Autoimmune cholangitis in twin sisters

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Dear Sir,

Autoimmune cholangitis is a controversial entity, which is considered either as antimitochondrial antibody (AMA) negative primary biliary cirrhosis (PBC), or a variant in a spectrum of autoimmune liver diseases (PBC, Autoimmune Hepatitis, Primary Sclerosing Cholangitis), or even an autonomous entity (1-3).

In our department, we have had the rare opportunity to confirm the concordance of autoimmune cholangitis in a pair of monozygotic twin sisters and to follow the very similar disease manifestation and subsequent course. They had been living in the same geographic region all their lives, having the same occupation (housewives) and very close social contact. The past medical history was unremarkable and negative for alcohol or tobacco consumption. The age at diagnosis, investigating fatigue and mild itching, was similar (57 years old in the first, 58 in the second) and the biochemical (raised alkaline phosphatase, ALT and low platelets) as well as the auto antibody profiles (positive ANA 1/160, weakly positive SMA 1/40, negative AMA, negative M2) were identical. The viral markers were negative in both patients and the iron studies, ceruloplasmin, a1-antithrypsin were within the normal range. Liver histology was alike in both sisters, characterised by predominantly portal inflammation, bile duct damage and development of significant fibrosis, compatible with autoimmune cholangitis stage III/IV. The disease course of the twin sisters was strikingly similar, characterised by decompensated liver disease approximately 3 years after the initial diagnosis, with multiple variceal haemorrhages and endoscopic sclerotherapy courses at that time. Liver transplantation was not a possible option for them because of socioeconomical limitations.

The first patient was diagnosed 3.5 years after the initial presentation with a 4 cm in diameter hepatocellular carcinoma (HCC) in the right liver lobe, confirmed by two imaging modalities (US and CT liver) and an aFP > 1000 ng/ml. Denying local ablation treatment, she participated in a randomised trial with octreotide (4) and 6 months later died after a massive pulmonary embolism. Her twin sister followed the same course with variceal bleeds and endoscopic sclerotherapy courses until 4.5 years after diagnosis of her liver disease, when she developed diuretic resistant ascites and right hydrothorax. She was treated with TIPS placement. Direct portography after transjugular intrahepatic catheterisation of the portal vein, disclosed multiple thrombi at main trunk of the portal vein, its right branch and the splenic vein. Nevertheless, the placement was successful and the clinical outcome as regards the hydrothorax was excellent. Unfortunately, the patient died 5 months after the TIPS placement, because of lower respiratory tract infection-septicaemia.

Notably again, roughly the same period after the initial diagnosis, both patients presented a critical event in their clinical course. The first a HCC and died from a thrombotic complication few months later, and the second presented with sudden onset of diuretic resistant ascites and extensive venous thromboses. At that time, screening with imaging and aFP of the second patient did not identify an HCC. Portal vein thrombosis in the context of liver cirrhosis frequently has been associated with HCC, and in a recently published study (5) our group showed that thrombophilic defects are common in patients with HCC. On the other hand, cholestatic liver diseases have been also proposed to be associated with hypercoagulable state (6,7). The premature death of the second patient did not offer the opportunity to follow her up long term and thus, to confirm or not the existence of the possible tumour. HCC mainly develops in elderly patients with advanced stage PBC, albeit its development was not found in a large study (8) to be associated with survival. As regards the occurrence of HCC in twins, this has been reported previously in the literature (9,10).

Current theories on the aetiopathogenesis of PBC, favour the hypothesis that the disease develops as a result of an inappropriate (genetically controlled) immune response, following stimulation by an environmental or infectious agent (11). The genetic basis for susceptibility to PBC is supported by four strands of evidence : the gender bias, the geographic and familial clustering of the disease, the co segregation with other autoimmune diseases and the studies of concordant rates for PBC in monozygotic twins (12). In our case's monozygotic twin sisters there are notable similarities with the concordant monozygotic twin pairs reported by

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Selmi *et al.* (13), which is the largest group of twins described up to now in PBC. Moreover, a single case of autoimmune cholangitis associated with dermatomyositis in monozygotic twin sisters has been also reported in the literature (14).

Undoubtly there is a major role of the genetics both in the induction of PBC and the subsequent clinical course and we believe that this is probably the case for autoimmune cholangitis.

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