Alpha-1-antitrypsin associated liver disease in rheumatoid arthritis

L.G. Teh, M.M. Steven and H.A. Capell

Centre for Rheumatic Diseases, 35 Baird Street, Glasgow, UK.

Summary: Two cases of alpha-1-antitrypsin associated liver disease occurring in patients with rheumatoid arthritis are described. Both presented with abnormal liver function tests and the true diagnosis was only apparent after liver biopsy and detailed serological studies. The concurrence of these two conditions is noteworthy because of the postulated role of proteolytic enzymes in producing the characteristic cartilaginous erosions of rheumatoid arthritis.

Introduction

Alpha-1-antitrypsin (A1-AT), a glycoprotein synthesized in the liver, is the major serum inhibitor of a wide range of proteolytic enzymes. Low levels of A1-AT are found in people with the ZZ, MZ and PZ phenotypes and are associated with childhood cirrhosis, emphysema of early adult onset, and more recently cryptogenic cirrhosis in adults (Triger & Milward-Sadler, 1979). Although the low levels of A1-AT associated with these phenotypes could theoretically be implicated in the pathogenesis of rheumatoid arthritis (Cox & Huber, 1976), typing studies have shown conflicting results (Sjöblom & Wolheim, 1977). We wish to report two patients with rheumatoid arthritis and liver diseases associated with the MZ phenotype and low serum levels of A1-AT.

Case reports

Case 1

A 47 year old hypertensive man with a nine year history of sero-positive rheumatoid arthritis was found to have abnormal liver function tests. Bilirubin was 25 $\mu\text{mol/l}$ (normal 3–22), aspartate transaminase (AST) 68 U/l (normal 12–48), alanine aminotransferase (ALT) 66 U/l (normal 8–55), alkaline phosphatase 654 U/l (normal 80–280), gamma glutamyl transpeptidase transferase (GGT) 163 U/l (normal < 36). He admitted to drinking approximately 210 g of alcohol a week. Current drug therapy included

indomethacin, nadolol, prazosin and glyceryl trinitrate. Examination showed nodules and active synovitis of many joints. Spider naevi were noted on the chest and bilateral Dupuytren's contractures, palmar erythema and hepatosplenomegaly were also present. Hepatitis B surface antigen (HBsAg), antinuclear antibody, smooth muscle antibody and anti-mitochondrial antibody were not detected. An isotope liver scan showed hepatosplenomegaly in keeping with parenchymal liver disease and portal hypertension. A liver biopsy showed micronodular cirrhosis with moderate amounts of fat present. There was ballooning of hepatocytes but no Mallory bodies were seen and the pattern was considered a low grade chronic active hepatitis and not related to alcohol consumption. In addition, PAS positive diastase resistant globules were noted in the liver cells (Fig. 1), and immunoperoxidase staining showed these globules to contain A1-AT. The serum level of A1-AT was 1.2 g/l (range 1.0–2.5 g/l). Genetic typing revealed the phenotype MZ.

Case 2

A 62 year old woman with a four year history of seronegative rheumatoid arthritis was found to have elevated alkaline phosphatase (880 U/l) and gamma-glutamyl transferase (68 U/l). She had previously received several non-steroidal anti-inflammatory drugs and was currently on flurbiprofen and had also commenced penicillamine 125 mg daily because of progression of disease. There was no history of previous liver disease, but she admitted to alcohol consumption of approximately 140 g a week over the previous seven years. Examination showed active synovitis in her fingers, shoulders and knees. Hepato

L.G. Teh, M.B., Ch.B.; M.M. Steven, M.B., Ch.B., M.R.C.P.; H.A. Capell, M.B., Ch.B., M.R.C.P.

Correspondence: L.G. Teh.

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Figure 1 A1-AT granules are shown within a number of hepatocytes but predominantly periportal. PAS/diastase $\times 460$.

splenomegaly was present but no other stigmata of chronic liver disease were detected. Serology (as in Case 1) was negative and an isotope liver scan showed hepatomegaly and patchy uptake of isotope with a normal spleen. A liver biopsy showed no evidence of acute or chronic liver disease but numerous PAS

positive, diastase resistant globules were present in the periportal hepatocytes. Immunoperoxidase staining confirmed this to be A1-AT. The serum level of A1-AT was 1.3 g/l with MZ phenotype.

Discussion

Deficiency of the protease inhibitor A1-AT found in the Z phenotypes could theoretically result in destruction of joint cartilage. In fact elevated levels of A1-AT, an acute phase reactant are more often seen. Studies of A1-AT phenotype in arthritis produced conflicting results (Cox & Huber, 1976; Sjöblom & Wolheim, 1977; Geddes *et al.*, 1977) but A1-AT deficiency would not appear to be pathogenetically important in the majority of patients with rheumatoid arthritis. Minor abnormalities of liver function are frequent in rheumatoid arthritis but the prevalence and cause of chronic liver disease in this condition are unknown. One case of rheumatoid arthritis was noted among 61 cases of A1-AT associated liver disease (Hodges *et al.*, 1982). In these cases, serum A1-AT was inappropriately low, characteristic globules were found in the liver and both were MZ phenotype. Although drugs or alcohol consumption could be contributory, the features are more suggestive of A1-AT deficient liver disease.

It is unlikely that A1-AT deficiency is of relevance to the pathogenesis of most cases of rheumatoid arthritis but careful investigation of patients with liver dysfunction is warranted. It is important to distinguish this entity from other causes of chronic liver disease such as chronic active hepatitis, alcoholic liver disease and drug induced conditions with their differing implications for prognosis and treatment.

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