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Review Article

Antimitochondrial Antibody Measurements in the Diagnosis of Antimitochondrial Antibody-negative and Alkaline Phosphatase-positive Primary Biliary Cholangitis: An Update and Review

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Abstract

Antimitochondrial antibody (AMA)-negative primary biliary cholangitis (PBC) is a rare presentation of PBC that comprises 5%–10% of all PBC patients. The pathogenesis of AMA-negative PBC appears to be similar to that of AMA-positive PBC. AMA-negative PBC presents similarly to AMA-positive PBC, with symptoms of cholestasis, fatigue, and pruritus most commonly reported. Defective bicarbonate production, resulting in acidification of bile and bile acids, has been proposed as the primary mechanism of damage to bile ducts and hepatocytes and is reflected in elevations of alkaline phosphatase and aminotransferases. Chronic damage can lead to the development of cirrhosis. The diagnosis is made by the finding of AMA negativity by ELISA or assays of similar sensitivity and a positive PBC-specific antinuclear antibody (ANA; anti-glycoprotein 210 and anti-speckled 100 kDa protein) test. In cases in which anti-glycoprotein 210 and anti-speckled 100 kDa protein assays are also negative, a liver biopsy is required to make the diagnosis after exclusion of other causes of cholestasis by magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography. Treatment for AMA-negative PBC is the same as for AMA-positive cases, with ursodeoxycholic acid as the first-line treatment. Current treatment is most effective in early stages, where it slows but does not eliminate progression. Risk stratification by validated tools such as the GLOBE and UK-PBC scores remains useful in AMA-negative PBC.

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Introduction

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by injury to the small- and medium-sized intrahepatic bile ducts, which often leads to liver fibrosis and ultimately cirrhosis if left untreated.[1] Antimitochondrial antibody (AMA)-negative PBC is defined by evidence of biochemical cholestasis on laboratory evaluation, histological findings on liver biopsy consistent with PBC, and AMA-negative testing. From our review of the subject, it is clear that AMA negativity is not a single entity, but a group of conditions that can be caused by several factors. These include laboratory issues, the natural history of the disease, and ursodeoxycholic acid (UDCA)-related seroreversion, in addition to true AMA-negative PBC. Most of these situations are not widely appreciated or addressed in guidelines. Therefore, the aim of this review is to focus attention on the pathogenesis, diagnosis, treatment, and outcomes of AMA-negative alkaline phosphatase (ALP)-positive PBC.

Measurement of AMA

The detectability of AMA in PBC depends on several factors, including the tests used and the immune responses of patients. There are five common strategies for detecting AMA: indirect immunofluorescence (IIF), immunoblotting, enzyme immunoassay, Luminex bead assay, and enzyme inhibition assay (Table 1).[2–13] The IIF method has the lowest sensitivity, with only 15% of AMA-negative sera showing reactivity to triple recombinant mitochondrial antigen (MIT3) (Table 2).[7–9,11–16] enzyme-linked immunosorbent assay (ELISA) and immunoblot tests detect preselected M2 antigens. These automated commercial kits have the advantage of convenience and increased sensitivity. Indeed, some patients originally tested AMA-negative by IIF were subsequently found to be positive by immunoblot or ELISA (Table 3).[6,11,14,17] For this reason, ELISA and immunoblot detection methods are considered superior to IIF for the detection of AMA.[18] ELISA and IIF are the most commonly used assays for AMA detection (Table 1).

