Case reports

Chronic intrahepatic cholestasis due to sarcoidosis

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SUMMARY Two West Indian patients with Kveim-biopsy proven sarcoidosis developed chronic cholestatic liver disease, clinically and biochemically similar to primary biliary cirrhosis. Liver histology revealed multiple granulomas with reduction in bile ducts and, in one patient, progression to biliary cirrhosis. Portal hypertension was present in both patients leading to severe variceal haemorrhage in one. Mitochondrial antibody was negative in both patients and when used in conjunction with the Kveim-Siltzbach skin test serves to differentiate chronic intrahepatic cholestasis secondary to sarcoidosis from primary biliary cirrhosis.

Hepatic involvement in sarcoidosis is common, consisting of multiple hepatic granulomas without clinically overt liver disease. Severe liver disease from sarcoidosis is rare, manifesting as hepatocellular failure and portal hypertension.^{1,2} A distinctly rare form of presentation is that of chronic intrahepatic cholestasis, which may mimic primary biliary cirrhosis. Attention was drawn to this variant of hepatic sarcoidosis by Rudzki *et al*³ who reported its occurrence in five American black males. However, confirmatory Kveim biopsies and cholangiographic data were lacking in that series.

We report chronic intrahepatic cholestasis in two West Indians with chronic sarcoidosis confirmed by Kveim-Siltzbach skin test biopsies and raised levels of serum angiotensin converting enzyme (SACE).

Case reports

CASE 1 A 50-year-old West Indian woman from St Vincent who had been living in the United Kingdom since 1961 was first seen at the Royal Free Hospital in October 1979 with persistent itching and jaundice.

Abnormal liver function tests had first been noted in 1968 when she was investigated for proteinuria.

There were no physical abnormalities at that time, but the alkaline phosphatase and 5'-nucleotidase were reportedly raised. The chest radiograph was normal, but a bone marrow biopsy showed multiple granulomas. The Mantoux test, VDRL, brucella agglutinins, Toxacara complement fixation test, and Casoni test were negative. The record of the Kveim test performed elsewhere at that time was unavailable.

The proteinuria resolved spontaneously, but she then developed iritis which was treated with steroid and atropine drops.

Pruritus began in 1970 and was initially intermittent. Liver disease became overt in 1976 when cholestatic jaundice and worsening pruritis developed. Hepatomegaly was noted and a liver biopsy showed portal inflammation and ductular proliferation, and a cluster of non-caseating granulomas. She was treated with antihistamines only. In May 1977 a laparotomy for persistent symptoms revealed an enlarged, soft liver. Biopsy again showed ductular proliferation but no granulomas were seen on this occasion.

On examination in October 1979 she had mild jaundice and numerous excoriations. There were no xanthelasmas or other cutaneous markers of chronic liver disease. The liver and spleen were both palpable, 4 and 3 cm below the costal margin respectively. Keloid formation was present in scars. There was no ascites. The heart, lungs, and nervous system were normal. Fundoscopy revealed evidence of previous right uveitis.

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Received for publication 1 September 1981

The full blood count was normal; the erythrocyte sedimentation rate was 70 mm/h Westergren (normal <20), the alkaline phosphatase was 71 KA/dl (normal 3–13), total bilirubin 43 μ mol/l (normal 3–17) (2.3 mg/100 ml (0.1–0.9)), aspartate transaminase 39 IU/l (normal 5–15), albumin 32 g/l (normal 36–50), and the prothrombin time was 15 seconds (control 13). Serum cholesterol level was 6.7 mmol/l (normal 3–6.5) (260 mg/100 ml (140–250)). Hepatitis B surface antigen, antinuclear antibody, smooth-muscle antibody, and mitochondrial antibody were negative. The VLDL was positive (titre 1:4), the TPHA positive in a titre of 1:1280 with a positive FTA (ABS). The cerebrospinal fluid was normal. The patient had had yaws in childhood. However, a full course of penicillin was given in 1979. No change in the symptoms, serological or biochemical tests was noted after treatment or over subsequent months.

