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Florid biliary duct lesions in an AMA -positive patient in absence of cholestatic liver biochemistry

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A B S T R A C T

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease, diagnosed by the presence of anti-mitochondrial antibodies (AMA) or highly PBC-specific anti-nuclear antibodies, in the appropriate context of cholestatic liver biochemistry.

We present a case with histological features of destructive granulomatous lymphocytic cholangitis affecting interlobular and septal bile ducts suggestive of PBC, with strong positive AMA, Anti-M2 and anti-nuclear dot, but with persistently normal alkaline phosphatase (ALP). On the contrary to previous reports suggesting that those individuals in whom ALP remains persistently below 1.5 times ULN appear to have a benign course and a better prognosis, our patient progressed to liver cirrhosis.

1. Background

PBC is a genetically predisposed disease, triggered by autoimmune event resulting in an inflammatory, predominantly T-cell mediated destruction of intrahepatic bile ducts [1]. In the context that most of the patients are advancing through the histological stages as rapidly as every 2 years and 30% of patients can have a severe, progressive form resulting in the early development of liver fibrosis and liver failure, so early diagnosis and treatment of PBC is essential [2].

The serologic hallmark of PBC is the anti-mitochondrial antibody (AMA), a highly disease-specific auto-antibody detected in 90–95% of PBC patients and less than 1% of non-diseased controls [3]. Alkaline phosphatase is a marker of cholestasis and a biliary source is inferred when ALP is associated with an elevated gamma-glutamyl transpeptidase (GGT), 5′-nucleotides, or leucine aminopeptidase. Chronic elevation of ALP is required to establish the diagnosis of PBC and those with ALP persistently below 1.5 times ULN, appear to have a better prognosis. Recently, the American College of Gastroenterology (ACG) Institute for Clinical Research & Education, reported that in some cases, the presence of AMA may be found some time before serum alkaline phosphatase becomes abnormal (“preclinical” phase). Also the panel recommended that, AMA positivity alone is not sufficient to make the diagnosis of PBC. These patients require follow up, but not additional intervention of treatment [4,5].

Hereby, we represent a case of clinically significant anti-mitochondrial antibody and histological pattern of PBC, progressed to liver cirrhosis in spite of persistent normal alkaline phosphatase and bilirubin.

2. Case

A 41 years, Qatari lady, known to have cervical and lumber disc bulge, migraine headache, otherwise no chronic illness and not on any regular medications. In May 27th, 2018, she was referred for the first time to hepatology clinic because of marginal increase in transaminases (ALT 45 U/L, AST 60 U//L). She was fairly asymptomatic with no itching and no jaundice. She has seven daughters and four sons and she reported occasional, non-significant, itch during pregnancy. Family history was irrelevant and she denies any alcohol intake, drug abuse or smoking. Clinical examination was fairly unremarkable, and her BMI was 30.5 kg/m2.

Initial laboratory investigations revealed, Hemoglobin 12.1 units?, platelet 175 units?, white blood cells 6.3 units?, INR 1.2, creatinine 18 Umol/L, bilirubin 12 μmol/L, albumin 30 gm/L, alkaline phosphatase 61 U/L, ALT 44U/L, AST 65 U/L and AFP 6 IU/ml. On reviewing her old records, we found that she has abnormal transaminases (with normal alkaline phosphatase) and low albumin since July 2017.

Autoantibody screening showed positive antimitochondrial antibody at the titer 1:640, antimitochondrial antibody- M2 > 220, ANA 1:320 Nuclear dots. Anti-smooth antibody is negative, antibody screening for celiac disease was also negative, IgG 2420 mg/dl.

Negative serology for both hepatitis B and hepatitis C virus was

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seen, and hepatitis B surface antibody was positive 18.02 mIu/ml.

All other investigations regarding the etiology of chronic liver disease was within normal range including ceruloplasmin 38.4 mg/dl, alpha-1 antitrypsin 423 mg/dl, iron is 17.1 μmol/L, TIBC 66 μmol/L,Fe saturation 26%.

Abdominal ultrasound scanning revealed, cirrhotic liver with no definite focal lesion.

Elastography assessment of the liver by ElasPQ ultrasound shear wave with 10 samples shows a stiffness average of 13.32 kPa which indicates moderate to severe liver fibrosis staging and the score F3- F4 by Metavir score.

