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CASE REPORT

Interferon-α induced severe thrombocytopenia: A case report and review of the literature

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Abstract

We report a case of severe thrombocytopenia following pegylated interferon-α 2a (Peg-IFN-α 2a) treatment of hepatitis C virus infection and summarize the clinical characteristics of 16 cases of IFN-α induced severe thrombocytopenia and its immune-mediated mechanism. Discontinuation of IFN-α and early administration of immunosuppressants are the effective therapy for IFN-α induced severe thrombocytopenia.

Key words: Interferon-α; Severe thrombocytopenia; Chronic hepatitis C

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INTRODUCTION

Interferon-α (IFN-α) and pegylated IFN-α 2a (Peg-IFN-α 2a) are the effective antiviral drugs for chronic liver diseases. However, IFN-α is associated with a number of side effects, including mild thrombocytopenia, a common adverse effect largely ascribed to bone marrow suppression. IFN-α treatment-associated severe thrombocytopenia, like immune thrombocytopenia or thrombotic thrombocytopenic purpura, has rarely been reported in the literature. Here, we report a patient who developed immune thrombocytopenia 3 mo following Peg-IFN-α 2a (Pegsys, Roch) treatment and report the clinical features of severe thrombocytopenia.

CASE REPORT

A 54-year-old female was diagnosed as chronic hepatitis C virus (HCV) infection in 1998. Laboratory test showed that her serum anti-HCV and HCV RNA were positive, viral genotype was 1b, and serum alanine aminotransferase (ALT) level was 60-100 U/L. The patient was treated with standard recombinant IFN-α 2a (Roch, 3 MU), 3 times per week, at a clinic in 2003. Hepatic cirrhosis was excluded before treatment. Her auto-antibodies including antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA) and anti-thyroid antibody were negative. HCV RNA turned negative 1 mo after treatment with IFN-α 2a. Three months later, IFN-α 2a was discontinued due to adverse effects, including poor appetite, fatigue, nausea and mild gingival bleeding. Her platelet (PLT) count was slightly decreased to 80×10^9/L. Six months later, her HCV RNA was positive again and she administered no antiviral drugs.

In May 2008, the patient felt mild fatigue. Laboratory test showed that the levels of HCV RNA, ALT, and AST were 1.5×10^5 copies/L, 67 U/L (normal < 40 U/L), and 42 U/L (normal < 40 U/L), respectively, while her PLT count was 110×10^9/L and the aforementioned autoantibodies were negative. One month after treatment with

Peg-IFN-α 2a (180 μg, *sc*, once a week), her HCV RNA turned negative with normal ALT and peripheral blood cell count. After discharged from hospital, she continued to administer the same dose of Peg-IFN-α 2a and was followed up. Three months later, the patient was admitted to our hospital again due to severe gingival bleeding, fatigue, poor appetite, and nausea. Laboratory test on admission showed that her haematocrit was 29.2%, leucocyte count was 3.23×10^9/L (including 76.5% of polymorphonuclear cells, 15.2% of lymphocytes, and 6.8% of monocytes), PLT count was 2×10^9/L, ALT was 53.6 U/L, AST was 44.9 U/L, total bilirubin was 5.2 μmol/L, prothrombin time was 10.5 s, activated partial thromboplastin time (APTT) was 30.9 s, fibrinogen was 2.82 g/L and HCV RNA was negative. Bone marrow aspirate showed a large number of megakaryocytes in her hypercellular marrow with few granules, scanty cytoplasm and no PLT around. Indirect immunofluorescence showed a high anti-platelet IgG titer (1:1280, normal < 1:80) and negative ANA and ASMA. Complements C_3 and C_4 were 0.79 g/L (range: 0.88-2.01 g/L) and 0.13 g/L (range: 0.16-0.47 g/L), respectively. B-mode gray scale ultrasonography showed no splenomegaly.

She was diagnosed as immune-mediated thrombocytopenia with Peg-IFN-α 2a highly suspected as its cause. Peg-IFN-α 2a was discontinued and two units of PLT was transfused on the day at admission. The PLT count was then increased to 27×10^9/L, but decreased to 1×10^9/L on the second day with a mild fever caused by rapid destruction of PLT. Immunoglobulin (400 mg/kg) and intravenous methylprednisolone (1 mg/kg per day) were administered during the following 5 d. On day 7, PLT count was increased to 33×10^9/L, and methylprednisolone was replaced with prednisone (30 mg/d). Two weeks later, her PLT count was increased to 107×10^9/L, and prednisone was withdrawn 1 mo later. Her PLT count remained normal during the follow-up, but her HCV RNA turned positive 3 mo after discharge. She has not received any other antiviral therapy since then.

