

Variants of Primary Biliary Cholangitis: An Updated Mini-Review

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Abstract: Primary biliary cirrhosis (PBC) is an autoimmune cholestatic disease of the liver which affects mainly middle-aged women characterized by progressive destruction and loss of the small intrahepatic bile ducts which in turn, may lead to end-stage liver disease. The typical clinical phenotype is characterized by a middle-aged female with elevated cholestatic enzymes and positive antimitochondrial antibodies (AMA). However, apart from this typical presentation, there are important variants in everyday clinical practice. These variants include the AMA-negative PBC, the isolated AMA positivity, the AMA-positivity in patients with well-established autoimmune hepatitis (AIH), the premature ductopenic PBC variant and the PBC variant with characteristics of AIH (PBC-AIH variant). In this mini-review, we summarize and discuss the literature data and our own experience on the PBC variants highlighting also the uncertainties and a potential new era of the research agenda.

Keywords: Primary biliary cholangitis, Antimitochondrial antibodies, Autoimmune hepatitis, Autoimmune liver diseases, Variant syndromes, Overlap syndromes.

INTRODUCTION

Primary biliary cholangitis (PBC) also known in the past as primary biliary cirrhosis, is the most frequent autoimmune liver disease, characterized by the detection of antimitochondrial antibodies (AMA) or specific antinuclear antibodies (ANA) and progressive destruction and loss of the small intrahepatic bile ducts [1-5]. The net result is the development of significant cholestasis, inflammation of the portal tracts, and fibrosis that may lead to end stage liver disease. The disease predominantly affects middle-aged females (female/male ratio: 8-10:1 between the 5th and 6th decade), although the last years a considerable number of younger patients are diagnosed [1,2,5,6]. The course of the disease is unpredictable although a prompt and timely diagnosis at early stages seems of utmost importance as treatment, even at the asymptomatic stage, can slow progression, delay liver decompensation, and improve survival [6-10].

PBC diagnosis is established by the presence of at least two of the following [1-4]: detection of AMA (positive in almost 95% of patients) or ANA PBC-specific antibodies (anti-sp100 or anti-gp210 antibodies in approximately 30% of patients) [11-13], unexplained biochemical cholestasis (raised alkaline phosphatase or γ -glutamyl transpeptidase) and compatible liver biopsy showing non-suppurative granulomatous

lymphocytic cholangitis affecting interlobular and septal bile ducts.

Although the vast majority of the PBC patients have a typical presentation (a female patient with combined raised cholestatic enzymes and seropositivity for AMA), there are important variants in everyday clinical practice. These variants include the AMA-negative PBC, the isolated AMA positivity, the AMA-positivity in patients with well-established autoimmune hepatitis (AIH), the premature ductopenic PBC variant and the PBC with characteristics of AIH (PBC-AIH variant; Table 1) [1,2,14-16]. In this mini-review, we summarize and discuss the literature data and our own experience on the PBC variants highlighting also the uncertainties and a potential new era of the research agenda.

AMA-NEGATIVE PBC

Depending on the kind of the initial laboratory screening, approximately 5% of PBC patients even though they have increased cholestatic enzymes are negative for AMA detection by indirect immunofluorescent assay using fresh frozen sections of rat kidney, stomach and liver tissues [3,4,14-17]. In these cases, the application of molecularly based assays, like ELISAs and immunoblot using the known antigenic targets of AMA can minimize the problem [3,4,18-20]. In addition, investigation for the PBC-specific ANA such as anti-sp100 and anti-gp210 antibodies is very helpful as they can establish PBC diagnosis when AMA is not detectable [3,4,11-13]. The accuracy of these antibodies for PBC diagnosis is equal to AMA detection and therefore, in these patients

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there is no need of liver biopsy to confirm the diagnosis.

