Gut, 1991, 32, 715–717

Azathioprine induced liver disease: nodular regenerative hyperplasia of the liver and perivenous fibrosis in a patient treated for multiple sclerosis

F Mion, B Napoleon, F Berger, M Chevallier, S Bonvoisin, L Descos

Abstract

Azathioprine hepatotoxicity has been described mainly in renal transplant recipients. Most reported cases are related to lesions of the venous system of the liver: peliosis hepatis, veno-occlusive disease of the liver, perisinusoidal fibrosis, and nodular regenerative hyperplasia of the liver. The most common clinical manifestation of these hepatic vascular lesions is portal hypertension. We present a case of nodular regenerative hyperplasia and perivenous fibrosis in a patient receiving azathioprine for multiple sclerosis. Histological abnormalities were similar to those described in renal transplant patients, and azathioprine was the only potential hepatotoxic agent present.

The hepatic toxicity of azathioprine, a widely used immunosuppressive drug, was first reported in an animal model[1] and has been reported after renal transplantation in man.[2] Cholestatic hepatitis,[3 4] peliosis hepatis,[5] hepatic sinusoidal dilatation,[6] veno-occlusive disease of the liver,[7 8] perisinusoidal and portal fibrosis,[9] and nodular regenerative hyperplasia of the liver[10 11] have been the major reported problems. Most of the cases were described in renal transplant patients. We now report a patient with nodular regenerative hyperplasia associated with perivenous fibrosis that developed after azathioprine treatment for multiple sclerosis.

Case report

A 37 year old white man was admitted to hospital in July 1988 for a first episode of haematemesis. He had been followed since 1980 for multiple sclerosis, the primary manifestation of which was a severe cerebellar syndrome. He had been treated since 1981 with a daily dose of azathioprine of 100 to 150 mg. Cyclophosphamide treatment, 500 mg administered intravenously every other month, was added in 1986. He received 1 g of methylprednisolone intravenously in 1982, 1985, and June 1988 because of disease relapses.

There was no history of alcohol abuse, hepatic disease, previous surgery, or blood transfusions. There was no sign of rheumatoid arthritis or other autoimmune disease. On physical examination, hepatomegaly and splenomegaly were the only noted abnormalities. Apart from anaemia caused by the bleeding and moderate thrombocytopenia (113 g/l, normal 150–300 g/l) other laboratory tests, including serum transaminases, alkaline phosphatase, bilirubin, prothrombin time, serum albumin, serum protein electrophoresis, and immunoelectrophoresis were within the normal range. Serum concentrations of ferritin, copper, ceruloplasmin, α_1 antitrypsin and α-fetoprotein were within the normal limits. Hepatitis B surface antigen (HBs Ag) and HBs and HBc antibodies were absent. Cytomegalovirus, Epstein-Barr, and herpes virus serologies were negative. Antimitochondrial, antinuclear, antismooth muscle, and antiendoplasmic reticulum antibodies were absent. Rheumatoid factor was negative.

The source of the bleeding, shown by upper gastrointestinal endoscopy, was oesophageal varices and this was initially controlled by conservative measures. Abdominal ultrasonography confirmed homogeneous hepatosplenomegaly. Portal and suprahepatic veins were well visualised. Portal vein patency was assessed by ultrasonographic pulsed doppler. A transparietal hepatic biopsy specimen was taken for histological examination. Azathioprine treatment was stopped. Despite the administration of propranolol, 120 mg per day, variceal bleeding recurred in December 1988. Injection sclerotherapy of the oesophageal varices was begun. Because of the patient's poor tolerance of endoscopic sclerotherapy, transection and devascularisation of the oesophagus was performed in March 1989. A hepatic wedge biopsy specimen was taken at that time. Since then the patient has been asymptomatic and only one session of injection sclerotherapy was needed to eradicate the remaining varices.

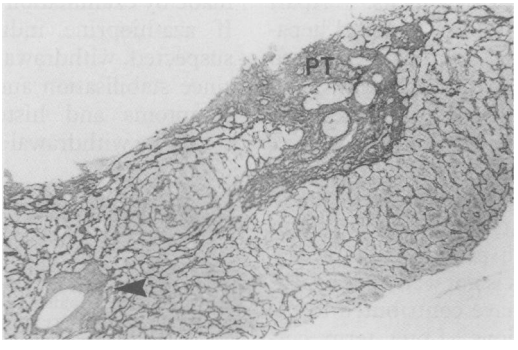

Figure 1: Needle biopsy specimen showing fibrosis around an hepatic (centrolobular) vein (arrow), in a portal tract (PT) and within the Disse space. No parenchymal necrosis or inflammatory infiltrate is seen (reticulin stain, original magnification ×25).

