PBC: an infectious disease?

Primary biliary cirrhosis (PBC) is characterised by progressive destruction of the middle sized intrahepatic ducts, leading to liver failure and, in the absence of transplantation, death. While ursodeoxycholic acid may slow progression, there is as yet no curative therapy. As the pathogenesis of PBC is unknown, it is difficult to develop a logical therapeutic strategy. PBC has been considered an autoimmune disease although immunosuppressive therapy is relatively ineffective; here we discuss the possibility that there may be an infectious aetiology.

Autoimmune features of PBC

There are clear autoimmune aspects to PBC: there is a strong association with extrahepatic autoimmune diseases such as thyroid disease. Overlap syndromes between PBC and autoimmune hepatitis have been well documented, although the response to immunosuppression is at best poor. One of the characteristic features of PBC is the association with disease specific autoantibodies: these include not only the antimitochondrial antibodies (AMA) but also antibodies to components of the nuclear pore complex (such as gp210). The antigens recognised by AMA have been identified (PDC-E2; OGDC-E2; E3BP; PDC-E1α; BCOADC-E2) and are located on the inner aspect of the mitochondrial membrane.3–7

AMA AND PBC

AMA may precede the clinical, biochemical, and histological features of PBC, suggesting that these antibodies may have a pathological role. However, these antigens are neither organ nor disease specific. Why the biliary epithelial cells are the main targets of disease may be explained by the observation that in PBC, but not other liver diseases and normal liver, biliary epithelial cells have E2 present on their plasma membrane. Several groups have attempted to generate animal models of PBC by immunising animals with antigens recognised by AMA: injections of tissue or recombinant mitochondrial antigens were given to murine mice, immunised with pyruvate dehydrogenase.9 There PBC-like bile duct lesions and AMA can be found in SJL mice, immunised with pyruvate dehydrogenase.1 There remains no clear evidence that AMA (or other PBC specific autoantibodies) are linked to the pathogenesis of the disease.

An infectious aetiology?

There are several observations that suggest the possibility that an infectious agent may result in PBC.

EPIDEMIOLOGICAL

Prevalence studies and the effect of migration

There is global variation in the reported prevalence of PBC and, although part of the variation in prevalence may reflect methodological factors, there is likely to be a true variation in incidence. This is supported by studies examining the effect of migration: people migrating between different geographical areas seem to take on the prevalence of the host population, thus in Britain, the prevalence is about 150–240 per million whereas among British immigrants to Australia the prevalence is 47 per million and for the endemic Australian community only 19 per million.10 Similarly, while PBC is almost absent in India, the prevalence of end stage PBC among first generation migrants to the UK from the Indian subcontinent is 14 per million.11

Clustering

Cases of PBC tend to “cluster” within areas. This phenomenon was first described in Sheffield where cases of PBC clustered in one area supplied by the Rivelin reservoir; the point prevalence here was 115 per million compared with 13 per million elsewhere in Sheffield.12 A subsequent study by Chetwynd showed significant evidence of spatial clustering;13 this clustering was unrelated to urban or rural location or to diagnostic activity, suggesting a true clustering effect.

GENETIC

There is a marked familial component to PBC, there is only a weak HLA association (with B8), and there is no childhood equivalent.14–16 The sibling relative risk of PBC (s.s) (10.5) is similar to that for rheumatoid arthritis5 and less than that for diabetes17 or systemic lupus erythematosus.18,19 When two members are affected, the disease tends to occur at the same time rather than at the same age, compatible with an external trigger.

THE TRANSPLANTATION MODEL

PBC specific autoantibodies (AMA and gp210) persist after transplantation in all subjects and histological evidence of recurrence is demonstrated in up to 20% of patients by 10 years.20 Within these grafts, aberrant distribution of E2, typical of PBC, occurs whether or not there is histological evidence of recurrence.21 Furthermore, both the risk and rate of recurrence after liver transplantation is related to increased immunosuppression.22 This situation is analogous to the universal recurrence of chronic hepatitis C virus infection in liver allografts following transplantation, which again may be enhanced by high doses of immunosuppressive agents.23 This observation strongly suggests that some factor(s) in the host induces aberrant E2 expression.

