

## Case Report

# Concurrent Autoimmune Hepatitis and Grave's Disease in Hepatitis C during Pegylated Interferon $\alpha$ -2a and Ribavirin Therapy

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## ABSTRACT

Classical interferon- $\alpha$  has been shown to be associated with the development of a variety of autoimmune disorders. A 34-year-old white woman with chronic hepatitis C virus infection who was treated with pegylated interferon  $\alpha$ -2a and ribavirin, developed Grave's disease and autoimmune hepatitis (AIH) at 32 and 44 weeks, respectively, following initiation of the therapy. The diagnosis of AIH was made based on the new development of anti-smooth muscle antibodies, anti-mitochondrial antibodies, and liver biopsy findings. It was confirmed by positive response to steroid challenge and was assessed according to the international AIH scoring system. Based on the previous case reports, we review the existing literature. Clinicians should be aware of the possibility of multiple autoimmune disorders during interferon-based therapy for chronic hepatitis.

**Key Words:** Autoimmune hepatitis, Grave's disease, hepatitis C, interferon

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Currently, a combination therapy with pegylated interferon (PEG-IFN) and ribavirin is being widely used for the treatment of chronic hepatitis C (CHC). We hereby describe a case of concurrent onset of autoimmune hepatitis (AIH) and Grave's disease during this therapy, via the autoimmune process. These findings suggest that clinicians should be conscious of the possible development of multiple autoimmune diseases during a combination therapy for CHC.

## CASE REPORT

A 34-year-old Caucasian woman, an active smoker with a history of vaginal lichen sclerosus, was evaluated for symptoms of fatigue. She denied alcohol, intravenous drug abuse, or blood transfusions and was in a monogamous relationship.

Workup revealed hepatitis C genotype 1b virus with a viral

load of 5720 IU/mL. Her pretreatment alanine transaminase (ALT) and aspartate transaminase (AST) were 72 and 74 U/L, with liver biopsy demonstrating mild inflammation in the liver and minimal fibrosis [Figure 1; Table 1].

The patient had normal thyroid function tests prior to initiating therapy with 180  $\mu$ g of PEG-IFN weekly and 400 mg of ribavirin twice daily. She had a rapid virologic response with her viral load reaching below 5 IU/mL within a month. After 32 weeks of treatment, she developed palpitations, tremors, weight loss, and insomnia. Laboratory evaluation revealed that thyroid stimulating hormone was suppressed at 0.02  $\mu$ IU/mL; free T3 and free T4 were elevated at 1007pg/dL and 3.45ng/dL, respectively. There was a diffuse and intense homogenous Iodine-123 uptake by the thyroid. In spite of negative thyroid stimulating immunoglobulin (TSI) antibodies, the presence of typical clinical manifestations along with the diffuse uptake in the scintigraphy was consistent with Grave's disease. She received radioiodine ablation for thyrotoxicosis without the discontinuation of antiviral therapy. At 44 weeks following initiation of her treatment, her liver enzymes became elevated with AST 652, ALT 432, and ALP 413 with normal bilirubin levels [Figure 2].

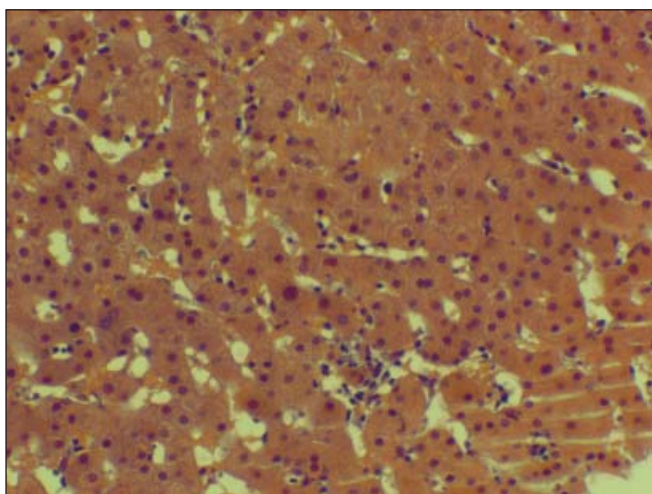
Serologic evaluation excluded viral hepatitis, the level of

