Autoimmune cholangitis

Autoimmune cholangitis is a term that has only recently appeared on the hepatology horizon and it may be best if the term were to be abandoned as its use has given rise to considerable confusion. Clearly the name infers inflammation of the bile ducts thought to be due to an autoimmune process. Primary biliary cirrhosis, primary sclerosing cholangitis, and graft versus host disease are all diseases of the bile ducts in which the pathogenesis is considered immune (often autoimmune) based. It is also possible that some drugs induce an immune mediated bile duct destruction and it has been postulated that viruses may do likewise.

The name “immune cholangitis” was introduced first by Brunner et al. to describe a condition seen in three women (two were mother and daughter) who had liver disease which clinically, biochemically, and histologically seemed to be typical of primary biliary cirrhosis, except that the serum antimitochondrial antibody (AMA) test was negative in all three; all three were antinuclear antibody (ANA) positive. Examinations of the bile ducts via endoscopic retrograde cholangiopancreatography (ERCP) disclosed no abnormalities. Treatment with prednisolone and azathioprine was said to be “successful”.

The non-organ, non-species specific mitochondrial antibody was first recognised as a hallmark for primary biliary cirrhosis in 1965 by Walker et al. Over time it has become recognised that the inciting antigen(s) are located on the inner part of the mitochondrial membrane. The specific antigens have been further defined using western immunoblotting techniques as being the 74 kDa E2 subunit of the pyruvate dehydrogenase complex (PDC-E2), the 52 kDa protein X, the 50 kDa branched chain 2-oxo-acid dehydrogenase complex (BOADC-E2), the 48 kDa (2-oxoglutarate dehydrogenase complex (OGDC-E2), and the 41kDa E1a subunit PDC. However, most laboratories still use the same immunofluorescence technique, which allows for single sample testing. Multiple samples are most easily tested with an enzyme linked immunosorbent assay (ELISA) using recombinant or purified antigens. The specificity of these tests has been assessed in healthy controls by Omasari et al., the sensitivity of immunoblotting by Mutimer et al., and ELISA by Fussey et al.

After the report of Brunner et al., Ben-Ari et al. described four more patients who seemed to have all the usual features of primary biliary cirrhosis but who also tested AMA negative even when using the sensitive immunoblotting method. These authors described their patients as having an autoimmune cholangiopathy because serum ANA and smooth muscle antibody (SMA) proved positive in all four cases. These patients were also treated with prednisolone with or without azathioprine and were shown to have at least short term biochemical and histological improvement (although there was no change in bile duct damage).

Once immunofluorescence testing for AMA detection was first introduced it was noted that about 5%-8% of patients with features otherwise typical of primary biliary cirrhosis tested negative. It was also noted in the early days of AMA testing that AMA was sometimes detected in the serum of patients with other forms of autoimmune liver disease. Similarly, the autoantibodies most commonly associated with autoimmune hepatitis – namely, ANA and SMA – were found in some patients who were AMA positive but who were otherwise thought from all the usual perspectives to have primary biliary cirrhosis. Now that primary sclerosing cholangitis can be diagnosed with absolute confidence via ERCP it has become recognised that these same non-organ, non-species specific auto-antibodies ANA and SMA are found in the serum of some patients with proven primary sclerosing cholangitis.

Hence, confusion as to the exact diagnosis in some cases of presumed autoimmune liver disease is an old problem. In 1976 Geubel et al. suggested that a three month trial of prednisolone therapy may help to distinguish autoimmune hepatitis from primary biliary cirrhosis in those patients who had features of both diseases.

The development of the highly sensitive and specific immunoblotting tests for AMA in the late 1980s might have been anticipated to clarify the definition of otherwise confusing cases of autoimmune liver disease. Thus we submitted serum samples from patients thought by all other criteria to have primary biliary cirrhosis (but who had been rejected from a therapeutic trial because their serum AMA tested negative by immunofluorescence), for AMA testing by immunoblotting. Seventeen of these 20 patients proved still to be AMA negative using this test. The clinical, biochemical, serological, and histological characteristics of these AMA negative cases were compared with AMA positive cases referred to the same therapeutic trial, matched for concentration of serum bilirubin. Certain other features distinguished the AMA positive and negative cases: the serum IgM concentrations were significantly lower in the AMA negative patients, and all had serum positive for ANA (often at high titres (1:160-1:1280)) whereas only three of the AMA positive patients were ANA positive. Similarly, more of the AMA negative cases were also SMA positive (seven of 17) compared with the AMA positive cases (one of 17). Aside from the AMA tests and IgM concentrations, these AMA positive and negative patients could not be distinguished. Their symptoms were comparable, the prevalence of other autoimmune diseases was no different, and their liver histology on needle biopsy (read by two independent pathologists blinded to AMA status) was indistinguishable. We coined the phrase “autoimmune cholangitis” to describe what is likely simply AMA negative primary biliary cirrhosis.

Several other centres have reported similar cases: Taylor et al. described nine cases, and Lacerda et al. performed serial testing for AMA by immunoblotting over several years. In all but one patient the AMA tests remained consistently negative. The Mayo group also noted lower IgM concentrations in their patients and Taylor et al. and
Lacerda et al\(^4\) both reported high titre ANA in all those tested.

