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Case Report

Rituximab for refractory autoimmune hepatitis: A case report

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ABSTRACT

Auto-immune hepatitis (AIH) is a chronic progressive hepatitis of unknown aetiology whose clinical presentation ranges from asymptomatic to fulminant hepatic failure. Corticosteroids and azathioprine, which are considered standard therapy for AIH, may, however, be associated with treatment failures and toxicities. Among the alternative medications under investigation, rituximab, used to treat successfully various auto-immune disorders, has fewer side effects. We report herein the case of a 68-year-old woman who developed AIH with worsening clinical, laboratory and histological features despite high-dose prednisone. On rituximab, the patient showed rapid and dramatic clinical improvement, suggesting a therapeutic role for this medication in severe AIH. Indeed, prospective controlled studies are needed to assess and validate this role.

Introduction

Auto-immune hepatitis (AIH) is an immune-mediated necro-inflammatory condition of the liver with a wide clinical presentation ranging from asymptomatic [1] to acute severe disease [2]. The diagnosis of AIH is based on a constellation of biochemical, auto-immune and histological features and requires the exclusion of other hepatic diseases [3,4]. As in most other auto-immune disorders, there is a female predominance (F:M = 3.6:1) [5].

Standard therapy, corticosteroids alone or combined with azathioprine (AZA), is efficacious in 80% of patients; [6] however, treatment failure, that is worsening of clinical, laboratory and histological parameters despite patient compliance with the therapy, occurs in at least 9% of patients and is usually observed within 3–6 weeks [7]. The consensus is that treatment failures should be managed with high-dose prednisone with or without AZA before considering alternative drugs [8]. Several alternative medications such as tacrolimus, ursodeoxycholic acid, 6-mercaptopurine and methotrexate have been used empirically to treat severe AIH [8]. However, most of these treatments are small anecdotal reports; none has been incorporated into standard management algorithms [8].

Rituximab is an anti-CD20 monoclonal antibody which depletes B-cells and has been used successfully to treat other auto-immune conditions [9]. It has been shown to induce remission of AIH in a patient treated for idiopathic thrombocytopenic purpura (ITP) [10] and in a patient with overlap syndrome, primary biliary cirrhosis and AIH and B-cell lymphoma [11]. The exact mechanism of action of rituximab in controlling AIH is not understood. It is theorised that rituximab induces B-cell depletion and thus suppresses the production of pathogenic antibodies [12].

Case report

A 68-year-old French-Canadian woman was referred to our institution for evaluation and management of steroid-refractory AIH and consideration for liver transplantation. She had presented initially to another hospital with jaundice, fatigue and weight loss of a few weeks' duration. The diagnosis of AIH was made based on the characteristic combination of biochemical, auto-immune and histological parameters and exclusion of other liver diseases. She was started on high-dose prednisone (60 mg day^{-1}), but despite treatment for 8 weeks, her serum aminotransferases remained elevated at 450 IU l^{-1} and bilirubin rose to 245 μmol l^{-1}. Her past medical history included hypertension, osteoporosis and a remote diagnosis of Waldenström macroglobulinaemia (WM). The patient was a non-smoker, and there was no significant alcohol or intravenous drug use. Her medications included candesartan 16 mg per day, vitamin D 400 IU twice per day, calcium carbonate 500 mg twice per day and prednisone 20 mg per day which was slowly tapered down. Her family history was non-contributory. Physical examination revealed normal vital signs, marked scleral icterus and an urticarial skin rash. Abdominal examination revealed neither tenderness nor hepatosplenomegaly. Laboratory data showed elevated alanine aminotransferase (ALT) 442 IU l^{-1}, aspartate aminotransferase

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(AST) 428 IU l^{-1}, alkaline phosphatase (ALP) 111 IU l^{-1}, total bilirubin 250.7 μM l^{-1} (direct bilirubin 180 μM l^{-1}) and an international normalised ratio (INR) of 1.35. Immunological tests showed elevated smooth muscle antibody (SMA, 1:80), serum immunoglobulin G (IgG; 29.10 g l^{-1}; range, 6.2–14.0 g l^{-1}) and IgM (3.30 g l^{-1}; range, 0.45–2.5 g l^{-1}) but negative antinuclear antibody (ANA) and antimitochondrial antibody (AMA) and negative serology for hepatitis viruses A, B and C. Alpha-1-antitrypsin and serum ceruloplasmin levels were normal, as were liver ultrasonography and magnetic resonance cholangiopancreatography (MRCP). A core biopsy of liver showed a portal and interface necro-inflammatory infiltrate composed of lymphocytes, moderate number of plasma cells and a few eosinophils, confirming the diagnosis of AIH with a grade of 3 (out of 4) and a stage of 2–3 (out of 4) (Figs. 1A–1C). Dermatological evaluation of the rash, including skin biopsy, revealed auto-immune urticaria.

The patient was put on prednisone 60 mg per day for 1 week without clinical or biochemical improvement. There was a question as to whether or not this was all due to WM causing infiltration of the liver by plasma cells, as the patient's IgM level was elevated. Therefore, in collaboration with the haematology, it was decided to start a course of rituximab (4 weekly infusions of 375 mg m^{-2}) while waiting for a repeat liver biopsy. The rationale behind using rituximab in this patient was to target both possibilities, WM and AIH.

