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Case report

Rapidly progressive obstructive jaundice due to Congo red negative amyloidosis

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Hepatic involvement in amyloidosis is common but obstructive jaundice is a very rare complication. Occasional patients with AL amyloidosis develop obstructive jaundice as a consequence of severe intrahepatic cholestasis, but review of the English literature reveals only 23 such cases. We report a further case of obstructive jaundice due to amyloidosis in which the diagnosis was particularly difficult to establish because the amyloid material was Congo red negative.

CASE REPORT. A 44-year-old previously healthy plumber was admitted to hospital with a three month history of progressive jaundice, pale stools, dark urine and itch. He complained of malaise and abdominal discomfort and had lost 14 lbs in weight. His alcohol intake was 18 units per week and he had no particular risk factors for viral hepatitis. His only medication was oxytetracycline 250mg twice daily for acne rosacea, which he had taken for five years.

Examination revealed deep jaundice. There were no stigmata of chronic liver disease. The liver was enlarged to 4cm below the costal margin, firm, smooth and non-tender. The kidneys and spleen were not palpable. There was no oedema, no peripheral neuropathy and no evidence of cardiac failure. He did not have macroglossia or bruising. Urinalysis revealed glycosuria but no proteinuria. Serum bilirubin was 315 μmol/l (usual range 3–18), alkaline phosphatase 441 U/l (35–120), gamma glutamyl transferase 1025 U/l (7–46) and aspartate transaminase initially 84 U/l (10–40). The prothrombin time was prolonged to 25·5 seconds (13–17), and serum creatinine was 151 μmol/l (40–110). Routine screening tests including plasma glucose were normal. The sedimentation rate was 54mm/hour, full blood count was normal and antinuclear antibody, anti-smooth muscle or anti-mitochondrial antibodies were not detected in serum. Serological tests for hepatitis A and B, cytomegalovirus, Epstein-Barr virus, leptospira and toxoplasma were all negative. Serum IgG was raised,

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19·9 g/l (5–16) but there was no reduction in the levels of the other immunoglobulins to suggest an immune paresis. An IgG paraprotein of 15 g/l was identified on electrophoresis of stored serum. Chest X-ray and electrocardiogram were within normal limits.

Ultrasound scan failed to identify any abnormality except thickening of the gallbladder. Computerised tomography confirmed hepatomegaly with minimal reduction in liver attenuation values; the spleen and pancreas appeared normal. After correction of the prothrombin time with fresh frozen plasma, percutaneous transhepatic cholangiography was attempted to exclude biliary obstruction. The procedure was technically difficult and three passes were made before the biliary tree was entered. There was no biliary dilatation but filling of the duodenum could not be demonstrated and an ampullary lesion was suspected. The procedure was complicated by abdominal pain and a fall in haemoglobin of 5 g/dl. Endoscopic retrograde cannulation of the pancreatic duct was therefore attempted but was unsuccessful due to distortion of the duodenum by extrinsic compression. At laparotomy the liver was found to be enlarged, but there was no evidence of extrahepatic biliary obstruction. A retroperitoneal haematoma was evacuated and a wedge liver biopsy performed. Postoperatively acute renal failure developed, characterised by oliguria and rapidly rising serum creatinine to greater than 500 μmol/l. Haemodialysis was complicated by hypotension. Serum bilirubin reached 600 μmol/l. The patient lost consciousness and required artificial ventilation but despite these measures died 32 days after admission to hospital.

Light microscopy of the operative liver biopsy (Fig 1) confirmed the presence of marked cholestasis, with slight bile duct proliferation. The hepatic architecture