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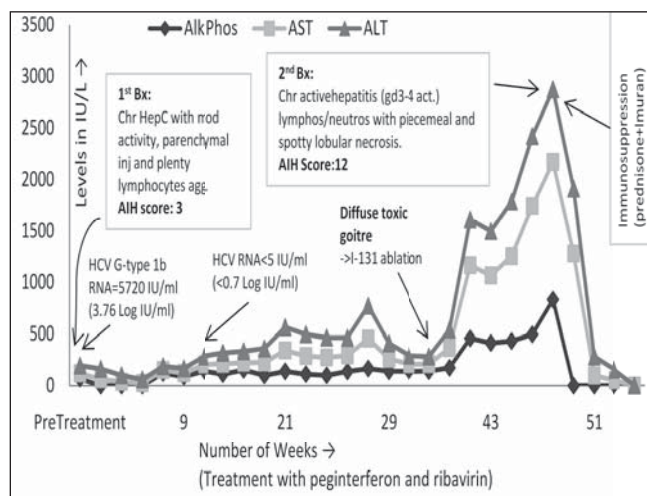
**Table 1: Laboratory findings at presentation**

|                  |                      |                             |                        |              |                  |
|------------------|----------------------|-----------------------------|------------------------|--------------|------------------|
| WBC              | 7.0 K/cmm (4.5–11.0) | BUN                         | 12 mg/dL (7–18)        | HCV Ab       | Positive         |
| Hb               | 12.8 g/dL (12–16)    | Creatinine                  | 0.75 mg/dL (0.6–1.0)   | HCV RNA      | 5720 IU/mL       |
| Plt              | 236 K/cmm (150–450)  | Uric acid                   | 3.9 mg/dL (3.6–8.3)    | HCV Genotype | 1b               |
|                  |                      | Na                          | 138 mmol/L (136–145)   | HBs-Ag       | Non-reactive     |
| PT               | 10.4 s (9–11.6)      | K                           | 4.7 mmol/L (3.5–5.1)   | HBs-Ab       | Non-reactive     |
| AST              | 52 U/L (15–37)       | Cl                          | 102 mmol/L (98–107)    | HB-core Ab   | Non-reactive     |
| ALT              | 74 U/L (30–65)       | Total cholesterol           | 206 mg/dL (<200)       | Hep A AB     | Non-reactive     |
| ALP              | 68 U/L (50–136)      | Glucose                     | 81 mg/dL (70–100)      | ANA          | Negative         |
| Total bilirubin  | 0.4 mg/dL (0.0–1.0)  |                             |                        | ASMA         | Negative         |
| Direct bilirubin | 0.07 mg/dL (0.0–0.3) | Ferritin                    | 86 ng/mL (<105)        | LKM-1        | Negative         |
| Total protein    | 7.2 g/dL (6.4–8.2)   | Ceruloplasmin               | 53 mg/dL (18–53)       | CRP          | 0.1 mg/dL (<0.8) |
| Albumin          | 3.4 g/dL (3.4–5.0)   | Thyroid stimulating hormone | 1.26 ng/dL (0.34–4.82) | RF           | 4 IU/mL (<14)    |

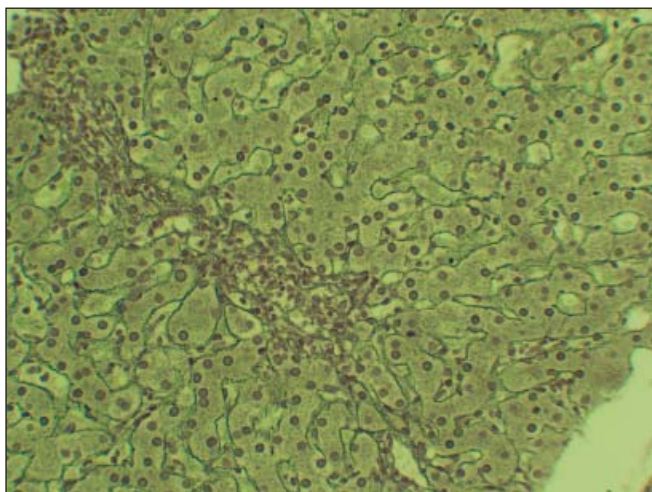
HCV, hepatitis C virus; HBs, hepatitis B surface; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody(anti-actin); LKM-1, liver–kidney muscle antibody. Normal values are indicated within parenthesis.



