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

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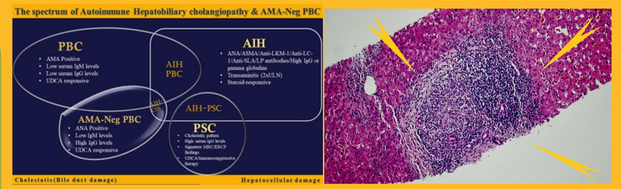
Introduction:

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.

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's vital signs were stable. 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 for a high antinuclear antibody (ANA) titer (>1:2560) 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, <1600 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 (Fig. 2) revealed a normal liver architecture with mild hepatomegaly. The patient underwent a core needle liver biopsy. Histopathology (Fig. 3A, 3B) 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. 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 3 months of therapy.



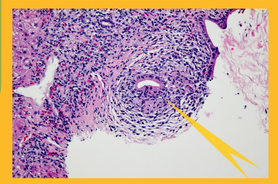


Figure: Histopathology: Two photomicrographs showing histologic features typical of the florid duct lesion seen in primary biliary cholangitis.. The portal areas show granulomatous inflammation and lymphocytic cholangitis of the bile ducts (pointed yellow arrows)(hematoxylin and eosin stain, 200X original magnification).

Table 1. Diagnostic criteria of AMA-pos PBC

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

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 & 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[16]

Discussion:

Brunner et al first published a case series of what they described as "immune cholangitis" in 1985, which resembled destructive, nonsuppurative biliary cholangitis. The study described three patients whose clinical presentation, biochemical 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[1].

The spectrum of AIHBC 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 ANA 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 (AHK) antibodies improves the diagnosis of PBC, particularly AMA-neg[7]. The clinical importance of these antibodies is avoidance of liver biopsy.

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. This case highlights the importance of recognizing AMA-neg PBC as a variant of AMA-pos PBC and distinguishing between them.

Conclusion:

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.

References:

[1] Brunner, G., & Klinge, O. (1987). Ein der chronisch-destruierenden nicht-eitrigen Cholangitis ähnliches Krankheitsbild mit antinukleären Antikörpern (Immun Cholangitis) [A chronic destructive non-suppurative cholangitis-like disease picture with antinuclear antibodies (immune cholangitis)]. Deutsche medizinische Wochenschrift (1946), 112(38), 1454–1458. https://doi.org/10.1055/s-2008-1068269
[2] Czaja A. J. (2013). Diagnosis and management of the overlap syndromes of autoimmune hepatitis. Canadian journal of gastroenterology = Journal canadien de gastroenterologie, 27(7), 417–423. https://doi.org/10.1155/2013/198070
[3] Rust, C., & Beuers, U. (2008). Overlap syndromes among autoimmune liver diseases. World journal of gastroenterology, 14(21), 3368–3373. https://doi.org/10.3748/wjg.14.3368
[4] Burak, K. W., Urbanski, S. J., & Swain, M. G. (2001). A case of coexisting primary biliary cirrhosis and primary sclerosing cholangitis: a new overlap of autoimmune liver diseases. Digestive diseases and sciences, 46(9), 2043–2047. https://doi.org/10.1023/a:1010620122567
[5] Kaplan, M. M., & Gershwin, M. E. (2005). Primary biliary cirrhosis. The New England journal of medicine, 353(12), 1261–1273. https://doi.org/10.1056/NEJMra043898
[6] Nakamura, M., Kondo, H., Mori, T., Komori, A., Matsuyama, M., Ito, M., Takii, Y., Koyabu, M., Yokoyama, T., Migita, K., Daikoku, M., Abiru, S., Yatsuhashi, H., Takezaki, E., Masaki, N., Sugi, K., Honda, K., Adachi, H., Nishi, H., Watanabe, Y., … Ishibashi, H. (2007). Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology (Baltimore, Md.), 45(1), 118–127. https://doi.org/10.1002/hep.21472
[7] Norman, G. L., Yang, C. Y., Ostendorff, H. P., Shums, Z., Lim, M. J., Wang, J., Awad, A., Hirschfield, G. M., Milkiewicz, P., Bloch, D. B., Rothschild, K. J., Bowlus, C. L., Adamopoulos, I. E., Leung, P. S., Janssen, H. J., Cheung, A. C., Coltescu, C., & Gershwin, M. E. (2015). Anti-kelch-like 12 and anti-hexokinase 1: novel autoantibodies in primary biliary cirrhosis. Liver international : official journal of the International Association for the Study of the Liver, 35(2), 642–651. https://doi.org/10.1111/liv.12690
[8] Lindor, K.D., Bowlus, C.L., Boyer, J., Levy, C. and Mayo, M. (2019), Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology, 69: 394-419. https://doi.org/10.1002/hep.30145
[9] Jin, Q., Moritoki, Y., Lleo, A., Tsuneyama, K., Invernizzi, P., Moritoki, H., Kikuchi, K., Lian, Z. X., Hirschfield, G. M., Ansari, A. A., Coppel, R. L., Gershwin, M. E., & Niu, J. (2012). Comparative analysis of portal cell infiltrates in antimitochondrial autoantibody-positive versus antimitochondrial autoantibody-negative primary biliary cirrhosis. Hepatology (Baltimore, Md.), 55(5), 1495–1506. https://doi.org/10.1002/hep.25511
[10] Sakauchi, F., Mori, M., Zeniya, M., & Toda, G. (2006). Antimitochondrial antibody negative primary biliary cirrhosis in Japan: utilization of clinical data when patients applied to receive public financial aid. Journal of epidemiology, 16(1), 30–34. https://doi.org/10.2188/jea.16.30
[11] Lacerda, M. A., Ludwig, J., Dickson, E. R., Jorgensen, R. A., & Lindor, K. D. (1995). Antimitochondrial antibody-negative primary biliary cirrhosis. The American journal of gastroenterology, 90(2), 247–249.
[12] Invernizzi, P., Crosignani, A., Battezzati, P. M., Covini, G., De Valle, G., Larghi, A., Zuin, M., & Podda, M. (1997). Comparison of the clinical features and clinical course of antimitochondrial antibody-positive and -negative primary biliary cirrhosis. Hepatology (Baltimore, Md.), 25(5), 1090–1095. https://doi.org/10.1002/hep.510250507