We describe a 72-year-old woman with chronic hepatitis C and autoimmune thrombocytopenic purpura (AITP) during pegylated interferon (PEG-IFN) α. Immunoglobulin G and antinuclear antibody were 2,113 mg/dL and 1,280 at the start, respectively. A liver biopsy negated autoimmune hepatitis. After a 48-week combination therapy with ribavirin, PEG-IFN α-2a was administered. At the 30th month, the platelet count was decreased to 1.1×10^4/μL. Bone marrow biopsy disclosed normocellular marrow compatible with AITP. The platelet-associated IgG (PAIgG) titer rose to 500 ng/10^7 cells. Corticosteroid therapy was successful, and the platelet count and PAIgG titer reverted to 6.4×10^4/μL and 57.3 ng/10^7 cells, respectively.

Key words: autoimmune thrombocytopenic purpura, interferon, platelet-associated immunoglobulin G, steroid therapy, chronic hepatitis C, immunological disorder

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Introduction

A number of autoimmune disorders attributed to interferon treatment such as thyroid disease and diabetes and others have been reported, among which are blood cell-related disorders including red blood cells and platelets. Here, we describe a case of autoimmune thrombocytopenic purpura (AITP) during pegylated interferon (PEG-IFN) α therapy.

Case Report

A 72-year-old woman (149 cm tall, weighing 54 kg) with chronic hepatitis C genotype 1b infection was started on PEG-IFN α-2b (80 μg/week) and ribavirin (600 mg/day) (PEG-IFN/RBV) in July 2006. Laboratory values were as follows: aspartate aminotransferase (AST) 43 (normal, 8-38) IU/L, alanine aminotransferase (ALT) 25 (4-43) IU/L, γ-glutamyl transpeptidase 47 (≤48) IU/L, bilirubin 0.6 (0.2-1.2) mg/dL, hepatitis C virus (HCV)-RNA 2,400 KIU/mL, hemoglobin 12.4 (11.3-15.2) g/dL, white blood cells count (WBC) 2,700 (3,500-9,100) μL, platelets 12.4 (13.0-36.9)×10^4/μL, immunoglobulin (Ig) G 2,113 (870-1,700) mg/dL, IgA 331 (110-410) mg/dL, IgM 334 (46-260) mg/dL, and antinuclear antibody (ANA) 1,280 (<40). A liver biopsy showed moderate inflammation and severe fibrosis (F3, A2) according to the new classification of Desmet et al (1) without plasma cell infiltration (Figs. 1a, 1b). Autoimmune hepatitis was ruled out. During the therapy, serum HCV-RNA remained positive and liver functions such as AST and ALT did not reach normal levels. After completing the 48-week course of PEG-IFN/RBV therapy in June 2007, the patient was put on PEG-IFN α-2a (90 μg) without ribavirin; however, liver functions were not normalized. During both treatment protocols, the number of platelets remained between 4 and 14×10^4/μL.

At the 30th month (October 2008), the platelet count rap-
idly declined to 1.1×10⁴/μL (just 1 week before 6.2×10⁴/μL), other values were WBC 1,500/μL, hemoglobin 9.0 g/dL, and hematocrit 26.8% and petechiae appeared on the patient’s upper extremities. PEG-IFN α-2a was discontinued, and bone marrow biopsy showed normocellular marrow with a myeloid : erythroid (M : E) ratio of 3:1 and an increased number of megakaryocytes (64/mm³) compatible with the diagnosis of AITP (Figs. 2a, 2b). Coagulation test results were normal, a direct Coombs’ test was negative, ANA was 1,280 times (cytoplasmic×160 times), the anticardiolipin antibody was negative and cryoglobulins were positive. The platelet-associated IgG (PAIgG) level on the platelet surface had increased to 500 (normal, 9.0-25.0) ng/10⁷ cells as measured by enzyme-linked immunoassay. The results of a ¹³C-urea breath test were negative for Helicobacter pylori infection, obviating bacteria removal therapy; instead, corticosteroid pulse therapy was started with the intravenous administration of 1,000 mg methylprednisolone sodium succinate for three days, followed by 30 mg of oral prednisolone for 2 weeks and gradually reduced to 5 mg per day. The platelet count reverted to 6.4×10⁴/μL in 14 days, and remained normal while the prednisolone dose was tapered off until the 39th month (July 2009). The PAIgG titer decreased to 57 ng/10⁷ cells in response to the corticosteroid therapy (Fig. 3). HCV-RNA remained positive and liver functions did not return to normal after the withdrawal of PEG-IFN α-2a.

Discussion

Mild-to-moderate thrombocytopenia is a common adverse event of treatment with conventional interferon or with PEG-IFN α, attributed primarily to bone marrow suppression, in patients with chronic hepatitis C. Nevertheless, severe, life-threatening AITP has rarely been associated with IFN treatment (2-8). The pathogenesis of AITP is not fully understood, but IgG-type antibodies against platelet membrane glycoproteins (IIb/IIIa, Ib/IX, etc.) are known to be involved (9).

AITP, an autoimmune disorder characterized by peripheral consumption of platelets and clinical manifestations of hemorrhagic diathesis (9), is a diagnosis of exclusion and often
difficult to establish. IFN-induced AITP has been reported to develop after 4 weeks to 12 months of therapy (3, 5) and even 6 months after the completion of therapy (7). AITP has been reported irrespective of the kind of IFN: IFN-α-2b, PEG-IFN-α-2a, and PEG-IFN with or without RBV (10).

The age of patients and baseline platelet count have varied widely, ranging from 27 (7) to 73 (6) years and from 8 (4) to 26 (5) × 10^12 /μL, respectively. The detection of circulating antiplatelet antibodies unbound to platelets is not sensitive enough for the diagnosis. Such autoantibodies can develop in patients immunized by pregnancy, allogenic transfusions or organ transplantation and are, thus, not specific for AITP. In contrast, direct assay of PAIgG is more useful in the diagnosis of AITP, with a sensitivity of 49-66% and a specificity of 78-92% (9). In the present case, PAIgG increased to 500 ng/10^7 cells (well above the normal range in the diagnosis of AITP) then decreased to 57.3 ng/10^7 cells (within the normal range) at the remission stage of AITP. As demonstrated in our patient, the response to steroid treatment was consistent with the diagnosis of AITP and PAIgG was also helpful in monitoring the response to corticosteroid therapy, and immunological disorders such as high γ-globulin levels of IgG and ANA positivity were found at the start of PEG-IFN/RBV therapy. Autoimmune hepatitis was ruled out by histological examination and the patient was started on PEG-IFN/RBV therapy. The clinical course was carefully monitored, focusing on the occurrence of autoimmune disease including diabetes, arthritis, sicca syndrome, vasculitis, thyroid abnormalities and others. Thirty months after the start of IFN therapy with PEG-IFN-α-2b/RBV and PEG-IFN-α-2a, AITP might have occurred by an autoimmune mechanism. Clinicians should be vigilant about the occurrence of AITP during and after IFN therapy, especially in the presence of immunological disorders (11).

**References**


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