Thrombotic thrombocytopenic purpura associated with pegylated-interferon alpha-2a by an ADAMTS13 inhibitor in a patient with chronic hepatitis C

A deficiency of ADAMTS13 leads to platelet clumping and/or thrombi formation, finally resulting in thrombotic thrombocytopenic purpura (TTP). In this study, a 62-year-old male with chronic hepatitis C developed TTP a month after long-term pegylated-interferon (PEG-IFN) treatment. The observed low level of activity of plasma ADAMTS13 following PEG-IFN treatment was shown to gradually increase with the improvement of TTP, while the titer of an inhibitory anti-ADAMTS13 IgG antibody decreased concomitant with the increase in ADAMTS13 activity. Serial determination of ADAMTS13 activity and its inhibitor may provide useful information for the diagnosis and treatment of IFN-associated TTP, as well as its pathogenesis.

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Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease, characterized by thrombocytopenia, microangiopathic hemolytic anemia, fluctuating neurological signs, renal dysfunction, and fever.[1] Recent studies have indicated that most TTP patients have deficient activity in von Willebrand factor-cleaving protease (VWF-CP/ADAMTS13), which specifically cleaves the multimeric von Willebrand factor (VWF) between Tyr1605 and Met1606 within the VWF A2 domain.[2,3] Deficiency of ADAMTS13 increases the plasma levels of ultra-large VWF multimer (UL-VWFM), which, under high shear stress, leads to platelet clumping and/or thrombi formation, finally resulting in TTP.[2-5] Various clinical conditions can induce TTP, including such conditions as infection, malignancies, autoimmunity, pregnancy, stem cell transplantation, and certain drugs such as interferon (IFN).[3-10] IFN is an essential component for treating hepatitis C virus (HCV)-related chronic hepatitis.[11] A number of adverse reactions to IFN have been reported, including pancytopenia, psychological symptoms, renal dysfunction and immunological disorders,[12] but it is clear that severe thrombocytopenia is one of the most important life-threatening adverse effects. Some of the cases were diagnosed as idiopathic thrombocytopenic purpura[13] and others were diagnosed as TTP.[8-10]

We here report on a patient with HCV-related chronic hepatitis who developed TTP a month after a full treatment course with pegylated-IFN (PEG-IFN). We demonstrate that TTP in this patient was caused by the absence of ADAMTS13 activity due to the presence of an inhibitory anti-ADAMTS13 immunoglobulin G (IgG) antibody.

A highly sensitive ELISA assay was used for measuring plasma ADAMTS13 activity and its inhibition, as recently described.[14] The inhibitor titer against ADAMTS13 activity was expressed in Bethesda units.[15] IgG was purified using a protein A column.

