Medicine®

CLINICAL CASE REPORT

OPEN

Late-Onset Immune Thrombocytopenic Purpura After Withdrawal of Interferon Treatment for Chronic Hepatitis C Infection

A Case Report

Chien-Hao Hsiao, MD, Kuo-Chih Tseng, MD, Chih-Wei Tseng, MD, and Chien-Hsueh Tung, MD

Abstract: Immune thrombocytopenic purpura (ITP) is a life-threatening complication following pegylated interferon alpha (PEG-IFN) plus ribavirin treatment, the standard treatment for hepatitis C virus (HCV) infection. We reported a rare case with late-onset ITP after withdrawal of PEG-IFN treatment.

A 53-year-old male with hepatitis C developed massive gum bleeding and a severe, reversible, immune thrombocytopenia 2 weeks after cessation of PEG-IFN treatment for HCV due to anemia and depression. The platelet count decreased to 4000 cells/μL. The HCV viral load was undetectable at the end of PEG-IFN treatment and during follow-up for 5 months. Other potential autoimmune disorders were ruled out. Late-onset ITP associated with PEG-IFN treatment was diagnosed.

The patient was treated successfully with steroid and azathioprine. Platelet count gradually increased to 117×10^3 cells/μL on the 18th day after admission.

ITP is a rare complication in patients with hepatitis C or in patients who received PEG-IFN treatment. The particular case supported that it may occur even after withdrawal of PEG-IFN treatment. Physicians should be aware of this late-onset complication.

(*Medicine* 94(34):e1296)

Abbreviations: EOT = end-of-treatment, HCV = hepatitis C virus, ITP = immune thrombocytopenic purpura, PEG-IFN = pegylated interferon alpha.

INTRODUCTION

The treatment of hepatitis C virus (HCV) infection has changed dramatically in recent years due to the development of many new drugs including direct-acting antiviral and host-targeted agents.[1] Interferon (IFN)-free regimens for treatment of different HCV genotypes could achieve high rates of sustained virologic response without the side effect of IFN. However, the cost of these new drugs is very high. Pegylated IFN alpha (PEG-IFN-α) plus ribavirin are still the standard treatment for HCV infection except the United States and several European countries.[1] PEG-IFN plus RBV are associated with numerous adverse drug effects, including thrombocytopenia, neutropenia, anemia, and autoimmune diseases, probably due to its bone marrow suppression and immunemodulatory effect.[2,3] Immune thrombocytopenic purpura (ITP) is rarely reported during the IFN treatment course.[5–11,15,21–24] Here, we reported a case who developed immune-mediated thrombocytopenia 2 weeks after withdrawal of IFN treatment.

CASE REPORT

This is a 53-year-old male patient who went to our hospital with chief complaint of massive gum bleeding for 1 day. The patient had a history of chronic hepatitis C. PEG-IFN-α-2a (180 μg) plus ribavirin (1200 mg/day) were prescribed to the patient since March 17, 2014. He denied any autoimmune conditions before treatment. The baseline virological data revealed high virus load (HCV RNA 2.1×10^6 IU/mL) with genotype 1b. Rapid virological response was not achieved at the fourth week (HCV RNA: 2.12×10^6 IU/mL). Partial early virological response (HCV RNA: 103 IU/mL at week 12) and delayed virological response (HCV RNA: <15 IU/mL at Week 24) were noted. However, fatigue, anemia, and depression syndrome were progressed at 30th week. The patient requested to stop treatment at Week 36. The viral load at the end-of-treatment (EOT) was undetectable. The platelet count at EOT was 92×10^3 cells/μL and elevated to 159×10^3 cells/μL 1 week later.

Two weeks following EOT, the patient developed massive gum bleeding. The physical examination showed the multiple petechiae on the extremities. There is no sign of intracerebral hemorrhage, gastrointestinal bleeding, or other internal bleeding. The initial platelet count was 4×10^3cells/μL. Coagulation profile showed normal prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, and fibrin degradation product. Peripheral blood smear showed neither fragmented red blood cells, helmet cells nor abnormal platelet aggregation. Concomitant autoimmune

