Primary biliary cirrhosis: historical perspective

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The first description of a liver disease that would probably be described as primary biliary cirrhosis (PBC) today, was reported in 1851 by Addison and Gull in Guys Hospital Report [1]. The title being “On a Certain Affectation of the Skin–Vitiligoidea–alpha plana, beta tuberosa”. A few years later (1892) Hanot reported on “La Cirrhosis hypertrophique avec ictere and chroniqe” [2]. It was Ahrens et al [3] who first coined the term Primary Biliary Cirrhosis in 1950. Unfortunately this name is often a misnomer because most individuals given a diagnosis of PBC today are in fact not cirrhotic, and the term may give rise to undue concern in the affected individual. However, all attempts to use different terminology, such as chronic non-suppurative granulomatous intrahepatic cholangiopathy have failed! Thus, the term primary biliary cirrhosis seems to be forever imprinted on the memory.

Clinical presentation

In 1959 Sheila Sherlock described 42 cases of PBC whom she had personally followed between 1944 to 1959 [4]. Twenty had presented with pruritus, which preceded overt jaundice by up to 11 years. However, in 14, jaundice was noted to precede the onset of pruritus. A few cases had been diagnosed on the incidental finding of hepatomegaly in the absence of any specific complaints (possibly the first description of asymptomatic disease). At that time, there were no helpful diagnostic tests to distinguish between intra and extrahepatic biliary obstruction. No patient gave a history of fever or abdominal pain. It was noted that stool color was variable, rarely being pale and often normal. Lacking the availability of ultrasound the diagnosis was usually made following surgical exploration of the biliary system or with a liver biopsy in a few (still a very “daring” procedure in the early 1950s). Only 5 of these 42 patients had a diagnosis made without surgical exploration.

Sherlock also recognized that a similar clinical picture could complicate Laennec's cirrhosis. She also noted that some young people with cirrhosis of the Waldenstrom type also presented with jaundice and pruritus but in the latter the biochemical picture most often reflected a hepatitis, and the histologic picture was very different. We have now gone full circle with the introduction of the concept of overlapping syndromes, which are addressed in this issue by Dr. Raoul Poupon's article, Autoimmune overlapping syndromes.

Xanthomatous skin lesions were common in this early series by Sherlock. They were reported in all but 16 of the 42 cases, some were flat xanthenasma and others tuberous deposits on extensor surfaces of the elbows, wrists, buttocks, knees, and ankles, but never in
tendon sheaths. It was noted that not all these patients with cholesterol deposits in skin had high serum cholesterol values. Vascular atheroma was not evident in 15 autopsies that were performed. She reported a clear-cut association between the degree of hyperbilirubinemia and the percentage of dietary fat absorbed. X-ray examination of the spine and ribs showed collapsed vertebrae and rib fractures in some, even though serum calcium levels were normal in all but 2 cases. Despite the administration of parenteral vitamin D, patients continued to have thin bones and so it was recognized that osteoporosis could complicate PBC as well as osteomalacia.

Gastrointestinal hemorrhage occurred in 16 of these 42 patients, but in 9 this was thought to be caused by peptic ulcer disease and only 7 were given a diagnosis of esophageal varices. Portal pressure measurements by way of the intrasplenic route were soon abandoned as this technique was complicated by hemorrhage. Measurements of the wedged hepatic vein pressure indicated that patients could have evidence of portal hypertension before the development of cirrhosis in this liver condition. The concept of presinusoidal portal hypertension in PBC was not fully recognized until this time.

Liver failure was the usual cause of death in these 42 patients and was generally a late manifestation of the disease, never occurring before 4 years after the initial diagnosis. A fall in serum cholesterol and disappearance of skin xanthomas was seen once liver failure ensued and sometimes even the serum level of the alkaline phosphatase was noted to return to normal preterminally.

A diagnostic test for primary biliary cirrhosis

A landmark observation in the history of PBC was made in 1965 by Walker et al [5]. These authors identified a specific granular cytoplasmic fluorescence pattern when they used a double layer of fluorescein on fixed and unfixed cryostat sections of thyrotoxic thyroid gland and human gastric fundal mucosa. All 32 cases of presumed PBC tested positive whereas no fluorescence was seen in 21 cases of common bile duct obstruction, 5 cases of cholestatic drug jaundice, 4 cases of cholestatic viral hepatitis and 3 cases of chronic cholestasis in individuals with ulcerative colitis. As there were no such tests as ultrasound, endoscopic retrograde cholangiopancreatography, CT scans, or magnetic resonance imaging, this serum test was indeed a major diagnostic breakthrough. Despite the subsequent recognition of the specific mitochondrial antigens [6,7], and thus our ability to use ELISA and immunoblotting methodology, the sensitivity and specificity of the simple immunofluorescence test for AMA has barely been surpassed. Thus most centers still use IF to detect AMA.