DISCUSSION

In this case, Peg-IFN-α 2a was considered the cause of autoimmune thrombocytopenia due to the following reasons[1]. First, thrombocytopenia presented following Peg-IFN-α 2a treatment and recovered after the drug was discontinued. Second, Peg-IFN-α 2a was the only candidate drug used before the onset of thrombocytopenia. Third, etiologies unrelated with drugs, such as splenomegaly, viral infection, acute hepatitis, and aplastic anemia, were excluded. Fourth, re-exposure to Peg IFN-α 2a resulted in recurrence of thrombocytopenia. Fifth, anti-PLT antibody was positive and bone marrow aspirate showed signs of megakaryocytic hyperplasia. All these factors suggest that immune-mediated mechanism is involved in thrombocytopenia.

IFN-α is one of the drugs inducing thrombocytopenia. Based on its pathogenesis, drug-induced thrombocytopenia is usually due to bone marrow suppression, immune-mediated destruction, and PLT aggregation[2]. Acute thrombocytopenia can often present as immune-mediated thrombocytopenia or PLT aggregation thrombocytopenia, whereas a slow decline of PLT often indicates a thrombocytopenia due to marrow suppression. In this case, the number of thrombocytes was rapidly decreased to 1×10^9/L after PLT transfusion due to acute damage of PLTs. Elevated level of anti-PLT antibody and decreased level of complements C_3 and C_4 support that immune-mediated mechanism is involved in the pathogenesis of thrombocytopenia.

Only few reports are available on IFN-α-induced severe thrombocytopenia (Table 1). A PubMed search with the key words 'interferon α' and 'thrombocytopenia' yielded 16 reports. Common IFN-α (9 cases) and Peg-IFN-α 2a (8 cases) were found to be associated with IFN-α-induced immune-mediated thrombocytopenia.

The mean age of the patients was 44.06 ± 14.27 years (range: 20-73 years). No significant difference was observed in gender. All the patients were infected with HCV. Serotype or genotype was examined in 7 cases. Of them, 4 had serotype 1b, 2 had genotype 3 and 1 had genotype 4. Since only a small number of cases were examined, whether the serotype 1b is more susceptible to immune-mediated thrombocytopenia than other types of thrombocytopenia needs to be further studied.

The median time from administration of IFN-α to the onset of thrombocytopenia was 3.6 mo (range, 1-36 mo). Fifteen out of 17 (83%) cases had epistaxis, gingival bleeding, oral mucosa bleeding, petechia, skin ecchymosis of trunk or lower extremies but no severe internal organ bleeding. The average PLT count was $(4.8 \pm 3.1) \times 10^9$/L. The anti-platelet antibody or platelet-associated IgG was positive in 12 and negative in 3 of the 17 (67%) cases, respectively, but not detected in 2 cases. Bone marrow aspirates showed signs of megakaryocytic hyperplasia with decreased platelet count in 16 patients. Besides the discontinuation of IFN-α/Peg-IFN-α 2a and administration of immunosuppressants (Table 1), two cases received platelet transfusion and ten cases received immunoglobulin simultaneously. The PLT count of all patients was gradually increased within 2 wk and recovered finally with no severe bleeding or death occurred, indicating that IFN-α induced severe thrombocytopenia can be reversed by discontinuing IFN-α/Peg-IFN-α 2a and giving immunosuppressant in time.