Potential contributors to AMA negativity in ALP-positive PBC cases

In considering the diagnosis of AMA-negative ALP-positive

Table 1. A summary of commonly reported AMA assays

Clinical assay type	Description	Clinical use/strengths	Limitations	Citations
IIF	Patient serum exposed to rodent kidney & stomach tissue rich in mitochondria. Binding to AMA-M2 antigens detected by IIF	Historical gold standard, widely available, can be used for initial screening in experienced labs	Reduced sensitivity compared to ELISA-based methods; requires fresh rodent kidney and stomach tissues as substrates; requires skilled interpretation of fluorescence patterns; unable to identify specific mitochondrial antigens	Han *et al*.[2]; Calise *et al*.[3]; Tanaka *et al*.[4,5]; Muratori *et al*.[6]
EliA-M2 IgG	Automated FEIA run on Thermo Fisher Phadia/ImmunoCAP250/ ImmunoCAP1000 analyzers detecting Ab to AMA-M2	Highly standardized; great reproducibility, automated.	Proprietary antigen formulation, expensive	Dähnrich *et al*.[7]; Poyatos *et al*.[8]; Bogdanos *et al*.[9]
ELISA using recombinant antigens	Solid-phase assay using recombinant/ purified mitochondrial antigens (e.g., MIT3, combining epitopes of PDC-E2, BCOADC-E2, OGDC-E2)	Optimal for initial screening, detects up to 44%–48% of IIF-negative cases	Varies by antigen manufacturer	Dähnrich *et al*.[7]; Poyatos *et al*.[8]; Bogdanos *et al*.[9]; Moteki *et al*.[10]; Gabeta *et al*.[11]
Anti–M2 ELISA	ELISA detecting Ab to M2 antigen complex	Automatic, widely used as screening assay.	Slightly less sensitive than MIT3 in AMA-negative cases	Dähnrich *et al*.[7]; Bogdanos *et al*.[9]; Gabeta *et al*.[11]; Lindor *et al*.[12]
Anti–PDC–E2 specific ELISA	Assay detecting Ab to PDC-E2 subunit	Useful for initial screening when PDC-E2 is primary target	Misses PDC-E2, BCOADC-E2, OGDC-E2 antigens	Bogdanos *et al*.[9]; Gabeta *et al*.[11]; Oertelt *et al*.[13]
Anti–M4 ELISA	Detects anti-M4 Ab by ELISA (can also be done via immunoblot)	Could be useful in PBC-AIH overlap	Limited standardization, not useful as primary diagnostic test	Lindor *et al*.[12]; Oertelt *et al*.[13]
Immunoblotting/ Dot-blot	Detection of antibodies against recombinant or native E2 subunits	Identifies subunit-specific AMA; useful for confirmatory test of positive ELISA	Labor-intensive; less standardized for routine clinical labs	Bogdanos *et al*.[9]; Gabeta *et al*.[11]; Lindor *et al*.[12]; Oertelt *et al*.[13]
Research tools				
Luminex bead-based multiplex assays	High-throughput bead-based multiplex immunoassay	Simultaneous detection of multiple autoantibodies; useful for initial screening in high volume labs	Limited clinical availability Research-focused	Lindor *et al*.[12]; Oertelt *et al*.[13]
Enzyme inhibition assays	Measures inhibition of mitochondrial enzyme activity	Used historically; detects functional antibody effects No established sensitivity	Not used in screening, lack standardization for routine diagnostic use	Lindor *et al*.[12]

IIF, indirect immunofluorescence; AMA, Antimitochondrial antibody; ELISA, enzyme-linked immunosorbent assay; EliA-M2, Enzyme-linked immunoassay; FEIA, fluorescence enzyme immunoassay; Ab, antibody; MIT3, triple recombinant mitochondrial antigen; PDC-E2, pyruvate dehydrogenase complex E2; BCOADC-E2, branched-chain 2-oxoacid dehydrogenase complex E2; OGDC-E2, 2-oxoglutarate dehydrogenase complex; PBC, primary biliary cholangitis AIH, autoimmune hepatitis.

Table 2. A summary of sensitivities and specificities of various AMA assays

Assay	Sensitivity (%)	Specificity (%)	Relevant citation
IIF	43.8–100	83.3–100	Hu *et al*.[15]
EliA-M2 IgG (FEIA)	87–94	95–98	Dähnrich *et al*.[7]; Poyatos *et al*.[8]; Bogdanos *et al*.[9]
ELISA using recombinant antigens (e.g., MIT3-based)	91–94	93.8–96.1	Hu *et al*.[15]
Anti-M2 ELISA	85–95	92–98	Lindor *et al*.[12]; Bogdanos *et al*.[9]; Dähnrich *et al*.[7]; Gabeta *et al*.[11]
Anti-PDC-E2 specific ELISA	87–94	95–98	Oertelt *et al*.[13]; Gabeta *et al*.[11]; Bogdanos *et al*.[9]
Anti-M4 ELISA	20–40	90–95	Oertelt *et al*.[13]; Lindor *et al*.[12]
Western blot (immunoblot)	85.0–94.9	84.8–100	Hu *et al*.[15]
Dot-blot	91	100	Bargou *et al*.[16]
Luminex bead-based multiplex assay	95	Not reported	Oertelt *et al*.[13]; Lindor *et al*.[12]
Enzyme inhibition assay	Not established	Not established	Lindor *et al*.[12]

IIF, indirect immunofluorescence; EliA-M2, enzyme-linked immunoassay M2 antigen; ELISA, enzyme-linked immunosorbent assay; AMA, antimitochondrial antibody; FEIA, fluorescence enzyme immunoassay; MIT3, triple recombinant mitochondrial antigen; anti-PDC-E2, anti-pyruvate dehydrogenase complex E2; anti-M4, anti-sulfite oxidase.

PBC, it is important to consider potential causes of false-negative AMA. These can be categorized as laboratory issues, the natural history of the disease, and pharmacological effects on AMA.