IN VIVO TRANSMISSION

There is no evidence for PBC being transmitted sexually or by blood transfusion. However, Hannan in a communication to the British Association for the Study of the Liver (1999) described two babies born of mothers with PBC who developed transient cholestatic liver disease associated with the appearance of AMA. While the authors suggested that transplacental transmission of AMA could be the cause of the liver damage, an alternative explanation is that there is transplacental or perinatal transmission of an infective agent.

IN VITRO EVIDENCE FOR A TRANSMISSIBLE FACTOR

Biliary epithelial cells isolated from patients with PBC, but not from patients with other liver diseases or normal subjects, show both in vivo and in vitro E2 staining on plasma membranes.

Abbreviations used in this paper: PBC, primary biliary cirrhosis; AMA, antimitochondrial antibodies; HIAP, human intracisternal A-type peptide; UTI, urinary tract infection.
controls and patients with chronic liver disease. However, mycobacterial protein could be demonstrated in the serum. Follow up studies concluded that antibody to a 65 kDa existence of AMA in genetically susceptible individuals. evoke a sequence of autoreaction events resulting in the induced humoral response to antigen from MYCOBACTERIA. Putative infectious agents

As granulomas, occurring either as aggregates of histiocytes or non-caseating lesions adjacent to damaged bile ducts, are commonly found in PBC, it was suggested that mycobacteria have a role in the pathogenesis of PBC. An initial study by Vilagut et al reported that all of 19 PBC sera reacted with an extract from the atypical mycobacteria M gordonae; identical recognition profiles were produced with two polypeptides of 70–65 and 55 kDa. There were no other reactions with nine other atypical mycobacteria or with controls. Two main mitochondrial antigens identified by sera from PBC patients, PDH-E2 and BCKDH-E2, were also recognised by eluted antimycobacterial antibodies, indicating that there is cross reactivity of these anti-M gordonae antibodies with the mitochondrial antigen against which AMA react in PBC. The authors proposed that an induced humoral response to antigen from M gordonae may evoke a sequence of autoreaction events resulting in the existence of AMA in genetically susceptible individuals. Follow up studies concluded that antibody to a 65 kDa mycobacterial protein could be demonstrated in the serum of patients with PBC as well as in serum from normal controls and patients with chronic liver disease. However, other studies have cast doubt on this hypothesis: in the first, there was no evidence of excess T cell responses to a mycobacterial antigen system in PBC patients. Thus in the absence of cross reactivity at the T cell level it would be difficult to sustain a role for responses to mycobacterial antigens in the pathogenesis of PBC. In the second, mycobacterial DNA was not detected in liver sections from patients with PBC or other liver disease. These data are still inconclusive as the detection sensitivity of the polymerase chain reaction may not detect mycobacteria in the archival liver tissue samples used and if mycobacteria do have a role in the pathogenesis of PBC they may only be necessary for initiating autoimmunity by molecular mimicry. Of note, treatment with the antimicrobial agent rifampicin had no effect on the course of the disease.