Pathology

The first hepatic needle biopsy specimen showed extensive perivascular fibrosis (Fig 1) that was most prominent around the hepatic veins and

Department of Gastroenterology, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France
F Mion
B Napoleon
S Bonvoisin
L Descos

Department of Pathology, Hôpital E Herriot, Lyon, France
F Berger

Department of Pathology, Institut Pasteur de Lyon, Lyon, France
M Chevallier

Correspondence to:
Professor L Descos, Centre Hospitalier Lyon-Sud, 69310 Pierre-Bénite, France

Accepted for publication 3 August 1990

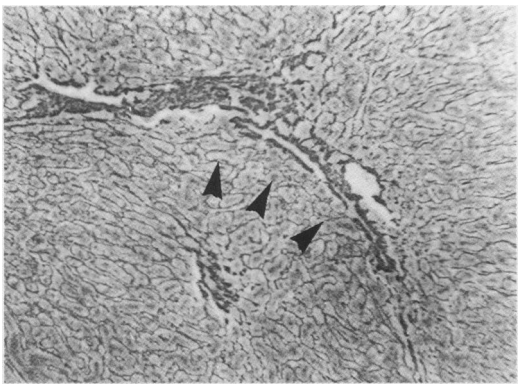

Figure 2: Open wedge biopsy specimen showing a typical aspect of nodular regenerative hyperplasia of the liver: the normal lobular architecture of the liver has disappeared and there is formation of large nodules of hepatocytes surrounded by reticulin fibres (arrows); (reticulin stain, original magnification ×10).

within the Disse space but was also seen in the periportal areas. There was no necrosis or inflammatory cell infiltration in the portal tracts or in the parenchyma. Bile ducts were intact. An immunofluorescence immunoperoxidase assay for the detection of HBs Ag and HBc Ag was negative. At laparotomy, the liver was enlarged and its surface was smooth, without visible nodulation. The liver was macroscopically fibrotic, without visible nodules. Microscopically, the wedge biopsy specimen showed nodules of normal hepatocytes surrounded by reticulin fibres which were detected by the appropriate stain (Fig 2). The absence of parenchymal necrosis, inflammatory infiltrate, and alteration of bile ducts were confirmed in this biopsy specimen. These abnormalities were interpreted as typical of nodular regenerative hyperplasia of the liver with accompanying perivenous fibrosis.

A second hepatic needle biopsy specimen obtained 19 months after the first one (February 1990) showed the persistence of the perivenous fibrosis together with the nodules of hepatocytes circled by reticulin fibres. No signs of inflammation or necrosis were seen.

Discussion

Hepatic toxicity is not a common side effect of azathioprine. Even after long term treatment, most series report a rate of hepatic abnormalities of between 3 and 10%, which are usually limited to abnormal liver function tests and minor changes seen on liver biopsy specimens.[12-15] Apart from a few cases of azathioprine induced hepatitis,[3 4] most severe liver injuries attributed to azathioprine occurred in renal transplant patients. Most hepatic lesions described are vascular, such as peliosis hepatis, veno-occlusive disease, perisinusoidal fibrosis, hepatoportal sclerosis, and nodular regenerative hyperplasia. The main clinical manifestation of these lesions is portal hypertension. The primary role of azathioprine in all these cases is not well established, since other factors may have contributed to the pathogenesis of the lesions. Long term corticosteroid treatment,[16] cytomegalovirus, or other viral infections[14] have been suggested as possible aetiological agents for these hepatic vascular changes. Our observation is of interest because it implicates azathioprine as the most probable aetiologic agent. Corticosteroid treatment had been intermittent and of short duration and cyclophosphamide has not been reported to cause vascular hepatic lesions,[17] although the role of these two drugs cannot be totally dismissed. A viral aetiology is doubtful in the absence of clinical symptoms, lack of histological evidence, and negative serological studies. Autoimmune diseases of the liver are also unlikely in the absence of autoantibodies or inflammatory infiltrate seen on the biopsy specimens. The hepatic histology of our patient is interesting because it brings together several features that can be related to a vascular lesion of the liver. The perivenous fibrosis noted here is present in all cases of azathioprine induced vascular lesions of the liver. The amount of fibrosis is variable, ranging from minute quantities visible only by electron microscopy[9] to extensive fibrosis around hepatic veins[5] or portal tracts.[8] Nodular regenerative hyperplasia is a lesion that has been attributed to azathioprine[11] and the role of perivenous fibrosis in its development has been discussed. We agree with the hypothesis of Wanless *et al*[18] and Haboubi *et al*[10] that azathioprine may damage endothelial cells lining the hepatic sinusoids, small hepatic, and portal veins, leading to extravasion of blood and development of fibrosis around the venous tracts. This fibrosis could cause portal hypertension, parenchymal hypoxia, and proliferative response of hepatocytes and result in the formation of nodules of hyperplastic hepatocytes typical of nodular regenerative hyperplasia. These nodules may also play a role in the development of portal hypertension by obstructing normal portal flow. In patients without renal transplants, a few reports describe azathioprine-induced hepatitis[19 20] but there is only one other case report of primarily vascular hepatic lesions caused by azathioprine. A patient receiving azathioprine for ocular panuveitis was found to have veno-occlusive disease of the liver.[7] Our report highlights the fact that these critical hepatic vascular complications of azathioprine treatment can indeed occur in patients other than those who have undergone renal transplantation. Unfortunately, hepatosplenomegaly is often the only symptom of underlying liver disease and liver function tests are usually normal. Therefore, the diagnosis is often made only after portal hypertension has developed. The diagnosis can only be made by examination of liver biopsy specimens. If azathioprine induced vascular disease is suspected, withdrawal of the drug is mandatory, since stabilisation and improvement of clinical symptoms and histologic lesions after azathioprine withdrawal has been reported.[10]