MRI abdomen showed, outline nodularity of the liver, Hypertrophy of the caudate lobe. Periportal T2 hyperintensity with delayed enhancement, likely representing periportal fibrosis. Multiple small, scattered foci of hyper enhancement measuring under 5 mm were seen in both lobes of the liver, which lack washout, probably represent micro-regenerative nodules, Li-RAD 2. All other organ examinations were reported as normal.

Gastroscopy showed mild antral gastritis, but no esophageal or fundal varices or any stigmata of portal hypertension.

Liver biopsy was performed and showed, disruption of the hepatic architecture by narrow and broad based fibrous bands, forming occasional nodules. Mild microvesicular and macrovesicular steatosis was noted. The portal tracts showed moderate chronic inflammation, predominantly lymphocytes with scattered plasma cells and eosinophils, along with expansion by fibrosis. Most portal tracts also revealed mild ductular reaction. One of the portal tracts contained a prominent epithelioid granuloma, present around a bile duct, surrounded by moderate to dense chronic inflammatory infiltrate, in keeping with a florid duct lesion (Figs. 1 and 2). Interface change and foci of lobular inflammation were easily identifiable. Cholestasis was absent. There was marked fibrosis, including portal fibrosis, periportal fibrosis and portal to portal bridging, imparting a nodular appearance, suggestive of incomplete cirrhosis (Ishak's Fibrosis score of 5/6 and Metavir fibrosis score of 3/4). In view of the presence of a florid duct lesion, positive autoantibodies and absence of other etiological features, the histological appearances were found to be consistent with primary biliary cholangitis.

3. Discussion

Primary biliary cholangitis is a chronic, slowly progressive, autoimmune, cholestatic liver disease, typically diagnosed by elevated cholestatic liver enzymes and a positive antimitochondrial antibody (AMA) test. The florid duct lesion, defined as a granulomatous destruction of the bile ducts, is the histological hallmark of PBC. The granulomatous inflammation may be either well-formed or vague, and is accompanied by lymphocytes and variable numbers of plasma cells, all of which are centered on the bile duct [6]. The clinical significance of AMA positivity in patients with normal cholestatic liver enzymes is uncertain.

In 1998, Mitchison et al. [7] reported, Twenty-nine AMA-Positive patients and who had a normal serum bilirubin, alkaline phosphatase and transaminase and almost 40% of them fulfilled histological diagnostic criteria for primary biliary cirrhosis [7].

In 2008, Brostoff et al. [8], reported a case of liver cirrhosis had a normal alkaline phosphatase and anti mitochondrial antibodies were strongly positive, as were anti nuclear antibodies, and the gamma glutamyl-transferase was shown to be elevated [8]. That case highlights that PBC can exist with an entirely normal ALP.

In 2007, Berdichevski et al. [9], reported, Six AMA-positive patients with normal cholestatic liver enzymes, but liver biopsy ranging between mild and non-specific histological findings and florid bile duct lesion compatible with early-stage PBC [9].

Previous reports suggested that patients with ALP persistently below 1.5 times ULN appear to have a benign course and a better prognosis [10]. However, from the previously reported cases and our case, we can suggest that patients with a disease-specific antimitochondrial antibodies may progress to histological destruction of intrahepatic bile ducts, which eventually lead to cirrhosis, in spite of presistnly normal ALP. This may be explained by the possible role of Genetics and epigenetics in the pathogenesis of primary biliary cholangitis. Exposure to environmental factors, such as infectious diseases and harmful chemicals, can produce epigenetic alterations in some individuals and subsequent PBC onset [11]. Also, maternal inheritance of PBC, presented with advanced liver fibrosis and mild increase in liver enzymes, has been reported [12].

Because of the well-established relationship between ALP and the ductular reaction and biliary metaplasia, which are hallmark of biliary injury. Moreover, as the levels of ALP correlates well with response to medical therapy and with the long-term outcome, serum total bilirubin and ALP are now considered the most robustly validated biomarkers of long-term outcome and treatment response in PBC [13]. This raises a dilemma about monitoring response to treatment and prognostic factors in this subgroup of patient with normal ALP. Carnitines and bile acid may be of value as PBC biomarkers for outcome prediction [14].

