Case Reports in Gastroenterology

Case Rep Gastroenterol 2023;17:14–20
DOI: 10.1159/000528437
Received: September 5, 2022
Accepted: November 17, 2022
Published online: January 06, 2023

Case Report

Distinction between Mitochondrial Antibody-Positive and -Negative Primary Biliary Cholangitis

Venkata Vinod Kumar Matli[a] David F. Dies[b] Sudha Pandit[d]
Gregory Wellman[c] James D. Morris[d]

[a]Department of Internal Medicine, Christus Highland Medical Center, Shreveport, LA, USA; [b]Department of Gastroenterology and Hepatology, Christus Highland Medical Center, Shreveport, LA, USA; [c]Department of Gastrointestinal and Liver Pathology, Christus Highland Medical Center, Shreveport, LA, USA; [d]Division of Gastroenterology and Hepatology, Louisiana State University Health Center, Shreveport, LA, USA

Keywords
Primary biliary cholangitis · Autoimmune cholangitis · AMA-negative PBC · AMA-positive PBC · Overlap syndrome · Antimitochondrial antibody

Abstract
Antimitochondrial antibody-positive primary biliary cholangitis (AMA-pos PBC) is an autoimmune disorder in which monoclonal antibodies are produced against epitopes in the mitochondrial membranes of biliary epithelial cells, resulting in progressive nonsuppurative biliary cholangitis. Up to 5% of patients lack these autoantibodies, termed antimitochondrial antibody-negative (AMA-neg) PBC. Although a somewhat new variant of AMA-pos PBC, it is not an overlapping syndrome. Few studies to date have described this phenomenon. An 87-year-old woman was referred to our clinic with elevated serum alkaline phosphatase (714 U/L). She reported fatigue but no other symptoms. A physical examination revealed a benign lesion and bilateral lower extremity swelling secondary to lymphedema. The serological profile was significant for a high antinuclear antibody titer (>1:2,560) with a centromere pattern and negative for antimitochondrial antibody (AMA). The hepatitis panel was negative for viruses A, B, and C. Her serum immunoglobulin G level was 871 mg/dL (normal, <1,600 mg/dL). The rest of the serological tests, including anti-smooth muscle antibodies (ASMA) and anti-liver/kidney microsomal antibodies, were negative. Computed tomography of the abdomen and pelvis without contrast showed normal liver parenchyma and no acute intra-abdominal pathology. Histopathology indicated florid duct lesions. The background parenchyma showed no significant steatosis, and inflammatory changes were limited to the portal areas. Periodic acid-Schiff staining revealed intact hepatic parenchyma and architecture. The patient was diagnosed

Correspondence to:
Venkata Vinod Kumar Matli, drvinmatli@yahoo.com

Case Rep Gastroenterol 2023;17:14–20
DOI: 10.1159/000528437

with AMA-neg PBC and responded well to ursodeoxycholic acid therapy. This case highlights the importance of recognizing AMA-neg PBC as a variant of AMA-pos PBC and differentiating between them. Autoimmune cholangitis is a vague and imprecise condition. All patients with AMA-negative PBC should be tested for other PBC-specific autoantibodies. Although the prognosis and bile duct damage and loss are worse in AMA-neg PBC for unknown reasons, treatment remains the same for both.

Introduction

Primary biliary cholangitis (PBC) is an autoimmune disorder in which mitochondrial antibodies are produced against the mitochondrial membranes of biliary epithelial cells, thereby causing biliary cholangitis. This is known as antimitochondrial antibody-positive (AMA-pos) PBC. However, up to 5% of PBC patients lack these antibodies but present in a clinically, biochemically, and histopathologically similar fashion; this condition is termed antimitochondrial antibody-negative (AMA-neg) PBC. This is a somewhat new variant of AMA-pos PBC rather than an overlapping syndrome. No studies to date have described this entity or its associated terminology.

The rationale for writing this case-based review stemmed from confusion regarding the terminology of "autoimmune cholangitis" and the position of the variant of AMA-neg PBC in the spectrum of autoimmune hepatobiliary cholangiopathy. This spectrum spans autoimmune hepatitis (AIH), which predominantly includes hepatocellular damage; PBC; and primary sclerosing cholangitis (PSC), which is predominantly related to bile duct damage. Overlap syndromes, such as AIH-PBC, AIH-PSC, and AIH-cholestatic syndrome, are located between the two ends of the spectrum. Figure 1 shows the spectrum and appropriate position of AMA-neg PBC.

