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LETTER TO THE EDITORS

Fulminant hepatic failure necessitating transplantation following the initiation of infliximab therapy: a cautionary tale times two

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Dear Sirs,

Infliximab (IFX) is a human-murine chimeric antibody with well-established efficacy in the treatment for several autoimmune diseases [1,2]. However, it is known to be hepatotoxic [3–6]. While the appreciation of IFX-associated liver disease is increasing, only one other documented case of IFX-related liver failure has been reported [7]. We herein report two patients with fulminant hepatic failure temporally linked to initiation of IFX, which likely precipitated a need for urgent liver transplantation.

A 40-year-old female with a lupus background complicated by hydradenitis suppurativa was started on IFX and 4 months after initiating this later treatment she developed fatigue, jaundice and encephalopathy. There was no prior history of alcohol abuse, and baseline liver and renal function were entirely normal (aspartate aminotransferase (AST) 27 U/l, bilirubin (Bili) 15 μM, alkaline phosphatase (ALP) 72 U/l and INR 0.6), although an abdominal ultrasound (US) showed moderate enlargement of the spleen (12 cm) at the time of IFX administration. At the time of presentation with liver failure, bloodwork showed severe cholestasis (Bili 262 μM, AST 292 U/l, ALP 193 U/l and INR 2.6), with a model for end-stage liver disease (MELD) score of 28 points.

Repeat US showed a small, shrunken, nodular liver without biliary obstruction, and marked ascites. Subsequent transjugular liver biopsy showed diffuse parenchymal collapse with extensive areas of lobular necrosis with ductal proliferation and portal fibrosis (Fig. 1a).

She deteriorated rapidly with encephalopathy and progressed to fulminant liver failure, requiring inotropic pressure, ventilatory and renal support followed by a whole liver transplant from a deceased donor. Her postoperative course was complicated by renal failure secondary to hepatorenal syndrome, pneumonia and acute cellular rejection. Over the next 2 weeks her renal and liver function normalized. She was discharged on a corticosteroid taper, with mycophenolate mofetil and tacrolimus for maintenance immunosuppression. Intensive care unit (ICU) stay was 27 days, and the total hospital stay was 58 days.

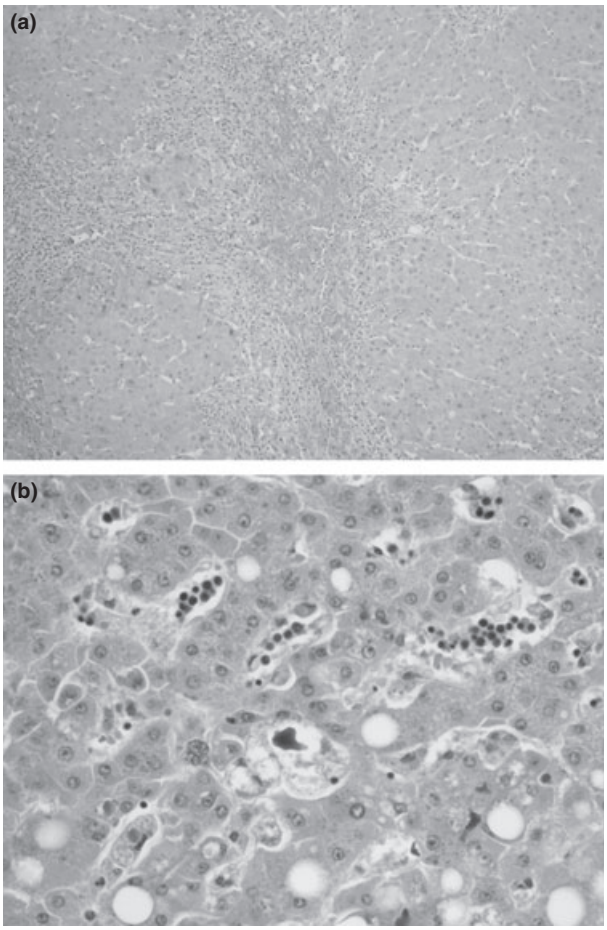

Figure 1 (a) Explant liver biopsy from patient 1 showing massive lobular hepatocellular injury, ductal proliferation, cholestasis and portal fibrosis (10× magnification). (b) Explant biopsy from patient No. 2 revealing massive, cholestasis, cholangitis and centrilobular necrosis (30× magnification).