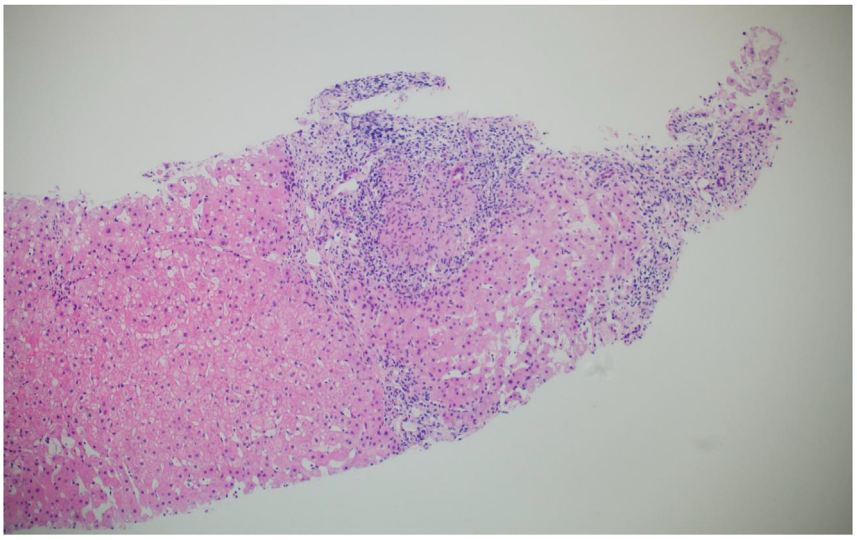

Fig. 1. Florid duct lesion. One of the portal tracts shows a prominent epithelioid granuloma around a bile duct with surrounding moderate chronic inflammation (H and E x 10).

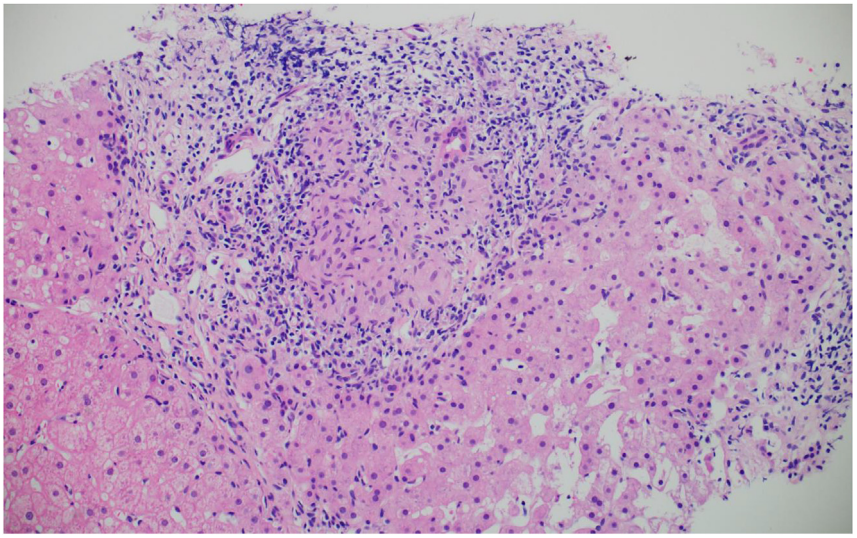

Fig. 2. Higher power view of the florid duct lesion (H and E x 20).

4. Conclusion

Patients with positive AMA and normal cholestatic liver enzymes, namely ALP, should still undergo stringent evaluation for PBC. This may even include performing a liver biopsy, although, this should mainly be considered in patients with high titer of AMA and significantly elevated IgM level.

More studies are needed to clarify how to best monitor this interesting group of patients as the traditional marker currently used to monitor disease progression (i.e ALP) is normal in these patients. Different markers indicating disease progression need to be established and these can be then used to monitor response to therapy instead of ALP. In addition, we do not know for certain whether these patients should be treated similarly to classic PBC or whether a different strategy of treatment (for example combination therapy with the ursodeoxycholic and Obticholic acid) is a better strategy to prevent progression of disease. Further follow up of such patients can hopefully shed some light on the differences between these patients as compared to patients with the classic form of PBC and this will likely help in better looking after this rare group of patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2019.04.004.

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