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

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 immunoglobin (TSH) 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...
a1-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,[1] 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
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. 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%. From Table 3 it is clear that the majority of cases have occurred in females. Nearly half of the reported patients, including ours were Caucasian. A majority of the patients (similar to our patient) were suffering from type 1b HCV infections. 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.

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. Further case reports 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.

The use of PEG-IFN and ribavirin for HCV recurrence post-liver transplant has also been associated with AIH. 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.

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. 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. Non-autoimmune IIT can manifest as destructive

| 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) |
| Pt 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) | Hb A1c 5.2% (4.8–6.0) | AMA Positive |
| Direct bilirubin 0.34 mg/dL (0.0–0.3) | Ferritin 396 mg/dL (<105) | ANA Negative |
| Total protein 8.3 g/dL (6.4–8.2) | TIBC 321 mg/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.
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-α 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 1 expression, and polarizes the adaptive immune response to Th1 (T helper cells). 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-α therapy.

REFERENCES

1. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: Review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929-38.

2. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. An update. Hepatology 2009;49:1335-74.

3. Durelli L, Bongioanni MR, Ferrero B, Oggero A, Marzano A, Rizzetto M. Interferon treatment for multiple sclerosis: Autoimmune complications may be lethal. Neurology 1998;50:570-1.

4. Steegmann JL, Requena MJ, García-Buey ML, Granados E, Romero R, Fernández-Raizada JM, et al. Severe autoimmune hepatitis in a chronic myeloid leukemia patient treated with interferon alpha and with complete genetic response. Am J Hematol 1998;59:95-7.

5. Lebiedz P, August C, Domschke W, Schmidt HH. Interferon (IFN) for malignant melanoma unmasking an autoimmune hepatitis. Eur J Intern Med 2009;20:e3-4.

6. García-Buey L, García-Monzón C, Rodriguez S, Borque MJ, García-Sánchez A, Iglesias K, et al. Latent autoimmune hepatitis triggered during interferon therapy in patients with chronic hepatitis C. Gastroenterology 1995;108:1770-7.

7. Lörke J, Erhardt A, Häussinger D. Induction of autoimmune hepatitis by pegylated interferon α-2b in chronic hepatitis C. Clin Gastroenterol Hepatol 2004;2:A20.

8. Kogure T, Ueno Y, Fukushima K, Nagasaki F, Inoue J, Kakazu E, et al. Fulminant hepatic failure in a case of autoimmune hepatitis in hepatitis C during peg-interferon-alpha 2b plus ribavirin treatment. World J Gastroenterol 2007;13:4394-9.

9. Vispo E, Maida I, Moreno A, Barreiro P, Soriano V. Autoimmune hepatitis induced by pegylated interferon in an HIV-infected patient with chronic hepatitis C. J Antimicrob Chemother 2008;62:1470-2.

10. Coriat R, Podevin F. Fulminant autoimmune hepatitis after successful interferon treatment in an HIV-HCV co-infected patient. Int J STD AIDS 2008;19:208-10.

11. Petropoulou KG, Dourakis SP, Delladetsima J, Archimandritis AJ. Autoimmune hepatitis, 2 years after successful peg-interferon-alpha 2b plus ribavirin treatment in a patient with chronic hepatitis C. Ann Gastroenterol 2010;23:142-5.

12. Kontorinis N, Agarwal K, Elhajj N, Fiel MI, Schiano TD. Pegylated interferon-induced immune-mediated hepatitis post-liver transplantation. Liver Transpl 2006;12:827-30.

13. Cazanave C, Rakotondravelo S, Morlat P, Blanco P, Bonnet F, Beylot J. Autoimmune hepatitis in a HIV-HCV co-infected patient: Diagnostic and therapeutic difficulties. Rev Med Interne 2006;27:414-9.

14. Cholongitas E, Samonakis D, Patch D, Senzolo M, Burroughs AK, Quaglia A, et al. Induction of autoimmune hepatitis by pegylated interferon in a liver transplant patient with recurrent hepatitis C virus. Transplantation 2006;81:488-90.

15. Berardi S, Lodato F, Gramenzi A, D’Errico A, Lenzi M, Bontadini A, et al. High incidence of allograft dysfunction in liver transplanted patients treated with pegylated-interferon alpha-2b and ribavirin for hepatitis C recurrence: Possible de novo autoimmune hepatitis? Gut 2007;56:237-42.

16. Merli M, Gentili F, Giusto M, Attili AF, Corradini SG, Mennini G, et al. Immune-mediated liver dysfunction after antiviral treatment in liver transplanted patients with hepatitis C: Allo or autoimmune de novo hepatitis? Dig Liver Dis 2009;41:345-9.

17. Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: Toward a new classification. Hepatology 2006;43:661-72.

18. Wong V, Fu AX, George J, Cheung NW. Thyrotoxicosis induced by alpha-interferon therapy in chronic viral hepatitis. Clin Endocrinol (Oxf) 2002;56:793-8.

19. Fernandez-Soto L, Gonzalez A, Escobar-Jimenez F, Vazquez R, Ocete E, Olea N, et al. Increased risk of autoimmune thyroid disease in hepatitis C vs hepatitis B before, during, and after discontinuing interferon therapy. Arch Intern Med 1998;158:1445-8.

20. Koh LK, Greenspan FS, Yeo PP. Interferon-alpha induced thyroid dysfunction: Three clinical presentations and a review of the literature. Thyroid 1997;7:891-6.

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