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# Etanercept Treatment as a Predisposing Factor for Acute Liver Injury Caused by HEV Infection - A Case Report

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## Abstract

We report a case of a 58-year-old patient with rheumatoid arthritis treated with Methotrexate (Mtx) and etanercept, who developed a sudden elevation of the liver enzymes during routine monitoring. Initial workup excluded common causes of hepatotoxicity. Further evaluation revealed acute Hepatitis E Virus (HEV) infection. Immunosuppressive therapy may have contributed to the atypical presentation. Transaminase activity levels nearly normalized after a short course of prednisone therapy. This case highlights the importance of considering HEV infection in immunosuppressed patients presenting with unexplained hepatic enzyme elevation.

**Keywords: Hepatitis E virus; Etanercept treatment; Liver injury; Hepatotoxicity**

## Introduction

Etanercept is a Tumour Necrosis Factor (TNF) inhibitor, widely used in the treatment of autoimmune disorders, including inflammatory rheumatic diseases, particularly in patients who exhibit an inadequate response to Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) [1].

TNF inhibitors may cause a variety of Adverse Drug Reactions (ADRs), with infections and malignancies being the most frequently reported ones [2,3]. Less common ADRs comprise gastrointestinal, pulmonary, haematological and neurological disorders [3,4].

Drug Induced Liver Injury (DILI) associated with etanercept may manifest in a spectrum of clinical presentations, ranging from mild elevations in serum transaminases activity to severe acute liver injury accompanied by hyperbilirubinemia and coagulation disturbances. Rarely, TNF inhibitors may cause drug-induced autoimmune hepatitis or secondary sclerosing cholangitis [5].

The diagnosis of DILI remains a clinical challenge and is frequently subject to overestimation due to the nonspecific nature of its presentation. Accurate identification of DILI requires a thorough evaluation and systematic exclusion of alternative ethology of hepatocellular injury, particularly hepatotropic viral infections, which may mimic or exacerbate drug-induced hepatic injury [6].

In this case report, we describe a patient treated with etanercept, who presented with acute liver injury, in whom an acute hepatitis E virus (HEV) infection was subsequently identified, highlighting the diagnostic complexity of hepatic injury in immunosuppressed patients.

## Case Presentation

A 46-year-old female patient with Rheumatoid Arthritis (RA) and type 1 diabetes mellitus was admitted to the Department of Rheumatology due to elevated transaminases activity.

One year before admission, subcutaneous MTX at a dose of 20 mg/week was introduced, however the improvement was incomplete. Consequently, the patient was enrolled in a clinical trial with etanercept and received the treatment for approximately six months. Two weeks before hospital admission, progressive elevation of transaminases was observed, leading to discontinuation of both etanercept and MTX. Despite drug withdrawal, laboratory tests showed further increase of liver enzyme activity.

On admission, the patient was in good general condition. Physical examination revealed no signs of synovitis and no other abnormalities. Laboratory tests revealed a continued elevation of transaminase activity - Alanine Aminotransferase (ALT) up to 1952 U/l, Asparagine

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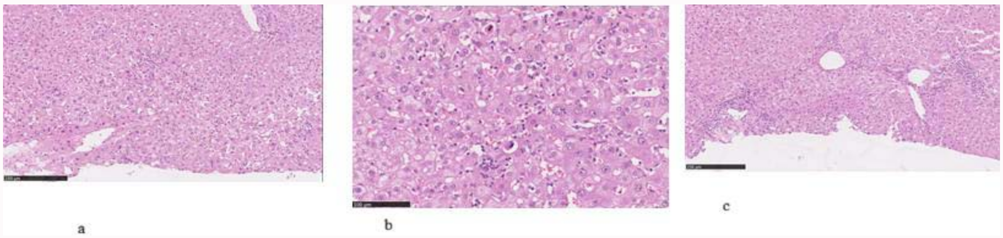


**Figure 1:** Liver biopsy, Haematoxylin and eosin staining: a: increased number of eosinophils, ceroid-laden macrophages, and overall lobular inflammation, scale bar x 250 um, b: Eosinophilic bodies scale bar x 100 um, c: Portal tracts with an infiltrate composed of plasma cells and Kupffer cells scale bar x 250 um.

**Table 1:** Dynamics of changes in the laboratory test results of the presented patient.

| Parameter | Reference Range | Day 1 | Day 2 | Day 5 | Day 7 | Day 9 | Day 35 |
|---|---|---|---|---|---|---|---|
| ALT | 0-35 U/l | 1541 | 1595 | 1952 | 1540 | 930 | 47 |
| AST | 0-35 U/l | 996 | 1069 | 1195 | 544 | 162 | 30 |
| ALP | 35-104 U/l | - | 317 | 338 | 291 | 256 | - |
| GGT | 5-36 U/l | - | 250 | 259 | 221 | 188 | 59 |
| Bilirubin | 0-1.2 mg/dl | 1 | - | 1.4 | - | - | 0.3 |
| INR | 0.8-1.2 | 0.96 | - | 1.02 | 1.04 | 1.01 | - |
| Albumin | 3.9-5.0 g/dl | 3.5 | - | - | 3.6 | 4 | - |
| HEV infection | Positive | Positive | Positive | Positive | Positive | Positive | Negative |