The patient was a 62-year-old male who had a history of blood transfusion in 1984 and was clinically diagnosed as having hepatitis C virus (HCV)-related chronic hepatitis on May, 1999. The circulating HCV was Ib in genotype and high in RNA concentration (1100×10^3 copies/mL, Amplicore HCV monitor assay: Roche Diagnostic System, USA). Liver biopsy was not performed because of the patient's request. Throughout a 5 year follow-up period serum transaminase levels were stable and within twice of the normal range. The patient received a series of 180 μg PEG-IFNα-2a every week for 48 weeks (from September 4, 2004 to July 28, 2005). Before beginning the PEG-IFN therapy, laboratory data revealed a normal range in trasnaminases, serum albumin (4.4 g/dL, normal range 3.8–5.1 g/dL), ZTT (13.7 U, normal range 4-15 U), and platelet count (168×10^9/L, normal range $130\text{-}369\times10^9$/L). No clinical findings indicative of liver cirrhosis were observed from the physical findings, abdominal ultrasonography, or gastro-fiberscope. During the IFN treatment period, transaminase levels had been within normal ranges and peripheral blood analyses showed mild pancytopenia without apparent adverse effects. Platelet count was 114×10^9/L two weeks after the final administration of IFN on August 11, 2005. Two weeks later on August 25 (a month after the final administration of IFN), the patient was admitted to our hospital because of high-grade fever and petechiae on the legs, which had been noticed three days before admission. Laboratory data demonstrated severe thrombocytopenia (6×10^9/L), anemia (Hb 10.0 g/dL, normal range: 13.0-18 g/dl) with numerous schistocytes, and elevations of lactate dehydrogenase (LDH)(1072 IU/l, normal range: 123-220 IU/L), creatinine (1.6 mg/dL, normal range: 0.6-1.1 mg/dl), and indirect bilirubin (1.6 mg/dl, normal range: 0.1-0.6 mg/dl). Reticulocyte count was 89×10^9/L (normal range: $30\text{-}94\times10^9$/L). Urinalysis demonstrated albuminemia, hematuria, and many hyaline and granular casts. Direct Coombs test and antinuclear antibody was negative. Lupus anticoagulant and anti-cardiolipin antibodies were also negative. Coagulation tests such as prothrombin time, activated partial thromboplastin time, fibrinogen, and fibrinogen degradation product were normal. Serum HCV-RNA was undetectable by RT-PCR. Magnetic resonance imaging examination demonstrated multiple small infarctions in the cerebellum. On bone marrow examination, findings showed a normal number of megakaryocytes without hemophagocytic reticulosis. Plasma ADAMTS activity on admission showed a marked decrease to less than 0.5% of normal. An inhibitor against ADAMTS13 was detected in both the patient's plasma (1.6 Bethesda units/ml) and purified IgG (0.19 Bethesda units/ mg IgG), thus confirming the diagnosis of acquired TTP caused by ADAMTS13 inhibitor (IgG autoantibody).

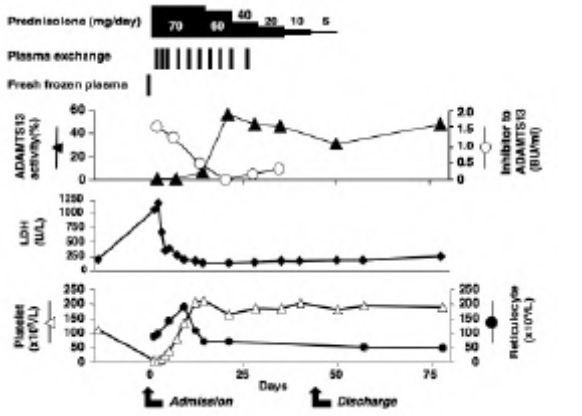

Figure 1. The clinical course of a patient with chronic hepatitis C who developed thrombotic thrombocytopenic purpura after pegylated-interferon treatment

The clinical course is shown in Figure 1. Six ml/kg of

fresh frozen plasma (FFP) and 1 mg/kg of prednisolone were administered on the first hospital day. After the second hospital day, plasma exchange (PE) was performed using 47 ml/kg/day FFP three times per week and periodically continued until the 23rd day (total 10 times). Prednisolone was tapered and stopped by the 56th day. The patient responded well to the PE and steroid treatment: platelet count immediately increased and LDH promptly decreased, both parameters of which normalized by the 9th day. Hb reached a nadir (7.9 g/dL) on day 4 after admission, then gradually increased to 9.5 g/dL, and serum creatinine normalized by the 14th day. The ADAMTS13 activity still remained below the detection limit on day 7, when platelet count recovered to 86×10^9/L and LDH was markedly decreased by 297 IU/L. Thereafter, ADAMTS13 activity gradually increased to 7% accompanied by the normalization of platelet count and LDH on the 14th day. The inhibitor of ADAMTS13 gradually decreased with concomitant increase of ADMTS13 activity, and became less than 0.5 Bethesda units/ml on the 21st day, when the ADMTS13 activity had recovered to 56%, and remained between 31% and 48% after discharge on the 41st day.