Table 1: Variant Syndromes of Primary Biliary Cholangitis (PBC)

<p><i>AMA-negative PBC</i></p> <p>Approximately 5% of PBC patients; Liver biopsy is necessary for diagnosis</p> <p>PBC-specific ANA may help; Clinical manifestations, natural history and response to treatment are similar to AMA-positive PBC patients</p>
<p><i>Isolated AMA positivity</i></p> <p>0.5-0.64% of healthy subjects have AMA; No treatment is required; 5-year development of PBC: 16%; Periodic monitoring of ALP is advised (yearly?)</p>
<p><i>AMA-positivity in AIH patients</i></p> <p>AMA prevalence in AIH patients: 5-35%; Most studies showed no correlation to cholestatic histological changes in follow-up biopsies or response to treatment</p> <p>Large multicenter study from the IAIHG is ongoing on this issue</p>
<p><i>Premature ductopenic variant of PBC</i></p> <p>Exceptional rare but severe PBC variant; Liver transplantation is required</p>
<p><i>PBC – AIH variant</i></p> <p>Many terms have been used so far; Absence of internationally accepted consensus for its definition</p> <p>The Paris criteria are currently in use but are very strict and differ from the respective criteria for PBC and AIH diagnosis</p> <p>Liver biopsy showing interface hepatitis is mandatory for the diagnosis</p> <p>No randomized trials for its management; However, combined treatment with immunosuppressants and UDCA seems rational</p>

AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; ALP, alkaline phosphatase; AIH, autoimmune hepatitis; IAIHG, international autoimmune hepatitis group; UDCA, ursodeoxycholic acid.

However, in true autoantibodies negative cases (AMA and PBC-specific ANA-negative patients) a liver biopsy is necessary to establish a firm diagnosis [1,2]. The clinical manifestations, natural course and prognosis as well as the response to ursodeoxycholic acid (UDCA) therapy of AMA-negative PBC patients seem similar to the AMA-positive PBC patients [1,2,5,21,22] although there is conflicting data regarding the progression and severity of the disease for those who have reactivity against the PBC-specific ANA [3,4,11-13,23-26].

ISOLATED AMA POSITIVITY

The detection of AMA in otherwise healthy subjects is not as rare as 0.5-0.64% of them may have isolated AMA in the absence of clinically obvious liver disease or elevated cholestatic enzymes [27-29]. Previous studies have shown histological evidence of PBC in about 40% of AMA-positive asymptomatic subjects with normal liver biochemistry, while long-term follow-up

showed that PBC would develop in most of them [30,31]. However, in the same long-term study of 18 years of follow-up, none of the patients developed cirrhosis, needed liver transplantation or died because of the presence of PBC [31]. In addition, a recent prospective study in AMA-positive individuals with non-established PBC diagnosis found that only 1 out of 6 subjects (16.7%) with AMA and normal alkaline phosphatase would develop PBC after 5 years of follow-up although the mortality rate of these subjects was unexpectedly higher compared to a control population matched for age and sex [32].

Taking together, all respective authorities agree that there is no need for treatment initiation in cases of isolated AMA seropositivity although a periodic screening every 6-12 months for the potential development of biochemical abnormality seems rational. If such abnormality is seen during follow-up then treatment should be the same as for classical PBC [1,2].

AMA-POSITIVITY IN PATIENTS WITH WELL-ESTABLISHED AIH

Although AMA is the serological hallmark for PBC diagnosis, they occasionally detected in patients with other liver disorders, including AIH but their clinical significance under these circumstances is obscure. In a recent systematic review of our group, the detection of AMA in patients with AIH was not uncommon, with a prevalence ranging from 5% to as high as 35% in some Japanese studies, depending mainly on the method employed [2]. However, most of the studies so far have shown that this finding represents simply a bystander phenomenon without any clinical significance, although there are serious limitations such as a short follow-up, infrequent sequential histological examination and inclusion of a small number of patients.

In this context, Montano-Loza *et al.* reported an AMA prevalence of 18% in AIH patients (24/130; follow-up: 123 months), but their presence was not associated with clinical or histological features of PBC at presentation, cholestatic histological changes at sequential liver biopsies, while remission and treatment failures were similar between AMA-positive and AMA-negative patients with AIH [33]. Similar findings have been reported by our group [34] and O' Brien *et al.* [35]. In the latter study, a very long-term follow-up of 27 years has been reported in 15 AIH patients with detectable AMA (15/126; 12%) but again no bile duct damage characteristic of PBC was seen on initial or

follow-up liver biopsies, while the clinical course remained typical of AIH and there was no difference on treatment response compared to AMA-negative patients with AIH [35].

