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Role of autoantibodies in the clinical management of primary biliary cholangitis

Eirini I Rigopoulou, Dimitrios P Bogdanos

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Eirini I Rigopoulou, Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Larissa 41110, Greece

Eirini I Rigopoulou, European Reference Network on Hepatological Diseases (ERN RARE-LIVER), General University Hospital of Larissa, Larissa 41110, Greece

Dimitrios P Bogdanos, Department of Rheumatology and Clinical Immunology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa 41110, Greece

Corresponding author: Eirini I Rigopoulou, MD, PhD, Professor, Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Mezourlo, Larissa 41110, Greece. eirigopoulou@med.uth.gr

Abstract

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterized by immune-driven destruction of small intrahepatic bile ducts leading to a proportion of patients to hepatic failure over the years. Diagnosis at early stages in concert with ursodeoxycholic acid treatment has been linked with prevention of disease progression in the majority of cases. Diagnosis of PBC in a patient with cholestasis relies on the detection of disease-specific autoantibodies, including anti-mitochondrial antibodies, and disease-specific anti-nuclear antibodies targeting sp100 and gp210. These autoantibodies assist the diagnosis of the disease, and are amongst few autoantibodies the presence of which is included in the diagnostic criteria of the disease. They have also become important tools evaluating disease prognosis. Herein, we summarize existing data on detection of PBC-related autoantibodies and their clinical significance. Moreover, we provide insight on novel autoantibodies and their possible prognostic role in PBC patients.

Key Words: Primary biliary cholangitis; Anti-mitochondrial antibodies; Primary biliary cholangitis-specific antinuclear antibodies; Anti-sp100; Anti-gp210; Prognosis

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Core Tip: The diagnosis of primary biliary cholangitis (PBC) relies on the detection of disease-specific autoantibodies, including anti-mitochondrial antibodies and disease-specific antinuclear antibodies targeting sp100 and gp210. In this review, we summarize existing data on detection of PBC-related autoantibodies and their clinical significance. Moreover, we provide insight on novel autoantibodies and their possible prognostic role in PBC patients.

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INTRODUCTION

Primary biliary cholangitis (PBC), known until 2014 as primary biliary cirrhosis, is a chronic autoimmune cholestatic liver disease, its main features being presence of anti-mitochondrial antibodies (AMA), female predominance and progressive destruction of small intrahepatic bile ducts[1]. A proportion of PBC patients progresses over the years to fibrosis and eventually to cirrhosis leading to hepatic failure. Diagnosis at early stages in conjunction with ursodeoxycholic acid (UDCA) treatment has been linked with prevention of disease progression in the majority of cases. Over the years, significant progress has been achieved in the armamentarium used for disease diagnosis and prognostication, including autoantibody testing and on-treatment prognostic indicators[1].

Originally PBC was reported in 1851 in a woman with jaundice and xanthomata and its clinical phenotype was described in 1949[2,3]. The first association of PBC with autoantibodies was reported by Mackay[4] in 1958 in a case with high titers of circulating complement-fixing antibodies to liver, kidney and other human tissue antigens[4]. Later on, in 1965, Walker *et al*[5] have reported the presence of AMA by indirect immunofluorescence (IIFL) in patients with PBC[5].

The discovery of AMA in conjunction with advances in their diagnostic testing and increased disease awareness has led to diagnosis at earlier stages. Moreover, treatment with UDCA, which is the standard of care for naïve PBC patients has been associated with improved long-term survival. All these factors have significantly contributed to the increase in prevalence rates throughout the years[6,7]. The highest incidence and prevalence rates have been reported in Europe and the United States (incidence and prevalence rates range from 3.3 to 32 per million person-years and 19 to 402 per million respectively)[8-11]. Discrepancies between regions may reflect differences in patients' accessibility to healthcare services, increased disease awareness depending on physician's expertise and widespread use of AMA and antinuclear antibody (ANA) testing during diagnostic work-up. Still, it is debatable whether increases in prevalence and incidence rates represent true changes over the years.

PBC is considered a prototype autoimmune disease, based on the abundance of AMA, female predominance and increased rate of other autoimmune diseases. Genetic and environmental factors are regarded as key players in the induction of immune tolerance loss to biliary epithelial autoantigens, a notion well appreciated also on work performed in animal models of the disease[12-15].

Higher disease rates between family members, especially siblings, formed the initial pathogenetic link between genetics and PBC. Genome wide association studies from Europe, North America, Japan and China have identified human leukocyte antigens (HLA) and non-HLA alleles that confer susceptibility to PBC, though discrepant results between ethnicities are apparent[16]. The majority of reported loci are encoding proteins implicated in the control of immune response mechanisms, including HLA, interleukin (IL)-12 production, B and T cell activation, interferon (IFN)- γ production and production of immunoglobulins. The contribution of genetics is also emphasized by the fact that monozygotic twins display significantly higher concordance rates compared to dizygotic twins (63% *vs* 0%)[17]. Still, lack of remarkable concordance rates between identical twins in PBC strongly supports the implication of environmental factors and epigenetics.

