Primary Biliary Cirrhosis: One Disease with Many Faces
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ABSTRACT: Primary biliary cirrhosis (PBC) is considered a model autoimmune disease because of the similarities between patients, their relative homogeneous presentation and natural history, and the presence of the signature autoantibody, the antimitochondrial antibodies. PBC also illustrates the potential role of genetic and environmental influence and is unique in having several well-defined animal models that recapitulate distinct features of the disease. The pathogenesis of the disease includes genetic predisposition, the production of both innate and adaptive immune responses, and cholangiocyte-specific biology that addresses the specificity of disease. In this review we highlight these features of PBC in comparison to other autoimmune diseases.

KEY WORDS: primary biliary cirrhosis, autoimmune disease, antimitochondrial antibodies, ursodeoxycholic acid

PBC = primary biliary cirrhosis

Primary biliary cirrhosis is the most common of the family of autoimmune liver diseases, and the prevalence in those populations that have been appropriately studied is estimated at 1 in 1000 women over the age of 40 [1]. A classic triad of features is used, by consensus, to diagnose patients and includes the presence of chronic biochemical cholestasis, demonstration of circulating specific anti-mitochondrial antibodies, and characteristic biopsy findings of destructive non-suppurative granulomatous/lymphocytic cholangitis [Figure 1]. Most patients now present without symptoms and are identified because routine biochemistry demonstrates anicteric cholestasis. This, however, is in striking contrast to the cohort described by Sheila Sherlock [2] in which only 4 of 100 patients between 1965 and 1972 were found because of incidental testing and 41% of patients underwent a perioperative biopsy [2]. Since the positive predictive value of liver biochemistry and positive immune serology is so high in PBC, treatment with the choleretic bile acid ursodeoxycholic acid is currently used, in the correct clinical context, without recourse to diagnostic or staging histology. In this review we summarize some salient features of PBC biology and highlight some challenges in our understanding of the disease.

PBC: GENES AND ENVIRONMENT

Descriptive and epidemiological studies have confirmed two important distinct aspects that contribute to the genesis of this chronic immunologically driven biliary disease. Firstly,

![Diagram of the multi-step pathogenesis of primary biliary cirrhosis](image-url)
PBC has an important genetic component, a concept clearly apparent to all autoimmune diseases. This is clear from the data showing an increased prevalence of other autoimmune diseases in patients and their families, namely, the presence – greater than predicted – of AMA in family members, and the strong disease concordance in identical twins, as well as raised prevalence of PBC itself in family members. Additionally, there are reported families with apparent PBC pedigrees [3-5]. The second epidemiological feature is the probable role of environmental triggers, which most likely lead to the specific loss of tolerance to the pyruvate dehydrogenase complex of mitochondrial enzymes, in those with an appropriate genetic predisposition. This is believed to occur either as a result of molecular mimicry or the chemical effects of xenobiotic exposure. Population level data report important associations for PBC that include smoking, recurrent urinary tract infections and possible chemical exposures [6], while time-space cluster analysis provides surrogate evidence of environmental challenges that presumably could be infective or toxic [7].

Genome-wide studies have now pinpointed the interleukin-12 axis as one key pathway in this disease, with genetic associations in particular with the IL12A and IL12RB2 loci [8], which are as important as the previously well-reported, but poorly understood, human leukocyte antigen disease associations [9]. Further studies identified additional risk loci including genes or loci already implicated in associated autoimmune diseases, e.g., IRF5, MMEL1, SPIB and 17q12.21 [10,11]. For sure additional loci will be discovered as study cohorts grow in size and their power to distinguish associations strengthens. However, genome-wide studies can likely explain only a proportion of genetic risk, and the application of whole-genome sequencing aimed at identifying highly penetrant but low prevalence mutations will take center stage. Nevertheless, the present genetic risk loci have clearly suggested that immunoregulatory pathways are important in disease, something that has also become apparent from an increasing array of targeted animal models of autoimmune cholangitis. These include the transforming growth factor-beta receptor II dominant-negative mouse [12], the IL-2 receptor alpha-deleted mouse [13], scurfy mice that have a mutation in the gene encoding the Foxp3 transcription factor that results in a complete abolition of Foxp3(+) Tregs, and a congenically bred non-obese diabetic c3c4 strain [14,15]. These models collectively highlight important roles for regulatory T cells, autoreactive CD8(+) cells, and natural killer cells in experimental autoimmune cholangitis. Intriguingly, the AE2 (Cl-/HCO3- anion exchange) knockout mouse also develops autoimmune cholangitis [16], although whether this really implicates biliary transporters in disease is not clear because the transporter is expressed in lymphocytes, and human studies have failed to show robust associations between AE2 and disease. Using murine models, investigators have also demonstrated the likely significance for chemical xenobiotics and bacteria in triggering characteristic disease-specific immunological signatures [17-19].

**BILIARY SPECIFICITY**

The biliary specificity of PBC is striking and not fully defined, but the evidence to date suggests this is driven by a specific facet of cholangiocyte apoptosis, in which the relevant autoantigen, pyruvate dehydrogenase E2, undergoes differential glutathiolation, increasing its immunogenicity. Biliary epithelial cells translocate immunologically intact PDC-E2 to apoptotic bodies and create apoptotic blebs, which present intact and immunoreactive antigen. In the context of a permissive immune system in which subtle changes in the checks and balances of normal immunoregulation are present, loss of tolerance occurs [20,21].