Laboratory issues

Some AMA-negative cases are actually false-negative due to the low sensitivity of assays used. In studies that analyzed AMA-negative cohorts, many cases have been found to be positive when retested with more sensitive assays. Michieletti *et al*.[19] reported that 3/20 patients initially found to be AMA-negative by IIF became AMA-positive with ELISA testing. Several other studies found that sera categorized as AMA-negative by IIF showed positivity when recombinant antigens were used (43% reclassification rate), e.g., MIT3 triple recombinant-based assays specific for pyruvate dehydrogenase complex E2 (PDC-E2), branched-chain 2-oxoacid dehydrogenase complex E2 (BCOADC-E2), and 2-oxoglutarate dehydrogenase complex (OGDC-E2). ELISA and immunoblot-based MIT3 combination assays have been reported to detect AMA-positive cases that are missed by IIF, with a reclassification rate of 42%–73% (Tables 1 and 3).[7–9,18] Thus, between 10% and 73% of cases initially AMA-negative by IIF were found to be AMA-positive upon retesting with more sensitive AMA assays.

Natural history of the disease

There are data suggesting that, especially early in the disease course, AMA may be negative but later become positive, indicating delayed seroconversion. Miyakawa *et al*.[17] reported on 21 symptomatic hospitalized, liver biopsy-proven PBC patients with serial monitoring of specific M2 autoantigens (PDC-E2, BCOADC-E2, and OGDC-E2) by IIF over a period of 3 years using the same assay for follow-up. Two patients who initially demonstrated AMA negativity to the anti-PDC-E2 IIF assay became positive between 1.5 and 2 years. The times to seroconversion for the following AMA-M2-associated epitopes of anti-protein X (3 cases), anti-BCOADC-E2 (1 case), and anti-OGDC-E2 (1 case) were reported to be 3 years, 2 years, and 3 years, respectively.[17] ELISA confirmation was not performed in the two AMA-negative cases.

One small case series noted that 10% of AMA-negative PBC patients (negative by IIF) were found to be AMA-positive on repeat IIF testing, with a mean follow-up period of 36 months. However, a specific time to seroconversion in these three cases was not determined.[20]

Table 3. A summary of studies reporting initial AMA-negative PBC reclassified as AMA-positive PBC by subsequent more sensitive tests

Initial test	Secondary test	Fraction (%) reclassified as AMA-positive	Study population	Reference
IIF	Recombinant-antigen ELISA	22/30 (73) by ELISA testing	30 AMA-negative, liver biopsy-proven PBC patients from Japan	Miyakawa *et al*.[17]
IIF	MIT3 ELISA (IgG ± IgA)	12/27 (44.5) by IgG MIT3 ELISA testing	27 AMA-negative, liver biopsy-proven PBC patients from Greece	Gabeta *et al*.[11]
IIF	WB (immunoblot) and ELISA	17/38 (44) by WB; 16/38 (42) when tested by ELISA	38 AMA-negative, liver biopsy-proven PBC patients from Italy	Muratori *et al*.[6]
IIF	"PBC screen ELISA" including pMIT3 (plus anti-gp210/anti-sp100)	43/100 (43) by "PBC Screen Assay" which combined pMIT3, gp210, sp100	100 AMA-negative, liver biopsy-proven PBC patients from Italy	Bizzaro *et al*.[14]

IIF, indirect immunofluorescence; ELISA, enzyme-linked immunosorbent assay; AMA, Antimitochondrial antibody; PBC, primary biliary cholangitis; WB, Western blot; MIT3 ELISA, enzyme-linked immunosorbent assay using the triple recombinant mitochondrial antigen; anti-gp210, anti-glycoprotein 210; anti-sp100, anti-speckled 100 kDa protein.

In another case series, 26% of AMA-negative, biopsy-proven PBC patients became AMA-positive during a mean follow-up time of 34 months as determined by IIF at baseline and follow-up.[21]

Overall, the data indicate that 10%–26% of initially AMA-negative PBC cases converted to AMA-positive status over a course of up to 3 years. It is important to note that most of the data reviewed are based on small cohorts and case series, possibly limiting generalizability.

Pharmacological effects on AMA titers

UDCA treatment for PBC has been documented to decrease AMA levels over time, referred to as UDCA-related seroreversion.[22,23] In some cases, AMA titers (IIF assay at baseline and follow-up) have even been reported to normalize.[24] In the latter study, 157 PBC patients were treated with UDCA, with follow-up of up to 28 years. UDCA responders showed significantly decreased AMA titers in the first year, although the majority remained positive. Ten patients had normalized AMA by the last follow-up. Specific time points of conversion were not mentioned.[24] Tang *et al*.[23] followed a cohort of 17 PBC patients treated with UDCA for 24 months. AMA titer levels significantly decreased by week 24 compared to baseline, with IgG-AMA levels decreasing as early as week 12.[23] However, the number of patients who had normalized AMA levels was not provided. Kisand *et al*.[25,26] reported an 11% mean decrease in IgG anti-Pyruvate dehydrogenase in a group of 23 UDCA-treated PBC patients, although none became AMA-negative at the time of reporting.