Numerous studies have revealed the important contribution of environmental exposures, including chemical xenobiotics, pollutants, cosmetics and also infectious agents, in immune tolerance loss and in the initiation of disease process[18-21].

Studies on animal models of the disease have underlined the likely input of specific environmental factors in the initiation and perpetuation of disease progression, adding further support for their significant input in genetically prone individuals[15].

DIAGNOSIS OF PBC

The cornerstone for PBC diagnosis is the detection of AMA and/or PBC-specific ANA when investigating a patient with cholestasis (Table 1)[6]. It is important to stress that AMA are one of the few autoantibodies being included in diagnostic criteria of a disease[6]. Liver histology is essential when AMA are not detected in a patient with cholestasis with high suspicion of PBC, or when indications of variant forms exist[6,22].

AUTOANTIBODIES

AMA

Since their first description in 1965 by Walker *et al*[5], AMA have been uninterruptedly used as the most reliable marker for the diagnosis of PBC[5]. This landmark paper did not showcase only the close association of AMA with PBC, but provided also a straightforward technique for its detection, which has been routinely used up to this time, namely IIFL[5]. Later on, in 1968, a trypsin-sensitive antigen was identified by Berg *et al*[23] to react *in vitro* with sera from PBC patients, which was located in the inner mitochondrial membrane and was called M2[23]. The same group proposed a classification of AMA antigens from M1 to M9[24]. This nomenclature was subsequently abandoned, as several studies have failed to link PBC with any of these antigens, except for M2[25,26].

M2 antigens consist of components of the 2-oxo-acid dehydrogenase multienzyme complexes; namely, pyruvate dehydrogenase (PDC), 2-oxoglutarate (OGDC) and branched-chain 2-oxo acid (BCOADC)[27]. Each complex is formed by several copies of at least three enzymes (E1, E2 and E3) that form high molecular-weight multimers and are localized in the inner mitochondrial membrane. The E2 enzyme, based at the structural core of the complex, contains the lipoyl group, which is bound to lysine and plays significant role in the catalytic cycle[27].

The next major breakthrough was the cloning and sequencing of a 74 kDa mitochondrial autoantigen, that led to the identification of E2 subunit of PDC-E2 as the major autoantigen in PBC[27,28]. Several reports were able to establish the fine characteristics of response to antimitochondrial antigens in PBC patients[29]. In detail, up to 95% of PBC patients show reactivity to PDC-E2 and to lesser extend (50%-70%) towards OGDC-E2 and BCOADC-32[29]. Few AMA positive PBC patients react only towards PDC-E2 and even less solely to OGDC-E2 or BCOADC-E2. The predominant anti-M2 reactivity is the one against the E2 component of PDC and also BCOADC and OGDC enzyme complexes, while less commonly reactivity to PDC-E1a and PDC-E1b subunits and also the dihydrolipoamide dehydrogenase (E3)-binding protein has been reported[29]. It is of interest that the E2 subunit of the OADC is highly conserved between species and also between various complexes. All immunodominant epitopes include a ExDKA motif with a lipoic acid attached to K at position 173, which is essential for T-cell antigen recognition[30].

Several studies have tried to elucidate mechanisms involved in loss of tolerance towards 2-OADC components located on the inner mitochondrial surface of biliary epithelial cells (BECs), finally leading to BECs injury and are reviewed elsewhere[31]. A multi-lineage loss of tolerance against major AMA epitopes appears to be one of the key features leading to progressive destruction of bile ducts in PBC where both CD4+ and CD8+ T cells orchestrate an immune response against the PDC-E2 complex in the liver as well as in the periphery[31]. IL-12 and IFN- γ prevail in PBC inducing Th1 immune responses at initial stages of the disease[32]. Perpetuation of liver injury during the disease process is linked with skewing towards a Th17 phenotype[31,32]. T follicular helper cells, known to assist B cell-specific antibody production, were found in increased numbers in livers of PBC patients, while T regulatory cells, that promote self-tolerance, were found numerically or functionally impaired in PBC patients[31].

Over the years, the role of BECs has been upgraded from regulators of fluidity and alkalinity of bile, to active participants of innate and adaptive immune responses contributing to bile duct injury and evolution of liver disease[1,33]. Why BECs are the targets of autoimmune attack, considering that PDC-E2 is not confined solely to these cells but is abundant in mitochondria of all nucleated cells, remains elusive. Several studies have proposed a hypothesis according to which small BECs, by undergoing apoptosis, transfer immunologically intact PDC-E2 to apoptotic bodies and form an apoptope (antigenic epitope). This apoptope in concert with macrophages and AMA can induce locally acting proinflammatory cytokines resulting in inflammation and surrounding apoptosis in PBC[14].