Interestingly, all the 17 cases had hepatitis C virus (HCV) infection rather than hepatitis B or other virus infections. Extrahepatic manifestations including thrombocytopenia were more frequently observed in HCV infection rather than in other virus infection[3]. HCV-related immune thrombocytopenia has been reported by Nakajima *et al*[4]. It was also reported that IFN-α can exacerbate thrombocytopenia by triggering the production of auto-antibodies in patients with HCV infection[5]. However, no patient with thrombocytopenia or positive anti-platelet antibodies has been reported in the literature

Table 1 Clinical characteristics of IFN-α-induced severe thrombocytopenia

Report source	Sex/ age (yr)	Liver disease/ treatment	HCV genotype/ serotype	Baseline/ Lowest PLTs (× 10^3/mL)	Duration of IFNα treatment	Bleeding tendency	Antiplatelets antibodies /PAIgG	Mgk in bone marrow	Treatment	Outcome
Shrestha *et al*[8]	M/41	HCV/IFNα	NR	6	NR	Yes	Negative	Increased	NR	CR
Dourakis *et al*[9]	M/39	HCV/IFNα	NR	→/14	8 mo	Yes	NR	Increased	Steriods/IvIg	CR
Dourakis *et al*[9]	F/64	HCV/IFNα	NR	→/10	6 mo	Yes	Positive	Increased	Steriods/IvIg	CR
Tappero *et al*[10]	F/NR	HCV/IFNα2a	NR	→/11	2 mo	NR	NR	NR	Steriods	CR
Jiménez-Sáenz *et al*[11]	M/46	HCV/IFNα2b	NR	→/3	3 yr	Yes	Positive	Increased	Steriods/IvIg	CR
Pockros *et al*[12]	M/61	HCV/IFNα	1b	→/9	4 mo	Yes	Positive	NR	Steriods	CR
Sagir *et al*[13]	M/45	HCV/Peg-IFNα2b	NR	147/9	10 wk	Yes	Negative	Increased	Steriods	CR
Sevastianos *et al*[14]	F/38	HCV, compensated cirrhosis/Peg-IFN2b	Group 4	141/5	4 wk	Yes	Positive	Increased	Steriods/IvIg	CR
Fujii *et al*[15]	F/24	HCV/IFNα	NR	→/1.1	4 wk	Yes	Positive	Increased	Steriods/IvIg	CR
Dimitroulopoulos *et al*[16]	F/20	HCV/IFNαcon-1	3a	→/11	28 wk	No	Positive	Increased	Steriods/IvIg	CR
Medeiros *et al*[17]	M/40	HCV/IFNα /PegIFNα2a	NR	→/6	6 mo	Yes	Positive	No performed	Steriods/IvIg	CR
Nakajima *et al*[4]	M/47	HCV/IFNα2a	1b	75/18	8 wk	Yes	Positive	Increased	IFN Discontinued	Not CR
Lambotte *et al*[18]	F/73	HCV/Peg-IFNα2a	1b	100/4	2 mo	Yes	Positive	Peripheral origin of the pancytopenia	Steriods/ IvIg/PT	CR
Demirtur *et al*[19]	F/40	HCV/Peg-INF	NR	217/6	13 wk	Yes	Positive	Increased	Danazol/IvIg	CR
Elefsiniotis *et al*[20]	M/27	HCV/Peg-IFNα2b	NR	150/10	48 wk (6 mo after IFN discontinued)	Yes	Positive	Increased	Steriods	CR
Alves Couto *et al*[21]	M/44	HCV/Peg-IFNα2b	Group 3	164/2	16 wk	No	Negative	Increased	Steriods	CR
Our hospital	F/54	HCV/Peg-IFNα2a	1b	100/1	3 mo	Yes	Positive	Increased	Steriods/ IvIg/PT	CR

F: Female; M: Male; IFN: Interferon; Peg: Pegylated; NR: Not reported; →: Normal; PAIgG: Platelet associated IgG; Mgk: Megakaryocytosis; IvIg: Intravenous Immunoglobulin; PT: Platelets transfusion; CR: Completed resolved.

before interferon treatment, indicating that interferon may increase the incidence of ITP in HCV-infected patients.

IFN-α has been widely used not only in treatment of viral infections but also in treatment of malignancies, skin diseases, and myeloproliferative disorders. IFN-α induced thrombocytopenia also occurs not only during antiviral treatment but also during treatment of other malignant diseases such as chronic myeloid leukemia[6], and renal cell carcinoma[7]. It is, therefore, essential for clinicians to recognize the disorder early and give patients appropriate treatment for a favorable prognosis.

In conclusion, severe immune-mediated thrombocytopenia may occur during IFN-α/Peg-IFN-α 2a treatment, especially in chronic HCV-infected patients. Discontinuation of IFN-α and administration of immunosuppressant is the key to the avoidance of severe bleeding or death due to thrombocytopenia.

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