Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9326-17
Intern Med 57: 741-744, 2018
http://internmed.jp

【 CASE REPORT 】

Thrombotic Microangiopathy Presenting with Intestinal Involvement Following Long-term Interferon-β1b Treatment for Multiple Sclerosis

Shusaku Omoto, Tomohiro Utsumi, Hiromasa Matsuno, Yuka Terasawa and Yasuyuki Iguchi

Abstract:
Thrombotic microangiopathies (TMAs) are systemic microvascular occlusive disorders. The present report describes a patient with relapsing-remitting multiple sclerosis who had been treated with interferon (IFN)-β1b therapy for eight years and developed TMA. The patient presented with headache, thrombocytopenia, renal dysfunction, severe hypertension, posterior reversible encephalopathy syndrome, and gastrointestinal involvement. After discontinuation of the medication and initiation of antihypertensive treatment, the patient rapidly improved. This is the first report of TMA with gastrointestinal involvement (intestinal TMA) induced by IFN-β. The new onset of hypertension or headache requires careful attention in cases of long-term administration of IFN-β1b.

Key words: thrombotic microangiopathy, intestinal thrombotic microangiopathy, interferon, multiple sclerosis, posterior reversible encephalopathy syndrome

(Intern Med 57: 741-744, 2018)
(DOI: 10.2169/internalmedicine.9326-17)

Introduction

Thrombotic microangiopathies (TMAs) are microvascular occlusive disorders that induce systemic or intrarenal aggregation of platelets, thrombocytopenia, and mechanical injury to erythrocytes. Acquired TMA syndrome is diverse and includes thrombotic thrombocytopenia purpura (TTP), Shiga toxin-mediated hemolytic uremic syndrome, drug-induced TMA, and complement-mediated TMA (1). The present report describes a patient with relapsing-remitting multiple sclerosis (RRMS) who had been treated with interferon (IFN)-β1b for eight years and presented with severe hypertension, posterior reversible encephalopathy syndrome (PRES), and gastrointestinal involvement due to drug-induced TMA.

Case Report

A 42-year-old woman was admitted to our hospital with headache, nausea, hypertension, and anemia. Eight years before this admission, the patient had been diagnosed with RRMS, which was maintained in remission with IFN-β1b at a dosage of 8 million IU every other day without other treatments. A health checkup 2 years before admission revealed mildly elevated systolic blood pressure (sBP) (140 mmHg), and 1 year later, her sBP was 150 mmHg. She had been experiencing severe headaches and nausea for one month before admission.

On admission, a physical examination showed severe arterial hypertension (226/138 mmHg) and tachycardia (116/min). She had headache and nausea but no edema. Laboratory investigations showed hemolytic anemia (hemoglobin 9.5 g/dL, elevated lactate dehydrogenase level 821 U/L, low haptoglobin level, and elevated reticulocytes), schistocytes, thrombopenia of 64×10^3/L, a slight increase in serum creatinine (0.86 mg/dL) compared with baseline (0.45 mg/dL), proteinuria (2.7 g/day), and a normal range of ADAMTS13 activity. Abdominal computed tomography and renal ultrasound were normal. Brain magnetic resonance imaging showed lesions with vasogenic edema involving the basal ganglia, brainstem, and bilateral cerebellum, suggesting

Department of Neurology, The Jikei University School of Medicine, Japan
Received: April 6, 2017; Accepted: July 5, 2017; Advance Publication by J-STAGE: November 20, 2017
Correspondence to Dr. Shusaku Omoto, s-omoto@jikei.ac.jp