Methods for AMA detection

IIFL: Since its discovery, IIFL is considered the “gold” standard technique for the detection of AMA and titers above 1/40 are regarded as positive[6,22]. The preferred tissue for the detection of AMA is liver, kidney and stomach substrates, which displays a fluorescence pattern unique to AMA. AMA stains the distal tubules on kidney sections, which contain more mitochondria compared to the proximal tubules, while it produces a bright granular pattern on gastric sections and a faint cytoplasmic pattern on liver sections[34]. Alternatively, on a substrate of human larynx epithelioma cancer cell line (HEp-2) cells, AMA give a diffuse, granular cytoplasmic pattern, that is not consistent with other methods of AMA

Table 1 Autoantibodies detected in primary biliary cholangitis and their clinical significance

Autoantibodies	Method	Prevalence	Specificity	Diagnostic relevance	Clinical significance
AMA	IIFL, ELISA, Blot	90%-95%. Varies according to method used	High (90%)	Yes	AMA presence and titer not associated with severity of PBC or prognosis of PBC
Antinuclear antibodies				Yes	
Against nuclear envelope antigens: Anti-sp100; anti-PML; anti-sp140; anti-SUMO	IIFL (MND pattern), ELISA	30%-50%	Very high (approximately 98%)	Useful in AMA-negative patients	Anti-sp100 is associated with more severe disease, faster disease progression and worse outcome
Against nuclear pore complex antigens: Anti-gp210; anti-np62; anti-LBR	IIFL (Rim-like perinuclear pattern; RL/M), ELISA, Immunoblot	30%-50%	Very high. Up to 100%	Useful in AMA-negative patients	Anti-gp210 is associated with more severe disease and worse outcome
Anticentromere antibodies	IIFL	10%-30%	Low	No	Limited data on their role as prognostic factor for complications related to portal hypertension
Anti-KLHL12 antibodies	ELISA	22%-36%	Very high	Yes. Useful in AMA-negative pts	Anti-HK1 is associated with worse outcome (needs validation)
Anti-HK-1 antibodies	Immunoblot				

sp100: Nuclear body speckled 100 kDa; sp140: Nuclear body speckled 140 kDa; SUMOs: small ubiquitin-related modifiers; PML: Promyelocytic leukemia proteins; LBR: Lamin B receptor antibody; KLHL12: Anti-kelch-like 12 protein; HK-1: Anti-hexokinase 1; AMA: Anti-mitochondrial antibodies; MND: Multi nuclear dot pattern; ELISA: Enzyme-linked immunosorbent assay; IIFL: Indirect immunofluorescence; PBC: Primary biliary cholangitis.

detection (*i.e.* IIFL with triple substrate or molecular based assays) and its use as a single method for AMA detection is not recommended. Still, HEp-2 cells is recommended to be used in parallel with the triple rodent substrate for the detection of PBC-specific ANA[34].

Data from few old studies have shown that AMA are not restricted to a specific immunoglobulin (Ig) G subclass, though IgG3 appears to be the most predominant[35,36].

Solid phase assays: The identification of AMA molecular targets has revolutionized the diagnostic approach of patients with PBC, since new molecular-based assays have been developed, which relay on the use of recombinant or purified antigens. Amongst them are microtiter plate Enzyme-linked immunosorbent assay (ELISA), chemiluminescence and fluorescent bead-based assays[37-43]. Commercially produced ELISA's have substantially gained ground over the years, considering they offer high grade of standardization and automation and don't require skilled personnel either for their application or interpretation[44].

Gershwin's group have created a recombinant fusion protein (MIT3), consisting of the major immunodominant epitopes of the three main AMA targets (PDC-E2, BCOADC-E2, OGDC-E2)[41]. An ELISA utilizing MIT3 had increased sensitivity compared to IIFL and ELISAs with conventional anti-M2, as it allowed the identification of AMA in 30%-50% of previously AMA-negative samples[39,45]. An improved technique, based on the coupling of the three recombinant mitochondrial autoantigens (PDC-E2, BCOADC-E2 and OGDC-E2) with beads, found 20% of AMA-negative by IIFL patients to be positive, while 100% of these new AMA positive patients were revealed as ANA positive[46]. The development of another assay (anti-M2-3E ELISA), which included antibodies to MIT3 and purified PDC to allow detection of additional less immunodominant mitochondrial antigens, like PDC-E1a and E1b, increased further the diagnostic accuracy of AMA compared to IIFL, conventional anti-PDC ELISA and also the anti-MIT3 ELISA[37].

Several studies have suggested that investigating individual AMA isotypes (IgG, IgM, IgA) could be of clinical relevance, as different isotypes may correlate with biochemical, clinical and histological features of the disease. As a secretory immunoglobulin, IgA is abundant in mucous membranes, while IgA AMA have been detected in bile, saliva and urine samples of PBC patients and have been suggested to contribute to bile duct injury[47,48]. Of relevance, PDC-E2 specific dimeric IgA, but not IgG resulted in induction of caspase activation in Madine-Darby canine kidney cells transfected with the human polymeric Ig receptor, in an experimental study[49]. Studies assessing the possible clinical significance of IgA AMA in PBC patients have produced conflicting results up to the present[39,50-52]. Even if we cannot recommend IgA AMA testing based on these remarks, we should stress that a minority of PBC patients (2%-3%) have only AMA of IgA isotype[39]. In this context, if a patient is suspected to have PBC based on clinical and biochemical features and IgG AMA are not detected, he should be tested for AMA of IgA isotype.