Editor: King-Wah Chiu.
Received: March 6, 2015; revised: July 8, 2015; accepted: July 11, 2015.
From the College of Medicine, Tzu Chi University (C-HH, K-CT, C-WT); Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (C-HH, K-CT, C-WT); Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, and National Yang-Ming University School of Medicine, Taipei (C-WT); and Division of Allergy, Immunology and Rheumatology; Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan (C-HT).
Correspondence: Chien-Hsueh Tung, Department of Internal Medicine, Division of Allergy, Immunology and Rheumatology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan, No. 2, Ming-Sheng Road, Dalin Town, Chia-Yi 622, Taiwan (e-mail: dm141820@tzuchi.com.tw).
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001296

connective tissue diseases such as systemic lupus erythematosus or cryoglobulinemia were excluded due to negative antinuclear antibody and cryoglobulin except for positive anticardiolipin IgG (116 GPL, normal range <20 GPL) and antiphospholipid IgG (165 U, normal range <15 U). Anti-phospholipid syndrome was excluded due to no previous thromboembolic events, according to 2006 Sapporo criteria.[12] Bone marrow biopsy was also performed, which revealed hypocellular marrow with even cellular distribution and without evidence of lymphoid neoplasia. The potential drugs that may cause platelet lysis were ruled out. Blood transfusion of platelet was performed, but poor response with rapid decline of platelet count in the next day of transfusion. A diagnosis of immune thrombocytopenic purpura was made.

We started intravenous methylprednisolone therapy (40 mg, 3 times daily) on November 27 combined with platelet transfusion treatments. It still showed no significant improvement. Azathioprine (100 mg, oral, once daily) was added since December 3. Hydroxychloroquine (400 mg, oral, once daily) was also prescribed due to positive anti-phospholipid antibodies. Platelet count gradually increased to 93×10^3 cells/μL 17 days after admission, so methylprednisolone was changed to oral form and slowly tapered off. On December 15, the patient was discharged due to stable condition with platelet counts elevating to 117×10^3 cells/μL (Figure 1). Followed laboratory data after 5 months revealed sustained virologic response, platelet count above 150×10^3 cells/μL, and decreased anti-cardiolipin IgG (30.5GPL) and anti-phospholipid IgG (73.21 U) levels.

METHODS

Informed consent was obtained from the patient for publication of this case report (according to the Declaration of Helsinki). The study was approved by the Institutional Review Board of the Buddhist Tzu Chi General Hospital.

DISCUSSION

ITP is a rare complication following chronic hepatitis C infection treatment with PEG-IFN-α therapy plus ribavirin, probably due to immune modulatory effect of IFN.[13] It can be seen at any time during IFN therapy, from the 4th week to the 12th month,[7,9] or even 6 months after the completion of therapy.[11] It can follow a course of gradual or sudden decline in platelet count. In the present case, platelet count raised to normal range 1 week after EOT. Severe thrombocytopenia developed 2 weeks later and was proved to be ITP by cautiously excluding other possible causes of thrombocytopenia. The delayed immune modulatory effects may be partially due to longer half-life and prolonged activity of pegylated form of IFN. The physicians must be aware that ITP can occur even after the end of treatment, as a late onset complication, especially when using the pegylated forms of IFN.

ITP was known to be mediated by autoantibodies, which bind to several platelet-surface glycoproteins and promote platelet clearance through Fcγreceptors that are expressed by tissue macrophages.[4] Neoantigens generated from degraded platelets further initiated CD4-positive T-cell clones, resulting in sufficient antibody production to cause thrombocytopenia.

