

Sclerosing cholangitis associated with Crohn's disease and autoimmune haemolytic anaemia

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Summary: A middle-aged man was found to have autoimmune haemolytic anaemia. Seven years after the first manifestations of the anaemia, he developed jaundice without haemolysis and a diagnosis of primary sclerosing cholangitis was made by endoscopic retrograde cholangiography. Crohn's colitis was later confirmed by X-rays and colonoscopy. This association is unique to the best of our knowledge and suggests that genetic and immunological mechanisms may be involved in the pathogenesis of these diseases.

Introduction

Previous reports have emphasized the association of inflammatory bowel disease and primary sclerosing cholangitis (PSC), mostly with ulcerative colitis.^{1–5} Autoimmune haemolytic anaemia was described in several cases of ulcerative colitis but not in Crohn's disease.^{6–26} Only two cases of autoimmune haemolytic anaemia together with PSC have been previously published. HLA-B8 phenotype was reported in 60% of PSC patients, compared with only 25% of controls, while HLA-DR3 was found in 70% of the patients.²⁹ This common haplotype is also present in an increased prevalence in several autoimmune diseases.³⁰

Case report

A 41 year old male engineer suffered from hepatitis A at the age of 19. For over 10 years he had recurrent, mild right upper quadrant abdominal pain. Liver function tests, complete blood count and cholecystography were carried out several times and proved normal.

In February 1982 he was hospitalized due to fatigue and jaundice. There was no history of fever, drug or alcohol ingestion.

Laboratory studies on admission disclosed haemoglobin 10.9 g/dl; mean corpuscular volume 105 fl, total bilirubin 32 µmol/l, direct bilirubin

14 µmol/l, haptoglobin below 50 mg/dl. Bone marrow studies showed marked erythroid hyperplasia. Direct Coomb's test was strongly positive with the specific test to IgG highly positive and to anti-C3 negative. Upper and lower bowel barium studies proved normal.

Abdominal ultrasound and computed tomography, ANA, rheumatoid factor, cold agglutinins and Donath–Landsteiner antibodies were negative. The diagnosis was idiopathic Coombs positive autoimmune haemolytic anaemia and treated with prednisone. There was a haematological response but due to constant infections the patient underwent splenectomy in August 1983. Steroids were then discontinued, but he still suffered occasional bouts of haemolysis.

In April 1989, jaundice appeared again without other symptoms. The haemoglobin was 12.8 g/dl, mean corpuscular volume 110 fl, platelets 670,000, bilirubin 470 µmol/l (normal up to 16), alkaline phosphatase 420 units (normal range up to 110), aspartate transaminase 74 U (normal up to 40) and alanine transaminase 87 U (normal up to 53).

The patient underwent ultrasound examination which revealed some enlargement of the gall-bladder without stones. Endoscopic retrograde cholangiopancreatography disclosed a firm stricture in the common hepatic duct, strictures and dilatation in the intrahepatic ducts (Figure 1). A biliary stent was introduced endoscopically into the common bile duct through the main stricture and the jaundice disappeared gradually.

In order to rule out cholangiocarcinoma, biopsies were taken from the stenotic area but no malignant changes were noted.

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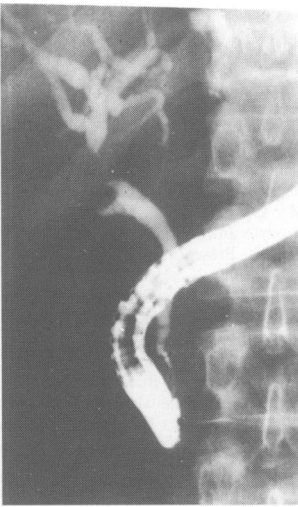


Figure 1 Endoscopic retrograde cholangiopancreatography showing a tight stricture of the common hepatic duct and several small strictures in intrahepatic bile ducts.

Between April and July 1989, the patient occasionally suffered from abdominal pain and from diarrhoea which was not bloody. At barium enema, colitis was suspected in transverse and ascending colon and, at colonoscopy, the mucosa of the caecum and ascending colon was granular with loss of the vascular appearance. No ulcers were seen. Histological examination showed colonic mucosa and submucosa sections with acute and chronic inflammation. The chronic inflammation was seen within the muscularis, but granulomas were not observed. The endoscopic, radiological and histological pictures were compatible with Crohn's colitis. HLA analysis revealed the following phenotypes: A1, A3, B8, Bw58, Cw7, DR3, DR7, DQw2, DRw52, DRw53.

Discussion

This patient illustrates a unique combination of autoimmune haemolytic anaemia, sclerosing cholangitis and Crohn's disease.

There is a recognized association between autoimmune haemolytic anaemia and ulcerative colitis,⁶⁻²³ but not to our knowledge with Crohn's

disease. The prevalence of auto-immune haemolytic anaemia was found to be one in 624 patients,²⁴ and one in 479²⁵ in patients with ulcerative colitis.

In a recent study of 112 consecutive patients with ulcerative colitis in two patients the Coombs test was positive (1.82%). The immunoglobulin was IgG, complement was not found on the erythrocyte. These two patients shared HLA-A1 with the patient presented here, but the other HLA antigens were different.²⁶

The connections between sclerosing cholangitis (PSC) and inflammatory bowel disease is well known. Between 50 and 70% of the PSC patients had ulcerative colitis as well.¹ On the other hand, the prevalence of Crohn's disease in PSC is very low and ranges between 0 and 4% in several series.^{2,3,5} Sclerosing cholangitis can precede the appearance of the inflammatory bowel disease and can appear even after total colectomy.

In a recent study, HLA was analysed in 29 (17 with ulcerative colitis) patients with primary sclerosing cholangitis before liver transplantation.⁴ Fifteen of the 29 patients with PSC (12 of the 17 with colitis) had a common haplotype: A1, B8, Cw7, DRw17, DR3, DQw2, DRw52a. In the remaining 14 patients (five with colitis) there was a loss of at least one of these antigens. However, all the patients were reported to carry the BRw52a subtype, based on the known linkage disequilibrium between the DRw52 allelic variant and DR3. Our patient had in addition the above common haplotype.

The association between PSC and autoimmune haemolytic anaemia is extremely rare and there are only two reported cases.^{27,28} Neither case had inflammatory bowel disease.

In conclusion, we report a patient with three diseases: autoimmune haemolytic anaemia, primary sclerosing cholangitis and Crohn's disease. Several autoimmune diseases, such as chronic active hepatitis, type I diabetes mellitus, myasthenia gravis and thyrotoxicosis, which are associated with the production of autoantibodies, have an increased prevalence of HLA-B8 and DR3.²⁹ Thus, the presence of an increased frequency of HLA-B8, DR3 and DRw52a alleles in PSC patients and also in our patient, and this particular combination of diseases suggests that both genetic and immunological mechanisms may be involved in their aetiology.

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