**Figure 1:** Pretreatment liver biopsy showing mild inflammation and minimal fibrosis



**Figure 2:** Clinical course of pegylated interferon  $\alpha$ -2 plus ribavirin therapy for hepatitis C virus infection



**Figure 3:** Liver biopsy following treatment with pegylated interferon  $\alpha$ -2 showing interface hepatitis and lymphocytic infiltrate

al-antitrypsin was normal and there was no evidence of Wilson's disease or hemochromatosis. She was not on any prescription or over-the-counter medications that could explain this unusual elevation of liver enzymes.

Further workup revealed newly elevated anti-mitochondrial and anti-smooth muscle antibodies with normal immunoglobulins. Repeat liver biopsy [Figure 3] revealed a periportal inflammatory lymphoplasmacytic infiltrates and piecemeal necrosis without biliary lesions and interface hepatitis consistent with a diagnosis of AIH [Table 2].

Applying the International Diagnostic Criteria for the Diagnosis of AIH,<sup>[1]</sup> we derived a score of 12; generating an interpretation of "probable" AIH. She was started on prednisone and azathiopurine with subsequent normalization of transaminases. The pattern of transaminase

**Table 2: Laboratory findings at the time of elevated transaminases**

|                  |                      |            |                      |               |                       |
|------------------|----------------------|------------|----------------------|---------------|-----------------------|
| WBC              | 2.6 K/cmm (4.5–11.0) | BUN        | 8 mg/dL (7–18)       | HCV RNA       | <5 IU/mL              |
| Hb               | 10.3 g/dL (12–16)    | Creatinine | 0.76 mg/dL (0.6–1.0) | HCV Ab        | Reactive (24.7)       |
| Plt              | 109 K/cmm (150–450)  | Uric acid  | 3.9 mg/dL (3.6–8.3)  | Hep A Ab      | Non-reactive          |
| PT               | 11.7 sec (9–11.6)    | Na         | 134 mmol/L (136–145) | Hep B Core Ab | Non-reactive          |
| AST              | 1245 U/L (15–37)     | K          | 5.7 mmol/L (3.5–5.1) | HBs-Ab        | Non-reactive          |
| ALT              | 496 U/L (30–65)      | Cl         | 100 mmol/L (98–107)  |               |                       |
| ALP              | 68 U/L (50–136)      | Glucose    | 87 mg/dL (70–100)    | ASMA          | 38 (high positive)    |
| Total bilirubin  | 0.7 mg/dL (0.0–1.0)  | Hgb A1c    | 5.2% (4.8–6.0)       | AMA           | Positive              |
| Direct bilirubin | 0.34 mg/dL (0.0–0.3) | Ferritin   | 396 ng/mL (<105)     | ANA           | Negative              |
| Total protein    | 8.3 gm/dL (6.4–8.2)  | TIBC       | 321 ug/dL (260–445)  | IgM           | 180 mg/dL (40–230)    |
| Albumin          | 3.2 g/dL (3.4–5.0)   | Iron       | 83 (50–170)          | IgG           | 1053 mg/dL (694–1618) |

HCV, hepatitis C virus; HBs, hepatitis B surface; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody (anti-actin); AMA, anti-mitochondrial antibody. Normal values are indicated within parenthesis.

elevation, positive anti-mitochondrial and anti-smooth muscle antibodies, histologic features and response to prednisone and azathiopurine confirmed the diagnosis of AIH. Multiple hepatitis C virus (HCV) RNA levels remained undetectable.

## DISCUSSION

The combination of PEG-IFN and ribavirin is the standard therapy for HCV.<sup>[2]</sup> The immunogenic activity of PEG-IFN may trigger the emergence, exacerbation, or de novo manifestation of a range of autoimmune disorders, including thyroid dysfunction, type 1 diabetes mellitus, immune-mediated thrombocytopenia, hemolytic anemia, psoriasis, rheumatoid arthritis, systemic lupus-like syndromes, autoimmune gastritis, primary biliary cirrhosis, AIH, and sarcoidosis, with their reported prevalence ranging between 4% and 19%.<sup>[3–5]</sup>

