

# Autoimmune Hepatitis Triggered by Treatment With Pegylated Interferon $\alpha$ -2a and Ribavirin for Chronic Hepatitis C

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## Abstract

Hepatitis flare is rarely observed during treatment with pegylated interferon alpha for hepatitis C virus (HCV) infection. A 49-year-old man receiving pegylated interferon  $\alpha$ -2a for HCV infection had icterus and hyperbilirubinemia in the 14th week of therapy, with HCV RNA undetectable after the 12th dose. Liver biopsy was suggestive of chronic hepatitis with cirrhosis without interface pattern. Pegylated interferon was discontinued; a few weeks later, his aminotransferases and immunoglobulin levels increased significantly. Antibody to cytosolic liver antigen-1 was positive, and liver biopsy revealed lymphoplasmacytic infiltrate with intense interface hepatitis, consistent with autoimmune hepatitis.

## Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide, with approximately 3% of the world population chronically infected.<sup>1,2</sup> The combination of pegylated interferon alpha and ribavirin is well-established therapy for HCV infection, but is associated with many side effects, and close monitoring of patients is required during therapy.<sup>2,3</sup> Interferon-induced flares have been attributed to the stimulatory effect of the treatment, though hepatitis flare is rarely observed.<sup>3,4</sup> Limited reports of hepatotoxicity or liver enzyme flares associated with interferon therapy have been published.

## Case Report

A 49-year-old man presented with episodes of melena for 1 month. Upper gastrointestinal endoscopy revealed large esophageal varices, which were band ligated. Physical examination revealed a body mass index of 24 kg/m<sup>2</sup>, a midline abdominal scar from prior exploratory laparotomy, and mild splenomegaly. Laboratory data revealed an infection with HCV (genotype 3, HCV RNA 1,794,981 IU/mL), alanine aminotransferase (ALT) 52 IU/L, aspartate aminotransferase (AST) 88 IU/L, alkaline phosphatase (AP) 243 IU/L, total bilirubin 0.8  $\mu$ mol/L, total protein 6.9 g/dL, serum albumin 3.1 g/dL, hemoglobin 12.4 g/dL, leukocyte count 5,800/mm<sup>3</sup>, and platelet count 98,000/mm<sup>3</sup>. Abdominal ultrasonography revealed coarse echotexture of liver, mild splenomegaly, and loss of phasicity in portal vein, suggestive of portal hypertension. His Child-Turcotte-Pugh score was 6, and his model for end-stage liver disease (MELD) score was 12. Pegylated interferon  $\alpha$ -2a 180  $\mu$ g per week and ribavirin 800 mg per day was started.

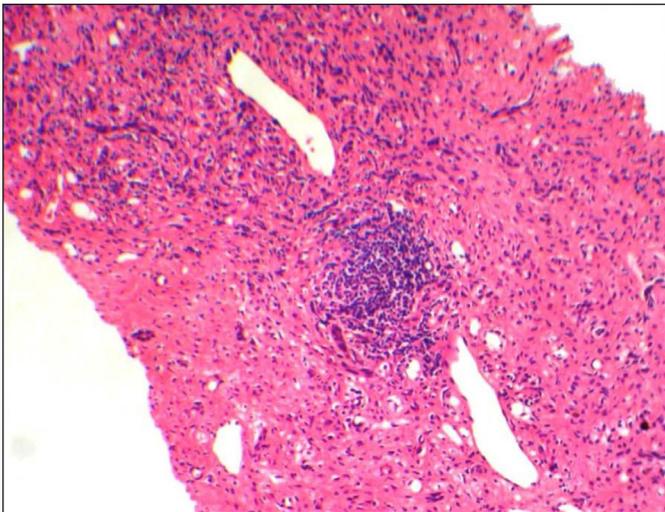
After 4 weeks, laboratory data revealed leukocytes 2,400/mm<sup>3</sup>, hemoglobin 11.2 g/dL, platelets 68,000/mm<sup>3</sup>, ALT 37 IU/L, AST 86 IU/L, and HCV RNA 432 IU/mL. His bilirubin increased to 2.6  $\mu$ mol/L with no evidence

