‘Relapse’ of chronic active hepatitis – not always what it seems

AF Muller, PJ Toghil, P Smith

Summary

Immune chronic active hepatitis is a disease notorious for its unpredictability. In a patient with chronic hepatitis who has already suffered relapses a search for a second cause of jaundice is not usually necessary. This report emphasises the essential role of liver biopsy.

Keywords: hepatitis, liver biopsy, jaundice, diflunisal

A 48-year-old woman became jaundiced initially in November 1978 when a diagnosis of infective hepatitis was made. Six months later she was still mildly jaundiced with abnormal liver function tests and a liver biopsy showed chronic active hepatitis without cirrhosis. She was started on steroids but was reluctant to continue because of Cushingoid features. Azathioprine 125 mg daily was introduced and continued and the steroids were withdrawn.

In 1981 when transferred to our care she was well with normal liver function tests (figure 1). The hepatitis B surface antigen (HbsAg) was negative. A liver biopsy showed mild chronic persistent hepatitis with no active inflammation. Auto-antibody screen showed smooth muscle antibody IgG class present at a titre of 800, antinuclear antibody IgM class titre of 50 and IgG class titre of 25. In 1981 azathioprine was stopped, but nine months later the liver function tests had deteriorated and further liver biopsy showed chronic acute hepatitis with fibrous bridging. Azathioprine was restarted at a dosage of 100 mg/day with a gratifying improvement in the liver function tests and liver biopsy appearances. In 1985, a further attempt was made to withdraw immunosuppressive therapy; this resulted in worsening of her condition, including joint pains, which necessitated restarting azathioprine. The deterioration in her clinical status was matched by changes of chronic aggressive hepatitis on liver biopsy. A further liver biopsy in 1989 to assess progress, whilst she was well clinically with normal biochemical tests, showed inactive hepatitis with intact limiting plates (figure 2).

Early in 1992, whilst on azathioprine, she became ill again with malaise, anorexia and mild jaundice. Liver function tests showed a bilirubin of 50 $\mu\text{mol/l}$ ($n < 17 \mu\text{mol/l}$), alkaline phosphatase 262 U/l (40–120 U/l), alanine transaminase 668 U/l ($< 50 \text{ U/l}$) and gamma glutamyl transferase 2005 U/l ($< 70 \text{ U/l}$). Testing for hepatitis C by anti-

HCV, anti-GOR¹ (an autoantibody found in hepatitis C infection which reflects HCV specific autoimmunity and which reacts against a fusion protein expressed by a cDNA clone {GOR 47-1} derived from a chimpanzee infected with non A, non B hepatitis) and polymerase chain reaction were negative. The liver was shown to be small on ultrasound. There were no gallstones or dilated bile ducts. Anticipating a further relapse of her hepatitis, another liver biopsy was performed under ultrasound control. Surprisingly this showed intrahepatic cholestasis, with no evidence of large duct obstruction, favouring a drug reaction; there was no evidence of relapse of the hepatitis (figure 3). She had not previously admitted to taking any unusual therapy, but further questioning disclosed the fact that she had been taking diflunisal (Dolobid) 250 mg bid for a month for her painful joints before the onset of this recent illness. With-

Figure 1 The clinical course of the illness indicating dates of liver biopsies. ALP=alkaline phosphatase; ALT=alanine transaminase; GGT= γ -glutamyl transferase

Departments of
Medicine and
Histopathology,
University Hospital,
Nottingham,
NG7 2UH, UK
AF Muller
PJ Toghil
P Smith

Correspondence to
Dr AF Muller, Consultant
Gastroenterologist, The
Kent & Canterbury
Hospital, Canterbury,
Kent CT1 3NG, UK

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Figure 2 Liver biopsy showing inactive chronic hepatitis with intact limiting plate

Figure 3 Liver biopsy showing (A) prominent intra-hepatic cholestasis and (B) no evidence of large duct obstruction in the portal tract and an intact limiting plate

Learning or summary points
<ul style="list-style-type: none"> • patients often fail to report, or deny, that they are taking medicines • diflunisal and other NSAIDs may cause abnormalities of liver function tests • in patients with chronic liver disease, such changes may mistakenly be thought to be due to relapse of the disease and be treated inappropriately • confirmation of the cause of deterioration in liver function tests in patients with chronic liver disease may need to be made by liver biopsy

drawal of diflunisal without any other change in therapy improved her general condition, though the joint pains remained. The liver function tests reverted to normal.

Discussion

There is no doubt that this patient's most recent episode of jaundice was drug induced. As with other nonsteroidal anti-inflammatory drugs (NSAIDs),² diflunisal is known to cause cholestatic jaundice.³ The liver biopsy changes were characteristic and the response to withdrawal of therapy appropriate. In clinical trials of NSAIDs, significant rises of liver enzymes by three times the upper limit of normal were detected in less than 1% and the data sheets advise caution in treating patients with known liver disease.⁴

The management of our patient's chronic liver disease is of interest because although initially managed with prednisolone and then azathioprine, further relapses were managed using azathioprine alone, because of the patient's wish not to be treated with steroids. The effectiveness of prednisolone either alone or in combination with azathioprine has been shown to improve liver biochemistry and

reduce mortality in controlled trials reported more than 20 years ago,^{5,6} whereas patients treated with azathioprine were shown to deteriorate. Our patients response to azathioprine was therefore unusual but suggests that some patients respond to this treatment alone.

In a patient with deteriorating liver function tests, an ultrasound of the liver is helpful before liver biopsy is performed, to exclude extra-hepatic causes such as choledocholithiasis. As previous ultrasonography in this patient had revealed a small shrunken liver, the liver biopsy was also performed under ultrasound guidance.

The management of immune chronic active hepatitis is notoriously difficult since the response to immunosuppressants is unpredictable and monitoring with serial liver function tests is often inadequate. Liver biopsies every one to two years offer a more reliable method of assessing disease activity. With this patient the initial assumption was that the worsening of her liver function was due to deterioration in her basic liver disease. At first, concurrent NSAID therapy was not admitted and without liver biopsy, a correct diagnosis could not have been established.

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4 ABPI Data Sheet Compendium 1993–4. London: Data-pharm Publications Ltd, p 1022.

5 Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. *Lancet* 1973; **I**: 735–7.

6 Soloway RD, Summerskill WHJ, Baggenstoss AH, *et al.* Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatment and early prognosis. *Gastroenterology* 1972; **63**: 820–33.