Case Presentation

An 87-year-old woman was referred to our clinic with an elevated alkaline phosphatase level of 714 U/L. The patient was asymptomatic; however, fatigue in the last few weeks was noted upon further interview. She denied experiencing abdominal pain, loss of appetite, pruritus, or weight loss. The patient reported being allergic to atorvastatin, lisinopril, irbesartan, and montelukast. The patient had a history of recurrent nodular malignant melanoma with metastasis to the left pelvis and bilateral femurs for which she previously underwent s/p-wide total excision and left inguinal lymph node resection. She was also previously diagnosed with type 2 diabetes, essential hypertension, hypothyroidism, and rheumatoid arthritis. The patient's vital signs were stable. Bilateral lower-extremity edema up to the thighs was noted. No abdominal distention, hepatosplenomegaly, or palpable masses were observed, and the liver span was normal. The remaining findings on physical examination were considered benign.

A complete blood count showed normal red and white blood cell and platelet counts. The hemoglobin and hematocrit levels were within normal limits like the coagulation profile. The patient's blood biochemical results, particularly those of serum transaminases, albumin, and globulin, were within normal limits except for alkaline phosphatase, which was elevated to 714 U/L, and gamma-glutamyl transferase at 193 U/L. The serological profile was significant

Case Rep Gastroenterol 2023;17:14–20
DOI: 10.1159/000528437

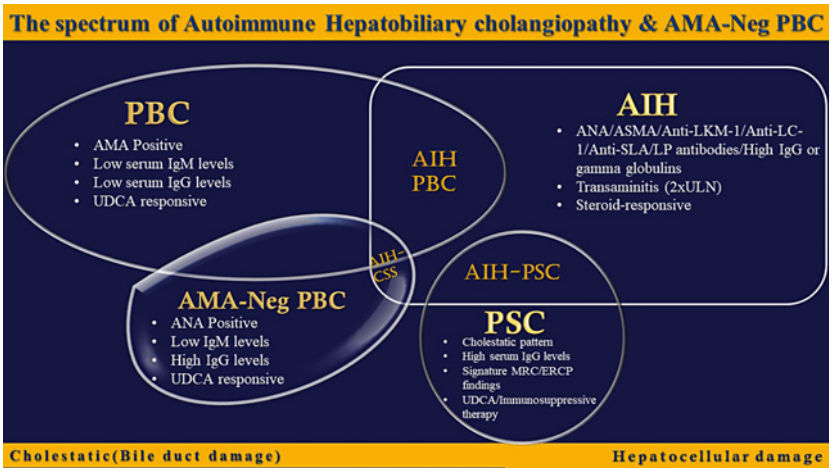

Fig. 1. The position of AMA-neg PBC in the spectrum of autoimmune hepatobiliary cholangiopathy. PBC, primary biliary cholangitis; ANA, antimitochondrial antibody; IgM, immunoglobulin M; UDCA, ursodeoxycholic acid; AMA-neg, antimitochondrial antibody negative; ANA, antinuclear antibodies; IgG, immunoglobulin G; ASMA, anti-smooth muscle antibody; anti-LKM-1, anti-liver kidney microsomal antibodies; Anti-LC-1, anti-liver cytosol antibodies; anti-SLA/LP antibodies, anti-soluble liver antigen/liver pancreas antibodies; MRCP, magnetic resonance cholangiogram; ERCP, endoscopic retrograde cholangiopancreatogram.

for a high antinuclear antibody titer (>1:2,560) with a centromere pattern and negative for AMA. The hepatitis panel was negative for viruses A, B, and C. Her serum immunoglobulin G level was 871 mg/dL (normal, <1,600 mg/dL). The rest of the serological tests, including anti-smooth muscle antibodies (ASMA) and anti-liver/kidney microsomal antibodies, were negative.