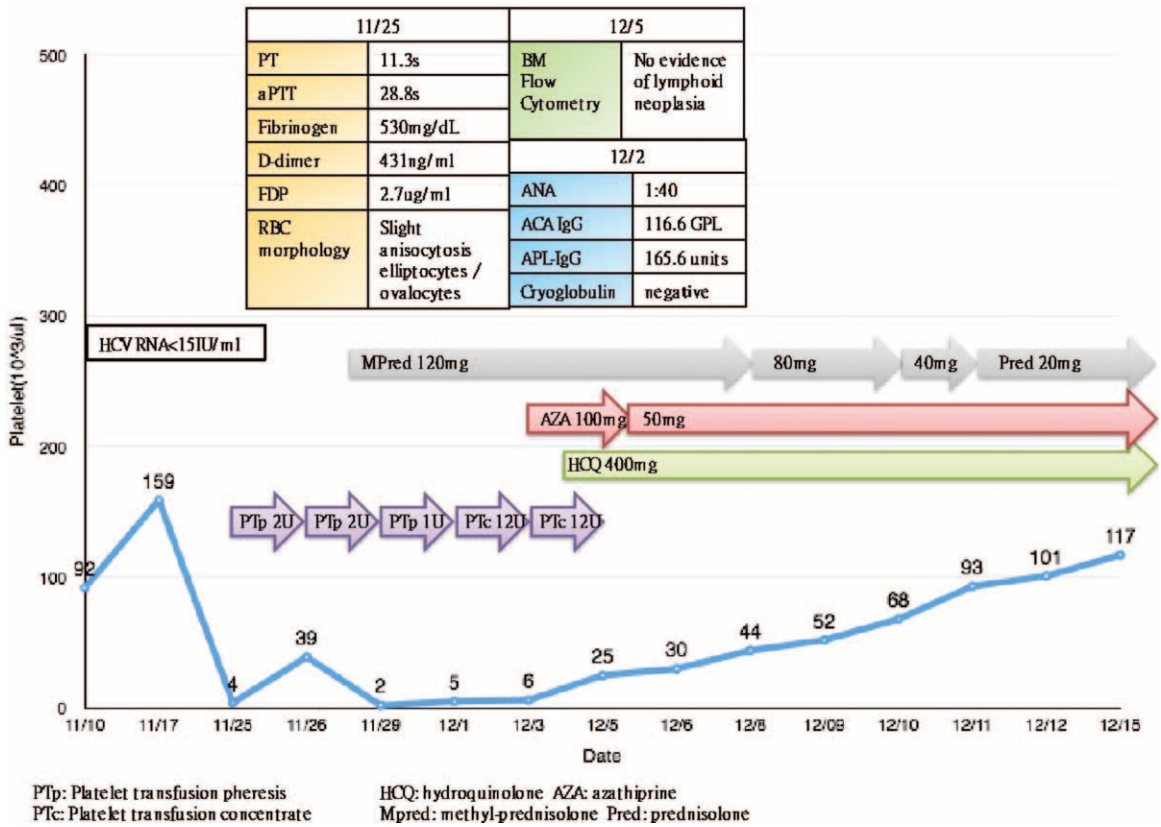

FIGURE 1. Clinical course of the present case.

IFN can promote the differentiation of macrophages, and the production of interleukin-1 and tumor necrosis factor-α, which may enhance the efficiency of antigen presentation of macrophage.[13] PEG-IFN alone or combined with ribavirin also induces strength of CD4+ T-cell responses.[25] This phenomenon may partially explain the mechanism of IFN-induced ITP.

ITP may be related to the HCV infection. The practice guideline for HCV-related ITP treatment suggested that antiviral therapy combined with intravenous immunoglobulin was the initial treatment instead of steroid, in concerning of the possibility of HCV reactivation after steroid treatment.[14] However in our case, at the end of IFN treatment, the viral load was undetectable. The HCV-related ITP was excluded.

In the literature, there were three case reports describing late-onset ITP associated with IFN treatment (one was written in Serbian) (Table 1).[11,21,24] The patients' age ranges from 27 to 37 years' old without significant difference in sex, and are all treated with pegylated form of IFN. After completion of IFN treatment course, the ITP occurred immediately or delayed up to 6 months. Though none of the patient had preexisting autoimmune disease, anti-platelet antibodies were detected in one of them, suggesting an autoimmune-mediated reaction even after discontinuation of the IFN therapy. This phenomenon was also found in our case presenting as elevated anti-phospholipid antibodies. In concerning of HCV reactivation, 2 reports avoid using steroid for ITP treatment. However, there was no remarkable difference in prognosis compared with the other report, as platelet counts all normalized to baseline after treatment without HCV flaring up. Due to limited case number, we could not conclude any risk factor to predict late-onset type of ITP. The physicians' awareness of late-onset ITP after completion of IFN treatment may favor prompt disease control and good outcome.

