1**

**Various laboratory parameters at the time of admission.**

| Parameter | Value (reference range) |
|---|---|
| 1. Hematology | |
| a. WBC | 13 100/cmm (4000–11 000) |
| b. RBC | 4.01 mill/cmm (3.5–4.5) |
| c. Hb | 12.5 gm% (12–16) |
| d. Platelets | 350 000/cmm (150 000–450 000) |
| 2. Liver function test | |
| a. Total bilirubin | 49 micromol/l (3–21) |
| b. Direct bilirubin | 34 micromol/l (0–5) |
| c. SGOT/AST | 169 U/l (0–35) |
| d. SGPT/ALT | 157 U/l (30–120) |
| e. ALP | 986 U/l (30–120) |
| f. Albumin | 37 gm/l (35–52) |
| 3. Renal function test | |
| a. Sodium | 137 mmol/l (135–145) |
| b. Potassium | 3.8 mmol/l (3.5–5.2) |
| c. Urea | 3.1 mmol/l (1.6–7.0) |
| d. Creatinine | 51 micromol/l (40–110) |
| 4. Tumor markers | |
| a. AFP | 3.0 (< 7.51) |
| b. CA-125 | 32.7 (< 35) |
| c. CEA | 1.8 (< 3.0) |
| d. CA-19.9 | 36.8 (< 37.0) |
| e. CA-15.3 | 20.1 (< 31.3) |

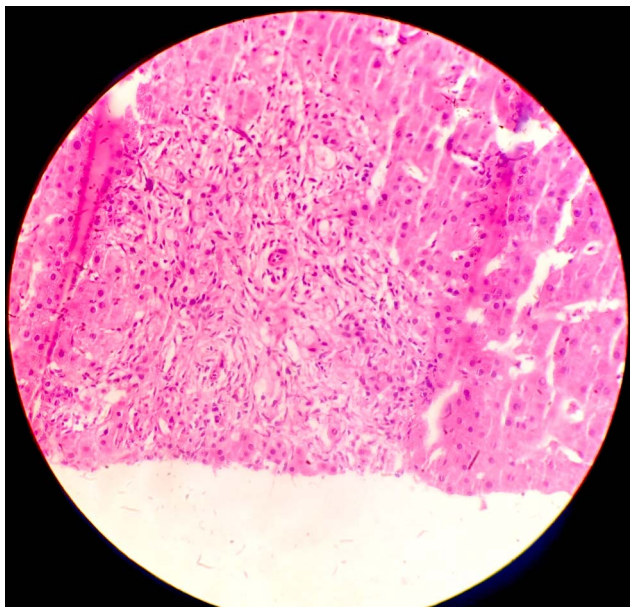

**Figure 1.** Section from liver shows hepatocytes with feathery degeneration, cholestasis and sinusoidal dilatation with mild lymphocytic infiltration in the portal tract along with areas of ill-formed granuloma.

**Table 2**

**ENA Profile of the patient with immunological work-up.**

| Parameter | Value/Titer | Inference with reference |
|---|---|---|
| dsDNA | 3.6 IU/ml | < 30 (Negative) |
| Complement | | |
| a. C3 complement | 229.3 mg/dl | 90–180 |
| b. C4 complement | 36.2 mg/dl | 10–40 |
| Smooth muscle antibody | 1:20 | Negative |
| Mitochondrial antibody | 1:10 | Negative |
| Extractable nuclear antigens (ENA) profile | | |
| Anti-nRNP | 1 | |
| Anti-smith | 0 | |
| Anti-RNP70 | 2 | |
| Anti-RNP A | 0 | |
| Anti-RNP C | 1 | |
| Anti-SS-A | 0 | 0–5: negative |
| Anti-Ro-52 | 77 | 6–10: borderline positive |
| Anti-SS-B (La) | 1 | 11–25: positive |
| Anti Scl-70 | 0 | |
| Anti-PM-Scl | 1 | 26–50: moderative positive |
| Anti Jo-1 | 1 | 51–256: strong positive |
| Anti-CENP-B | 1 | |
| Anti-PCNA | 1 | |
| Anti-Ds-DNA | 0 | |
| Anti-nucleosomes | 1 | |
| Anti-histones | 0 | |
| Anti-Rib-P proteins | 1 | |

## Discussion

The etiological causes of autoantibody synthesis in PBC are still unknown. There is evidence that genetic and environmental factors interact to affect PBC susceptibility. There is currently

evidence to support the pathogenesis of PBC being influenced by infectious agents like bacteria, retroviruses, and xenobiotics[9]. Xenobiotics are foreign substances that can interact with their own proteins. *Escherichia coli*, *Chlamydia pneumoniae*, *Lactobacillus*, and *Helicobacter pylori* are examples of infectious agents. It is believed that exposure to certain substances, especially xenobiotics, might change the composition of native proteins and trigger an immunological reaction against one's own proteins. This process is known as molecular mimicry[10].

Because PBC is a rare disease and many individuals present with an asymptomatic increase of liver enzymes, timely diagnosis of the condition can be difficult. PBC has a very diverse clinical trajectory, in part because it is now more frequently detected in its initial stages. After diagnosis, over one-third of individuals experience no symptoms for a long time[11]. Fatigue and pruritus are the most frequent symptoms in people who do experience them. On the other side, jaundice occurs later and is linked to a worse prognosis. 10% of patients report experiencing stomach pain in the right upper quadrant. In fact, only a small portion of patients actually exhibit nonspecific symptoms like pruritus, upper right quadrant stomach pain, and exhaustion at the time of diagnosis[12]. Numerous genetic investigations have demonstrated that the risk loci for PBC are also those that predispose to RA, SS, SSc, SLE, IBD, and psoriasis[13]. As a result, it is frequently important to check for extrahepatic autoimmune diseases such as autoimmune thyroiditis, SS, and other illnesses. These extrahepatic autoimmune diseases are more prevalent in females and are more usually associated with AMA, ANA, and/or SMA seropositivity[1].