During hospitalisation, one infusion of rituximab produced a dramatic clinical and biochemical improvement within few days. A transjugular liver biopsy was performed on the day of discharge.

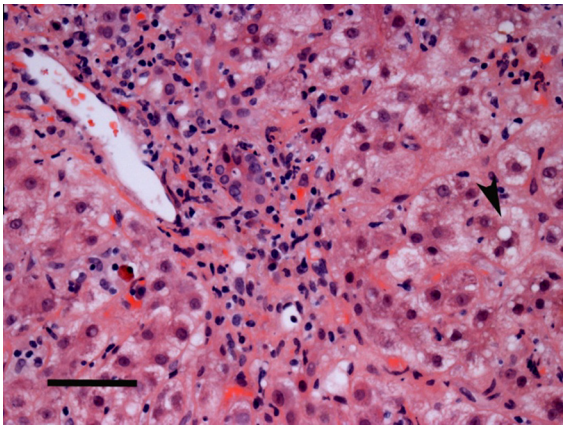

Fig. 1A. Medium-power photomicrograph of liver biopsy showing portal tract (extending from upper left towards the centre) with prominent interface hepatitis and disarray of hepatocytes. Note small pseudoacinus in centre right (arrowhead). Haematoxylin and eosin stain. Scale indicates 25 μm.

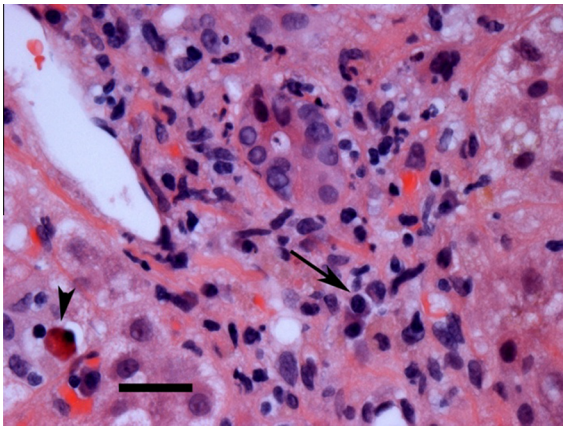

Fig. 1B. Higher-power photomicrograph of the same portal tract showing inflammatory cells composed mostly of lymphocytes, with a trio of plasma cells (arrow) and an apoptotic body (arrowhead). Haematoxylin and eosin stain. Scale indicates 10 μm.

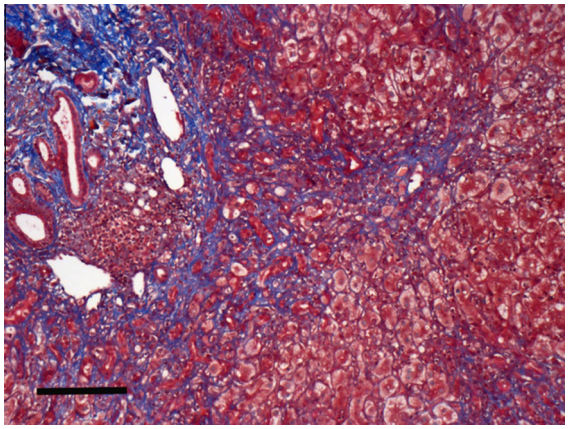

Fig. 1C. Low-power photomicrograph of a section stained with Masson trichrome outlining nodules of hepatocytes (dark red) separated by variably prominent fibrous septa (blue), consistent with a stage of 2–3 out of 4. Masson trichrome stain. Scale indicates 50 μm.

Table 1
Modified diagnostic criteria for the diagnosis of AIH [3, 4].

Parameter/Feature	Score	Parameter/Feature	Score
Female gender	+2	Drug history	
		Positive	−4
		Negative	+1
ALP:AST (or ALT) ratio		Average alcohol intake	
<1.5	+2	<25 g/day	+2
1.5–3.0	0	>60 g/day	−2
>3.0	−2		
Serum globulins or IgG above normal		Liver histology	
		Interface hepatitis	+3
>2.0	+3	Predominantly	
1.5–2.0	+2	Lymphoplasmacytic infiltrate	+2
1.0–1.5	+1	Rosetting of liver cells	+1
<1.0	0	None of the above	−5
		Biliary changes	−3
		Atypical features	−3
ANA, SMA or LKM-1		Other autoimmune disease(s)	
>1:80	+3	In either patient or first degree	+2
1:80	+2	relative	
1:40	+1		
<1:40	0		
AMA positive	−4	Optional additional parameters	
		Seropositivity for other defined antibodies	+2
		HLA DR3 or DR4	+1
Hepatitis viral markers		Response to therapy	
Positive	−3	Remission alone	+2
Negative	+3	Remission with relapse	+3
		Interpretation of aggregate scores	
		Pre-treatment: Definite AIH	>15
		Probable AIH	10–15
		Post-treatment: Definite AIH	>17
		Probable AIH	12–17

Abbreviations: ALP, serum alkaline phosphatase level; AST, serum aspartate aminotransferase level; ALT, serum alanine aminotransferase level; IgG, serum immunoglobulin G level; AMA, antimitochondrial antibodies; HLA, human leucocyte antigen.