There was no consensus in management of IFN -induced ITP, or even late-onset ITP associated with IFN treatment. Immediate withdrawal of IFN therapy and treatment with immunosuppressants were administered in previous reports.[6,15] In our case, we initially gave high-dose methylprednisolone therapy without intravenous immunoglobulin in concerning of financial reason and the evidence of undetectable viral load at the end of treatment. Though poor response was revealed in the first week, the treatment response was noted 12 days after methylprednisolone treatment. A previous report showed the treatment response of prednisolone for ITP initiates in 4 to 14 days and peaks in 7 to 28 days.[14] Azathioprine is an immunosuppressive agent recommended as one of second-line drugs for ITP. The treatment response of azathioprine starts in 30 to 90 days and peaks in 30 to 180 days.[14] Hence, the treatment response of this case may be related to the effect of methylprednisolone.

From the previous reports of IFN-related ITP, platelet count may rapidly improve within 1-week treatment of steroid pulse therapy plus intravenous immunoglobulin treatment following cessation of IFN therapy,[16] or being refractory until second-line therapy such as anti-RhD or rituximab treatment for 16 months.[6,7] No mortality occurred in all cases. It indicated that, despite different and individual response to treatment, ITP after IFN seemed to perform an optimistic prognosis upon prompt diagnosis and appropriate treatment, as well as late-onset type.[11,21,24]

High serum level of anti-cardiolipin antibodies (ACA) and anti-phospholipid antibodies without anti-b2- glycoprotein-I antibodies was detected in our case. Chronic hepatitis C infection has been associated with higher detection rate of ACA, especially following IFN-α treatment.[17] However, previous studies do not support the hypothesis that HCV plays a specific

TABLE 1. Clinical Characteristics of Late-onset ITP

Authors	Age/Sex	HCV Genotype	Anti-HCV Regimen	ITP Occurrence Time, wk (From 1st Dose)	PLTs Baseline/During IFN Treatment/Lowest ($\times 10^3$ cells/mL)	Auto-antibodies Before/After ITP	Treatment	Resolve Time
Papakonstantinou et al[21]	27/M	3a	pIFN + RBV	24wk (at the time of discontinuation of treatment)	150/80/4	NR/negative	IVIG/rituximab	4 wk
Elefsiniotis et al[11]	27/M	NR	pIFN-α2b + RBV	48wk (24 wk after discontinuation of treatment)	NR/150/1	Negative/anti-PLT Ab	Steroid	2 wk
Hajder et al[24]	37/F	Ib	pIFN + RBV	28wk (4 wk after discontinuation of treatment)	NR/66/2	Negative/negative	IVIG	NR
Present case	53/M	1b	pIFN-α2a + RBV	38wk (2 wk after discontinuation of treatment)	150/92/2	Negative/ACA IgG, APL IgG	Steroid/AZA/HCQ	2 wk

ACA IgG = anti-cardiolipin immunoglobulin G, APL IgG = anti-phospholipid immunoglobulin G, AZA = azathioprine, F = female, HCQ = hydroquinolone, IVIG = intravenous immunoglobulin, M = male, NR = not reported, pIFN = pegylated interferon alpha, PLTs = platelets, RBV = ribavirin.

role in the production of ACA and even the pathogenesis of anti-phospholipid syndrome.[18,19] ACA production seems to be a nonspecific, transient phenomenon of liver damage, characterized by low titer and absence of associated anti-b2- glycoprotein-I.[20] Though anti-phospholipid antibodies were associated with thromboembolic events,[23] hydroxychloroquine had the protective effect against thrombosis in patients with positive anti-phospholipid antibodies.[22,26] In our case, we used hydroxychloroquine for primary prevention. No clinical or laboratory evidence of thromboembolic events occurred despite the high positive titer of ACA, which gradually decreased during following up. This epiphenomenon may not be clinically meaningful.

CONCLUSION

In conclusion, ITP is a rare but life-threatening complication following PEG-IFN-α treatment for chronic hepatitis C patients. It could occur at any time following IFN treatment and even after withdrawal of treatment. Physicians should be aware of this late-onset complication after PEG-IFN treatment.

ACKNOWLEDGMENTS

This report is based on the medical records from the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation.