A second case involved a 51-year-old female with a previous ulcerative colitis (UC), and steatohepatitis, presented to a peripheral hospital with fatigue, progressive appetite loss and shortness of breath. Initially her UC had been managed with a course of prednisone, but IFX therapy was begun 5 months prior to admission. This patient had normal liver function prior to the introduction of IFX (AST 36, Bili 19, ALP 59, INR 0.7), and a previous US showed severe fatty infiltration with mild hepatomegaly and a normal spleen.

On presentation, she had febrile neutropenia (40.2 °C, neutrophil count 0.4 cells/μl) complicated by cholestatic liver failure (Bili 98 μM, AST 568 U/l, ALT 140 U/l, ALP 527 U/l and INR 2.5). She required intensive care for a generalized seizure, hepatic encephalopathy (ammonia 69 μM) and respiratory failure. This was an unusual form of presentation with a clinical picture suggestive of infectious source. Yet, no positive blood cultures were ever received during this patient's hospital stay. The only positive culture was *Escherichia coli* bacteriuria, which did not account for a systemic inflammatory response syndrome.

She became progressively more cholestatic over the next 6 weeks, with declining liver function (Bili 654 μM, AST 149 U/l and ALP 896 U/l). Immunologic investigation was positive for anti-actin, while antinuclear antibody, extractable nuclear antigen, anti-SSA auto-antibodies, anti-dsDNA and antimitochondrial antibodies were all negative. US-guided liver biopsy revealed moderate to severe steatohepatitis with features of acute parenchymal inflammation with intracellular cholestasis and necrosis (Fig. 1b).

Given the subfulminant hepatic failure, a whole liver transplant from a deceased donor was performed on post-admission day 17. Her postoperative course was complicated by acute renal failure requiring dialysis.

Following transplant, her hepatic function tests slowly normalized, and she was discharged for ongoing care. Immunosuppression consisted of sirolimus, mycophenolate mofetil and prednisone. The ICU stay was 35 days, and the overall hospital stay was 141 days.

Both cases presented with elevated INR (around 2.5), which was artificially corrected with fresh frozen plasma (to 1.2) within two or 3 days until transplant. Six weeks after transplant both patients showed normal INR values. Similarly, both subjects also showed almost identical explant pathology reports, with massive lobular confluent hepatocellular injury with ductal proliferation, cholestasis and cholangitis; favouring drug-induced aetiology.

We herein describe two cases of subfulminant hepatic failure necessitating urgent liver transplantation beginning approximately 5 months after the initiation of IFX. Both patients had pre-existing mild underlying liver disease but with normal liver function prior to starting IFX, and IFX treatment appeared to temporally coincide with precipitation of subfulminant hepatic failure. Previous experience suggests that hepatic dysfunction may occur between months 1 and 19 after IFX [7]. Our two cases are consistent with previous, IFX-associated cholestasis, with the unique exception that both progressed to subfulminant hepatic failure requiring urgent liver transplantation [3,4,8].

A recent Cochrane review did not show statistical difference in the incidence of adverse outcomes associated with IFX versus control [9]. However, IFX has been linked to rare instances of idiosyncratic acute liver injury and is a well-known cause of reactivation of hepatitis B [10]. The pathogenic mechanism of the use of IFX and its associated hepatic toxicity remains unknown. However, there is increasing evidence of acute autoimmune hepatitis potentially triggered by IFX treatment [11–13].

In our experience, both cases presented with cholestasis around the fifth month of treatment, confirming the possibility of liver dysfunction well into the treatment scheme. Pre-existing mild liver disease in these two patients may have potentiated the risk of IFX treatment leading to irreversible liver failure requiring urgent liver transplantation.

Current consensus guidelines recommend baseline liver function tests with a hepatic risk factor screen (hepatitis serology, auto-antibodies) prior to onset of therapy. Ongoing screening for liver dysfunction at 4-month intervals is suggested with a low threshold for discontinuation of therapy if transaminase levels reach three times the upper limit of normal [14].

This study highlights an important and potentially lethal complication of IFX therapy, especially in patients with underlying mild liver disease. We present these two cases to reinforce need for caution and increased vigilance in prescreening and ongoing surveillance for patients on IFX.

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