However, Dinani *et al.* [36] reported three persistently AMA-positive patients with AIH who developed PBC over time. Of note, one of these three patients had been previously reported in the above-mentioned cohort by O' Brien *et al.* [35], indicating perhaps that much longer follow-up is needed to detect late development of PBC in AMA-positive AIH patients. Finally, in a very recent multicentre study on 47 AMA-positive AIH cases, it was shown in the univariate analysis that AMA reactivity was significantly associated with older age and a better response to immunosuppression compared with 264 AMA-negative AIH patients [37]. However, after multivariate logistic regression analysis using AMA as a dependent variable, there was no statistically significant difference while none of the AMA-positive patients with AIH showed signs of PBC manifestations after a median follow-up of 4 years [37]. In summary, these patients should be treated as for AMA-negative patients with AIH according to the common clinical practice guidelines for the management of AIH [14-17].

We should emphasize herein, however, that the International AIH Group (IAIHG) is currently running a large multicentre retrospective study based on prospectively collected data on AMA issue in patients with AIH in order to definitely address first, the prevalence of AMA in AIH patients at presentation and long-term follow-up, second, the significance of AMA seropositivity in AIH in terms of demographic, clinical, serological, biochemical and histological characteristics of the patients at baseline and during follow-up and third, the long-term outcome and treatment response of AMA-positive patients with AIH compared to age and sex-matched AMA-negative AIH patients.

PREMATURE DUCTOPENIC VARIANT OF PBC

A rare premature ductopenic PBC variant has been reported, in which severe pruritus is associated with progressive cholestasis with jaundice [38,39]. Of note, this variant is not responsive to UDCA treatment. Liver biopsy shows extensive bile duct loss but without significant fibrosis or cirrhosis while, the affected patients usually are rapidly in need for liver transplantation either because of persistent and intractable itching or progressive jaundice [1,2]. Therefore, the referral of these patients to expert

centers is highly recommended. As pregnancy may add cholestasis during the last trimester and post-partum, this fact could also be deleterious for those women with an already established ductopenic PBC variant.

PBC – AIH VARIANT

a. Definition and Diagnosis

A small proportion of around 8-10% of PBC patients exhibits also clinical characteristics of AIH [1,2,14-17]. This happens either simultaneously or consecutively (patients with established PBC who develop features of AIH) while some patients with AIH may also present PBC characteristics (patients with established AIH who develop features of PBC). Many terms have been used in the past to describe this syndrome like “hepatitic form of PBC”, “PBC with secondary AIH” and “PBC-AIH overlap syndromes”. However, the previous term “*overlap*” used for years to describe these disorders strongly suggests the simultaneous presence of two distinct diseases, which is not the case for all patients and therefore, this term could be a misnomer [15,16,40-42]. Recently, the term “*variant*” has been proposed by the European Association for the Study of the Liver (EASL), which is thought to be more precise for these conditions [15].

In the absence of internationally accepted consensus criteria for the precise definition of PBC - AIH variant its diagnosis is usually difficult. The “Paris criteria” are still the most frequently used in everyday clinical practice (Table 2) [43]. However, these criteria are robust and from our experience less than 50% of patients with AIH fulfil these criteria (in particular for the cut-off of serum levels of IgG). In this context, a recent study from China showed that the PBC – AIH variant may be identified very efficiently using the Paris criteria, but after lowering the IgG threshold to 1.3 times the upper limit of normal instead of 2.0 times, further supporting the concerns for underestimation of diagnosis of this condition by using the original criteria published in 1998 [44]. Moreover, it should be kept in mind that the Paris criteria are different from the respective definitions for PBC and AIH [1,2,15,16]. Notably, both the revised (Table 3) [45] and the simplified score (Table 4) [46] for the diagnosis of AIH have not been developed to diagnose these variant forms of PBC and therefore, they should not be used in routine clinical practice for the diagnosis of PBC-AIH variants [1,2,14-17,40,47,48]. Testing of autoantibodies against soluble liver antigen/liver pancreas (anti-

SLA/LP) by immunoblotting or ELISA should be considered in the laboratory workup of patients with PBC and suspected AIH as these autoantibodies have been reported in patients with PBC-AIH variant [49-51].