The IgG was 28.5 g/l (normal 8–18), the IgA and IgM were normal. The SACE level was raised to 83 nmol/min/ml (normal 16–52) (2.22 mg/min/100 ml (0.45–1.39)). A percutaneous liver biopsy (Fig. 1) showed many epithelioid-cell granulomas throughout, both singly and in clusters. Some granulomas contained large multinucleated giant cells and there was a variable degree of central necrosis. A few crystalline, birefringent inclusions were seen. There were irregular fibrous septa in associations with the granulomas, but, although lobular architecture was distorted, cirrhosis was not evident. Bile ducts were markedly reduced in number. Abundant copper-associated protein was seen on orcein staining. Liver copper content was raised at 332 g/g dry liver (normal 5–55) as measured by neutron activation analysis. Biopsy of the keloid scars did not reveal sarcoid infiltration.

A radiograph of the chest was normal but pulmonary function studies showed a mild obstructive and restrictive defect. Serum and urinary calcium and phosphate were normal. A Kveim-Siltzbach skin test biopsy was positive, providing sarcoid histology and indicative of active sarcoidosis. Endoscopy during retrograde pancreatography showed oesophageal varices and demonstrated a normal pancreatic duct. Transhepatic percutaneous cholangiography showed a non-dilated biliary tree with no obstruction. The intrahepatic bile ducts were tortuous and appeared stretched in places; this was compatible with distortion of liver architecture but not with sclerosing cholangitis.

The itching was relieved by cholestyramine and on follow-up there have been no further problems apart from increasing dyspnoea due to lung involvement. This necessitated the use of prednisolone,

Fig. 1 Case 1. Part of a live biopsy showing coalescing granulomas with a multinucleated giant cell (arrow), adjacent to liver parenchyma (below right). Haematoxylin and eosin, $\times 140$.

which has not altered the liver function tests or relieved itching when cholestyramine was temporarily stopped.

CASE 2 A 46-year-old West Indian man, who had been living in the United Kingdom since 1961, was first seen at the Royal Free Hospital in March 1980 with bleeding oesophageal varices.

In 1963 he experienced malaise with cough and a radiograph of the chest showed bilateral hilar lymphadenopathy. The Kveim-Siltzbach test was positive and he was treated with steroids with a good response. He developed jaundice, hepatomegaly, and generalised lymphadenopathy a year later, and liver biopsy showed multiple granulomas consistent with a diagnosis of sarcoidosis. Steroid treatment was continued until 1972 and then withdrawn after improvement in his jaundice. A Kveim biopsy was still positive in 1970. In 1977 he presented with haematemesis and melaena and large oesophageal varices were seen on endoscopy. In 1979 he experienced itching with deepening jaundice, pale stools, and dark urine.

On endoscopic retrograde cholangiography, the intrahepatic biliary tree showed distortion compatible with cirrhosis, with a normal undilated extrahepatic biliary tree. The patient complained of pain in the ankles in February 1980 and was noted to have developed gross clubbing of fingers and toes with typical radiographic changes of hypertrophic pulmonary osteoarthropathy. His limb pain was treated with indomethacin but he returned in March with bleeding varices seen on endoscopy.

On admission, he was jaundiced, with clubbing, excoriations, bilateral parotid enlargement, soft crepitations at both lung bases, a palpable liver 6 cm below the costal margin, a palpable spleen 3 cm below the costal margin, and minimal ascites. The heart was normal, and apart from drowsiness and flapping tremor, the nervous system was normal.