A study from China, has suggested that salivary AMA-M2, tested by ELISA is a useful biomarker for the diagnosis of PBC. It is a non-invasive method, providing high specificity, as salivary AMA-M2 were detected only in serum AMA-M2 positive PBC patients and none of the controls[53].

In PBC, SDS-PAGE followed by western blotting has been used in the past as a sensitive and specific method in identifying individual mitochondrial antigens based on their molecular weight (74 kDa band for PDC-E2, 52 kDa band for BCOADC-E2 and 48 kDa band for OGD-E2). Preparations of mitochondrial fractions of primate and/or liver or bovine heart are usually used as source of AMA antigens, though recombinant proteins are suggested to produce less background[54,55]. Immunoblotting with recombinant protein results in 91% positivity in sera from PBC patients, compared to 81% when recombinant PDC-E2 fusion protein is utilized[54]. Similar to ELISAs, the fact that a small portion of PBC patients demonstrate reactivity only to BCOADC-E2 and/or OGD-E2 could account for this variance in sensitivity. A study applying computer-assisted imaging technology showed correlation between AMA titers by IIFL and number and intensity of immunofixed 1-OADC bands in sera from PBC patients[55]. However, immunoblotting is time consuming and in routine practice its usage has been abandoned giving space for the most reliable and fully automated antigen-specific assays or automated IIFL.

Data from a recent study suggests that M2-AMA dot blot is more specific than IIF-AMA[56]. This study demonstrated increased sensitivity and specificity with increasing number of M2-AMA specificities detected.

In recent years automated particle-based multi-analyte technology (PMAT) assays have been used for the detection of autoantibodies, including those related to PBC. Data evaluating the performance of this assay have been convincing and commercial assays based on this technology are widely available, as they allow the concurrent detection of several antigen-specific autoantibodies[57].

AMA AND THEIR CLINICAL CORRELATIONS

AMA is the most characteristic feature of PBC, as up to 95% of patients are tested positive for these autoantibodies. A 2014 meta-analysis including 24 studies showed that the pooled sensitivity and specificity of AMA in the diagnosis of PBC is 84.5% and 97.8%, respectively[58]. The specificity of AMA for PBC has been initially revealed in two small longitudinal studies, where the majority of AMA positive patients with no evidence of cholestatic liver disease developed full blown PBC[59,60]. Still, recent studies have shown a small proportion of AMA positive individuals to develop PBC through the years[61,62]. These data should be interpreted with caution, as follow up duration might have been not long enough in these latter studies to allow clinical presentation of PBC that is known to progress slowly.

Data from Sun *et al*[63], though, have shown that 80% of AMA positive individuals with normal alkaline phosphatase have histological features of PBC, stressing that cholestasis is not a prerequisite for the establishment of PBC[63]. The pathogenic role of AMA is further supported by the case of two newborns where liver disease had developed after transfer of AMA from their mothers *via* the placenta, while liver pathology subsided when the autoantibodies disappeared.

However, AMA have been reported in up to 1% of healthy individuals[64,65]. Considering the substantially lower PBC prevalence, only a small percentage of those AMA positive individuals is going to advance to PBC. Moreover, longitudinal data on AMA kinetics in patients transplanted for PBC show these autoantibodies to persist, though biochemical or histological features of PBC recurrence have been reported in 36% 10 years post liver transplantation[66,67]. As autoantibodies can arise years before disease presentation only long-term observational studies spanning a period of decades will be able to elucidate this issue further.

Kisand *et al*[68] have suggested that development of PBC might arise in those who have or will develop high titer AMA overtime of various specificities and subclasses compared to AMA positive individuals with low titer antibodies of only one Ig class reactivity[68].

Whether AMA titers is a prognostic indicator for PBC needs to be assessed further, as several studies up to the present have produced conflicting data. Early studies from the 80s and 90s have shown AMA titers to correlate to disease activity and progression[69,70]. Another study demonstrated that PBC patients had significantly higher AMA titers, tested by IIFL and higher anti-PDC-E2 avidity compared to AMA positive individuals with normal biochemistry[71]. Moreover, Gabeta *et al*[39] have demonstrated IgG and IgA AMA titers to positively correlate with the Mayo risk score[39].

Whether testing by IIFL for individual IgG AMA subclasses could assist in identifying prognostic features of PBC patients remains obscure. Another study stressed that AMA of the IgG3 subclass positively correlate with more advanced liver disease, as manifested by higher frequency of cirrhosis and higher Mayo risk score[36].

Furthermore, treatment with UDCA was associated with a decrease in AMA titers in one of the first trials of UDCA in PBC patients, while in a recent study from China, response to UDCA treatment at 1 year was linked to decreased AMA titers[72,73]. However, several other studies failed to prove AMA titers or their longitudinal changes as prognostic markers of PBC progression[74-76]. In line with this, a

small study on 9 asymptomatic PBC patients with inadequate response to UDCA, who continued with combination of UDCA and fenofibrate, showed a decrease in AMA titers in 4 of these patients. These data could suggest that AMA production may be regulated by peroxisome proliferator-activated receptor α in PBC patients. Still, this is a hypothesis that needs to be confirmed in the future, as it was not reproduced by other studies[77].

