CASE REPORT

Autoimmune hepatitis: a histological variant associated with prominent centrilobular necrosis

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Abstract

A patient presented with pruritus and recent elevation of aminotransferases. The case fulfilled most of the criteria for the diagnosis of autoimmune hepatitis and achieved clinical and complete biochemical response to steroid therapy. However, the liver biopsy specimen revealed an unusual histological pattern consisting of severe centrilobular necrosis demarcated by a thin rim of hepatitic reaction. In contrast, the portal tracts appeared almost normal. This histological appearance has not been associated with autoimmune hepatitis. This presentation and the histology may represent an early pattern of autoimmune injury to the liver. (*Gut* 1997; 41: 269–271)

Keywords: autoimmunity; hepatitis; chronic active hepatitis; histology

Autoimmune hepatitis (AIH) is an unresolving inflammation of the liver characterised by the presence of autoantibodies, hypergammaglobulinaemia, and the histological evidence of periportal hepatitis.¹ Since its formal recognition about 40 years ago,^{2,3} its definite diagnosis remains a challenge due to the absence of pathognomonic features of the disease.^{1,4} The availability of better diagnostic assays to detect viral markers in the past few years has aided its distinction from chronic viral hepatitis,^{4,5} although false positive results have also confounded the problem in some cases.^{6,7} Periportal hepatitis with piecemeal necrosis has been the hallmark lesion of AIH^{8,9}; however, this came to be recognised as only a part of a wide spectrum of morphological inflammatory patterns, ranging from lobular hepatitis to cirrhosis.¹⁰

We describe a case that presented with an unusual histological pattern of AIH characterised by zonal centrilobular necrosis resembling that seen in toxic liver injury. To our knowledge few other similar cases have been recently reported in the literature.¹¹

Case report

A 39 year old woman was referred for evaluation of abnormal liver tests. Fourteen

weeks earlier she had been diagnosed with Raynaud's phenomenon and was found to have an antinuclear antibody (ANA) titre of 1:2560 with an anticentromere pattern. The physical examination was unremarkable and liver function tests were then normal. Three months later the patient complained of pruritus with significantly raised aminotransferase levels (aspartate aminotransferase (AST) 243 IU/l, alanine aminotransferase (ALT) 484 IU/l, gamma glutamyltranspeptidase (GGT) 74 IU/l) and normal alkaline phosphatase, total bilirubin, albumin, and globulin levels. Hepatitis A, B, and C serologies were all negative. She had no previous history of hepatobiliary disease, and denied exposure to hepatotoxic drugs, alcohol, or chemicals. There was also no parenteral exposure or history of transfusion of blood products.

During the next three weeks the patient reported fatigue, low grade fever, and arthralgias of both hands and knees. At that time, liver enzymes had further risen to AST 376 IU/l, ALT 705 IU/l, GGT 79 IU/l, and the ANA titre was now 1:5120. Serological tests for anti-smooth muscle antibody, cryoglobulins, anticardiolipin antibodies, Sjogren's antibodies, and gammaglobulin levels were all negative. An ultrasound scan of the liver and biliary tree was normal, and a Doppler study of the hepatic vessels showed no vascular abnormalities at the level of the hepatic veins or the portal vein and its branches. A decision was made to start corticosteroid therapy immediately, with the presumptive diagnosis of autoimmune hepatitis; a liver biopsy specimen was first taken.

Histological examination of the biopsy specimen showed that the overall pattern of acinar architecture was preserved (fig 1). Necrosis bridging the centrilobular areas was seen focally (fig 2). All the centrilobular regions showed lytic necrosis, sharply demarcated by a distinct rim of necroinflammatory activity featuring many acidophilic bodies and a dense lymphocytic inflammatory infiltrate (fig 3). The rest of the parenchyma and most of the portal areas were virtually unaffected. Occasional portal tracts showed mild non-specific inflammation. None of the portal tracts showed piecemeal necrosis, plasmacytosis, fibrosis, or significant expansion (fig 4). No veno-occlusive changes were noted.

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Figure 1: The pattern of acinar architecture is preserved and there is no evidence of cirrhosis. Central veins are indicated by arrows, portal tracts by arrowheads (original magnification $\times 5$).

Figure 2: Centrilobular necrosis. An unremarkable portal tract is noted (arrowhead). Central vein is indicated by an arrow (original magnification $\times 20$).

Figure 3: Centrilobular lytic necrosis with a marginal zone of prominent necroinflammatory activity. Note that lobular regions away from the zonal lesion show only an increase of sinusoidal cells, not significant necroinflammatory activity (original magnification $\times 50$).

The patient was started on methylprednisolone at a dose of 40 mg/day. Two weeks later the aminotransferases had returned to normal levels (table 1) and her symptoms had resolved. She was then started on azathioprine 1 mg/kg/day and the steroids were slowly tapered. The patient continued to do well and liver enzyme levels have been normal up to the present time (May 1997).