Computed tomography of the abdomen and pelvis revealed a normal liver architecture with mild hepatomegaly. The patient underwent a core needle liver biopsy. Histopathology (Fig. 2a, b) revealed mixed eosinophilic and lymphocytic inflammatory infiltrates, primarily in the portal tracts. Portal-based granulomas and lymphocytic cholangitis were also observed. This pattern was consistent with that of a florid duct lesion. No significant steatosis was observed in the background parenchyma. Periodic acid-Schiff staining revealed an intact intrahepatic parenchyma and architecture.

We reexamined the pathological sections and concluded that the pathology was consistent with PBC but negative for AMA. The final diagnosis of the case was AMA-neg PBC. The patient was treated with ursodeoxycholic acid. The patient responded to the above therapy, and her alkaline phosphatase level decreased from 714 U/L to 413 U/L after 6 months of therapy. Unfortunately, the patient was initially nonadherent to the treatment regimen in the first month of therapy, but no complications and no compliance issues have been reported after 6 months of follow-up.

Discussion

AMA-neg PBC is a variant of AMA-pos PBC that presents clinically, biochemically, and histopathologically similarly to it; however, it differs serologically because it lacks AMA, an essential criterion for PBC. Brunner et al. [1] first published a case series of what they described as “immune cholangitis” in 1985, which resembled destructive, nonsuppurative biliary cholangitis. The study described 3 patients whose clinical presentation, biochemical

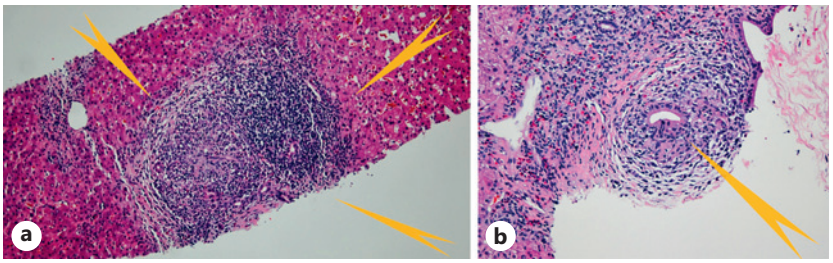

Fig. 2. a, **b** Histopathology two photomicrographs showing histologic features typical of the florid duct lesion seen in primary biliary cholangitis. The portal areas show granulomatous inflammation and lymphocytic cholangitis of the bile ducts (pointed yellow arrows) (hematoxylin and eosin stain, ×200 original magnification).

indices, and histopathology were the same as those of PBC, except for a lack of antibodies against the mitochondrial membranes of biliary ductal epithelial cells.

The spectrum of autoimmune hepatobiliary cholangiopathy comprises three principal disorders (AIH, PBC, and PSC) and three distinct overlap syndromes (AIH-PBC, AIH-PSC, and AIH-cholestatic syndrome) [2]. The most common overlap syndrome is AIH-PBC, with a prevalence of 7–13% in AIH or PBC patients, whereas AIH-cholestatic syndrome has a prevalence of 5–11% and previously exists as autoimmune cholangitis [2, 3]. There are no reported cases of AIH-PBC-PSC overlap, although cases of mixed PBC-PSC characteristics have been reported [4].

AMA is an immunoglobulin A product of B lymphocytes produced against lipoic acid located in the inner mitochondrial membrane of bile duct epithelial cells, thereby causing ductular damage. AMA is present in 95% of AMA-pos and 5% of AMA-neg PBC patients, with antinuclear antibody and ASMA occurring in 50% of cases [5]. Other PBC-specific autoantibodies, such as anti-glycoprotein 210 (anti-gp 210) and anti-sp100, are present in 30% of AMA-neg PBC cases [6]. Anti-kelch-like-12 antibodies and anti-hexokinase-1 antibodies were reportedly identified in 35% and 22% of AMA-neg PBC patients, respectively. Serological testing for anti-human kidney antibodies improves the diagnosis of PBC, particularly AMA-neg [7]. The clinical importance of these antibodies is avoidance of liver biopsy. Unfortunately, we did not test these antibodies in our patient.