Anti-M2 AMA can also occur in the context of overlapping diseases, such as the autoimmune hepatitis/PBC variant, metabolic associated fatty liver disease/PBC variant, viral hepatitis (hepatitis B virus, hepatitis C virus)/PBC variant and other rheumatic diseases, such as systemic sclerosis[6,78,79]. Their presence should be evaluated in the appropriated clinical context.

ANA IN PBC

Various ANA specificities have been reported in up to 70% of PBC patients[80]. HEp-2 cells are preferred compared to the triple tissue substrate for the detection of ANA, as large nuclei and high rate of mitosis of these cells permit the discrimination of different staining patterns[34]. A variety of staining patterns, often coinciding, have been described in PBC patients, including rim-like (RLM), nuclear dot, speckled, homogeneous and centromere staining pattern[81,82]. For diagnostic purposes, ANAs are categorized into those not specific for PBC and those specific for the disease.

According to the official categorization of ANA patterns issued by the International Consensus on ANA Patterns initiative, 2 IIFL patterns are defined as PBC-specific, namely the multiple nuclear dot (MND) pattern (AC-6) and the punctuate nuclear envelope pattern (AC-12)[83].

ANA not specific for PBC

Anticentromere antibodies (ACA) and those against extractable nuclear antigens (anti-ENA), recognizing various molecular targets, including nuclear ribonucleoproteins (nRNP), ribosomal phosphoproteins and cellular enzymes such as DNA topoisomerase I (Scl-70) and histidyl-tRNA synthetase (Jo-1) are non-specific ANA and can be detected up to 30% of PBC patients, at times indicating co-existing autoimmune rheumatic diseases[80,84].

Originally, IIFL on HEp-2 cells was used for ACA detection and counter immunoelectrophoresis on thymic and spleen extracts for anti-ENA detection. More sensitive methods, like ELISA and immunoblot were developed for the detection of various molecular targets (*i.e.* nRNP, Sm, SSB/La, SSA/Ro 60 and 52). Their application has revealed anti-ENA reactivities in up to 30% of PBC patients, anti-SSA/Ro-52kD being the most frequent one. The presence of anti-SSA/Ro-52 kD was associated with active and advanced disease in one study[84]. ACA have been reported in 20%-30% of PBC patients and 80% of patients with a PBC/Systemic Sclerosis overlap syndrome[81,84-86].

The diagnostic and clinical significance of ACA positivity in patients with PBC without SSc has recently been under investigation, though with discrepant results[86-88]. Data from two studies have suggested ACA to be a predictive factor for the development of complications related to portal hypertension in PBC patients, though not for the progression to liver failure[86,88]. As both studies were conducted in PBC patients of Asian origin, large scale data are needed to explore this hypothesis further.

PBC-specific ANA

PBC-specific ANA have been reported in up to 50% of PBC patients, with wide variation in the prevalence rate between studies depending on the method used[80]. They demonstrate high specificity, though low sensitivity for PBC and is a valuable tool during diagnostic work-up of patients with suspicion of PBC, especially in those tested negative for AMA[6,22]. Their identification is optimized when HEp-2 cells are used as a substrate, as these cells have large nuclei and during their mitotic phase ACA stain their chromosomes[34].

PBC-specific ANA display two distinct immunofluorescence patterns: A perinuclear/RLM and a MND pattern[80,83]. The RLM pattern gives a distinctive punctuated pattern of the nuclear surface that corresponds to a nuclear complex. This pattern is generated by reactivity to nuclear pore complexes (NPC), which are multi-protein structures that mediate nucleocytoplasmic transport. Gp210 is the main antigenic targets in PBC and is currently used for diagnostic purposes. Less immunodominant antigens, not incorporated in the diagnostic work-up, are those of nucleoporin p62 and lamin B receptor. The MND pattern consists of 3-20 dots scattered throughout the nucleus, but sparing the nucleoli and is produced by reactivity to the nuclear body speckled 100 kDa (sp100) protein and the promyelocytic leukemia (PML) protein, while more recently sp140 and small ubiquitin-related modifier (SUMO) protein has been reported as additional antigenic targets[80,89,90].

The visualization of ANA can be hindered by AMAs presence and other ANA specificities[34]. This could justify the perception that prevailed based on the results of early studies reporting of the presence of PBC-specific ANA especially in AMA-negative patients[81]. For example, the MND pattern can be easily mistaken with that produced by ACA; the anti-MND pattern consist of dots of various size and numbers, while the ACA pattern is characterized by dots of equal size. ACA stain the cells'

chromosome, whereas anti-MND don't.

A multicenter study showed that the diagnostic performance of the conventional IIFL improved further by the use of individual IgG (IgG1-4) isotypes instead of anti-total IgG sera, leading to increased recognition of PBC-specific ANAs[91]. In detail, 65% and 15% of PBC patients were MND and/or RLM positive using IgG isotype-specific antisera and anti-total IgG antiserum respectively[91].

