CASE REPORT

Autoimmune hepatitis unmasked by nimesulide

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SUMMARY

A 49-year-old woman presented at the emergency department, with acute hepatic failure, 2 weeks after taking nimesulide. Presenting with a MELD score of 25.0, the patient was transferred to a specialised liver transplant unit, with the probable diagnosis of toxic hepatitis. After a clinical improvement with supportive care and acetylcysteine, a liver biopsy was executed. The histology revealed micronodular cirrhosis associated with acute hepatitis, with features suggestive of autoimmune hepatitis. The patient was then started on azathioprine 50 mg/day and prednisolone 30 mg/day, and tapering of prednisolone was carried out in the following months. Twenty eight months after treatment, another liver biopsy was performed, showing almost full remission of the disease, with only mild fibrosis and no significant inflammatory infiltrate.

BACKGROUND

Autoimmune hepatitis (AIH) is a disease of unknown cause, characterised by chronic hepatic inflammation, presence of autoantibodies (antinuclear antibody (ANA), antismooth muscle antibody (SMA) and liver kidney microsomal (LKM) antibody), a female preponderance and elevated serum γ globulins, especially IgG.¹ AIH starts with continuous hepatocellular inflammation and necrosis and tends to progress to cirrhosis.

AIH can have an insidious presentation or it can be an example of an acute-on-chronic liver disease, presenting as subacute or even fulminant liver failure.^{2–5} Clinical features of AIH may become overt after usage of various medications such as nitrofurantoin, minocycline, interferon and tumour necrosis factor α blocking agents.^{6–8} Nimesulide, a non-steroidal anti-inflammatory drug, is referred to in various published reports as a hepatotoxic drug,^{6 9 10} but its association with autoimmunity or with the triggering of AIH symptoms, as in this case, is rare.

In the past years, a few reports about the reversibility of cirrhosis have been published, contradicting the earlier idea that it was a final stage in liver disease.¹¹ Our clinical case reports an unusual presentation of AIH and its successful treatment, with almost total reversibility of cirrhosis after 2 years.

CASE PRESENTATION

A 49-year-old woman presented to the emergency department, with worsening jaundice. She had been prescribed with 100 mg of nimesulide two times a day for 3 days, for an oral pain, 2 weeks before admission. Following drug intake, the patient started having soft stools three times a day, without blood or mucus, accompanied by dark

urine. One week later, she developed new-onset jaundice.

The patient's medical history included unspecified reaction to a non-steroidal anti-inflammatory drug (NSAID), 25 years before. She did not report of abdominal pain, pruritus, fever or nausea. She had no sick contacts, no recent antibiotics and no recent travel. She took no medications or herbal supplements on a daily basis, nor did she use tobacco or alcohol. There was no family history of liver disease. Her physical examination revealed only jaundice, with no signs of chronic liver disease or encephalopathy.

INVESTIGATIONS

The initial laboratory findings were as follows (reference ranges provided parenthetically): haemoglobin 14.4 g/dL (11.9–15.6 g/dL), white cell count $13.7 \times 10^3/\mu\text{L}$ ($4\text{--}11 \times 10^3/\mu\text{L}$), platelets $243 \times 10^3/\mu\text{L}$ ($150\text{--}400 \times 10^3/\mu\text{L}$), C reactive protein 41.3 mg/L (<3.0 mg/dL), creatinine 0.6 mg/dL (0.6–1.2 mg/dL), alanine aminotransferase (ALT) 2558 U/L (12–78 U/L), aspartate aminotransferase (AST) 2255 U/L (15–37 U/L), alkaline phosphatase 174 U/L (50–136 U/L), total bilirubin 12.98 mg/dL (0.1–1 mg/dL), direct bilirubin 9.57 mg/dL (0–0.2 mg/dL), albumin 2.6 g/dL (3.4–5.0 g/dL), ammonia $134.1 \mu\text{g/dL}$ (18.7–54.5 $\mu\text{g/dL}$), lactate dehydrogenase 589 U/L (84–246 U/L), prothrombin time 26.6 s (8.0–14.0 s) and International Normalised Ratio 2.2. Serum protein electrophoresis showed a 'swell-like' elevation in the γ zone. IgG was 2970 mg/dL (700–1600 mg/dL) and IgA 529 mg/dL (70–400 mg/dL). The patient had the following positive antibodies: anti-ANA 1/80 with a cytoplasmic pattern, anti-SMA 1/80 and anti-M2 mitochondrial. Other antimitochondrial antibodies, anti-LKM-1, antineutrophil cytoplasmic antibody, antidouble-stranded DNA antibody and antisoluble extractable nuclear antigens were negative. Antihepatitis A IgM, hepatitis B surface antigen, antihepatitis B core antigen IgM, antihepatitis C virus antibodies, anticytomegalovirus IgM, antiEpstein-Barr virus IgM, anti-HIV and venereal disease research laboratory test were all negative. Ceruloplasmin, copper and iron indices were normal. Abdominal ultrasound showed a liver with regular contours, shape and dimensions preserved, and uniform texture. The pancreas and spleen were normal. No enlarged lymph nodes and no intra-abdominal free fluid were visualised.