In addition to treatment for PBC, UDCA has reportedly been used off-label to treat sclerosing cholangitis, graft-versus-host disease, cholestasis of pregnancy, and liver disease in cystic fibrosis.[27] PBC patients who receive UDCA or other similar agents for other conditions may exhibit false-negative AMA levels due to drug effects.[28]

True AMA-negative PBC

When all situations of false-negative AMA status have been ruled out, true AMA-negative PBC remains.

Epidemiology and prevalence of AMA-negative PBC

Up to 5%–10% of PBC cases have been reported to be AMA-negative,[12] while some smaller studies have shown even higher rates of AMA-negative confirmed PBC cases. In a large non-white Brazilian cohort of 464 PBC patients, 17% (80/464) had biopsy-proven AMA-negative PBC.[29] Notably, the AMA-negative patients in this study were younger than AMA-positive patients, with a mean age of 52.2 years compared with 59.6 years in AMA-positive cases. In addition, initial symptoms occurred at an earlier age than in AMA-positive cases (43.2 years compared with 49.5 years).[29] Southeast Alaska Natives have been shown to exhibit a relatively high proportion of biopsy-proven AMA-negative PBC cases (5 AMA-negative cases out of 18 total PBC patients; 27.7%). In this population, the combined prevalence of AMA-positive and AMA-negative PBC was reported to be 21 per 100,000.[30] When compared with two predominantly white European populations, this prevalence was similar to that observed in Norway (14.6 per 100,000) but lower than the rate reported in northern England (25 per 100,000).[30] In a US-based cohort study that included 45 AMA-negative cases, 35 were Caucasian, 6 African American, and 4 Hispanic, although this study did not report whether these patients had biopsy-proven PBC and did not specify how the diagnosis was made.[31] Evidence from these diverse cohorts showed that the prevalence of biopsy-proven AMA-negative PBC among particular ethnic groups was considerably higher (ranging from 17%–30%) than in typically diagnosed PBC among the Caucasian population.[29]

AMA-negative PBC generally affects women at a rate 10 times higher than men at the population level, which is similar to rates seen in AMA-positive PBC.[32] In a retrospective review that included 290 cases of biopsy-proven PBC, AMA-negative PBC was found in 16% of females and in 0% of males.[33] In a study by Peters *et al*.,[31] 95.5% (43/45) of patients were female. Given the low rate of PBC seen in males and the rarity of AMA negativity, it is not surprising that the male-to-female ratio is also high in AMA-negative PBC, although the small sample size may limit the reliability of these findings.

Pathogenesis of AMA-negative PBC

Current theories of the pathogenesis of PBC propose a triggering event caused by xenobiotic modification or the appearance of a microbial mimic of dihydrolipoyl transacetylase of PDC-E2 in mitochondria. Presentation of these antigens on antigen-presenting cells activates both T-cell and B-cell responses. The former attacks and damages biliary epithelial cells (BECs). The latter results in the development of circulating AMAs (loss of immune tolerance) against the antigenic component of PDC-E2. However, AMAs are thought not to be responsible for damage to BECs. Rather, BEC damage is thought to be triggered by the production of proinflammatory cytokines by antigen-presenting cells, which leads to decreased function of anion exchanger 2 (AE2), a chloride–bicarbonate exchanger (1 Cl^-:1 HCO_3^-) in the membrane of cholangiocytes of small bile ductules. Reduced bicarbonate secretion acidifies the bile duct lumen, protonating bile acids, which makes them capable of permeating BECs. These toxic bile acids damage membranes through detergent action, affecting both BECs and hepatocytes.[18,34] This proposed mechanism is consistent with the observed limitation of ductal damage to the small intrahepatic bile ducts and hepatocytes.[13] There is no evidence that AMAs are involved in the damage or destruction of BECs.[35,36]

In AMA-negative PBC, for some reason, immune modification of the PDC-E2 antigen does not activate the B-cell response, resulting in negative AMA assays despite damage to BECs from accumulation of acidified bile acids that is indistinguishable from that in AMA-positive cases.[37,38] The expression of PDC-E2 antigen on BECs was found to be the same in AMA-negative and AMA-positive cases.[38] Thus, the mechanism of cholangiocyte damage appears to be independent of AMA status. This accounts for the lack of observed differences in histopathology, symptomatology, disease progression, and outcomes between AMA-negative and AMA-positive patients.[18,38]