AMA, present in up to 95% of PBC patients, has been established as a highly specific marker for the disease, and its presence is a characteristic criterion for PBC diagnosis, with increasing sensitivity at increasing titers[14]. Major international recommendations state that if a patient tests positive for AMA and has clinical, biochemical, or radiological evidence of intrahepatic cholestasis, the diagnosis of PBC can be made with confidence. However, the diagnosis must be based on the characteristic clinical signs of this illness in patients who test negative for AMA, which accounts for around 5% of PBC cases[15]. However, a meta-analysis involving 400 patients who had PBC and an AMA-negative status showed that ANAs had a very good specificity for PBC and an AMA-negative status. Anti-gp210 and anti-sp100 ANAs, among others, showed extremely high specificity but limited sensitivity for the diagnosis of AMA-negative PBC and could thus be utilized as trustworthy biomarkers to lessen the need for liver histology[16]. However, several investigations showed that PBC that tested negative for AMA was linked to worse clinical outcomes and more extensive histological bile duct damage[17]. Therefore, liver biopsy is advised for this group of patients to confirm the diagnosis of AMA-negative PBC and to rule out the presence of AIH or NASH without unduly delaying the course of treatment[18]. Our patient had AMA-negative PBC which was diagnosed with liver biopsy and also had positive ANA like in other reported 'ANA negative PBC' cases. Patients with PBC who do not have antimitochondrial antibodies exhibit the same clinical trends, serum biochemistry profiles, and liver histological characteristics as those who do. On the other hand, UDCA treatment and a postponed diagnosis may cause a more advanced disease in AMA-negative people[17].

Once a diagnosis of PBC is established, regardless of whether it is positive or negative for AMAs, the most widely accepted treatment is UDCA. Ursodeoxycholic acid is well tolerated in most patients[19]. At intervals of 3–6 months, liver testing should be periodically monitored[20]. It has been demonstrated through numerous randomized trials, combined analyses, and extensive observational studies that this medication not only enhances biochemical indicators but also slows the course of histology and increases survival without transplantation[21,22]. Furthermore, Liu's research found that treating AMA-negative and AMA-positive PBC with UDCA led to comparable improvement in ALP, IgM, and glutamyl transpeptidase levels[23]. Even though UDCA is a successful treatment and has helped PBC become a manageable chronic condition, it does not alleviate typical symptoms like fatigue and pruritus[24]. Other treatments for pruritus include cholestyramine, rifampicin, and opioid antagonists[20].

Although the rate of disease progression varies widely from patient to patient, in the majority of cases, there is a development of cirrhosis and its sequelae. Data on the untreated natural history are scarce, but one of the first clinical trials in PBC showed a rather fast histological progression in the absence of effective treatment. Within 4 years, progression towards cirrhosis was observed in 40% of patients with an early histological disease stage (stage I or II) and in 68% of patients with advanced disease (stage III)[25]. A fraction of patients have liver failure and end-stage liver disease despite receiving optimal care. A liver transplant (LT) is the only available form of treatment for these people. Hepatocellular carcinoma and refractory pruritus are two other, less common indications for LT in PBC[12]. Therefore, regardless of the patient's AMA status, LT should be taken into consideration once UDCA stops controlling the disease and the patient advances to end-stage liver disease. After a median follow-up of 36 months, Lee et al. looked at the clinical results of orthotopic LT in patients with PBC who tested negative for AMA. According to the investigators, patients with PBC who tested positive for AMA had similar graft and patient survival rates as well as subsequent histological alterations, such as disease recurrence and steroid-resistant or late rejections[26].

SS has been reported in varying frequency upto ~ 40% of cases of PBC[27]. The term autoimmune epithelitis has been suggested as a replacement label for PBC and SS, which are both characterized by immune-mediated tissue injury, particularly in biliary and exocrine gland epithelia[20]. Although a clear correlation between the two disorders has been shown, SS's prognostic importance in PBC is still unclear. The main treatment for sicca symptoms is supportive therapy. Artificial tears are the primary option for dry eyes. Second-line treatments include cholinergic drugs like pilocarpine and cevimeline. In cases that are unresponsive, cyclosporine may be considered. As dental caries are usually linked to dry mouth, it is important to practice good oral hygiene and visit the dentist frequently. The use of moisturizers may be advised for a dry vagina. Systemic immunosuppressive therapy may be considered if sicca symptoms are resistant to supportive treatment[24]. PBC shares similarities with our patient in that it is linked to dyslipidemia, but there is no proof that it increases the risk of cardiovascular disease. Due to this, recommendations for lipid-lowering therapy are now made on an individual basis rather than on a regular basis[4].

## Conclusion

Antimitochondrial antibody-negative and AMA-positive PBC share similar clinical, biochemical, and histopathological

features. Detection of AMAs alone should not influence the diagnosis or treatment of PBC, and the disease should be managed like other PBC patients.

## Ethical approval

Not applicable as ethical approval is not required for writing the case report from the institutional review board in our institute.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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## Author contribution

S.A,: writing – original draft, data curation, conceptualization; S.S., E.P., A.N., R.K., and S.R.M.: writing – original draft, writing – review and editing; M.L.: data curation, writing – review and editing; R.P.: writing – review and editing, conceptualization, supervision.

## Conflicts of interest disclosure

The authors declare that they have no financial conflicts of interest with regard to the content of this report.

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All the necessary information is provided within the manuscript.

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