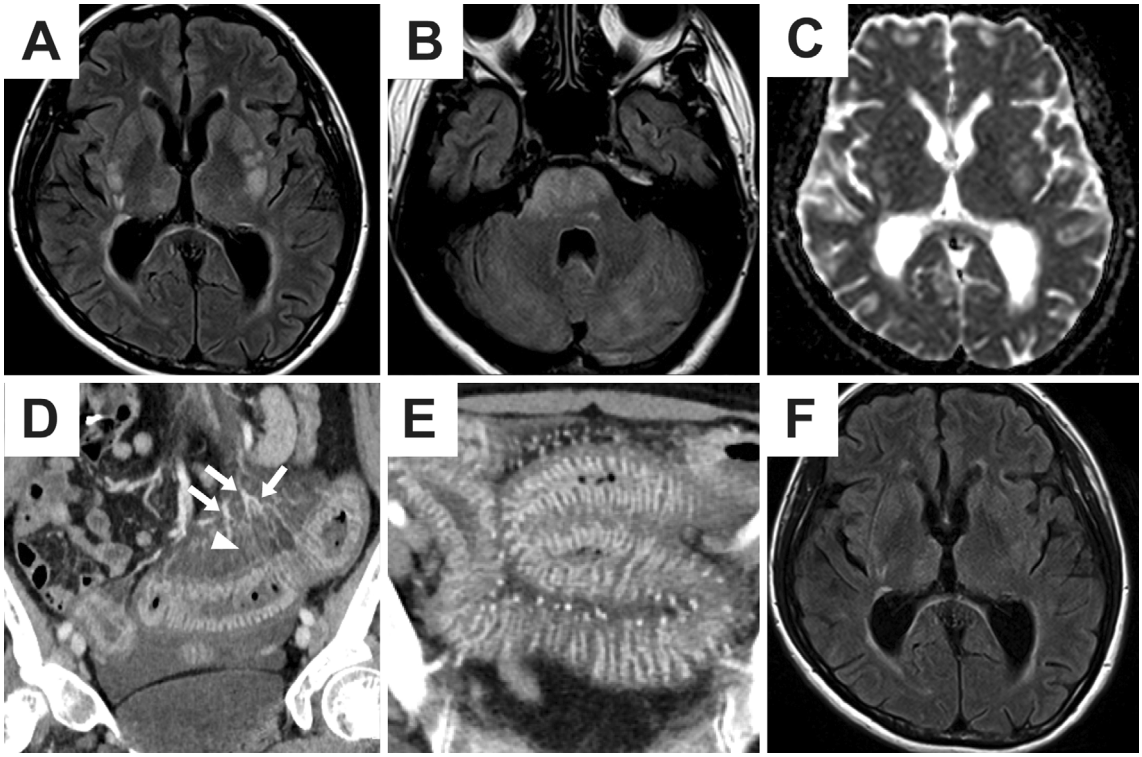

Figure. **FLAIR brain images (A, B) on admission show hyperintense lesions in the bilateral basal ganglia (A), brainstem, and cerebellum (B). An ADC map (C) on admission shows increased values in the areas of FLAIR abnormalities. Coronal (D) and axial (E) sections of enhanced abdominal computed tomography on the 4th hospital day reveal diffuse wall thickening with intestinal mucosal enhancement and vasa recta engorgement (arrowhead) as well as dilation of the mesentery blood vessels (arrows) and ascites. Six days after initiation of antihypertensive therapy, the FLAIR hyperintense lesions in the bilateral basal ganglia are markedly decreased (F). FLAIR: fluid attenuated inversion recovery**

PRES (Figure A-C). We ultimately diagnosed her with TMA associated with IFN-β1b because her hypertension had gradually progressed over two years with no signs of infection, malignancy, or autoimmune diseases.

The drug was withdrawn, and antihypertensive therapy was initiated with intravenous nicardipine infusion (2 mg/h). Her headache and nausea disappeared within a few days. On the 4th hospital day, the patient developed severe abdominal pain and nausea. Enhanced abdominal computed tomography showed marked intestinal edema, dilation of the mesentery blood vessels, and ascites (Figure D and E). These abnormalities were presumably caused by microangiopathy in mesentery blood vessels, as no evidence of potential causes such as ischemia or infection was found on clinical findings, laboratory data, or imaging. She had no fever, and her serum C-reactive protein and lactic acid levels were normal. A fecal culture was negative. The abdominal pain disappeared within a few days without specific treatment. Three weeks after the initiation of antihypertensive treatment, the laboratory abnormalities and elevated blood pressure returned to normal levels except for mild anemia (hemoglobin 9.8 mg/dL). The patient needed 2 antihypertensive drugs (nifedipine 40 mg/day and losartan 75 mg/day). PRES also improved, as seen on brain magnetic resonance imaging performed on the 6th hospital day (Figure F).