The identification of the molecular targets of PBC-specific ANA has led to the development of molecular based techniques, including ELISA and immunoblot, that are more sensitive and observer-independent[80,92,93]. Accordingly, Invernizzi *et al*[92] demonstrated reactivity to NPC by immunoblotting in 22% of 105 patients known to be ANA negative by IIFL. There was no significant difference in the percentage of anti-NPC positive amongst those being AMA positive and negative PBC patients with the use of immunoblotting[92]. Similarly, Muratori *et al*[81] have reported on the increased sensitivity of ELISA in detecting PBC-specific ANAs compared to IIFL, though they were more often detected in AMA negative compared to AMA positive PBC patients[81].

Still, a major limitation of the molecular based assays is the selection of specific targets and exclusion of others that might be of potentially equal importance, especially if reactivity to those subdominant antigens is of diagnostic relevance (such is the case of single specificities).

The sensitivity of anti-gp210 has been reported between 5.71% and 55.88%, whereas specificity ranged from 61.70% to 100% depending on the method used and the population studied[94-98].

ANA AND THEIR CLINICAL CORRELATIONS

Several studies have evaluated whether PBC-specific ANAs have a prognostic role in PBC patients. Discrepant results between studies can be justified by differences in study design (*i.e.* methods to evaluate the presence of antibodies, different antigenic preparations used), as well as heterogeneity of patients investigated[86,94].

Early studies, based mainly on IIFL detection of autoantibodies, had failed to establish a link between presence of PBC-specific ANAs and disease' prognosis[99,100]. During the last 20 years, several reports relaying mostly on ELISA, western blot and line blot data, delineated the correlation of PBC-specific ANAs with more severe disease and worse outcome, though differences between studies exist. Most studies underline that positivity for anti-NPC antibodies and especially for anti-gp210 are associated with more severe disease and worst disease outcome[81,87,91,92,97,101].

One of these studies using IIFL for the identification of autoantibodies, revealed anti-RLM of the IgG3 isotype to correlate with more severe liver disease[91]. A meta-analysis encompassing 5 studies in Asian patients demonstrated anti-gp210 antibodies to be associated with worst disease outcome and suggested their use as optimal predictors of PBC prognosis at the time of diagnosis[102].

Nakamura *et al*[103] reported that persistently positive anti-gp210 antibodies during follow up in Japanese PBC patients under UDCA treatment confer a strong risk for progression to end-stage liver disease, whereas these patients had histologically more severe interface hepatitis, lobular inflammation, and ductular reaction[103]. These findings were not confirmed in a study assessing autoantibody patterns during follow up in Greek PBC patients[104].

Anti-np62 antibodies are detected in 22%-31% of PBC patients, though their significance is not well documented and their diagnostic relevance remains unclear[105,106]. A Japanese study suggested that anti-np62 antibodies are associated with advanced disease. These results need to be confirmed by other studies[105].

Anti-sp100, the most frequent amongst antibodies displaying the MND pattern, is detected in 8%-44% of PBC patients, its specificity ranging from 63.8% to 100%[81,107-109]. The pooled sensitivity of anti-sp100 for PBC has been estimated at 23.1% and the pooled specificity at 97.7%[98]. Importantly, subgroup analysis could not identify significant differences in pooled specificity across the strata of geographical regions or across various methods used for their identification[98].

The prevalence of anti-lamin B receptor antibodies have been reported in 9%-15% of PBC patients and are considered highly specific[105,110]. Given their rarity and their unknown prognostic role, they are not routinely tested in every day clinical practice.

Anti-MND and anti-sp100 antibodies tested by IIF and by ELISA respectively have been associated with more severe disease, as attested by biochemical and histological features, faster disease progression and worse outcome[91,107]. Moreover, anti-MND of the IgG3 isotype was associated with longer disease duration and more severe histological picture[91].

Autoantibodies against PML are less frequently detected in PBC patients (12%-19%), and largely co-exist with anti-sp100, though cases with single reactivity to PML have been also reported[93,107]. Double reactivity to sp100 and PML was suggested to be associated with unfavorable outcome of PBC patients[93,107]. SUMOs have been exclusively linked to presence of anti-sp100 and anti-PML, suggesting antigen spreading as a possible mechanism for anti-SUMO generation[90].

Züchner *et al*[107] reported anti-sp100 levels to remain stable during the course of the disease. Of interest, alteration in the sp100 epitope recognition pattern in some patients during the natural course of the disease was noted in a proportion of patients under UDCA treatment, which indicates that UDCA

can modify immunoglobulin expression[107]. In accordance with these findings are those from a study in 110 Greek patients, where serial determination of autoantibodies titers demonstrated that a decrease in anti-sp100 levels was associated with response to UDCA treatment and improvement of the Mayo risk score[104]. Akin to AMA, PBC-specific ANA are shown to persist after liver transplantation without signs of disease recurrence[106,111].