AMA-neg PBC is a different entity than that previously known as autoimmune cholangitis and now termed AIH-CSS. AMA-neg PBC is a variant of AMA-pos PBC rather than an overlap syndrome. The phrases “autoimmune cholangitis” or “autoimmune cholangiopathy” cannot be used interchangeably to describe AMA-neg PBC because they are vague and imprecise [8]. Although autoimmune cholangitis has been used in the literature, no specific criteria or diagnostic guidelines have been published in hepatology or gastroenterology journals. It also cannot be considered an AIH-cholestatic syndrome because it has no features of AIH, such as transaminitis greater than five times the upper limit of normal (ULN); however, it has cholestatic features such as elevated alkaline phosphatase twice the ULN and gamma-glutamyl transferase greater than five times the ULN, interface hepatitis, and bile duct damage evident on liver biopsy. The diagnosis of AMA-pos PBC can be established when two of the criteria listed in Table 1 are met [8].

Cell-mediated immune intolerance reportedly plays a role in the pathogenesis of AMA-neg PBC. Jin et al. [9] compared portal cell infiltrates in AMA-neg and -pos PBC patients and found increased infiltrations of cluster of differentiation (CD) 5+ cells and CD20+ cells in the portal tracts, particularly the biliary ductules that damaged the biliary epithelial cells. Differences between AMA-pos and -neg PBC patients are listed in Table 2.

The response to treatment is similar in patients with AMA-pos PBC. If left untreated, both PBC types may worsen to advanced fibrosis and end-stage liver disease requiring liver

Table 1. Diagnostic criteria of AMA-pos PBC: the diagnosis of AMA-pos PBC can be established when two of the criteria listed in the following are met [8]

Evidence	Criteria
1) Biochemical evidence of cholestasis	Elevated alkaline phosphatase levels
2) Serological	
AMA-pos PBC	Antimitochondrial antibody-positive
AMA-neg PBC	Antimitochondrial antibody-negative or presence of other PBC-specific autoantibodies, e.g., sp100 or gp210
3) Histopathological	Nonsuppurative destructive cholangitis and destruction of interlobular bile ducts

AMA, antimitochondrial antibody; PBC, primary biliary cholangitis.

Table 2. Differences between AMA-positive PBC and AMA-negative PBC

	AMA-pos PBC	AMA-neg PBC
Sex		Female preponderance [10]
Symptoms	Frequent pruritus	Less frequent pruritus [10]
Biochemical profile		ALP and GGT levels lower than in positive patients [10]
Serology		
AMA	95%	5–10%
IgM levels	High	Low [11]
IgG levels	High	Low [11]
ANA and ASMA	56%	96% (higher prevalence and higher titers than AMA-pos patients) [12]
Other PBC-specific autoantibodies		Anti-HK-1 and anti-Kelch-12 antibodies are present in 40% of cases. Anti-gp210 and anti-sp100 are also present. These are considered future novel biomarkers. [13]
Associated autoimmune diseases		Rheumatoid arthritis, Sjögren's syndrome, progressive systemic sclerosis, and CREST syndrome [14]
Prognosis		Worse than AMA-pos PBC. Reason is unclear but could be secondary to delayed diagnosis [14]
Quality of life	Better	Worse [15]
Histopathology	Less bile duct damage and loss	Greater bile duct damage and loss [9]

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibodies; CREST, calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; IgM, immunoglobulin M; PBC, primary biliary cholangitis.

transplantation [16]. The CARE checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000528437).

Conclusion

This case highlights the importance of recognizing AMA-neg PBC as a variant of AMA-pos PBC and distinguishing between them. Up to 5% of PBC patients lack these antibodies but

Case Rep Gastroenterol 2023;17:14–20
DOI: 10.1159/000528437

present clinically, biochemically, and histopathologically similar; this condition is termed antimitochondrial antibody-negative PBC (AMA-neg PBC). Autoimmune cholangitis is a vague and imprecise term that cannot be used to describe AMA-neg PBC. AMA-neg PBC is a variant of AMA-pos PBC, with a slight difference due to serological deficiency of mitochondrial antibodies. Thus, AMA-neg PBC is not an overlap syndrome, as it does not share the features of AIH or PSC. All AMA-neg PBC patients should be tested for other PBC-specific autoantibodies such as anti-gp210, anti-sp100, anti-HK-1, and anti-kelch like-12 antibodies. Although histopathologically similar and bile duct damage and loss are worse in AMA-neg than -pos PBC, treatment remains the same for both conditions. However, the prognosis is slightly worse for AMA-neg PBC for unknown reasons.