Table 2: Paris Criteria for the Diagnosis of PBC – AIH Variant Syndrome (Adapted from ref. [43])

PBC
ALP \geq 2 xULN or γ -GT \geq 5 xULN AMA detection (cut-off titer: \geq 1:40) Liver biopsy showing florid bile duct lesions
AIH
ALT \geq 5xULN Serum IgG \geq 2 x ULN or SMA detection Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis (interface hepatitis)

PBC-AIH variant syndrome requires the presence of at least 2 out of 3 key criteria for each disease. PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ULN, upper limit of normal; γ -GT, gamma-glutamyltranspeptidase; AMA, antimitochondrial antibodies; ALT, alanine aminotransferase; IgG, immunoglobulin G; SMA, smooth muscle antibodies.

Table 3: Revised Scoring System for Autoimmune Hepatitis Diagnosis (Adapted from [45])

Parameter/Features	Score
Gender: Female/Male	+2/0
Degree of elevation above ULN of alkaline phosphatase vs. aminotransferases	
- <1.5	+2
- 1.5 – 3.0	0
- >3.0	-2
Total serum globulins, γ-globulins, or IgG above normal	
- >2.0	+3
- 1.5 – 2.0	+2
- 1.0 – 1.5	+1
- <1.0	0
ANA, SMA or LKM-1 titers by immunofluorescence	
- >1 : 80	+3
- 1 : 80	+2
- 1 : 40	+1
- <1 : 40	0
- AMA positive	-4

(Table 3). Continued.

Parameter/Features	Score
Hepatitis markers (IgM anti-HAV, HBsAg, IgM anti-HBc, anti-HCV, HCV RNA)	
- Positive/Negative	-3/+3
Recent or current use of known or suspected hepatotoxic drugs	
- Yes/No	-4/+1
Average alcohol intake	
- <25 g/day / >60 g/day	+2/-2
Other autoimmune disease(s) in patient or first degree relatives	
- Yes/No	+2/0
Additional parameters (only if ANA, SMA or LKM-1 are negative)	
- HLA DR3, DR4, or other HLA with published association with AIH	+1
- Positivity for any of ANCA, anti-LC1, anti-SLA/LP, anti-ASGPR and anti-sulfatide	+2
Liver histology	
- Interface hepatitis	+3
- Predominant lymphoplasmacytic infiltrate	+1
- Rosetting of liver cells	+1
- None of the above	-5
- Biliary changes	-3
- Other changes	-3
Response to therapy: Complete/Relapse	+2/+3

Definite AIH if greater than 15 before treatment or greater than 17 post-treatment; probable AIH if between 10-15 before treatment or 12-17 post-treatment; IgG, immunoglobulin G; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-LKM1, anti-liver/kidney microsomal antibody type-1; AMA, antimitochondrial antibodies; HLA, human leukocyte antigens; AIH, autoimmune hepatitis; ANCA, anti-neutrophil cytoplasmic antibodies; anti-LC1, antibodies against liver cytosol type-1 antigen; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas; anti-ASGPR, antibodies against the asialoglycoprotein receptor; IgM anti-HAV, hepatitis A virus IgM antibody; HBsAg, surface antigen of hepatitis B virus; IgM anti-HBc, IgM antibody against the core antigen of hepatitis B virus; ULN, upper limit of normal.

Unlike several uncertainties, the recent clinical practice guidelines on PBC diagnosis and management of EASL and the British Society of Gastroenterology (BSG) [1,2] recommend liver histology as a mandatory tool for the assessment of patients with this variant form of PBC. Particularly, liver biopsy with expert histopathology review seems crucial because of potential therapeutic implications in the PBC cases that

Table 4: Simplified Criteria for Autoimmune Hepatitis Diagnosis (Adapted from [46])

Parameter/Feature	Finding	Points
<i>ANA or SMA pos</i>	≥ 1:40	+1
<i>ANA or SMA pos or anti-LKM pos or anti-SLA/LP pos</i>	≥ 1:80 ≥ 1:40 Positive	+2*
<i>Liver histology (presence of hepatitis is necessary)</i>	Typical AIH** Compatible with AIH** Atypical**	+2 +1 0
<i>Serum IgG levels</i>	> Upper normal limit > 1.1 x Upper normal limit	+1 +2
<i>Absence of viral hepatitis***</i>	Yes No	+2 0
<i>Sum</i>		≥ 6: probable AIH ≥ 7: definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points). **Definition of typical lesions: presence of interface hepatitis, hepatocyte rosetting and emperipolesis; Compatible liver histology: chronic hepatitis with lymphocytic infiltration without all the features considered typical; Atypical: histological lesions supporting another diagnosis. ***In chronic cases absence of hepatitis B and C viral markers; in acute cases absence of serological markers of acute hepatitis A, B, C, D and E is needed. ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-LKM, anti-liver/kidney microsomal antibody; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas; AIH, autoimmune hepatitis; IgG, immunoglobulin G.

do not respond to UDCA having also disproportional elevations of alanine aminotransferase (ALT) and/or IgG [1,2].