DIFFERENTIAL DIAGNOSIS

Presenting with a MELD score of 25.0, the patient was transferred to a specialised liver transplant unit, where she was prescribed acetylcysteine

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Figure 1 Liver biopsy histology at the initial presentation showing hepatocyte ballooning, lymphocytic inflammatory infiltrate and micronodular cirrhosis—(A) H&E stain at ×100 magnification, (B) H&E stain at ×400 magnification, (C) reticulin stain at ×100 magnification).

according to unit protocol, for 5 days, with a favourable outcome, downward profile of markers of liver lysis and improvement of coagulation tests.

Before receiving the laboratory results, an acute drug-induced liver disease seemed to be the most probable diagnosis. After the results of positive ANA, SMA and anti-M2 mitochondrial antibodies, and after excluding other main possible causes of acute hepatitis, such as viral hepatitis or Wilson disease, the diagnosis needed to be clarified. In order to do so, a liver biopsy was performed, revealing the presence of architectural distortion of the liver parenchyma, with the formation of fibrous septa and regenerative nodules, major lymphocytic inflammatory infiltrate and interface hepatitis. Pseudoacinar formations were identified in the nodules, as well as significant hepatocyte ballooning and the presence of mega mitochondria. Polymorphonuclear neutrophils were also observed in the septa and in the nodular parenchyma. In conclusion, histopathology was consistent with micronodular cirrhosis associated with acute hepatitis, with features suggestive of autoimmune hepatitis (figure 1).

TREATMENT

The patient was treated with azathioprine 50 mg/day and prednisolone 30 mg/day. Two weeks after initiating treatment, AST decreased to normal range. IgG remained elevated for 8 weeks. During the following 2 years of treatment, prednisolone was gradually tapered to a daily dose of 2.5 mg, with the patient continuously showing clinical and biochemical remission.

OUTCOME AND FOLLOW-UP

A transient elastography (FibroScan), performed 18 months later, showed a liver stiffness of 4.3 kPa, with a 63% (10/16) success rate and an IQR of 0.7 kPa, corresponding to a stage F0-F1 fibrosis (using the Metavir grading system). Another liver biopsy was performed after 28 months of treatment (while taking 2.5 mg/day of prednisolone and 50 mg/day of azathioprine), which showed preserved trabecular architecture, normal portal spaces with mild fibrosis and no significant inflammatory infiltrate (figure 2). No steatosis, no siderosis and no necrosis were found in the lobular parenchyma.

DISCUSSION

The majority of adult patients diagnosed with AIH have an insidious onset of symptoms,¹² while in 30–40% of patients, the onset of AIH can mimic that of acute hepatitis due to other causes.^{13 14} In our clinical case, there seems to be a temporal association with the intake of nimesulide and the appearance of the first symptoms, suggesting a drug-induced liver injury as the most plausible diagnosis.

In 2002, Liu and Kaplowitz¹⁵ distinguished two types of drug-induced liver injury (DILI) associated with AIH and, later, in 2011, Weiler-Normann and Schramme established another classification of DILI and AIH, proposing three possible connections with suggested diagnoses and clinical characteristics.¹⁶ In fact, there can be many more combinations, since an overlap between these entities is also possible. In terms of prognosis, it is important to distinguish drugs as triggers of a self-perpetuating autoimmune liver disease from immune-mediated drug-induced liver injury, since the last condition nearly always resolves¹⁷ or becomes quiescent when drugs are withdrawn.

Figure 2 Follow-up liver biopsy histology, 28 months later, after treatment with prednisone and azathioprine—(A) H&E stain at ×40 magnification, (B) H&E stain at ×400 magnification, (C) reticulin stain at ×100 magnification).

