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CASE REPORT

# Precore mutant hepatitis B virus-associated fulminant hepatitis during infliximab therapy for rheumatoid arthritis

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**Abstract** A 73-year-old female, who suffered from rheumatoid arthritis for 10 years, developed precore mutant hepatitis B virus-associated fulminant hepatitis after 1 year of infliximab therapy and subsequent methotrexate withdrawal. We emphasize the importance of preemptive antiviral therapy before starting infliximab administration and withdrawing immunosuppressive drugs.

**Keywords** Fulminant hepatitis · HBV · Infliximab · MTX · Rheumatoid arthritis

## Introduction

Infliximab, a tumor necrosis factor-α (TNF-α) inhibitor, has become the standard therapy for active rheumatoid arthritis (RA), but also has influences on bacterial, viral, and tuberculous infections [1]. In particular, the reactivation of hepatitis B virus (HBV) is problematic [2] and HBV-induced fulminant hepatitis following infliximab treatment has been reported in patients with Crohn's disease and Still's disease [3–6]. Here, we describe an autopsy case of RA who developed precore mutant HBV-associated fulminant hepatitis after 1 year of infliximab therapy and subsequent methotrexate (MTX) withdrawal.

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## Case report

A 73-year-old female, with a 10-year history of RA, had been treated with prednisone (5–10 mg/day) and MTX (5–8 mg/week) for 10 and 6 years, respectively. These were ineffective, and infliximab (150 mg every 8 weeks, 3 mg/kg) was added between June 2004 and May 2005, with liver function tests at each infusion. A pretreatment screening test showed that HBsAg and HBcAb were positive, and hepatitis C virus antibody was negative. Liver tests and images showed no abnormalities. MTX and prednisone were tapered, and prednisone was withdrawn in April 2005. An effective clinical improvement of joint disease was observed, and C reactive protein became normal. After the eighth infusion of infliximab, the liver function was found to be abnormal (AST 291 IU/L (normal <40), ALT 331 IU/L (<40)), and MTX therapy was withdrawn. Her liver function progressively worsened (AST 1690 IU/L, ALT 1390 IU/L), and she was admitted to our hospital in June 2005.

On admission, she had jaundice and mild hepatic encephalopathy. Laboratory data revealed AST 393 IU/L, ALT 544 IU/L, γGTP 130 IU/L (<30), LDH 364 IU/L (115~245), total bilirubin 15.7 mg/dL (<1.0), prothrombin time 8% (>70), and $NH_3$ 168 μg/dL (30~80). Her serological status was as follows: HBsAg, HBeAb, and IgM HBcAb were positive, while HBsAb and HBeAg were negative. HBV-DNA was present with a level of 4.3 log copies per milliliter (<2.6) by polymerase chain reaction assay. HBV was of genotype B and the precore mutant was 100%. She had no HIV and IgM hepatitis A virus antibodies. An abdominal computed tomography (CT) scan showed atrophic liver. Therefore, a diagnosis of fulminant hepatitis due to the reactivation of HBV from a previously asymptomatic HBV carrier state was made, and lamivudine (a reverse-transcriptase inhibitor of viral DNA polymerase)

therapy (150 mg/day) and plasma exchange were immediately performed. Her condition temporarily improved, and liver transplantation was considered. However, her liver function deteriorated and an abdominal CT showed more atrophic liver. She died of liver failure 18 days after admission. A postmortem examination was performed, and the ascites volume was 170 mL. The liver was remarkably atrophied, weighing just 508 g, and more than 80% of the hepatocytes were necrotic. CD8-positive cytotoxic T lymphocytes had predominantly infiltrated, and amyloid A protein deposition as a result of RA was seen in the hepatic artery (Fig. 1). Vessels in most organs showed amyloid A protein deposition.

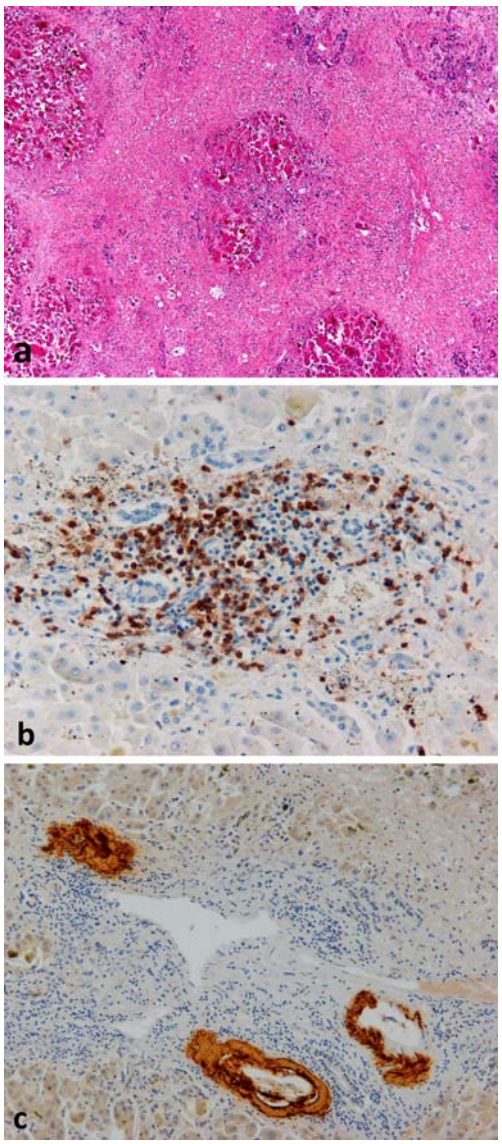


**Fig. 1** Liver histology. **a** Massive hepatocytic necrosis (H&E stain, 4×). **b** Predominantly infiltrated CD8 positive lymphocytes (20×). **c** Amyloid A immunoreactivity of the hepatic artery (10×)

## Discussion

Our case suggests that infliximab treatment induces HBV precore mutation and the destruction of HBV-infected hepatocytes by CD8-positive cytotoxic T lymphocytes. The HBV precore mutation is involved in the pathogenesis of fulminant hepatitis [7], and the reactivation of a precore mutant HBV during infliximab therapy has been reported [8]. TNF-α has antiviral properties by inhibiting the replication of HBV DNA and mediates apoptosis of cytotoxic T lymphocytes [9, 10]. TNF-α inhibitors may induce fulminant hepatitis following the reactivation of precore mutant HBV and the proliferation of cytotoxic T lymphocytes. In addition to infliximab, long-term MTX treatment and subsequent withdrawal may accelerate HBV reactivation. HBV-positive patients are at increased risk of fulminant hepatic failure after withdrawing immunosuppressive drugs such as MTX because of the hepatocytic attack following sudden reaction of the immune system [11].

Preemptive antiviral therapy with lamivudine is recommended as part of infliximab therapy for HBV-positive patients, even if they have normal liver function or an undetectable viral load [8, 12]. The delayed onset of antiviral therapy in our patient may have been responsible for the fatal outcome. This case shows that infliximab therapy in an HBV-positive patient with RA can lead to fulminant hepatitis, possibly through the reactivation of precore mutant HBV and the proliferation of cytotoxic T lymphocytes. In addition, this case illustrates the importance of anti-HBV therapy before starting infliximab administration and withdrawing immunosuppressive drugs.

**Disclosures** None



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