BACTERIA

It has been proposed that AMA and PBC are induced by exposure to enterobacterial antigens. Immunoblotting studies have shown that PBC specific antibodies recognise enterobacterial proteins which correspond to mitochondrial target proteins with a molecular weight of 50–70 kDa. Rabbits immunised with enterobacterial R mutants generate AMA although enterobacteria wild forms, which are not R mutants, do not. Although some studies have indicated that there is an increased prevalence of R forms of Escherichia coli in the stools of patients with PBC, this has not been confirmed by others. Other evidence implicating E coli includes an increased incidence of asymptomatic E coli urinary tract infections (UTIs) in patients with PBC, and the observation that patients with recurrent UTIs also have an increased incidence of positive AMA. A possible explanation (“the endosymbiont theory”) is that mitochondria have evolved from free living prokaryocytes taken up by amoeboïd cells; thus the structure and function of mitochondria and aerobic bacteria are similar. R mutants differ from wild-type enterobacteria mainly in the defective synthesis of the saccharide protein of lipopolysaccharide. This results in the different molecular organisation of the cell membrane and the possibility that R mutants might possess different characteristics, especially those related to immunogenic properties. Phylogenetic conservation and wide prevalence of bacterial and mitochondrial polypeptides suggests immune tolerance to antigen in humans. Immune tolerance may be terminated when polypeptides are presented in a strong immunogenic form or when a defect in the immune system occurs; for example, R forms of enterobacteria in the gut may induce AMA in PBC patients. Again, this hypothesis linking E coli infection and PBC cannot be sustained as the association between recurrent UTI and PBC has not been confirmed by all studies and AMA found in patients with UTI are of low titre and of different specificity. Furthermore, Tanaka et al were unable to find evidence of bacterial or mycobacterial genomic products in livers from patients with PBC.

An infectious cause for PBC?

Many of the clinical and serological features of PBC are compatible with an environmental trigger but all of these factors are circumstantial. The environmental factor could either induce an autoimmune disease after an acute infection or induce autoimmunity with persisting infection. It is not clear, however, if this distinction is valid. For example, chronic hepatitis C virus infection, where biliary epithelial cells as well as hepatocytes are infected and where bile duct damage is a significant component of liver damage, is associated with immunological abnormalities such as cryoglobulinemia and autoantibodies, including antinuclear antibody, liver-kidney microsomal antibody, anti-GOR, and rheumatoid factors. These associated conditions are more frequent when the infection is treated with interferon. Anti-GOR is an antibody found in chronic hepatitis C infections in humans and primates directed at a host antigen and it is therefore an autoantibody. However, this antigen shows significant homology with part of the hepatitis C virus nucleocapsid which may point to an explanation for induction of autoimmunity by the virus. Anti-GOR is thought to reflect specific hepatitis C induced autoimmunity and GOR is therefore a hepatitis C virus specific autoantigen (or epitope).

PBC is characterised by elevated levels of serum IgM. Raised levels of polyclonal IgM may be a consequence of polyclonal B cell activation by lipopolysaccharide or viruses, such as Epstein Barr virus. The association of the sex linked immunodeficiency and hyper IgM syndrome with a cholangiopathy is probably not relevant to the pathogenesis of PBC as the former condition is associated with abnormal CD40 levels on biliary epithelial cells but are normal in PBC.

That non-infectious environmental factors can trigger autoimmunity is evidenced by coeliac disease where gliadin triggers an immune response but tissue transglutaminase is
the autoantigen. Gliadin is a substrate for the transglutaminase; Molberg et al. showed that transglutaminase may deaminate gliadin to create an epitope that binds efficiently to DQ2. A possible analogy is the immune response to the drug metabolizing enzymes seen in some drug induced immune mediated hepatitis (such as tienilic acid and antibodies to CYP2E6). Dietary factors have also been suggested to trigger type I diabetes in genetically susceptible individuals. However, PBC differs from these, and other autoimmune diseases, in that it has not been recognised in children.

Initiation of autoimmunity can be considered as a three stage process: the development of an autoimmune cellule repertoire is followed by activation of these autoreactive cells in response to a local target; the third step is failure of the immune system to regulate these self-reactive processes. It is beyond the scope of this article to review the molecular mimicry and bystander activation. Molecular mimicry, where host lymphocytes or antibodies recognise antigens that are shared between self and microbial antigens, is thought to be important in multiple autoimmune diseases, including diabetes mellitus, Guillain-Barré syndrome, and autoimmune hepatitis (such as tienilic acid and antibodies to DQ2).

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