Liver histology

It was in 1965 that Rubin et al [8] first described the spectrum of liver histology associated with PBC. In a subsequent report by Scheuer in 1967 [9] four histologic stages: (1) the florid duct lesion, (2) ductular proliferation, (3) fibrotic septa, and (4) cirrhosis were described in detail. Despite various amendments, this staging system continues to be used many decades later. It is now recognized that the typical albeit early lesions of PBC may be found on examination of liver tissue from individuals whose only other feature of the disease is that their serum tests positive for AMA [10].
Natural history of primary biliary cirrhosis

In 1851 when this disease was first recognized the concept of asymptomatic PBC was unimaginable. It was the advent of diagnostic tests such as the AMA and the introduction of more widespread use of routine screening of liver biochemistry that the true prevalence of asymptomatic and even sub-clinical disease has become realized [11]. Now the percentage of cases of asymptomatic PBC outnumber symptomatic cases. Asymptomatic PBC is often described in the older individual in whom it may not always be presymptomatic because nearly 50% die of non-hepatic causes [12]. So in 2003 a diagnosis of PBC may not and should not presume early death from liver failure.

Pathogenesis of primary biliary cirrhosis

Following the recognition that AMA was a hallmark for PBC, it was recognized that this serum marker was sometimes present in relatives of index cases but never in controls [13]. A familial risk of PBC is now well recognized. The affected offspring of the propositus generally develops PBC at a younger age [14].

The apparent association of PBC with several other disorders believed to have an autoimmune basis (eg, Hashimoto's thyroiditis) would suggest that the pathogenesis for this chronic liver disease may be promoted by immune dysregulation. Thus, evidence for genetic polymorphisms of genes associated with the control of antigen processing and cytokine production have been sought. However, to date, any associations reported have been weak. But now with the complete identification of the human genome, more extensive genetic evaluation is possible.

The environment

In 1972 Douglas and Finlayson [15] reported that a mother and neighbor who cared for an index case of PBC both subsequently developed PBC. This observation was the first indication that environmental and genetic factors may play a role in the pathogenesis of PBC. Shortly after this case report, David Trigger [16] observed that cases of PBC were more prevalent in an area served by a specific water reservoir. Similar case clustering has been reported from Japan in the area of Hiroshima [17], suggesting that exposure to the atomic bomb may be a risk factor for PBC. In another recent report from North East England, case clustering has also been observed [18]. Two reports, one from the United Kingdom [19] and the other from the United States [20] indicate that a current or past history of cigarette smoking is more common in individuals with PBC (RR2.04–3.5). A recent experiment suggests that xenobiotic induced alterations of endogenous PDC-E2 protein (AMA substrate) reacted with serum testing positive for AMA [21]. There have also been several reports documenting a possible association of various infections, mostly bacterial, with individuals with PBC. Both hepatic granulomas and eosinophils are non-specific markers of an immune mediated reaction to infection or a foreign body, and they are often seen on liver histology in PBC.

Treatment for primary biliary cirrhosis
Despite the aggressive pursuit by many investigators to identify the immunopathogenesis of PBC the inciting antigens have yet to be identified. Thus the treatment for this disease remains non-specific. Therapies have included agents that address specific symptoms associated with this chronic cholestatic liver disease, such as agents to relieve pruritus, or prevent the long-term complication of osteoporosis. Subsequent articles will address these issues in detail.

Specific therapies aimed at preventing progression of the liver disease have been restricted to immunosuppressive agents, anti-fibrotics, and choleretics. Unfortunately most attempts to identify an effective therapy for PBC have failed, in part because of the great difficulty in conducting therapeutically trials for this disease. The disease remains rare (14.1/10^6 in 1994 in the United Kingdom) thus making it difficult to recruit an adequate sample size unless large multi-center studies are conducted (these are extremely expensive). The more asymptomatic cases with early disease the larger and the longer the trials would need to be if the primary measure of outcome were to be death or need for liver transplant. Instead one could use one of the several prognostic risk scores developed in PBC, but their validity has only been demonstrated in the individual with symptomatic disease. So at present we have no good surrogate markers of survival to use to measure drug efficacy in early disease. Perhaps molecular markers of liver disease progression will become the surrogate marker for the future. The development of targeted therapy, once the common trigger for this disease is identified, should enhance treatment efficacy. Meanwhile, investigators need to establish how they can distinguish those individuals with currently early asymptomatic disease, who are likely to progress to decompensated liver disease, from those who will remain stable.

Summary

PBC is an old disease first described in 1851. It's predilection for women and its association with other autoimmune diseases suggests an immune based pathogenesis, but epidemiologic studies indicate that genetic and environmental factors play a role in the pathogenesis of PBC. The serologic hallmark for PBC, namely the antimitochondrial antibody, was first identified in 1965 and remains the most sensitive and specific hallmark for this disease. When first described, primary biliary cirrhosis was universally fatal but asymptomatic cases now represent more than 60% of cases diagnosed, less than half of whom will die of their liver disease. No specific therapy that effectively stops or reverses disease progression has been identified, thus it behoves investigators to aggressively pursue identification of the etiology of PBC.

References


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