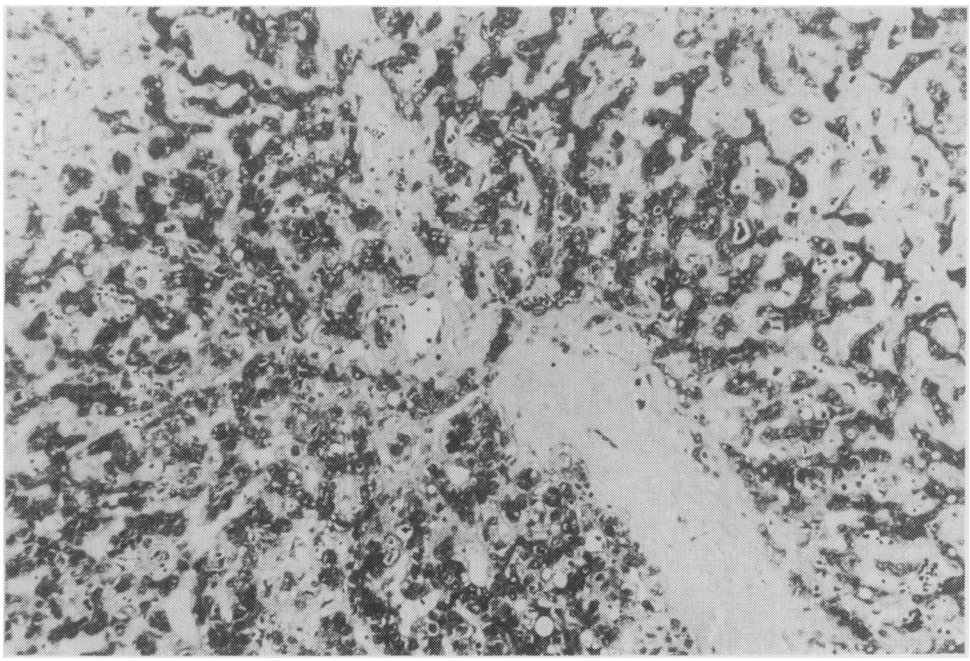

Fig 1. Liver. The architecture is disrupted and the hepatocytes compressed by amorphous material. (Masson trichrome × 100).

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was grossly distorted by bands of fibrous tissue but there was no regenerative activity to establish a diagnosis of cirrhosis. The sinusoids and hepatocytes were compressed and the appearances were suggestive of amyloid, but Congo red staining was negative on several occasions. It was felt that extrahepatic biliary obstruction or sclerosing cholangitis could not definitely be excluded on the basis of this wedge biopsy.

At the subsequent necropsy the body was deeply jaundiced. The liver was enlarged, weighing 3150 g. The liver capsule was intact, apart from the sutured biopsy site. It had a finely nodular external and cut surface. The extrahepatic biliary tree was patent, with no evidence of obstruction or dilatation. The pancreas appeared macroscopically normal, with no evidence of tumour. The ampulla was normal. The remains of a retroperitoneal haematoma was present behind the duodenum in close relation to the lower end of the common bile duct. No definite bleeding point could be identified and there was no perforation of the common bile duct or duodenum. The spleen was enlarged, weighing 319 g. It had a slightly firm consistency on cut section.

Histologically the postmortem liver was similar to the biopsy. Sections from both were stained repeatedly with Congo red, Thioflavine T and Sirius red but results were consistently negative. Immunoperoxidase staining of liver for AA amyloid was also negative. Stains for kappa and lambda light chains showed no evidence of light chain restriction. Electron microscopy of the biopsy and postmortem liver showed similar features (Fig 2). There was widespread deposition of extracellular fibrillar material in the perisinusoidal space of Disse and between hepatocytes. This material was composed of aggregates of non-branching fibrils, 9 nm in diameter in a felt-like meshwork. The appearances supported a diagnosis of Congo red negative amyloidosis.

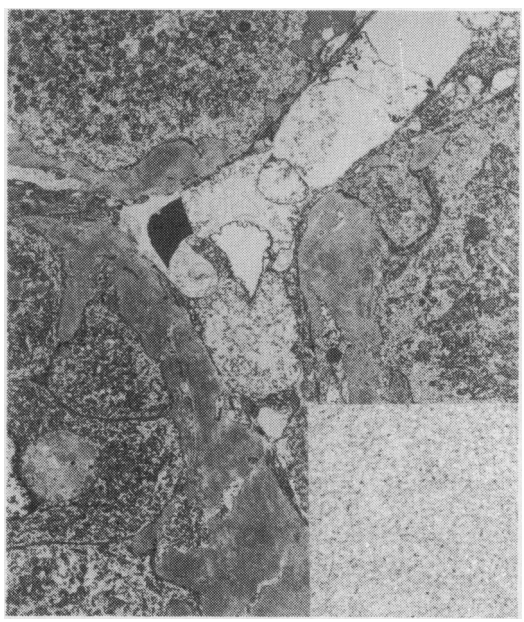

Fig 2. Electron micrograph of liver showing amyloid material lining the space of Disse. (Uranyl acetate, lead citrate × 3500).
Inset: High power of the amyloid fibrils (× 10^5).

