SHORT REPORT

Autoimmune hepatitis during infliximab therapy for Crohn's disease: A case report

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Abstract

We present the case of a 60-year-old Caucasian male with Crohn's disease treated with infliximab. Within 14 weeks of treatment induction, an asymptomatic acute hepatitis was detected. Elevated autoantibodies and liver biopsy findings supported the diagnosis of autoimmune hepatitis. No competing aetiologies were present. The hepatitis completely responded to infliximab cessation and administration of corticosteroids. This case is the most compelling to date of an infliximab-induced autoimmune hepatitis. Although the role of liver enzyme monitoring is unclear, an awareness of this adverse effect is important, given the potential for a rapid and complete response to specific treatment.

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1. Introduction

Infliximab is a chimeric humanised murine monoclonal antibody against tumour necrosis factor-alpha (TNFα) that is used in the treatment of chronic inflammatory conditions such as Crohn's disease, ulcerative colitis and rheumatoid arthritis. Whilst mild abnormalities of liver enzymes are a recognised potential adverse effect from the use of infliximab, the development of significant liver dysfunction is a much rarer phenomenon, with only a small collection of cases reported in the existing literature. For many of these existing cases the precise role of infliximab is compromised by the presence of other potential aetiologies.

We describe a case of acute hepatitis due to infliximab as treatment for Crohn's disease, with no other concurrent medications or causative agents that might have otherwise contributed to this disorder.

2. Case report

A 60-year-old Caucasian male with a history of prior hepatitis B virus (HBV) infection (hepatitis B surface antigen negative, surface antibody positive, core antibody positive) presented to his general practitioner and colorectal surgeon in June 2008 with anal discomfort and a firm, painless mass in the right perianal region. He was found to have peri-anal abscesses and ulceration of the anal canal. These abscesses were incised with some short-term benefit to the patient's symptoms. Relapse in symptoms led to a referral to our service. Subsequent colonoscopy performed in September 2008 identified the presence of deep, irregular ulceration of the...
distal rectum adjacent to the anorectal margin, with histopathology showing changes in keeping with Crohn’s disease.

Prednisolone (50 mg daily) and azathioprine (2 mg/kg daily) failed to completely relieve symptoms; a follow-up flexible sigmoidoscopy confirmed persistent rectal ulceration. Prednisolone and azathioprine therapy were ceased. Infliximab therapy was then commenced with an induction regimen of 350 mg (5 mg/kg) administered at zero, two and six weeks, and the first dose of a planned regimen of eight-weekly maintenance infusions administered thereafter. Complete resolution of symptoms occurred by week four of infliximab therapy.

Given the patient’s prior hepatitis B infection, serial HBV DNA levels were performed and remained undetectable both before and during treatment with infliximab. Liver function tests prior to infliximab were normal (bilirubin 15 umol/L, alanine transaminase [ALT] 30 U/L, alkaline phosphatase [Alk Phos] 65 U/L, gamma glutamyl transpeptidase [GGT] 24 U/L) and an autoimmune screen revealed a normal anti-nuclear antibody (ANA) level (1 U/mL [normal range <7 U/mL]).

Elevated levels of ALT were identified at 14 weeks after the initiation of infliximab. Over the next 7 weeks, the patient’s ALT continued to rise to over 10 times normal (1307 U/L) (Fig. 1). Alk Phos (272 U/L), GGT (182 U/L) and aspartate transaminase (AST) (718 U/L) showed lesser degrees of elevation. We confirmed the patient did not consume alcohol and had taken no other prescribed or non-proprietary medications. The patient remained asymptomatic throughout this time.

In order to determine the aetiology of the hepatitis, an autoimmune panel was repeated, revealing elevated levels of ANA (10 U/mL) and anti-dsDNA (14 U/mL [normal range <7 U/mL]), positive antibodies against F-actin, as well as elevated IgG (24.5 g/L), IgM (2.8 g/L), and IgA (4.4 g/L). Other tests, including C3, C4, smooth-muscle antibody, and anti-liver-kidney-microsomal antibody were negative. HBV DNA was undetectable and serological markers for hepatitis B re-activation were negative (hepatitis B surface antigen and hepatitis B core IgM negative). Serology for hepatitis C, cytomegalovirus, Epstein–Barr virus, and delta virus were also negative. An abdominal ultrasound was normal.