Aminotransferase (AST) up to 1195 U/l, as well as an increase in Alkaline Phosphatase (ALP) activity to 338 U/l. Moreover hypoalbuminemia 3.5 g/dl, hyperbilirubinemia 1.4 mg/dl and the INR within the normal range were noted (Table 1). Infections with HAV, HBV, HCV, HIV, CMV and EBV were excluded. Serological tests for anti-HEV antibodies were not available, therefore only HEV RNA detection was performed, and the result was pending throughout the hospitalization. Two abdominal ultrasounds revealed no abnormalities. Given a progressive rise in transaminase activity more than a month after discontinuing MTX and etanercept, along with presence of other autoimmune diseases, Autoimmune Hepatitis (AIH) was suspected. Prednisone at a starting dose of 30 mg/day was introduced (day 5$^{th}$ after admission, Table 1), resulting in rapid decrease in transaminase activity. Serologic testing for autoimmune liver and biliary diseases was negative. Due to the unclear mechanism of hepatic injury, a liver biopsy was performed. In the histopathological examination ballooning, feathery and acidophilic degeneration of hepatocytes and over all lobular inflammation were described (Figure 1a,1b). Moreover, numerous Kupffer cells were present both intralobular and in portal tracts and plasma cells were scattered in portal tracts and within the lobules (Figure 1c). The findings were indicative of nonspecific acute hepatitis, potentially drug induced.

Based on the overall clinical context the liver injury deemed most likely to be drug induced. Given the progressive normalization of transaminase activity following initiation of corticosteroid therapy, the patient was discharged with a recommendation for gradual tapering of prednisone.

One week after discharge, previously pending laboratory results were reported, confirming the presence of HEV RNA. The patient was referred to an infectious diseases outpatient clinic and continues to be followed by both gastroenterology and rheumatology specialists.

Almost complete normalization of transaminases was achieved after one month of treatment with prednisone, while subsequent HEV RNA testing after prednisone withdrawal confirmed spontaneous elimination of HEV infection. On day 35th, spontaneous resolution of HEV infection was observed (Table 1). Ultimately, the acute liver failure was attributed to a combination of drug-induced injury and superimposed viral hepatitis.

## Discussion

Drug-induced liver injury is a well-recognized complication, which may be associated with tumour necrosis factor- inhibitors. Etanercept has been reported to carry a relatively low risk of hepatotoxicity, and its latency period may range from a few weeks to several months following treatment initiation [6,7]. The clinical course is generally mild and self-limiting, with most patients experiencing full recovery after discontinuation of the drug.

However, in patients with more pronounced liver enzyme elevations, treatment with systemic corticosteroids may accelerate recovery and prevent progression to severe liver dysfunction. Concomitant administration of methotrexate has been shown to exert a protective effect against DILI in patients treated with TNF inhibitors [6]. In the diagnostic evaluation of DILI, the Roussel Uclaf Causality Assessment Method (RUCAM) is a validated tool commonly used to assess the likelihood of a causal relationship between the suspected drug and liver injury. In the present case, the calculated R value, used to classify the pattern of liver injury, was 5.8-consistent with a hepatocellular type of damage. The total RUCAM score was 1, corresponding to a classification of 'unlikely' for drug-related hepatotoxicity [8].

Recent evidence suggests that up to 8% to 12% of cases of acute liver injury initially attributed to DILI are, in fact, attributable to previously unrecognized acute hepatitis E virus infection [9]. HEV typically causes a self-limiting infection in immunocompetent individuals; however, in immunosuppressed patients, it may progress to acute liver failure or chronic hepatitis [10]. Infection most commonly occurs through the consumption of contaminated water or animal-derived food products, such as raw pork meat, milk, and seafood. In recent years, an increase level of HEV infections has been observed in developed countries [11].

The European Association for the Study of the Liver (EASL) guidelines recommend testing for hepatitis HEV infection using both anti-HEV IgM serology and HEV RNA PCR in all patients with suspected DILI, particularly those presenting with atypical symptoms or significantly elevated serum ALT activity. Laboratory test results can provide valuable assistance in establishing a definitive diagnosis. In a comparative study, Dalton et al. observed that patients with acute HEV infection exhibited significantly higher serum ALT (>300 IU/L), elevated ALT/ ALP ratio (≥2), and lower serum bilirubin concentrations compared to patients with confirmed DILI. [9,12-15].

Although non-invasive investigations are essential first steps, liver biopsy can provide definitive diagnostic clarification in patients with persistently elevated aminotransferase levels despite empirical treatment, particularly when autoimmune or cholestatic etiologist are under consideration [16].

In patients with active HEV infection, specific antiviral therapy is usually not necessary, however, in patients with immunosuppression antiviral intervention may be justified. Current clinical practice typically endorses a 3-month course of ribavirin or in selected circumstances pegylated interferon α [17,18].

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