Histological examination showed infiltration of multiple organs with amyloid material. The heart, thyroid gland, adrenal glands, pancreas, spleen and kidneys were all involved. The appearances of the kidneys on light microscopy were typical (Fig 3). Amyloid material was noted around renal arterioles, in the interstitium and to a lesser extent, focal glomerular infiltration. The renal tubules showed a significant degree of flattening of the tubular epithelium with tubular dilatation indicative of acute tubular necrosis. In the thyroid gland there was striking separation of the follicles by the amyloid material. Immunoperoxidase

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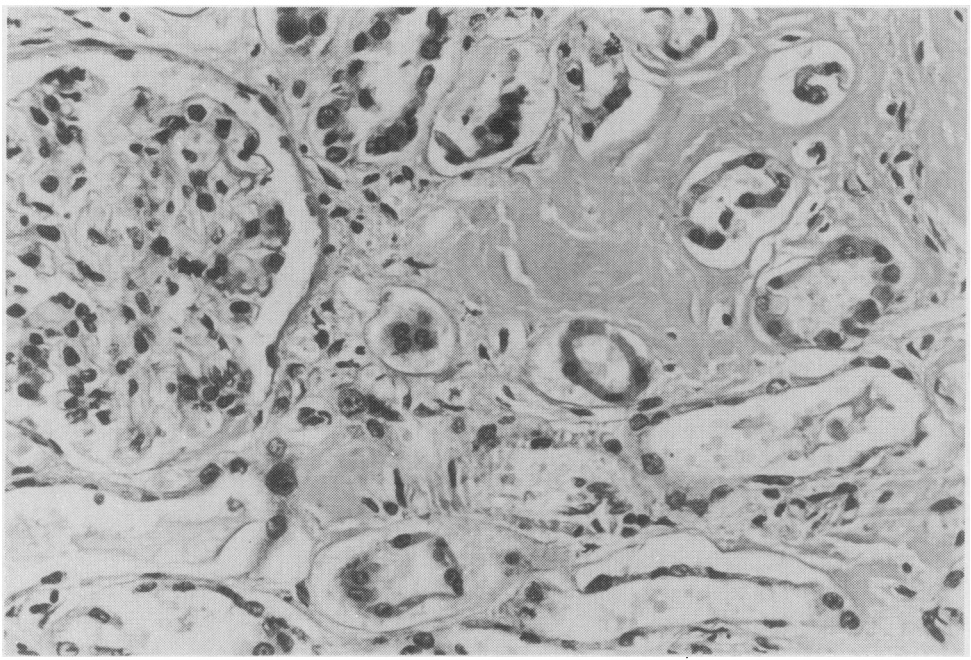

Fig 3. Kidney. There is interstitial deposition of amorphous material which electron microscopic examination confirmed to be amyloid. The appearances in several other organs were similar (see text). (Haematoxylin and eosin × 250).

staining for calcitonin was negative as were the conventional light microscopical stains for amyloid. Involvement of the adrenal glands was confined to the medulla with compression atrophy of the medullary parenchymal cells and a notable sparing of the adrenal cortex. Within the pancreas the ducts and blood vessels were infiltrated by same material. The splenic arterioles were involved along with diffuse infiltration of the splenic red pulp. The heart showed diffuse interstitial infiltration.

DISCUSSION

Although the liver is frequently involved in amyloidosis, obstructive jaundice due to severe intrahepatic cholestasis is a very rare complication. In this case, the cause of the jaundice only became apparent when electron microscopy of liver tissue revealed the ultrastructural appearance of amyloidosis. Oxytetracycline is recognised to cause microvesicular fatty metamorphosis. This complication usually occurs within a few days of starting large doses administered parenterally.[1] It is unlikely that oxytetracycline was the cause of liver dysfunction and withdrawal of the drug on admission to hospital was not associated with any improvement. There was no evidence at autopsy of sclerosing cholangitis, cholangiocarcinoma or drug-induced hepatic injury which had earlier been considered in the differential diagnosis.

There was no clinical or pathological evidence of chronic disease which might have given rise to secondary amyloidosis, and the absence of clinical features of multiple myeloma and the presence of an IgG paraprotein indicate that this was

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a case of primary or immunocyte-related (AL) amyloidosis.[2] In these cases the amyloid protein is derived from light chain fragments of immunoglobulins. Primary AL amyloidosis involves the liver in 65–70% of cases,[3] but significant liver dysfunction is very rare and death is usually due to renal insufficiency, cardiac failure or sudden cardiac death.