Presentation and clinical course of AMA-negative, ALP-positive PBC

Asymptomatic AMA-negative PBC

Prince *et al*.[39] stratified PBC patients by symptom status. The AMA-negative rate was reported to be 9.7% in the initially asymptomatic group and 10.7% in the symptomatic group. In a prospective study with a 24-year follow-up of 279 biopsy-proven PBC patients, 36/279 (12.9%) were asymptomatic.[40] In this group, 19% were AMA-negative.[40] Long *et al*.[41] followed 20 patients with asymptomatic biopsy-proven PBC and

Table 4. Positivity rates of anti-gp210 and anti-sp100 in AMA-negative PBC (ANA-related markers)

Anti-gp210 positivity in AMA-negative PBC (Approx. %)*	Anti-sp100 positivity in AMA-negative PBC (Approx. %)*	References
10	10	Milkiewicz *et al*.[52]
60	60	Xiao *et al*.[49]
33	0	Saito *et al*.[53]
20	6	Hu *et al*.[51]
15	38	Muratori *et al*.[54]
57	60	Wu *et al*.[55]
9	23	Bizzaro *et al*.[14]

*The extreme variability in reported anti-gp210 and anti-sp100 antibody positivity is likely due to study-specific factors such as cohort size, ethnicity, availability of liver biopsy, and type of assay. Xiao *et al*. and Wu *et al*. used immunoblot-based assays, Bizzaro *et al*. used ELISA-based assays, and Milkiewicz *et al*. used enzyme-linked immunoassays for anti-gp210/anti-sp100 testing. In addition, cohort sizes varied widely, and some studies included few AMA-negative patients. AMA, antimitochondrial antibody; PBC, primary biliary cholangitis; anti-gp210, anti-glycoprotein 210; anti-sp100, anti-speckled 100 kDa protein.

found that 2/20 (10%) were AMA-negative. Another study of 36 initially asymptomatic biopsy-proven PBC patients reported 6/36 (16.6%) to be AMA-negative at the time of diagnosis.[42] Finally, in a retrospective study on long-term outcomes of AMA-negative biopsy-proven patients, 26% were noted to be initially asymptomatic.[43] In asymptomatic AMA-negative cases, ALP elevation may be the only indication of underlying cholestasis and possible PBC. ALP elevation is not related to the presence or absence of AMA.

Symptomatic AMA-negative PBC

In a study of 301 initially symptomatic biopsy-proven PBC patients, 10.9% were found to be AMA-negative.[39] Out of 243 symptomatic biopsy-proven PBC patients, 18% were AMA-negative.[40] In a Japanese national public-aid registry cohort of 5,805 initially symptomatic biopsy-proven PBC patients, 19.4% were AMA-negative.[44] Altogether, it appears that the incidence of AMA-negative biopsy-proven initially asymptomatic PBC cases is similar to that of initially symptomatic cases, ranging from 9.7% to 19%.

AMA-negative PBC patients have the same clinical features of cholestatic liver disease as AMA-positive PBC, including pruritus and fatigue early, and jaundice, ascites, encephalopathy, and variceal bleeding late in the disease course.[12] In the past, AMA-negative patients often presented at later disease stages, resulting in poorer prognosis and more advanced disease at UDCA initiation.[18] AMA-negative PBC was reported to have more severe bile duct damage and loss due to increased portal inflammation characterized by higher numbers of $CD5^+$ and $CD20^+$ lymphocytes compared with AMA-positive PBC.[29,45] However, a comparative study showed no difference between AMA-positive and AMA-negative PBC patients in rates of cirrhosis, liver failure, or liver transplantation.[46] Recent data have confirmed no difference in aggressiveness or outcomes between AMA-positive and AMA-negative PBC.[47] Furthermore, the clinical response to UDCA was found to be generally similar between AMA-negative and AMA-positive patients.[45]

Diagnosis of AMA-negative, ALP-positive PBC

The American Association for the Study of Liver Diseases (AASLD), British Society guidelines, and European Association for the Study of the Liver (EASL) guidelines primarily rely on elevation of ALP and positive AMA titers to make a diagnosis of PBC.[14,48]

If AMA is negative and false negatives and other causes of cholestasis have been ruled out, PBC-specific antinuclear antibodies (anti-sp100 and anti-gp210) are recommended for confirmation. Anti-gp210 and anti-sp100 antibodies have shown positivity rates of up to 60% in AMA-negative cases, although there is variability in the data (Table 4).[9,14,49–55]

There is no recommended positivity cutoff for anti-sp100 or anti-gp210 in current guidelines. Rather, current AASLD and EASL guidelines recommend that AMA positivity be determined as specified by assay manufacturers, without the need for liver biopsy.[18,12] However, because ELISA-type assays are more sensitive than IIF assays, in situations where anti-sp100 and anti-gp210 antibody assays have limited availability and/or affordability, our review of assay data suggests that ELISA AMA assays may be useful in identifying IIF AMA false negatives (Fig. 1).