The haemoglobin was 10.2 g/dl, the white count normal and platelet count $80 \times 10^9/l$. The alkaline phosphatase was 38 KA/dl, aspartate transaminase 76 IU/l, albumin 29 g/l, total bilirubin 455 $\mu\text{mol/l}$ (26.8 mg/100 ml (0.1–0.9)). The prothrombin time was 15 seconds (control 13). Serum cholesterol was normal, and serum and urinary calcium and phosphate were normal. The VDRL, hepatitis B surface antigen, antinuclear antibody, smooth-muscle antibody, and mitochondrial antibodies were negative. Immunoglobulins were all normal. The SACE level was raised to 72 nmol/min/ml (1.93 mg/min/100 ml). The radiograph of the chest showed bilateral hilar lymph node enlargement and bilateral pulmonary infiltration. Splenoportography demonstrated a large splenorenal collateral and hepatic and superior mesenteric arteriography revealed arterialisation of the intrahepatic portal venous system with rapid retrograde portal flow. A transhepatic sclerosis of the bleeding varices was successfully achieved. The portogram revealed an extensive portal collateral circulation with large varices. After the sclerosis, the patient made an uneventful recovery with resolution of fluid retention and portosystemic encephalopathy. The cholestasis, however, has persisted. Liver biopsies taken between 1964 and 1980 were reviewed, and showed granulomas, abundant at first and later scanty, and gradual development of cirrhosis of biliary pattern (Fig. 2). Granulomas contained giant cells, some with asteroid bodies, but no necrosis.

Bile ducts were strikingly reduced in numbers, ductular proliferation was a prominent feature, and much copper-associated protein was seen.

Discussion

The clinical spectrum of hepatic involvement in sarcoidosis extends from asymptomatic granulo-

Fig. 2 Case 2. Cirrhosis of biliary type has developed, with ductular proliferation in a perinodular zone of oedematous connective tissue. A small granuloma is seen within a nodule. Haematoxylin and eosin, $\times 70$.

matosis to overt hepatic disease manifested by hepatocellular failure or portal hypertension or combinations of both.¹ Intrahepatic cholestasis has been reported as another rare manifestation of long-standing hepatic sarcoidosis by Rudzki *et al*,³ although confirmatory Kveim biopsies could not be performed in their series of five young American negro males.

The two cases reported here, both of whom had the diagnosis of sarcoidosis confirmed on Kveim biopsy, show many similarities to the cases previously described.³ Both patients are immigrant West Indians, a racial group sharing with American blacks an exceptionally high incidence of sarcoidosis. Systemic granulomatous disease preceded the onset of cholestasis in both patients. This feature, together with the long natural history of the disease (22 and 27 years in cases 1 and 2 respectively, both of whom are still alive, and 10 to 18 years in the series reported by Rudzki *et al*³), serves to differentiate the conditions of chronic intrahepatic cholestasis of sarcoidosis from primary

biliary cirrhosis in which patients who usually present with cholestasis thereafter survive for a mean period of six to 11 years.^{5,6} An additional point of note is the high male:female ratio in cholestasis due to sarcoidosis, which contrasts with the female preponderance of primary biliary cirrhosis.

The most reliable means for differentiating sarcoid cholestasis from primary biliary cirrhosis are the Kveim-Siltzbach skin test and the mitochondrial antibody titre, and both cases in this report conform fully to these criteria needed to distinguish them from primary biliary cirrhosis. Other differentiating features include normal IgM levels (usually raised in primary biliary cirrhosis) and histological features.⁷ In primary biliary cirrhosis eccentric infiltrates of plasma cells, lymphocytes, and eosinophils are seen in relation to damaged bile ducts. Granulomas are common, but are usually few in number and often poorly defined. In sarcoidosis, on the other hand, bile duct damage, even when present, is less conspicuous, while granulomas are abundant and well-formed. The lesions are often clustered, and healing may result in substantial scars. In spite of these differences, the two conditions are occasionally histologically similar, or even indistinguishable. Firm differentiation between sarcoidosis and primary biliary cirrhosis may, on rare occasions, prove to be impossible and both conditions may, apparently, coexist. Both a positive Kveim test and low titres of anti-mitochondrial antibody were reported in one patient with mediastinal lymph node enlargement and chronic granulomatous biliary cirrhosis.⁸ Another patient has been described with intrahepatic cholestasis secondary to a chronic granulomatous biliary cirrhosis histologically typical of sarcoidosis, in whom both the Kveim test and mitochondrial antibodies were negative.⁹ Furthermore, widespread granulomas suggestive of sarcoidosis have been found in the lungs, lymph nodes and spleens of patients with serologically proven primary biliary cirrhosis, and negative Kveim-Siltzbach tests.¹⁰ SACE levels were increased in both our patients, and, although SACE measurement is not a specific test for sarcoidosis, raised levels help to corroborate the diagnosis of this disease.^{11,12}