The occurrence of AIH has been reported in patients receiving IFN for multiple sclerosis,<sup>[3]</sup> chronic myeloid leukemia,<sup>[4]</sup> and more recently in, malignant melanoma.<sup>[5]</sup> In CHC patients, initial case reports of exacerbation of liver disease during treatment with IFN were ascribed to AIH, after being incorrectly diagnosed as viral hepatitis and aggravated by the immunostimulating effects of IFN. However, in a study early last decade, García-Buey *et al* reported 7 women out of 144 patients initially diagnosed as true HCV, in whom IFN- $\alpha$  treatment resulted in the aggravation of liver disease, which successfully responded to corticosteroids plus azathiopurine.<sup>[6]</sup> They concluded that in female patients with HCV, a genetic susceptibility to AIH may exist, possibly triggered by immunostimulating effects during interferon therapy.<sup>[6]</sup> Since then there have been sporadic case reports in the english literature [Table 3] with biopsy-proven AIH following PEG-IFN treatment, which was successfully managed by steroids or azathiopurine.

From Table 3 it is clear that the majority of cases have occurred in females.<sup>[7–11]</sup> Nearly half of the reported patients, including ours were Caucasian.<sup>[8,9,12]</sup> A majority of the patients (similar to our patient) were suffering from type 1b HCV infections.<sup>[8,10,12]</sup> However, unlike our patient, the rest of the patients were treated with PEG-IFN type 2b. Recently a case of AIH, which developed nearly 2 years after viral clearance with IFN, was reported, signifying the importance of long-term follow-up even after sustained virologic response, at least in those patients with underlying autoimmune diathesis.<sup>[11]</sup> IFN-induced AIH culminated into fulminant hepatitis in two of the reported cases.<sup>[8,10]</sup>

In general, because of the general attenuation of immune response in HIV subjects, autoimmune diseases were believed to be infrequent. However in 2006, Cazanave reported AIH in HCV–HIV co-infected patient who was treated with IFN.<sup>[13]</sup> Further case reports<sup>[9,10]</sup> confirmed that early initiation of anti-retroviral therapy leads to the preservation of good immune status, thus predisposing HIV-positive patients to autoimmune diseases similar to the general population.<sup>[9]</sup>

The use of PEG-IFN and ribavirin for HCV recurrence post-liver transplant has also been associated with AIH.<sup>[12,14]</sup> Furthermore, the occurrence of a new type of graft dysfunction in liver-transplanted patients receiving PEG-IFN and ribavirin, not related to rejection but due to de novo AIH has been confirmed by two independent studies.<sup>[15,16]</sup>

The fascinating spectrum of thyroid disease associated with PEG-IFN therapy has been recently classified into autoimmune interferon-induced thyroiditis (IIT) and non-autoimmune IIT.<sup>[17]</sup> Autoimmune IIT can manifest as a clinical disease, that is, as Grave's disease or Hashimoto's thyroiditis, or as a subclinical disease, that is, the production of thyroid autoantibodies (TAb) without abnormal thyroid functions.<sup>[17]</sup> Non-autoimmune IIT can manifest as destructive