More recently, anti-kelch-like 12 and anti-hexokinase 1 have been reported in 35% and 22% of AMA-negative PBC patients, respectively.[56] However, these are experimental assays, are not widely available, and should be interpreted with caution.[57] Current guidelines do not support a PBC diagnosis based on non-AMA, non-ANA antibodies. In the absence of positive AMA or ANA tests, AASLD guidelines recommend a liver biopsy to establish the diagnosis.

Differential diagnoses

Cholestasis due to drug reactions and infectious processes should be screened by appropriate blood tests. Mechanical obstructions are best evaluated by magnetic resonance cholangiopancreatography (MRCP) or, if necessary, endoscopic retrograde cholangiopancreatography (ERCP). Primary sclerosing cholangitis (PSC) is perhaps the disease most symptomatically similar to PBC. While it typically affects both intra- and extrahepatic bile ducts, PSC can be limited to the intrahepatic ducts and should be considered in AMA-negative cases.[58] To exclude intrahepatic PSC, especially in AMA-negative cases, imaging by MRCP is recommended to identify characteristic multifocal strictures and dilatations of the intrahepatic bile ducts.[59] MRCP can also identify biliary dilatation secondary to tumors or stones and is therefore recommended by AASLD guidelines.[60] In most cases, a diagnosis of PSC can be made by MRCP or ERCP alone. However, if these studies are inconclusive, a liver biopsy is recommended to distinguish AMA-negative PBC from PSC.[60] The absence of periductal concentric "onion-skin" fibrosis argues against PSC, and the presence of classical florid duct lesions and granulomas supports a diagnosis of PBC.[59] Importantly, negative ANA, smooth muscle antibody, or perinu-