Goodman and colleagues\(^5\) examined this dilemma from the pathologist's point of view. They reviewed the notes of 200 patents whose liver biopsy specimens they had studied and whom they considered had primary biliary cirrhosis from a morphological standpoint. The number of florid bile duct lesions, the degree of ductopenia, portal inflammation, and piecemeal necrosis were present with equal frequency in the four groups categorised by autoantibody status – namely, AMA negative-ANA negative: AMA negative-ANA positive: AMA positive-ANA negative, and AMA positive-ANA positive. The only histological difference was the rate of cirrhosis, which they found to be only 1 in 40 in the AMA negative-ANA positive cases, whereas 12% of the other 160 patients were cirrhotic. However, this was a retrospective study and hence, subject to all the biases inherent in retrospective analyses.

Other features which may distinguish AMA positive from AMA negative primary biliary cirrhosis have been examined. Carbonic anhydrase is an enzyme found in epithelial cells including the bile ducts and in this context may promote cholestasis. Antibodies to this enzyme were reported by Gordon et al\(^6\) to be present using western blotting in five of six cases of presumed “autoimmune cholangitis” (all but one anti-PDC negative – that is, AMA negative), whereas only one of 12 PDC positive cases of primary biliary cirrhosis and 10 of 10 hepatitis cases tested positive for carbonic anhydrase antibodies. Few healthy controls (except for eight cases of Gilbert’s syndrome) were tested. These results could not be confirmed by ourselves or by Professor FB Bianchi (personal communication).

It has been noted that in patients with AMA sero-positive primary biliary cirrhosis, the E2 subunit of PDC, or another molecule which cross reacts with it, can be detected in the apical region of biliary epithelial cells in liver biopsy specimens. It remains unknown as to why this inner mitochondrial membrane antigen should be present in this location.\(^7\) It seems to appear before the appearance of MHC class II expression on the biliary epithelium in primary biliary cirrhosis.\(^8\) The central concept that AMA may have a role in the pathogenesis of primary biliary cirrhosis. In a later paper by Tsuynamaya\(^9\) PDC-E2 expression was found in the bile ducts in seven of nine AMA seropositive primary biliary cirrhosis (autoimmune cholangitis) patients.

A recent study by Kitami et al\(^10\) subjected serum from patients who were AMA positive and negative by ELISA to exhaustive immunoblotting studies. They examined the immunoglobulin fractions IgG, IgA, and IgM for the different inner mitochondrial membrane (M2) antibodies and found that 17 ELISA negative cases of presumed primary biliary cirrhosis were indeed anti-M2 positive suggesting that there is no true AMA negative primary biliary cirrhosis. These data provide further support for the premise that AMA may be linked to the pathogenesis of primary biliary cirrhosis.

The results of several randomised controlled trials using ursodeoxycholic acid in AMA positive primary biliary cirrhosis have universally shown that treatment leads to a rapid fall in all the biochemical markers of cholestasis – namely, serum bilirubin, alkaline phosphatase, and \(\gamma\)-glutamyl transpeptidase.\(^11\) Similar trials will never be possible in “autoimmune cholangitis” due to the paucity of cases. Early reports by Taylor et al\(^12\) claimed there was no apparent benefit in four of five patients treated with ursodeoxycholic acid, but in a recent report by Kim et al\(^13\) the beneficial biochemical effect of ursodeoxycholic acid therapy given to eight patients with AMA negative primary biliary cirrhosis (autoimmune cholangitis) was thought to be comparable with that found in their patients with AMA positive primary biliary cirrhosis.

The study of Goodman et al\(^5\) would suggest that from a histological standpoint the typical features of primary biliary cirrhosis may be seen in patients both with and without the serum markers of autoimmune liver disease – namely, AMA and ANA. However, aside from granulomatous bile duct destruction the other histological features of primary biliary cirrhosis are not specific and hence histology, certainly from needle biopsy samples, cannot be the gold standard for the diagnosis of primary biliary cirrhosis. Now that the highly sensitive and specific serum tests for AMA using western immunoblotting techniques have been developed they could be the gold standard for diagnosis. However, with the exception of the study of Kitami et al\(^10\) it seems that not all patients with otherwise classic primary biliary cirrhosis are seropositive even via immunoblotting.

It is now recognised that different pathogenetic mechanisms may give rise to a histological pattern sometimes hard to distinguish from primary biliary cirrhosis – for example, graft versus host disease, sarcoidosis, and even primary sclerosing cholangitis. It is probable that autoimmune cholangitis is a cholestatic liver disease with a natural history similar to AMA positive primary biliary cirrhosis despite some differences in serology and that it should be treated similarly that is, with ursodeoxycholic acid. Perhaps after all it would be less confusing if autoimmune cholangitis was referred to as “AMA negative primary biliary cirrhosis”.

JENNY HEATHCOTE

9EN – 222, The Toronto Hospital, University of Toronto, 200 Elizabeth Street, Toronto, Ontario, Canada M5G 2C4

11 Gershof AB, Baggenstoss AH, Summerskill WHJ. Responses to treatment can differentiate chronic active liver disease with cholestatic features from the primary biliary cirrhosis syndrome. *Gastroenterology* 1976; 71: 444–9.