**TOWARDS DISEASE PHENOTYPES**

With so many new insights, much remains to be done to piece together the full biological process in our patients. Added to this is the need to address some of the differences seen in patients related to their clinical course and outcome, beyond the sole fact that they have PBC [Table 1]. In what some might perhaps argue is an over-simplistic view but which reflects simple day to day observations from the clinic, one can conceptualize a number of broad patient descriptors for those now living with PBC. Firstly there is the middle-aged woman with early disease and few if any symptoms, who has a good biochemical response to UDCA and an excellent and apparently benign outcome. Second are those who do not respond to treatment and in whom disease progresses slowly towards cholestatic liver failure. This group does seem distinct from a smaller cohort of patients who appear to have quite modest disease with reasonable biochemistry over many years or decades on treatment, but who in their seventies and eighties develop progressive portal hypertension, ascites and then liver failure. This itself is in further contrast to some very elderly patients who have PBC, usually with few symptoms or concerns, but

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**Notes:**

- AMA = anti-mitochondrial antibodies
- IL = interleukin
- IRF5 = interferon regulatory factor 5
- MMEL1 = membrane metalloendopeptidase-like 1
- SPIB = signal transducer and activator of transcription binding protein
- 17q12.21 = chromosome 17q12.21
- UDCA = ursodeoxycholic acid
- PDC-E2 = pyruvate dehydrogenase E2
- UDCA = ursodeoxycholic acid
The clinical features of disease are heterogeneous with varying clinical outcomes and response to treatment. A biochemical response to UDCA predicts a favorable long term outcome.
disease course. Patients with scleroderma/systemic sclerosis and PBC are indeed reported to have a slower disease progression as well. The detailed surveillance of immune serology in patients with PBC may be insightful mechanistically and may prove to be a way of identifying patient subtypes [24].

Histologically, PBC transpires to be more than just a duct disease, and interface hepatitis can be present and quite marked, even sometimes misleading pathologists to a mistaken diagnosis of autoimmune hepatitis [25]. The factors that determine why some patients have more inflammatory activity histologically are unknown, but it seems there are two processes that are distinct: so-called piecemeal necrosis (inflammatory destruction of hepatocytes similar to AIH) and biliary piecemeal necrosis in association with ductopenia (increase in the frequency of ductular profiles extending periportally). It has been argued that the degree of interface hepatitis drives the progression to cirrhosis. Overall estimates also suggest that 5–10% of patients with PBC have features of AIH, and regardless of whether one calls this an overlap syndrome or just a florid hepatitic PBC, greater understanding of this and other “overlap” presentations might be insightful regarding all patients with PBC [26].

It has become clearer that the biochemical response to UDCA treatment is a useful clinical means to evaluate outcome, but universally applicable and well-validated definitions are lacking and predictors of response are not adequately understood. Whether a reflection of disease heterogeneity (including the possibility that some disease is always destined to be mild and non-progressive) or treatment efficacy, it nevertheless appears to distinguish patients with more benign outcomes from those on a trajectory to liver failure. Disease severity, including stage of fibrosis and degree of ductopenia, appear relevant but other factors are likely at play. Examples of treatment response algorithms, in practice usually applied at varying time points after treatment with UDCA, include the Mayo criteria (alkaline phosphatase < 2 times the upper limits of normal) [27], the French criteria (ALP < 3 x ULN, and aspartate aminotransferase < 2 x ULN, and bilirubin < 17.1 μmol/L), the Spanish criteria (decline in ALP of more than 40% of baseline or to a normal value) [28], and our Toronto criteria (patients whose ALP is < 1.67 x ULN after 2 years of UDCA treatment have less than one stage of fibrosis progression at 10 years, or those whose ALP is < 1.76 x ULN have less than two stages of fibrosis progression at 10 years) [29]. Patients meeting the Spanish criteria had a similar survival to that of the matched control population, while those meeting the French criteria are predicted to have a 10 year transplant-free survival rate of 90% (compared with 51% for those who did not). Understanding further the basis of treatment response, not just to UDCA but to other drugs such as fenofibrate, will aid disease classification.

PBC: CONTRASTS AND COMPARISONS

PBC is considered a model autoimmune disease. For one thing, there are greater similarities in the onset and natural history of disease, unlike other organ-specific autoimmune diseases [30]. Moreover, PBC illustrates the clustering and commonalities found among other autoimmune diseases, including some of the common environmental triggers that have been postulated [31,32]. In contrast, however, PBC does not respond well, if at all, to immunosuppressive agents. This is in sharp distinction to several other autoimmune diseases and raises the possibility that some of the pathology is mediated other than by an adaptive response [33-35]. Finally, the genetics of PBC, including genome-wide and microRNA experimental studies, are yielding exciting data pointing to potential therapeutic targets [8,11,36]. In this respect we note the increasing emphasis on the molecular consequences of apoptosis and the use of epigenetics and proteomics in autoimmunity and suggest that this will become a focus for further study not only in PBC but other autoimmune diseases as well [37-40].

CONCLUSIONS

PBC, like all diseases, has a lot more to it than meets the eye, and while three cardinal features may be relevant for diagnosis, there remain many other clinical and laboratory aspects of disease that need more extensive definition. With improved methods of patient phenotyping, greater progress will follow biologically, and hopefully translate into new, effective and specific therapies.

The biologic processes are increasingly being revealed by genomic testing and development of targeted animal models: subtle immunoregulatory changes appear likely to drive this classic autoimmune disease

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References