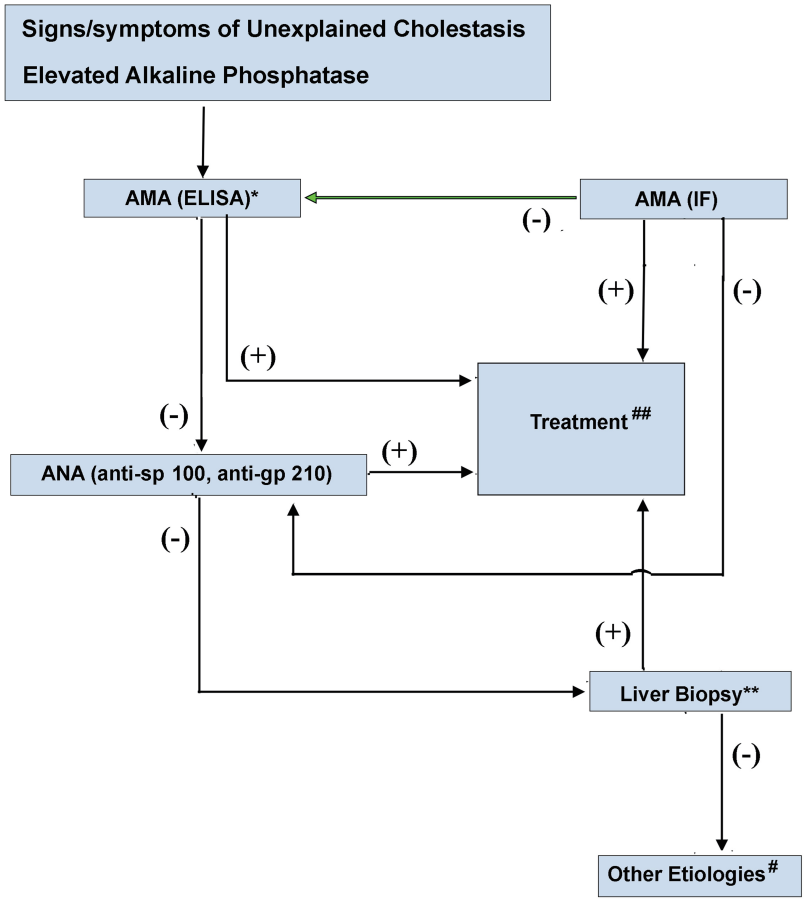

Fig. 1. Proposed diagnostic algorithm for AMA-negative patients with cholestatic symptoms or elevated alkaline phosphatase. If AMA is negative by IIF, retest by AMA ELISA or other assay with similar sensitivity and specificity. If negative by ELISA, then retest by ANA (anti-gp210 and anti-sp100). For any positive results, a PBC diagnosis is confirmed. If all tests are negative, a liver biopsy is needed to make a diagnosis of PBC. Rather than cutoff titers, most guidelines recommend that positive and negative AMA and ANA (anti-gp210 and anti-sp100) criteria be used as specified by the test manufacturers. The green arrow indicates our recommendation of AMA ELISA testing in AMA-negative cases determined by IIF AMA in situations where ANA (anti-gp210 and anti-sp100) assays have limited availability and/or affordability. *ELISA or other assay such as Western blot with equivalent sensitivity/specificity, **liver histopathology consistent with PBC, e.g., nonsuppurative damage to small and medium bile ducts, ductopenia, with possible granulomas and fibrosis. #Other etiologies to consider include bile duct obstruction, space-occupying lesions, drug-induced cholangiopathy, and other autoimmune diseases such as PSC or IgG4-related cholangitis. Other appropriate workup includes CT scan, MRCP, other relevant serological testing (i.e., IgG4 levels, serum tumor markers), and if necessary, referral for ERCP, interventional radiology, or surgery. ##Treatment includes initiation of UDCA as a first-line agent with consideration of elafibranor and seladelpar as second-line agents; see Treatment section. AMA, antimitochondrial antibody; PBC, primary biliary cholangitis; ELISA, enzyme-linked immunosorbent assay; ERCP, endoscopic retrograde cholangiopancreatography; ANA, antinuclear antibody; anti-gp210, anti-glycoprotein 210; anti-sp100, anti-speckled 100 kDa protein; IIF, indirect immunofluorescence; PSC, primary sclerosing cholangitis; CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; UDCA, ursodeoxycholic acid; +, positive; –, negative.

clear anti-neutrophil cytoplasmic antibody testing does not rule out PSC, as these tests lack specificity. Thus, MRCP and liver biopsy remain the definitive diagnostic tools when PSC is suspected.[60] Any extrahepatic biliary lesions exclude PBC as the diagnosis.

Other differential diagnoses to consider include autoimmune hepatitis, which typically presents with a hepatocellular injury pattern, elevated IgG levels, and positive antinuclear, anti–liver-kidney microsomal, soluble liver antigen, or anti–smooth muscle antibodies.[12,61] Drug-induced cholestatic liver injury is common, presenting with elevated cholestatic serum markers, including ALP, gamma-glutamyl transferase (GGT), and bilirubin, with a temporal relationship to administration of a culprit drug.[12] Any intrahepatic space-occupying lesion, benign or malignant, can cause intrahepatic cholestasis by compression of intrahepatic bile ducts. These should be considered in the differential diagnosis and worked up initially by abdominal ultrasound.

Biliary obstruction secondary to choledocholithiasis and malignancy is generally characterized by clinical presentations that differ from PBC and should be evaluated by abdominal ultrasound followed by computed tomography or magnetic resonance imaging. Obstructions may require ERCP and/or endoscopic ultrasound (EUS).[62]

Treatment of AMA-negative PBC

The AASLD recommends UDCA at a dose of 13–15 mg/kg/d as initial treatment for AMA-positive PBC, regardless of baseline ALP levels.[12] Recent data indicate that treatment outcomes in AMA-negative cases are similar to those in AMA-positive PBC patients. A study that included eight AMA-negative biopsy-proven symptomatic PBC patients found that sequential liver biochemistries were comparable between AMA-negative and AMA-positive patients while on UDCA treatment.[21] Invernizzi *et al*.[46] also reported no statistically significant difference in biochemical response to UDCA between AMA-negative cas-

es and AMA-positive controls, with a mean follow-up of 53 months. More recent data have confirmed the lack of biochemical differences between these groups. UDCA has been shown to slow disease progression and delay the need for liver transplantation.[12,63] Most studies on UDCA treatment have primarily focused on ALP responses.

Obeticholic acid is recommended for UDCA non-responders. Bezafibrate is used as an alternative. In a multicenter study of "difficult-to-treat" PBC cases, adding a fibrate to UDCA plus obeticholic acid ("triple therapy") was associated with greater improvements in biochemical response and a higher likelihood of normalizing liver biochemistry.[64] This study did not specifically report treatment outcomes in the AMA-negative population.

Elafibranor and seladelpar are peroxisome proliferator-activated receptor agonists that have been approved by the U.S. Food and Drug Administration for the treatment of PBC that has not adequately responded to UDCA or in patients who cannot tolerate UDCA. There are no data on the use of these agents in AMA-negative PBC.