A subsequent liver biopsy performed 21 weeks after first commencing infliximab, and 7 weeks after his last dose of infliximab, revealed moderate to severe active hepatitis with portal and lobular activity, and mild prominence of plasma cells and eosinophils. These findings were consistent with an autoimmune hepatitis or drug-induced hepatic injury. Given this result, further infliximab was withheld, and prednisolone (50 mg daily for 2 weeks, then 40 mg daily for 2 weeks) was commenced. ALT levels completely normalised within 4 weeks (bilirubin 14 umol/L, ALT 39 U/L, Alk Phos 45 U/L, and albumin 39 g/L).

After the normalisation of the liver biochemistry, azathioprine therapy was re-introduced in order to maintain the clinical remission of Crohn’s disease that had been obtained with infliximab. 2 weeks later, the patient developed an asymptomatic flare of hepatitis (bilirubin 19 umol/L, ALT 573 U/L, Alk Phos 214 U/L, GGT 374 U/L, albumin 32 g/L). HBV DNA was undetectable. Biochemistry normalised over 2 weeks with the cessation of azathioprine and a transient reintroduction of prednisolone (bilirubin 35 umol/L, ALT 16 U/L, Alk Phos 64 U/L, and GGT 34 U/L).

Since this time, the patient has been successfully weaned from prednisolone, and currently experiences minimal symptoms from Crohn’s disease; he has a normal biochemistry with

![Figure 1](https://academic.oup.com/ecco-jcc/article-abstract/5/3/253/469003)
no immunosuppressive therapy. ANA levels normalised upon reassessment at 26 weeks following the last dose of infliximab.

3. Discussion

We report the case of a patient developing an asymptomatic, acute severe biochemical and histological hepatitis following infliximab therapy for inflammatory bowel disease, with subsequent resolution of the hepatitis after drug cessation and corticosteroid therapy. This case is one of the most convincing reports to date to demonstrate an induced hepatitis as an adverse effect from infliximab. The pathogenesis of the hepatitis in this instance had an autoimmune basis, as evidenced by the positive ANA, elevated immunoglobulin levels, liver histology, and absence of viral markers. The presence of antibodies against F-actin, a highly specific marker for type 1 autoimmune hepatitis, also supports this pathogenesis. Applying the International Diagnostic Criteria for Autoimmune Hepatitis we would derive a score of 17 before treatment and 20 after treatment giving a diagnosis of "definite" autoimmune hepatitis.1

This case report builds upon the growing literature supporting the possibility of severe hepatotoxicity as an adverse effect of infliximab. The majority of existing case reports on hepatotoxicity with infliximab have inferred mechanisms of autoimmune hepatitis2-7 or direct drug-mediated hepatotoxicity.8-13 Only a few of these reports have involved patients with inflammatory bowel disease,3,5,9,12 and most cases are compoundable by possible contributing hepatotoxic medications or alcohol,2,4,7,10 or absence of liver biopsies to confirm aetiology.7,9-11,13

Our case is notable for the reasons that there were no concomitant medications that might have contributed to the hepatitis, that we thoroughly investigated and excluded other causes for hepatitis, and that the hepatitis responded so rapidly to the administration of corticosteroids. Although this patient had a history of prior infection with hepatitis B, serial monitoring of HBV DNA levels throughout his illness excluded a flare of HBV as a cause of the hepatitis. The secondary azathioprine-related flare of hepatitis is also curious, as earlier administration of azathioprine in identical doses had occurred in this patient without evidence of hepatotoxicity. It remains possible that a premature cessation of prednisolone rather than a direct azathioprine hepatotoxic reaction, contributed to a flare from the primary infliximab-induced hepatitis. Normalisation of liver biochemistry with the cessation of azathioprine and reintroduction of prednisolone is consistent with either explanation.

Whether such hepatotoxicity might occur with other anti-TNFα agents is unclear. Adalimumab, another anti-TNFα monoclonal antibody approved for the treatment of inflammatory bowel disease has only one reported case of possible induced hepatotoxicity in the published literature.14 The aetiology of this case of hepatotoxicity was also consistent with an autoimmune hepatitis, and responded completely to adalimumab withdrawal and corticosteroid administration. The potential for cross reactivity between anti-TNFα agents with respect to hepatotoxicity remains uncertain.

Severe hepatotoxicity from infliximab is uncommon, and the utility of routine monitoring of liver function tests during infliximab therapy is unclear. In our patient, it can be argued that the relatively early detection of a severe hepatitis was fortuitous, by nature of his history of HBV infection, and consequent liver monitoring. However, awareness of the possibility of autoimmune-like hepatitis secondary to infliximab is important, because of the need for infliximab withdrawal and the potential for steroid responsiveness.

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AD collected patient information and completed the first draft of the manuscript. GF and NK provided the clinical interpretation of investigation results and participated in subsequent revisions of the manuscript. All authors read and approved the final manuscript.

References