Previously reported cases of cholestatic jaundice associated with sarcoidosis have also mimicked primary biliary cirrhosis in the development of hypercholesterolaemia and skin xanthomas.^{3,13-15} In contrast, case 1 in this report had only mildly raised serum cholesterol, while in case 2, cholesterol levels were normal. These findings may reflect a relatively early phase of disease in case 1 and a late phase (during which cholesterol levels may fall) in case 2.

Another interesting feature in case 2 was the presence of hypertrophic 'pulmonary' osteoarthropathy. Clubbing and hypertrophic osteoarthropathy are not features of sarcoidosis. However, clubbing may occur in most forms of liver disease, hypertrophic osteoarthropathy being more frequently associated with chronic cholestatic liver disease.¹⁶

The coexistence of portal hypertension with intrahepatic cholestasis of sarcoidosis was established in both cases; varices were present in both and bleeding presented a major problem in case 2. Portal hypertension also developed in 4/5 of the cases reported by Rudzki *et al.*³ Portal hypertension would thus seem to accompany this syndrome frequently, although the converse statement does not hold true.¹ It is also apparent that the natural history of the condition is one of progression to cirrhosis of a 'biliary' pattern (case 2), although portal hypertension may antedate this appearance on liver biopsy as in other forms of biliary disease as in case 1. It thus seems likely that, in chronic intrahepatic cholestasis of sarcoidosis, the same process of granulomatous and subsequent fibrous destruction of bile ducts leads to compression and destruction of portal venous radicles, with early evolution of portal hypertension. An additional contribution towards the development of portal hypertension in sarcoidosis may result from increased portal blood flow secondary to the formation of intrahepatic arteriovenous shunts in the regions of granulomas.¹ This proposal is supported by the findings in case 1 of an arterIALIZED intrahepatic portal system with hepatofugal portal blood flow seen during hepatic arteriography.

Sarcoidosis may produce jaundice by other mechanisms than intrahepatic cholestasis. Increased splenic red blood cell destruction, hepatocellular failure, and obstruction of the extrahepatic bile ducts by granulomatous hepatic hilar lymph nodes have been proposed as possible mechanisms producing jaundice.¹ There was no evidence of excessive haemolysis in either of the two patients, and non-obstructed biliary trees were demonstrated in both by cholangiography. Case 2 had additional features of hepatocellular failure, but these were not sufficient to explain the predominantly cholestatic clinical picture.

Long-term benefit from corticosteroid therapy in hepatic sarcoidosis is difficult to assess because of great variations in both the natural history of the disease and the stage of the disease at the time of instituting therapy. In case 1, no short-term benefit from steroids on liver function tests was evident. Cholestyramine was effective in relieving pruritis, but steroids alone did not affect this symptom. In case 2, overt liver disease appeared to develop

during steroid therapy, although later progression occurred after steroids were stopped. These findings bear out earlier observations^{1,2} that no consistent clinical or pathological effect of corticosteroids is demonstrable in patients with advanced hepatic sarcoidosis.

We thank the Department of Histopathology at Wycombe General Hospital for providing histology specimens and Dr Roger Bird for performing the SACE estimations.

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