Few studies have suggested infectious agents to have acted as potential triggers for the development of anti-MND antibodies in PBC patients. Bogdanos *et al*[112] have demonstrated a strong correlation of anti-sp100 reactivity and presence of AMA only in those PBC patients with recurrent urinary tract infections[112]. Molecular mimicry between T-cell epitopes, first implicating mitochondrial and afterward nuclear proteins, has been proposed[113].

A study conducted in a Han Chinese population demonstrated significant genetic predisposition for sp100 but not for gp210. In detail, HLADRB1*03:01, DRB1*15:01, DRB1*01, and DPB1*03:01 alleles were associated with antibody production against sp100[114]. Whether this difference is indicative of diverse roles of anti-sp100 and anti-gp210 in PBCs pathogenesis needs to be elucidated in the future. Besides, as data of this study is confined to Chinese patients, these results need to be confirmed in other PBC cohorts.

AMA NEGATIVE PBC

The percentage of AMA negativity by IFL widely varies amongst studies, ranging from 5%-20%. Soon after the identification of the molecular targets of AMA and the development of molecular based assays, it has become apparent that such assays can considerably increase the sensitivity for AMA detection, leading to a significant drop of “true” AMA-negative cases[37,39,40,45,46,115]. By immunoblotting testing, IgG antibodies against PDC-E2 are detectable in 97% of AMA positive PBC and in 66% of AMA negative PBC[116].

Others have reported even higher prevalence of antigen-specific AMA in IFL AMA-negative PBC patients, reducing even more the percentage of AMA negative PBC[117-119]. In our hands, only 16% of IFL AMA-negative PBC patients had reactivity against mitochondrial autoantigens using a sensitive immunoblot technique[55].

Nevertheless, even when the most sensitive AMA tests are used, still a proportion of PBC patients may not have AMA. While some studies indicated that seronegative cases may convert to AMA seropositive over the years, some others have elegantly shown that there are still patients that will never develop these autoantibodies over the course of the disease. This is of fundamental importance as it implies that breaking of immunological tolerance to the mitochondrial autoantigens of AMA is not the sole cornerstone of PBC pathogenesis, and other non-mitochondrial antigen-driven mechanisms are potentially involved. It is also of diagnostic importance because it highlights the importance for the proper identification and routine use of diagnostic surrogate markers which can assist the diagnosis of PBC in AMA negative cases. It also raises the question as to whether AMA positive and AMA negative PBC are two entities with distinct characteristics or not.

It must be noted, that over the years and with the wealth of data provided, a consensus has been reached that “true” AMA-negative PBC is an entity indistinguishable from AMA-positive PBC, in terms of demographic, biochemical, clinical and histopathological features[117,118,120]. Though the total number of AMA negative cases with PBC included in various studies can be considered small, and despite the lack of multi-centre studies investigating in greater detail the features of AMA negative PBC, the current evidence supports the notion that the natural history as well as the prognosis of AMA-negative PBC is analogous to AMA-positive PBC[121,122]. Current guidelines indicate the therapeutical and clinical management of AMA negative PBC should be the same with AMA positive PBC. Early studies have reported that aside AMA status, some immunoserologic features may be different between AMA-negative and AMA-positive PBC, such as lower IgM and higher gamma globulin in the former rather than the latter group[117,118,120,123].

Several studies have published data reporting a significantly higher rate of positivity for ANA in AMA-negative compared to AMA-positive PBC. Original studies were based on IFL testing, while most recently such assays included ANA-specific antigen testing against sp100 and gp210. The wide range of ANA positivity is attributed to technical reasons, such as the sensitivity of the assay used for autoantibody detection and cohort selection bias or geographic/ethnic disparities. Early IFL studies reported the prevalence of ANA to range between 71% to 100%, in AMA-negative PBC patients, compared with 18% to 33% in AMA seropositive PBC patients[117,118,120,123].

The first point that at times is overlooked by the clinicians is that PBC-specific ANAs are not confined to AMA-negative PBC and therefore disease-specific ANA is by no means a characteristic feature of this form of the disease. It has now become apparent that this striking over-representation was due to the practical limitations imposed by IFL on tissue sections because ANA positivity could be obscured by the simultaneous presence of AMAs, which could perplex the reading by the immunodiagnostician. This is indeed true in weak AMA positive cases where ANAs become more visible and can be present in frequencies comparable to AMA negative PBC cohorts[81]. With the advent of assays using as antigenic

substrate recombinant sp100 and gp210, a more accurate estimation of the respective autoreactivities has been achieved, though great variation is still seen amongst studies. In a consecutive cohort, Muratori *et al*[81] found ANA of any pattern in 53% of patients, including 27% with anti-Sp100, and 16% with anti-gp210 antibody reactivity[81].

Most studies fail to report significant differences of anti-gp210 and anti-sp100 between AMA-positive and AMA-negative PBC cohorts[124].

The relatively recent identification of novel autoantigens in AMA negative patients with PBC has provided further hints regarding the diagnostic and clinical challenges of AMA-negative patients with PBC and their relevance to the presence of disease-specific autoantibodies.