Acknowledgments

The authors express their deepest appreciation to Mr. Dustin Hadley, PA, Department of Gastrointestinal Medicine, and Jason Campbell, MD, Diagnostic and Interventional Radiologist, Christus Highland Medical Center, who provided insightful comments about this research.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report including patient's imaging studies. Institutional Review Board ethics approval was not required in accordance with local guidelines.

Conflict of Interest Statement

Authors have no conflicts of interest to declare.

Funding Sources

This study received no funding.

Author Contributions

Matli V. obtained all of the required data and drafted the article after performing the literature review. Wellman G., a gastrointestinal and liver pathologist, reviewed the slides and revised the article. Pandit S. revised the article. Dies D. and Morris J. critically revised the manuscript and approved the final version of the article for publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Brunner G, Klinge O. [Ein der chronisch-destruierenden nicht-eitrigen Cholangitis ähnliches Krankheitsbild mit antinukleären Antikörpern (Immuncholangitis)]. Dtsch Med Wochenschr. 2008;112(38):1454–8.
2 Czaja AJ. Diagnosis and management of the overlap syndromes of autoimmune hepatitis. J Gastroenterol. 2013;27(7):417–23.
3 Rust C, Beuers U. Overlap syndromes among autoimmune liver diseases. World J Gastroenterol. 2008;14(21):3368–73.
4 Burak KW, Urbanski SJ, Swain MG. A case of coexisting primary biliary cirrhosis and primary sclerosing cholangitis: a new overlap of autoimmune liver diseases. Dig Dis Sci. 2001;46(9):2043–7.
5 Kaplan MM, Gershwin ME. Primary biliary cirrhosis. N Engl J Med. 2005;353(12):1261–73.
6 Nakamura M, Kondo H, Mori T, Komori A, Matsuyama M, Ito M, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology. 2007;45(1):118–27.
7 Norman GL, Yang C-Y, Ostendorff HP, Shums Z, Lim MJ, Wang J, et al. Anti-kelch-like 12 and anti-hexokinase 1: novel autoantibodies in primary biliary cirrhosis. Liver Int. 2015;35(2):642–51.
8 Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance from the American association for the study of liver diseases. Hepatology. 2019;69(1):394–419.
9 Jin Q, Moritoki Y, Lleo A, Tsuneyama K, Invernizzi P, Moritoki H, et al. Comparative analysis of portal cell infiltrates in antimitochondrial autoantibody-positive versus antimitochondrial autoantibody-negative primary biliary cirrhosis. Hepatology. 2012;55(5):1495–506.
10 Sakauchi F, Mori M, Zeniya M, Toda G. Antimitochondrial antibody negative primary biliary cirrhosis in Japan: utilization of clinical data when patients applied to receive public financial aid. J Epidemiol. 2006;16(1):30–4.
11 Mendes F, Lindor KD. Antimitochondrial antibody–negative primary biliary cirrhosis. Gastroenterol Clin North Am. 2008;37(2):479–84, viii.
12 Invernizzi P, Crosignani A, Battezzati PM, Covini G, De Valle G, Larghi A, et al. Comparison of the clinical features and clinical course of antimitochondrial antibody-positive and -negative primary biliary cirrhosis. Hepatology. 1997;25(5):1090–5.
13 Reig A, Norman GL, Garcia M, Shums Z, Ruiz-Gaspà S, Bentow C, et al. Novel anti–hexokinase 1 antibodies are associated with poor prognosis in patients with primary biliary cholangitis. Am J Gastroenterol. 2020;115(10):1634–41.
14 Juliusson G, Imam M, Björnsson ES, Talwalkar JA, Lindor KD. Long-term outcomes in antimitochondrial antibody negative primary biliary cirrhosis. Scand J Gastroenterol. 2016;51(6):745–52.
15 Raszeja-Wyszomirska J, Wunsch E, Krawczyk M, Rigopoulou EI, Kostrzewa K, Norman GL, et al. Assessment of health related quality of life in polish patients with primary biliary cirrhosis. Clin Res Hepatol Gastroenterol. 2016;40(4):471–9.
16 Heathcote J. Autoimmune cholangitis. Gut. 1997;40(4):440–2.