A recognised subgroup of patients with AL amyloidosis do develop severe intrahepatic cholestasis. Review of the literature reveals 23 previous cases.[4,5] Including this case, there is a majority of males (15:9) and the age range is 29–80 years. The serum bilirubin at presentation was in excess of 300 μmol/l in only six out of the twenty-four cases and a monoclonal paraprotein band was detected in the serum in eight of twelve cases where it was sought. Multiple myeloma was diagnosed in only one case[6] and in one case the M band was due to free lambda light chains. Death was due to renal failure in seventeen of twenty cases where the cause was recorded. Median survival was only 12 weeks (range 3–52 weeks). The cause of cholestasis in this subgroup is unclear. It has been postulated that the pattern of amyloid deposition in these cases interferes with the passage of bile from canaliculi and/or small intrahepatic bile ducts to septal bile ducts.[7] The microscopic findings in our case would support this hypothesis.

This case also illustrates the difficulty which has frequently been encountered in diagnosis. Ultrasound and CT scans are typically non-diagnostic. The negative staining with Congo red and other amyloid stains increased our difficulty. Melato et al noted variable affinity for Congo red in their series of cases of hepatic amyloidosis.[8] We confirm that conventional stains for amyloid may be falsely negative and that electron microscopy is a more sensitive diagnostic technique. The presence of a paraprotein band in a jaundiced patient with no stigmata of chronic liver disease and no radiological evidence of biliary tract obstruction should raise the possibility of hepatic AL amyloidosis. Percutaneous liver biopsy is the procedure of choice to obtain a histological diagnosis.[9] There is some added risk of bleeding complications with invasive procedures, as illustrated by this case, even when the prothrombin time has been corrected, probably as a result of involvement of blood vessels by amyloid.

There is no established effective therapy for primary hepatic amyloidosis. Several authors have reported regression of hepatomegaly following treatment with a combination of melphalan and prednisone.[6, 10, 11, 12, 13] In one case amyloid was present in a liver biopsy specimen before treatment and absent after treatment.[10] Colchicine and dimethylsulphoxide have also been tried[14] but no treatment has been reported to be of benefit in cases of severe cholestasis.[5] The prognosis in such cases is very poor.

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REFERENCES

1. Sherlock S. Diseases of the liver and biliary system, 8th edition. Oxford: Blackwell Scientific Publications, 1989: 488-91.
2. Kyle RA, Greipp PR. Amyloidosis (AL): clinical and laboratory features in 229 cases. *Mayo Clin Proc* 1983; **58**: 665-83.

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3. Levy M, Polliack A, Lender M, Eliakim M. The liver in amyloidosis. *Digestion* 1974; **10**: 40-51.
4. Skander MP, Harry DS, Lee FL. Severe intrahepatic cholestasis and rapidly progressive renal failure in a patient with immunocyte-related amyloidosis. *J Clin Gastroenterol* 1987; **9**: 219-22.
5. Konikoff F, Mor C, Stern S, Shaklai M, Halevy J, Theodor E. Cholestasis and liver failure with lambda-AL amyloidosis. *Gut* 1987; **28**: 903-6.
6. Calomeni JA, Smith JR. Obstructive jaundice from hepatic amyloidosis in a patient with multiple myeloma. *Am J Haematol* 1985; **19**: 277-9.
7. Rubinow A, Koff RS, Cohen AS. Severe intrahepatic cholestasis in primary amyloidosis. *Am J Med* 1978; **64**: 937-46.
8. Melato M, Manconi R, Magris D, Morassi P, Benussi D, Tiribelli C. Different morphologic aspects and clinical features in massive hepatic amyloidosis. *Digestion* 1984; **29**: 138-45.
9. Gertz MA, Kyle RA. Hepatic amyloidosis (primary AL, immunoglobulin light chain): the natural history in 80 patients. *Am J Med* 1988; **85**: 73-9.
10. Gertz MA, Kyle RA. Response of primary hepatic amyloidosis to melphalan and prednisone: a case report and review of the literature. *Mayo Clin Proc* 1986; **61**: 218-23.
11. Horne MK. Improvement in amyloidosis (letter). *Ann Intern Med* 1975; **83**: 281-2.
12. Bradstock K, Clancy R, Uther J, Basten A, Richards J. The successful treatment of primary amyloidosis with intermittent chemotherapy. *Aust NZ J Med* 1978; **8**: 176-9.
13. Farhangi M, Thakur VM, Durham JB. Objective response in amyloidosis treated with intermittent chemotherapy. *South Med J* 1984; **77**: 755-7.
14. Scheinberg MA, Pernambuco JC, Benson MD. DMSO and colchicine therapy in amyloid disease. *Ann Rheum Dis* 1984; **43**: 421-3.

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