In summary, it should be kept in mind that PBC-AIH variants should not be over-diagnosed in order not to make vulnerable PBC patients to the risk of side effects of immunosuppressive therapy but on the other hand, physicians should also be aware that it is unclear whether the use of strict cut-offs of the Paris criteria is efficient to identify all PBC patients who would potentially benefit from immunosuppression. For this reason, patients with autoimmune liver diseases are better to be categorized initially as AIH, PBC, or primary sclerosing cholangitis, taking into account the predominant manifestations and those with additional features should not be considered as being distinct diagnostic and clinical entities [14-17,40,41].

b. Natural History and Management

Problems on the precise definition of PBC-AIH variant along with their low prevalence have resulted in the inability of carrying out controlled trials concerning their management. Most retrospective studies, however, albeit the small number of patients suffering from a PBC-AIH variant, have shown a more severe course compared to patients with PBC alone as attested by the earlier development of portal hypertension, decompensated cirrhosis and the need of liver transplantation or death [52-59]. Taking into

account the above findings, treatment with a combination of UDCA and immunosuppressive therapy in order to treat both disease elements seems reasonable as, besides inherent problems in definition and diagnosis, recent meta-analyses have shown that combination therapy was more effective than UDCA alone [58,60].

In line with the abovementioned findings, the recent EASL and BSG clinical practice guidelines for PBC management have recommended adding immunosuppression (steroids alone or in combination with azathioprine) to UDCA in previously diagnosed PBC cases if at least moderate interface hepatitis is present at the histological level [1,2]. However, the recent EASL clinical practice guidelines for AIH diagnosis and management recommend treatment for AIH patients even at lower cut-offs of ALT or IgG and a histological activity index as low as 4 indicating further the difficulties in managing patients with these variant syndromes [15]. In particular, in patients with dominant AIH characteristics, an alternative approach is to start with immunosuppression only and then add UDCA if the response is insufficient [15,16].

Of note, it has been reported that PBC-AIH patients appear to respond to fewer immunosuppression dosages and maintain remission after treatment withdrawal at higher rates than patients with AIH only [53,58]. In non-responders after the initial immunosuppressive therapy, alternative agents like

mycophenolate mofetil, cyclosporin or tacrolimus can be used [14,16,17,58,61,62]. It is not certain if AIH patients who develop manifestations of PBC will benefit from UDCA addition but it seems logical under real-life conditions, particularly in young patients, because of the potential long-term benefit of UDCA administration, which may subsequently protect the patients from the development of ductopenia and biliary cirrhosis during their lifetime.

CONCLUDING REMARKS AND RESEARCH AGENDA

Apart from the typical presentation of a female patient with combined raised cholestatic enzymes and seropositivity for AMA, there are important variants in everyday clinical practice including the AMA-negative PBC, the isolated AMA positivity, the AMA-positivity in patients with AIH, the premature ductopenic PBC variant and the PBC-AIH variant. Because of their relative rarity, these variant forms of PBC and in particular, the PBC-AIH variant suffer from several inherent difficulties in definition, diagnosis, investigation of pathogenesis and management. The following uncertainties in PBC-AIH variant may help scientists to design well organized, concentrated and pioneer multicenter research collaborations that can guide to better understanding of its pathogenesis and treatment options.

- Do we need new criteria apart from the Paris criteria with “lower cut-offs” of IgG and aminotransferases in order to proceed to liver biopsy in a PBC patient with suspicion of PBC-AIH variant presence?
- Which patient with PBC will benefit from immunosuppression? (grade of necroinflammatory activity – other markers e.g. anti-SLA/LP antibodies)
- Validation of the old criteria and the unmet need for a specific diagnostic scoring system for the diagnosis of PBC-AIH variants
- Which is the degree of histological bile duct lesion that defines PBC in patients with an already established AIH diagnosis?
- Do these patients require additional UDCA treatment?
- Do we need randomized controlled trials for the management of PBC-AIH variants?

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