1 Haxhe JJ, Alexander GPJ, Kestens PJ. The effect of Imuran and Azaserine on liver function tests in the dog. *Arch Intern Pharmacodyn* 1967; **168**: 366–72.
2 Sopko J, Anuras S. Liver disease in renal transplant recipients. *Am J Med* 1978 **64**: 139–46.
3 De Pinho RA, Goldberg CS, Lefkowitch JH. Azathioprine and the liver. Evidence favoring idiosyncratic, mixed cholestatic-hepatocellular injury in humans. *Gastroenterology* 1984; **86**: 162–5.
4 Sparberg M, Simon N, Del Greco F. Intrahepatic cholestasis due to azathioprine. *Gastroenterology* 1969; **57**: 439–41.
5 Degott C, Rueff B, Kreis H, Duboust A, Potet F, Benhamou JP. Peliosis hepatis in recipients of renal transplants. *Gut* 1978; **19**: 748–53.

6 Gerlag PGG, van Hooff JP. Hepatic sinusoidal dilatation with portal hypertension during azathioprine treatment: a cause of chronic liver disease after kidney transplantation. *Transplant Proc* 1987; **29**: 3699–703.

7 Weitz H, Gokel JM, Loesche K, Possinger K, Eder M. Veno-occlusive disease of the liver in patients receiving immunosuppressive therapy. *Virchows Arch [A]* 1982; **395**: 245–56.

8 Katzka DA, Saul SH, Jorkasky D, Sigal H, Reynolds JC, Soloway RD. Azathioprine and hepatic veno-occlusive disease in renal transplanted patients. *Gastroenterology* 1986; **90**: 446–54.

9 Nataf C, Feldmann G, Lebrec D, *et al.* Idiopathic portal hypertension (perisinusoidal fibrosis) after renal transplantation. *Gut* 1979; **20**: 531–7.

10 Haboubi NY, Ali HH, Whitwell HL, Ackrill P. Role of endothelial cell injury in the spectrum of azathioprine-induced liver disease after renal transplant: light microscopy and ultrastructural observations. *Am J Gastroenterol* 1988; **83**: 256–61.

11 Jones MC, Best PV, Catto GRD. Is nodular regenerative hyperplasia of the liver associated with azathioprine therapy after renal transplantation? *Nephrol Dial Transplant* 1988; **3**: 331–3.

12 du Vivier A, Munro DD, Verbov J. Treatment of psoriasis with azathioprine. *BMJ* 1974: i: 49–51.

13 Kissel JT, Levy RJ, Mendell JR, Griggs RC. Azathioprine toxicity in neuromuscular disease. *Neurology* 1986; **36**: 35–9.

14 Mourad G, Bories P, Berthelemy C, Barneon G, Michel H, Mion C. Peliosis hepatis and nodular regenerative hyperplasia of the liver in renal transplants. Is cytomegalovirus the cause of this severe disease? *Transplant Proc* 1987; **19**: 3697–8.

15 Whisnant JK, Pelkey J. Rheumatoid arthritis: treatment with azathioprine (Imuran). Clinical side-effects and laboratory abnormalities. *Ann Rheum Dis* 1982; **41** (suppl 1): 44–7.

16 Zafrani ES, Pinaudeau Y, Dhumeaux D. Drug-induced vascular lesions of the liver. *Arch Intern Med* 1983; **143**: 495–502.

17 Menard DB, Gisselbrecht C, Marty M, Reyes F, Dhumeaux D. Antineoplastic agents and the liver. *Gastroenterology* 1980; **78**: 142–64.

18 Wanless IR, Godwin TA, Allen F, Feder A. Nodular regenerative hyperplasia of the liver in hematologic disorders: a possible response to obliterative portal venopathy. A morphometric study of 9 cases with an hypothesis on the pathogenesis. *Medicine* 1980; **59**: 367–79.

19 Zarday Z, Veith FJ, Gliedman ML, Soberman R. Irreversible liver damage after azathioprine. *JAMA* 1972; **222**: 690–1.

20 Barrowman JA, Kutty PK, Ra MU, Huang SN. Sclerosing hepatitis and azathioprine. *Dig Dis Sci* 1986; **31**: 221.