Two commonly used prognostic models are the GLOBE score and the UK-PBC score. The GLOBE score incorporates age at start of therapy, total bilirubin level, ALP, albumin, and platelet count after one year of UDCA treatment.[12] A score of 0.30 or less indicates a better prognosis, while a higher score predicts the likelihood of death or the need for liver transplantation at 5 and 10 years.[65] Assessment of the UK-PBC score also predicts the risk of liver transplantation or liver-related death within 5, 10, or 15 years.[66] This is determined by baseline patient albumin and platelet counts combined with serum ALP, aminotransferases, and bilirubin levels after 20 months of therapy.[67] Many large studies have validated these scores and found that both reliably predict UDCA treatment response in both AMA-positive and AMA-negative cases. John *et al*.[68] reported no difference in UDCA response between AMA-negative and AMA-positive cases using the GLOBE score in a cohort of 521 PBC patients, of whom 65 were AMA-negative. Marenco-Flores *et al*.[69] conducted a prospective validation study of the GLOBE and UK-PBC scores that included biopsy-proven AMA-negative cases, thereby supporting their use.

Discussion

The current review revealed that the incidence of biopsy-proven AMA-negative PBC is low, ranging from 9.7% to 20% of all PBC cases, and is similar in symptomatic and asymptomatic cases. Of these AMA-negative cases, the vast majority remain negative indefinitely. However, 10% to 26% of biopsy-proven AMA-negative cases have been reported to seroconvert to AMA-positive status, taking up to 3 years to complete this change. From a clinical management perspective, delayed AMA seroconversion is not very relevant because ANA (anti-gp210 and anti-sp100) serology, or if necessary, liver biopsy, provides a diagnosis of AMA-negative PBC in the vast majority of cases.

Current AASLD and EASL guidelines state that repeated AMA testing is not indicated or useful once an initial assay is found to be negative. Repeated AMA testing is also not indicated for monitoring disease progression.[12,48] Testing for ANA (anti-gp210 and anti-sp100) is recommended to confirm a diagnosis of AMA-negative PBC, so that liver biopsy is usually unnecessary. However, if the initial AMA-negative result was obtained using a low-sensitivity assay such as IIF, or in situations where anti-gp210/anti-sp100 antibody assays have limited availability and/or affordability, repeat testing with a more sensitive AMA assay (e.g., ELISA AMA assays) may be useful in identifying false-negative IIF results. This recommendation is based on our review of assay performance data and is not a formal guideline of any liver society (Fig. 1).

In the past, the lack of AMA often delayed diagnosis and treatment. As a result, AMA-negative PBC cases were frequently diagnosed at late stages, giving the impression of a more aggressive form of the disease. However, more recent studies of AMA-negative PBC diagnosed by ANA (anti-gp210 and anti-sp100) positivity have permitted earlier detection and treatment. As a result, there does not appear to be a difference in aggressiveness or outcomes between AMA-positive and AMA-negative PBC.[47]

Finally, AMA-negative PBC has often been described as an "atypical" entity separate from AMA-positive PBC. However, the fact that the progression and outcomes of AMA-positive and AMA-negative PBC are virtually identical confirms that the presence or absence of AMA is unrelated to disease development or progression. Therefore, labeling AMA-negative PBC as "atypical" is somewhat misleading.

The existing literature has important limitations. Many studies were small, retrospective, geographically or ethnically concentrated, and primarily based on Western cohorts. There is a lack of data on the persistence of AMA negativity in AMA-negative patients. Future clinical trials should include studies on longitudinal changes in AMA and anti-gp210 or anti-sp100 antibodies, development and validation of new specific PBC biomarkers related to disease progression, and more effective therapies targeting pathogenic mechanisms.

Conclusions

False-negative AMA-negative PBC can be due to insensitive AMA tests, delayed seroconversion, or medication-induced suppression of AMA. These should be considered and excluded, and true AMA-negative PBC should be confirmed by ANA (anti-gp210 and anti-sp100).

The presentation, progression, and response to treatment of AMA-negative PBC have been shown to be similar to those of AMA-positive PBC.

Liver biopsy is not necessary to make a diagnosis of AMA-negative PBC except in the few cases where ANA (anti-gp210 and anti-sp100) are also negative.

GLOBE and UK-PBC scores remain useful clinical tools for prognostication and can be applied to AMA-negative cases, as such cases were included in validation studies of these tools.

Although AMA-negative PBC is often discussed as an "atypical" entity separate from AMA-positive PBC, the fact that progression and outcomes are virtually identical indicates that the presence or absence of AMA appears not to significantly influence disease development or progression. Therefore, labeling AMA-negative PBC as "atypical" is somewhat misleading.

The findings indicate that future research on PBC should focus on improving un-derstanding of its pathogenesis and on the discovery of new targeted therapies, including for AMA-negative cases.

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Conflict of interest

GYW has been Editor-in-Chief of the *Journal of Clinical and Translational Hepatology* since 2013. He has no role in the publisher's decisions regarding this manuscript. The other authors have no conflict of interests related to this publication.

Author contributions

Review concept (GYW), information collection, drafting of the manuscript (KS), and revision of the manuscript (GYW, KS). All authors have approved the final version and the publication of the manuscript.

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