We demonstrated the absence of ADAMTS13 activity due to the presence of an anti-ADAMTS13 antibody in a case of TTP occurring a month after a series of PEG-IFN therapy for chronic hepatitis C. To date, patients who developed TTP during IFN therapy have been reported; however, the plasma ADAMTS13 activity has not been determined.[8,9] In our case, ADAMTS13 activity was dramatically decreased, reaching an undetectable level, and thereafter gradually increased with the improvement of TTP. It is notable that the activity of ADAMTS13 remained below the detection limit on day 7 after treatment by PE, when the platelet count recovered to 86×10^9/L and the LDH markedly decreased, suggesting rapid consumption of the enzyme to cleave a large amount of UL-VWFM during the initial treatment period for TTP. The antibody against ADAMS13 contained within the IgG fraction detected at the occurrence of TTP gradually decreased with concomitant increase of ADAMTS13, and fell to less than 0.5 Bethesda units, thus indicating a close relationship between the presence of an ADAMTS13 inhibitor and the development of TTP. This is the first patient associated with IFN therapy for whom serial determination of ADAMTS13 activity and its inhibitor was assessed.

We previously encountered a patient with HCV-related liver cirrhosis who was complicated by fetal TTP following the development of an ADAMTS13 inhibitor.[16] This case showed advanced liver cirrhosis and tense ascites without IFN therapy. In advanced cirrhotics, the levels of VWF antigen were remarkably high,[17] and plasma activity of ADAMTS13 was low, most likely because of the consumption of the enzyme used for the degradation of increased levels of VWF,[17] and/or the decreased production or secretion of ADAMTS13 that is exclusively produced in the hepatic stellate cells.[18] The imbalance of an increased amount of VWF over a deficiency of ADAMTS13 activity may, therefore, result in TTP in advanced cirrhotics, which certain triggers, including infection or endotoxemia, may precipitate. The presence of an ADAMTS13 inhibitor may enhance the situation.

In contrast, the present case of IFN treatment for 48 weeks showed chronic hepatitis, but not liver cirrhosis. Interestingly, IFN-induced thrombotic microangiopathy (TMA) occurred after much longer IFN administration,[9] indicating that higher cumulative doses of IFN may be one of the risk factors for the development of IFN-induced TTP. In our case, TTP onset may be associated with IFN therapy, but there is no direct evidence to prove the development of TTP by IFN itself. It is unclear whether anti-ADAMTS13 antibodies could be present before IFN therapy, but there remains the possibility that IFN might induce autoimmune reactions, resulting in the generation of autoantibodies against ADAMTS13.[12]. We have shown that an ADAMTS13 inhibitor in the plasma was detected in 13 (48%) of 27 patients with autoimmune-associated TTP, and in all (100%) of 7 patients with ticlopidine-associated TTP.[6] Furthermore, irrespective of IFN therapy, HCV infection itself might contribute to the development of TTP. HCV infection was, indeed, confirmed in all 4 patients with chronic hepatitis including our present case who developed TTP after IFN therapy[8,9] and in five of 10 patients (50%) who developed TMA after living-donor liver transplantation.[19]

Pegylated-IFN is currently widely used for the treatment of patients with chronic hepatitis C, because its tolerability and efficacy are superior to conventional IFN.[20] Discontinuation of therapy because of thrombocytopenia was required in 2% of the patients receiving 180ug of PEG-IFN-α2a for the treatment of chronic hepatitis C that displayed cirrhosis or bridging fibrosis.[20] Due attention should be paid to the development of TTP during IFN therapy, especially in the case of PEG-IFN, which has a longer action than conventional IFN.

Kiyoshi Kitano,[1] Yukio Gibo,[1] Atsushi Kamijo,[1] Kiyoshi Furuta,[1] Satohiro Oguchi,[1] Satoru Joshita,[1] Yasufumi Takahashi,[1] Fumihiro Ishida,[3] Masanori Matsumoto,[4] Masahito Uemura,[5] Yoshihiro Fujimura[4]

[1]Department of Internal Medicine, Matsumoto National Hospital, Matsumoto, Japan, [2]Gibo Liver Clinic, Matsumoto, Japan, [3]Second Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan, [4]Department of Blood Transfusion Medicine, and [5]Third Department of Internal Medicine, Nara Medical University, Kashihara, Nara, Japan

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Correspondence: Kiyoshi Kitano, M.D., Ph.D. Matsumoto National Hospital, Matsumoto, 399-8701, Japan.
Tel: +81-263-58-4567, Fax: +81-263-86-3183
E-mail: kiyoshikitano@mac.com

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