Discussion

The establishment of a definite diagnosis of autoimmune chronic hepatitis has been problematic in some cases. The International Autoimmune Hepatitis Group proposed a formal set of criteria on the histological appearance that includes piecemeal necrosis, with or without lobular hepatitis, in the absence of biliary lesions, granulomas, metal deposits, or other alterations suggestive of a different aetiology.¹² However, inability to fulfil these criteria completely does not invalidate the disease entity, and a diagnosis of probable AIH can still be made.

The predominant histopathological pattern in AIH has been reported to be periportal piecemeal necrosis, with or without lobular hepatitis.^{5, 12-15} Syncytial multinucleated giant hepatocytes may be suggestive of the disease,⁴ but not pathognomonic since they can also be seen in other diseases. In the absence of portal lymphoid aggregates, steatosis, bile duct damage, and ground glass hepatocytes which are features associated with chronic viral hepatitis, the composite pattern of moderate to severe piecemeal necrosis, lobular hepatitis, and moderate to severe plasma cell infiltration of the portal tracts has rendered a specificity of 81% and a positive predictive value of 68% for AIH. Its sensitivity, however, was only 40%,¹⁶ suggesting that patients with the diagnosis lack the characteristic morphological pattern and, perhaps, may present with a variety of individual features.

The patient described here did not demonstrate the typical histological features of AIH. In fact, centrilobular necrosis had not been associated with the disease until it was reported in five cases of steroid responsive AIH.¹¹ In two patients in whom initiation of therapy was delayed, the diagnostic histological appearance of AIH evolved into the typical pattern seen in repeat biopsy specimens. After treatment with corticosteroids, marked improvement or complete resolution of the lesions were found in follow up biopsy specimens. Of the five patients, only two had manifested hypergammaglobulinaemia.¹¹ This patient likewise had normal gammaglobulin levels, which may explain the lack of plasmacytosis on histological examination. The clinical presentation, the laboratory findings, and the remarkable response to steroid therapy otherwise fulfilled the diagnostic criteria for AIH.¹²

Centrilobular necrosis has also been documented in hepatic injury secondary to hepatotoxic drugs and chemicals such as halothane, paracetamol, thioacetamide, tetrachloride, and carcinogens such as nitrosamines.¹⁷ This specific localisation reflects the area of high

Figure 4: Portal tract with mild inflammation, mostly lymphocytes, no plasmacytosis, no significant expansion or fibrosis, and no features of piecemeal necrosis. Prominent "glycogenated" nuclei are seen (original magnification $\times 50$).

TABLE 1 Summary of liver function tests

Test (normal values)	Week -14	Week 0*	Week 3†	Week 5	Week 6	Week 12	Week 26
AST (5–45 IU/l)	27	243	376	52	29	26	25
ALT (5–37 IU/l)	16	484	705	181	44	48	21
GGT (12–60 IU/l)	17	72	79	96	64	65	22
LDH (90–220 IU/l)	284	237	257	197	159	228	195
Alkaline phosphatase (35–110 IU/l)	81	74	73	75	72	60	54
Total bilirubin (3–22 μ mol/l)	5	10	11	15	11	6	6
Albumin (35–47 g/l)	41	44	ND	41	41	37	43
Globulin (25–35 g/l)	30	25	ND	26	24	24	22

*Onset of symptoms.

†Followed by onset of corticosteroid treatment.

ND, not done.

concentration of the enzyme system which metabolises the substance to its hepatotoxic metabolite. Vascular insults, particularly veno-occlusive diseases, similarly lead to a picture of centrilobular and mid-zonal necrosis and congestion, with hepatocyte survival confined mainly to the portal rim areas.¹⁷ Our patient had no history of such drug exposure and no evidence of clinical vascular hypoperfusion or venous occlusion. No other aetiological agent for the acute hepatic dysfunction was identified. The predilection of the disease to affect the centrilobular zone instead of the periportal area in these cases is not clearly understood at this time. It is possible that this pattern represents an early lesion in AIH that precedes portal involvement, as was suggested by the course of the two initially untreated patients in the case series.¹¹ This theory, however, would suggest that the pattern should have been demonstrated more frequently during the evaluation of the disease than has been reported. It may be the failure to associate the pattern with AIH that prevented its recognition as a part of the entire histological spectrum of the disease. In a study of murine models of

AIH immunised intraperitoneally with syngeneic liver homogenate, the histological inflammatory infiltrates that developed were initially localised in the centrilobular or portal areas, but as the hepatitis progressed and peaked the increase in the inflammatory density preferentially occurred around the central vein.¹⁸ These results seem to contrast with the experience in humans, obscuring its relevance to medicine. More studies involving animal models and an increasing awareness on the part of the clinicians are needed to delineate further the actual mechanism involved in the pathogenesis of AIH and its various histological features.

In summary, we present a case of AIH with an unusual histopathological pattern consisting of centrilobular necrosis with a virtually unaffected portal tract. The recognition of the morphological spectrum of the disease is of great importance in facilitating a timely diagnosis and allowing the prompt institution of the proper treatment in patients who are most likely to benefit from it.

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