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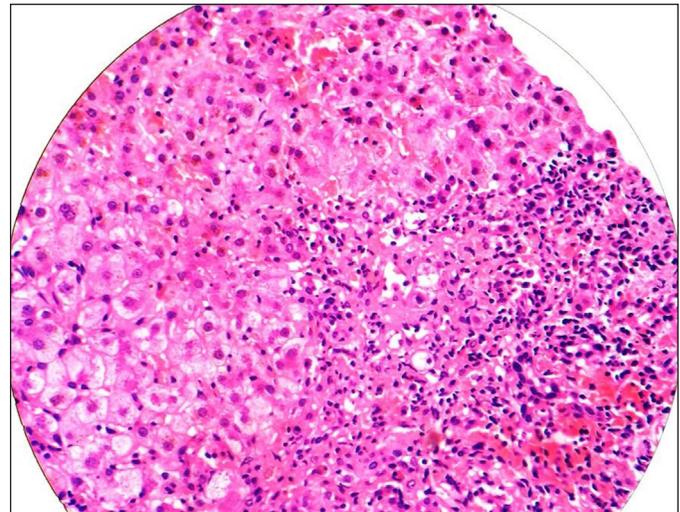


**Figure 1.** Initial liver biopsy with H&E stain showing ongoing chronic hepatitis with fibrous septa containing moderate inflammation. Inflammatory cells consist of mainly lymphocytes and few plasma cells.

of hemolysis. The dose of interferon was decreased from 180  $\mu$ g to 135  $\mu$ g to continue treatment. After 12th week of therapy, his HCV RNA was undetectable. In the 14th week, he complained of yellow discoloration of eyes and urine associated with nausea. Bilirubin was 6.5  $\mu$ mol/L, though leukocyte count, platelet count, and hemoglobin levels had decreased to 2,200/mm<sup>3</sup>, 60,000/mm<sup>3</sup>, and 10 g/dL, respectively. Pegylated interferon and ribavirin treatment were discontinued, with decreases in AST and ALT but persistent elevation in bilirubin.

Hepatitis B surface antigen, hepatitis B virus (HBV) DNA, anti-nuclear antibody, anti-mitochondrial antibody, anti-liver kidney microsome 1 antibody, anti-double stranded DNA antibody, anti-hepatitis A virus IgM antibody, and anti-hepatitis E virus IgM antibody were negative. Thyroid stimulating hormone was normal. HCV RNA was undetectable after termination of therapy until 6 months of follow-up. Liver biopsy was suggestive of chronic hepatitis with cirrhosis, without any evidence of steatosis, significant interface, or pseudoacinar pattern (Figure 1).

A few weeks later, aminotransferase levels increased to more than 10 times above normal. Serum total immunoglobulin G was 2,630 IU/mL. Antibody to cytosolic liver antigen 1 (Anti LC1) was positive. Repeat liver biopsy revealed lymphoplasmacytic infiltrate with intense interface hepatitis (Figure 2). The International Autoimmune Hepatitis Group scoring system score was 12 (probable).<sup>5</sup> The patient was started on oral prednisolone, and his aminotransferase levels declined significantly after a few days of treatment. He is being monitored with aminotransferase levels and HCV RNA, and remains on maintenance prednisolone 10 mg per day.



**Figure 2.** Repeat liver biopsy with H&E stain revealed dense lymphoplasmacytic infiltrate and intense interface hepatitis.

## Discussion

The combination of pegylated interferon alpha and ribavirin is a well-established therapy for chronic HCV infection in countries where newer drugs like sofosbuvir are not available.<sup>2,3</sup> Pegylated interferon alpha has several antiviral mechanisms, but its role in hepatitis C treatment seems to be related to its immunomodulatory effect. About 10–14% of the patients discontinue HCV infection therapy due to adverse effects. Most common effects are flu-like symptoms such as fatigue, headache, and fever, psychiatric side effects (depression, irritability, and insomnia), and laboratory abnormalities.<sup>3</sup>

The European Association for the Study of the Liver (EASL) guidelines recommend stopping treatment after severe hepatitis flares, which occur due to stimulatory effects of interferon on T-cell cytolytic activity and natural killer cell function.<sup>2</sup> Detecting the cause of hepatitis flare is usually difficult.<sup>5</sup> Autoimmune disorders are observed in 4–19% of patients receiving interferon alpha.<sup>2,6</sup> Interferon-induced autoimmune hepatitis flare during treatment has been observed in 25–40% of HBV patients, and though unusual in HCV patients, induction of autoimmune hepatitis by pegylated interferon  $\alpha$ -2b in chronic HCV has been reported.<sup>4,7</sup> Hepatitis flares have been reported with enzymes 10–20 times above the upper limit of normal during interferon and ribavirin therapy.<sup>8</sup> Anti-Golgi complex antibody has been detected in one of these.<sup>9</sup> Our patient's autoantibodies were negative before he started treatment, and histology was inconsistent with underlying autoimmune disease. Although autoimmune hepatitis is a rare complication during interferon therapy, it should be considered when there is an increase in aminotransferase levels.

## Disclosures

Author contributions: All authors contributed equally to the manuscript. CD Rathi is the article guarantor.

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