The potential hepatotoxicity of common therapeutic drugs is widely recognised as a major challenge in contemporary hepatology. Among these, NSAIDs are among the drugs most responsible for DILI.^{10 18–22} More specifically, nimesulide's safety was reviewed in 2007 and again in 2010 by the European Medicines Agency (EMA), because of concerns with liver injury.^{18 23} The Agency's Committee for Medicinal Products for Human Use concluded that nimesulide was associated with an increased risk of liver toxicity compared with other anti-inflammatory treatments and that systemic nimesulide should not be used for long-term treatment.²⁴

Distinguishing DILI from AIH can be clinically challenging,²⁵ but regarding histology, Suzuki *et al*²⁶ showed that, while a histological overlap occurs for these pathologies, there are sufficient differences that allow us to achieve the correct diagnosis: interface hepatitis, focal necrosis and portal inflammation were present in all of the evaluated cases but were more severe in AIH than in hepatocellular DILI.²⁶

Among the many possible options described formerly, we consider that our patient's case is better explained by the possibility of a previously existing quiescent AIH, undiagnosed until nimesulide triggered a new acute liver injury. According to the revised scoring system for diagnosis of autoimmune hepatitis,²⁷ the pretreatment score is 13 and the post-treatment score is 15, both compatible with probable AIH. Considering the simplified criteria,²⁸ the score is 7, consistent with definite diagnosis of autoimmune hepatitis. Interface hepatitis and a predominant lymphocytic inflammatory infiltrate²⁷ are key histological features of autoimmune hepatitis, while the presence of polymorphonuclear neutrophils in the septa and in the nodular parenchyma is characteristic of acute inflammatory liver injury. The fact that cirrhosis was present at the time of diagnosis, and the short duration of the NSAID intake, support the diagnosis of a pre-existing autoimmune hepatitis, with years of evolution.

Nonetheless, it is still clinically accurate to characterise this clinical presentation as acute liver failure despite the presence of pre-existing disease, as some authors do for similar presentations of other chronic liver diseases such as Wilson disease, in which cirrhosis is often present at the time of initial diagnosis.^{29 30} Acute-on-chronic liver failure is an increasingly recognised entity encompassing an acute deterioration of liver function in patients with cirrhosis, either secondary to superimposed liver injury or due to extrahepatic precipitating factors.³¹

One of the most interesting and revealing facts present in our clinical report is the reversibility of cirrhosis. Cirrhosis was traditionally accepted as a passive and irreversible outcome of chronic inflammatory injury to hepatocytes in conjunction with the accumulation of extracellular matrix proteins.³² In AIH, at least a third of patients, regardless of the mode of presentation, have histological evidence of cirrhosis at the time of diagnosis, indicating that they probably have had subclinical disease for a long time.^{33 34} However, there are some remarkable reports in the literature, which indicate that advanced liver fibrosis and even cirrhosis are potentially reversible after successful treatment.¹¹ Recent developments in understanding the process of hepatic fibrogenesis confirm that the process is a dynamic one, and suggest that a capacity for recovery from any degree of fibrosis, including those associated with cirrhosis, is possible.³⁵ A return towards architectural normality has been documented in advanced fibrosis and cirrhosis; this has been most clearly documented in autoimmune disease,³⁶ but is paralleled by observations of haemochromatotic patients after venesection, and patients with hepatitis B and C after successful interferon therapy.^{32 37–39} Rapid institution of treatment with high-dose

corticosteroids may rescue patients whose autoimmune hepatitis ultimately would have progressed to either fulminant hepatic failure or cirrhosis.⁴⁰ Dufour *et al* reported a series of eight patients with autoimmune hepatitis and cirrhosis, treated with glucocorticoids and/or immunosuppressive drugs, with a second liver biopsy taken years after starting treatment. The median (Knodell) fibrosis score decreased from 3.3 to 0.8.³⁸ There is also a case report of an autoimmune hepatitis patient with documented liver cirrhosis who attained a biochemical response to immunosuppressive therapy and a repeat liver biopsy after 14 years revealed normal liver histology.⁴¹

The clinical case presented here supports the emerging evidence that, in some circumstances, with an effective treatment for autoimmune hepatitis, remodelling of the liver scar tissue can occur, and cirrhosis may revert into a stage with less fibrosis.

Learning points

- ▶ The diagnosis of autoimmune hepatitis should be considered in patients presenting with acute liver failure, as prompt treatment with steroids and liver transplantation may be lifesaving.
- ▶ It is possible that a hepatotoxic substance, such as nimesulide, can trigger the clinical manifestation of an underlying autoimmune hepatitis.
- ▶ Contrary to what was thought until very recently, liver cirrhosis in autoimmune hepatitis is potentially reversible after successful treatment.

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Patient consent Obtained.

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