REFERENCES

1. Pawlotsky JM. New hepatitis C therapies: the toolbox, strategies, and challenges. *Gastroenterology.* 2014;146:1176–1192.
2. Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology.* 2002;36(5 Suppl 1):S237–S244.
3. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009;49:1335–1374.
4. Cines DB, Blanchette S, Chir B. Immune thrombocytopenic purpura. *N Engl J Med.* 2002;346:995–1008.
5. Kim SR, Imoto S, Kudo M, et al. Autoimmune thrombocytopenic purpura during pegylated interferon alpha treatment for chronic hepatitis C. *Intern Med.* 2010;49:1119–1122.
6. Demirturk N, Cevik F, Demirdal T, et al. Autoimmune thrombocytopenia induced by PEG-IFN-alpha plus ribavirin in hepatitis C. *Platelets.* 2006;17:340–343.
7. Weitz IC. Treatment of immune thrombocytopenia associated with interferon therapy of hepatitis C with the anti-CD20 monoclonal antibody, rituximab. *Am J Hematol.* 2005;78:138–141.
8. Lambotte O, Gelu-Simeon M, Maigne G, et al. Pegylated interferon alpha-2a-associated life-threatening Evans' syndrome in a patient with chronic hepatitis C. *J Infect.* 2005;51:e113–e115.
9. Sevastianos VA, Deutsch M, Dourakis SP, et al. Pegylated interferon-2b-associated autoimmune thrombocytopenia in a patient with chronic hepatitis C. *Am J Gastroenterol.* 2003;98:706–707.
10. Dourakis SP, Deutsch M, Hadziyannis SJ. Immune thrombocytopenia and alpha-interferon therapy. *J Hepatol.* 1996;25:972–975.
11. Elefsiniotis IS, Pantazis KD, Fotos NV, et al. Late onset autoimmune thrombocytopenia associated with pegylated interferon-alpha-2b plus ribavirin treatment for chronic hepatitis C. *J Gastroenterol Hepatol.* 2006;21:622–623.
12. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006;4:295–306.
13. Dumoulin FL, Leifeld L, Sauerbruch T, et al. Autoimmunity induced by interferon-alpha therapy for chronic viral hepatitis. *Biomed Pharmacother.* 1999;53:242–254.
14. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood.* 2011;117:4190–4207.
15. Fujii H, Kitada T, Yamada T, et al. Life-threatening severe immune thrombocytopenia during alpha-interferon therapy for chronic hepatitis C. *Hepatogastroenterology.* 2003;50:841–842.
16. WHO. Guidelines for the screening, care and treatment of persons with hepatitis C infection. 2014.
17. Leroy V, Arvieux J, Jacob MC, et al. dev and significance of anticardiolipin, anti-beta2 glycoprotein I and anti-prothrombin antibodies in chronic hepatitis C. *Br J Haematol.* 1998;101: 468–474.
18. Munoz-Rodriguez FJ, Tassies D, Font J, et al. Prevalence of hepatitis C virus infection in patients with antiphospholipid syndrome. *J Hepatol.* 1999;30:770–773.
19. Ordi-Ros J, Villarreal J, Monegal F, et al. Anticardiolipin antibodies in patients with chronic hepatitis C virus infection: characterization in relation to antiphospholipid syndrome. *Clin Diagn Lab Immunol.* 2000;7:241–244.
20. Mangia A, Margaglione M, Cascavilla I, et al. Anticardiolipin antibodies in patients with liver disease. *Am J Gastroenterol.* 1999;94:2983–2987.
21. Papakonstantinou PI. Monoclonal antibody Rituximab for severe immune thrombocytopenia after pegylated interferon for hepatitis C infection. *Hippokratia.* 2014;4:370–372.
22. Belizna C. Hydroxychloroquine as an anti-thrombotic in antiphospholipid syndrome. *Autoimmun Rev.* 2015;14:358–362.
23. Espinosa G, Cervera R. Antiphospholipid syndrome: frequency, main causes and risk factors of mortality. *Nat Rev Rheumatol.* 2010;6:296–300.
24. Hajder J, Stanisavljević N, Marković O, et al. Late onset of severe thrombocytopenia during Interferon treatment for chronic hepatitis C infection - case report. *Srp Arh Celok Lek.* 2010;138:240–243.
25. Kamal SM, Fehr J, Roesler B, et al. Peginterferon alone or with ribavirin enhances HCV-specific CD4 T-helper 1 responses in patients with chronic hepatitis C. *Gastroenterology.* 2002;123:1070–1083.
26. Wallace DJ, Gudsoorkar VS, Weisman MH, et al. New insights into mechanisms of therapeutic effects of antimalarial agents in SLE. *Nat Rev Rheumatol.* 2012;8:522–533.