**Table 3: Previous case reports of AIH following PEG-IFN therapy reported in the english literature**

| Author<br>Year<br>Country             | Age | Sex | HCV<br>genotype | Preexisting<br>antibody      | Time interval<br>prior to AIH | Type of<br>interferon | Diagnostic features  | Special highlights   |
|---------------------------------------|-----|-----|-----------------|------------------------------|-------------------------------|-----------------------|--|--|
| Lorke<br>2004<br>Germany              | 56  | F   | NA              | Negative                     | 9 months                      | PEG-IFN2b             | Positive ANA, ASMA,<br>Anti-LKM type 1,<br>hypergammaglobulinemia<br>AIH score was 13                          |  |
| Kontorinis<br>2006<br>USA             | 55  | M   | Type1           | NA                           | 9 months                      | NA                    | Elevated ASMA, elevated<br>IgG and liver biopsy<br>compatible with AIH<br>AIH score was 18                     | AIH following treatment<br>for recurrent HCV post-<br>liver transplant for early<br>hepatocellular carcinoma |
| Cholangitas<br>2006<br>United Kingdom | 52  | M   | NA              | Low (1:100)<br>titers of ANA | 11 months                     | PEG-IFN 2b            | Elevated IgG, ASMA with<br>anti-actin specificity and liver<br>biopsy compatible with AIH.<br>AIH score was 14 | AIH following treatment<br>for recurrent HCV<br>post-liver transplant for<br>cirrhosis                       |
| Kogure<br>2007<br>Japan               | 27  | F   | Type 1b         | Negative                     | 6 months                      | PEG-IFN2b             | Elevated ANA, Anti-LKM-1<br>and IgG and liver biopsy<br>compatible with AIH.                                   | Fulminant hepatic<br>failure due to AIH during<br>treatment for HCV.   |
| Coriat<br>2008<br>Spain               | 48  | F   | Type 1b         | NA                           | 4 months                      | PEG-IFN2b             | Elevated IgG, ASMA and<br>liver biopsy compatible<br>with AIH<br>AIH score was 13                              | Fulminant AIH after<br>successful treatment in<br>a HIV-HCV co-infected<br>patient leading to death.         |
| Vispo<br>2008                         | 20  | F   | Type 4          | Negative                     | 15 months                     | PEG-IFN2b             | Elevated ANA, polyclonal<br>IgG elevation and liver<br>biopsy compatible with AIH<br>AIH score was 14          | AIH after successful<br>treatment in a HIV-HCV<br>co-infected patient.                                       |
| Petropoulou<br>2010<br>Greece         | 76  | F   | Type2a/2c       | Antithyroid<br>antibodies    | 2 years                       | PEG-IFN2b             | Positive ANA, ASMA, anti-SLA<br>and liver biopsy compatible<br>with AIH. AIH score was >15                     | A 2 year interval between<br>cessation of treatment and<br>the appearance of AIH.                            |
| Trikudanathan<br>2010<br>USA          | 34  | F   | Type 1b         | Negative                     | 44 weeks                      | PEG-IFN2a             | Positive ASMA, AMA and<br>liver biopsy compatible with<br>AIH. AIH score was 12.                               | Dual onset of Grave's<br>disease and autoimmune<br>hepatitis following viral<br>clearance                    |

ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; anti-LKM-1, anti-liver-kidney microsomal antibody; anti-SLA, anti-soluble antigen.

thyroiditis or non-autoimmune hypothyroidism.<sup>[17]</sup> The frequency of interferon-induced Grave's disease has been estimated to be around 1%.<sup>[18]</sup> Well-established predisposing factors for the development of IIT include female sex, hepatitis C, higher doses and longer duration of IFN therapy.<sup>[18]</sup> Interestingly, thyroid disease is less likely to develop in patients with chronic hepatitis B infection who are treated with interferon alfa than in those with chronic HCV infection, despite the use of higher doses of interferon alfa for the treatment of hepatitis B virus. This finding suggests that HCV and interferon alfa may have a synergistic role in inducing thyroid disease during antiviral therapy.<sup>[19]</sup> Studies have shown that the risk of hypothyroidism is higher when compared with hyperthyroidism (3.8% vs 2.8%)<sup>[20]</sup> and thyroid dysfunction is more common in females when compared with males (13% vs 3%).<sup>[20]</sup> The time of onset of thyroid dysfunction is extremely variable—from 8 to 23 months following commencement of interferon.<sup>[20]</sup> In general, thyrotoxicosis is usually seen earlier than hypothyroidism.<sup>[18]</sup>

The presence of lichen sclerosis in our patient suggests that she had an underlying autoimmune diathesis. The simultaneous onset of two autoimmune disorders suggests a vigorous triggering of the immune system by pegylated IFN- $\alpha$  in a genetically predisposed individual. HCV infection itself may perpetuate the immune cascade, which leads to autoimmune disease, especially in genetically predisposed subjects. It reflects disturbances in self-tolerance due to the molecular mimicry between viral proteins and autoantigens. IFN plays a vital role in eradicating virally infected hepatocytes, but could also enhance recognition of autoantigens, leading to an increased risk for autoimmune diseases. It stimulates natural killer cells and cytotoxic lymphocytes, by stimulating major histocompatibility complex class I expression, and polarizes the adaptive immune response to Th1 (T helper cells).<sup>[12]</sup> This imbalance toward the Th1-mediated response induced by IFN may be the potential pathogenic mechanism in both Grave's disease and AIH.

To conclude, AIH, which could lead to fulminant hepatitis,



should be considered as one possible reason for an increase of transaminase levels during IFN therapy. A high clinical awareness is recommended in patients with known genetic susceptibility or positive autoimmunity markers prior to or during IFN- $\alpha$  therapy.

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