NOVEL AUTOANTIBODIES

During the last decade, antibodies against kelch-like protein (KLHL12) and hexokinase 1 (HK-1) were proposed as novel biomarkers in PBC patients, especially those lacking AMA[125,126]. While KLHL12 is a nuclear protein that is implicated in collagen export and ubiquitination of various proteins, HK-1 is an enzyme that is localized in the outer mitochondria membrane, phosphorylates glucose and modulates susceptibility to cellular apoptosis. Both display high specificity ($\geq 95\%$), while their combination improved their overall sensitivity from 48.3% to 68.5% by ELISA and from 55% to 75% by immunoblot in AMA-negative PBC patients[125]. Recently, a study in Spanish PBC patients has confirmed the aforementioned data on the utility of these autoantibodies to diagnose AMA-negative patients by demonstrating anti-HK1 or anti-KLHL12 in a third of AMA negative and in 40% those negative for AMA, anti-gp210 and anti-sp100[127]. Furthermore, anti-HK1 positivity was associated with significantly higher possibility of liver decompensation and lower liver-related survival free of transplantation[127]. A more recent study assessed the prevalence of anti-KLHL12 and anti-HK-1 antibodies by ELISA at 5 sites within Europe and North America and documented the presence of these antibodies in patients with PBC in all geographies, irrespectively of the origin of the sera failing to identify geographic factors which could imply that the genetic make-up of the patients is responsible for the induction of these autoantibodies[128]. A Polish study reported the highest prevalence of anti-KLHL12 antibodies so far (36%) in both AMA-positive and AMA-negative patients and confirmed their high specificity for PBC diagnosis[110]. Their presence was linked to higher bilirubin levels and advanced fibrosis[110]. The prognostic significance of these autoantibodies needs to be evaluated in larger cohorts of PBC patients.

Bombaci *et al*[129] have proposed SPATA31A3 and GARP, as novel autoantigens in PBC, as PBC sera demonstrated high reactivity to these antigens irrespective of AMA and PBC-specific ANA presence [129]. Their combination with PDC-E2 assisted in discrimination of PBC from other diseases with high sensitivity and specificity. The authors offer in addition pathophysiological evidences on GARP expression in human cholangiocytes, which underlines the potential implication of this autoantigen in the induction of the disease[129].

MULTIPLEX ASSAYS

Considering that the repertoire of autoantibodies related to several autoimmune diseases is increasing, multiplex assays have become available in order to facilitate their simultaneous detection in a reliable, automated fashion, without consuming substantial amount of time. Such an example is that reported by Liu *et al*[130] in 2010 on a new PBC-screening assay that allows simultaneous detection of MIT3, sp100 and gp210 of IgG and IgA isotype by ELISA and compared these results with those from distinct IgG ELISAs[130]. Testing of 1175 PBC patients and 1232 non-PBC controls revealed sensitivity and specificity of PBC screen to be 83.8% and 94.7%, respectively, which is similar to that found from the evaluation of the combined data from individual MIT3, sp100, and gp210 IgG ELISAs[130].

Furthermore, assessment of 253 AMA-negative PBC patients by IIFL with this assay, resulted in positivity for PBC-specific autoantibodies in almost half of them (44.7%). Based on these data, PBC screen has been proposed as a reliable first line test for the diagnosis of PBC[130]. Comparable were the results from an Italian study, where examination of 100 AMA-negative PBC patients by IIFL showed reactivity in 43% of these patients with the use of the PBC screen[131].

Data from a study using a multiplex line blot assay, designed for autoimmune liver diseases, that contained AMA-M2, M2-E3 (a recombinant fusion protein including the E2 subunits of PDC, BCOADC and OGDC), as well sp100, PML and gp210 recombinant proteins had an overall sensitivity and specificity for PBC of 98.3% and 93.7% respectively. IIFL displayed lower sensitivity (86.2%), though comparable specificity (97.9%)[132]. Recently, a new automated PMAT assay on the Aptiva instrument, which includes MIT3, sp100, gp210, HK1 and KLp, facilitated the recognition of higher frequency of AMA- negative PBC patients compared to conventional immunoassays[57]. Even though multiplex technology seems to be a promising tool in the diagnosis of PBC, its use in the diagnostic algorithm of PBC needs to be further evaluated.

CONCLUSION

In conclusion, thorough discussion of the available literature reveals important aspects of the diagnostic, clinical and prognostic significance of disease-specific autoantibodies in AMA positive and AMA negative PBC patients[133]. Overall, identification of AMA and PBC-specific ANA is the cornerstone for the diagnosis of PBC. PBC-specific ANA, including anti-gp210 and anti-sp100, have a pivotal role in PBC diagnosis in AMA-negative individuals with high suspicion of the disease. Moreover, they have an established role as predictive factors for more advanced disease and worse outcome. The role of novel autoantibodies as diagnostic and prognostic tools in the management of patients with PBC needs to be assessed further.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Eirini I Rigopoulou 0000-0003-1978-4602; Dimitrios P Bogdanos 0000-0002-9697-7902.

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