Discussion

IFN-β is a widely prescribed immunomodulatory agent for RRMS and includes IFN-β1a and IFN-β1b. TMA induced by IFN-β1b is rare compared with that induced by IFN-β1a (2). Only one case in which IFN-β1b-induced TMA was described in detail has been reported among multiple sclerosis (MS) patients in Japan (3).

Several mechanisms have been suggested to explain how IFN-β induces TMA. The pathogenesis of TMA may include a reduction in vascular endothelial growth factor (VEGF). A low level of VEGF inhibits appropriate renal endothelial formation and promotes the development of microvascular injury and TMA (4). In addition, VEGF is a major factor in the regulation of the production of endothelial nitric oxide. Nitric oxide plays a key role in maintaining local vasodilatation, reducing the risk for local thrombosis, and protecting endothelial cells from toxicity due to circulating cytokines, such as tumor necrosis factor-alpha, the circulating levels of which are elevated after injection of IFN (5, 6). Indeed, the inhibition of VEGF with the monoclonal VEGF antibody bevacizumab may cause TMA in pa-

tients with proteinuria and hypertension (4). A previous report showed that IFN-β inhibits the production of VEGF protein (7). For efficient angiogenesis, VEGF promotes phosphorylation-dependent ubiquitination and degradation of the IFN receptor and subsequent attenuation of IFN-α/β signaling (8).

In the present case, the patient's hypertension gradually progressed over two years. Systemic complications, such as hematological abnormalities and PRES due to intercurrent severe hypertension, probably developed just before admission and may have affected the disease status. In addition, microangiopathy itself presumably also affects the development of PRES. For instance, cisplatin has a cytotoxic effect on the vascular endothelium, leading to brain capillary leakage and acute blood-brain barrier disruption, which may trigger vasogenic edema (9). Indeed, previous reports have shown that some patients with PRES are normotensive (10).

Plasma exchange is an essential treatment for acquired TTP, which is characterized by severe ADAMTS13 deficiency attributed mostly to the presence of autoantibodies to ADAMTS13. Because of the high mortality due to TTP, plasma exchange should be considered as an immediate intervention if a diagnosis of acquired TTP cannot be ruled out. However, plasma exchange is less effective for other types of TMA, according to evidence-based recommendations regarding the indication for apheresis advocated by the American Society for Apheresis (11). In the present case, discontinuation of IFN and best supportive care were selected as the initial treatment for TMA because we had high confidence in the diagnosis of drug-induced TMA, even though no specific diagnostic test exists for TMA, and the organ damage was not severe at admission, aside from PRES.

Late-onset TMA following initiation of IFN therapy may reflect cumulative endothelial toxicity induced by IFN. Indeed, IFN-α and IFN-β therapies are known to directly cause TMA in a dose-dependent manner, and the IFN protein itself can directly damage small blood vessels, as shown in a transgenic mouse model of IFN toxicity (12). In particular, the duration of exposure to IFN-β for MS patients is longer than that of chronic myelocytic leukemia and hepatitis C virus patients treated with IFN-α (13). IFN acts as an immune modulator in MS but as an immune escalation factor in chronic myelocytic leukemia and hepatitis C virus. These differences may account for the delayed development of TMA in MS (13).

To our knowledge, this is the first report of TMA with gastrointestinal involvement (intestinal TMA: iTMA) induced by IFN-β. No pathologic criteria have been established for the diagnosis of iTMA. El-Bietar reported that the histopathological changes in iTMA after hematopoietic stem cell transplantation include mucosal hemorrhaging, loss of glands, endothelial cell swelling and separation, intraluminal schistocytes, fibrin, and microthrombi (14). The onset of iTMA occurred several days after admission in the present case, as the patient's platelet counts rapidly increased after the initiation of treatment. Rapid elevation of platelets due to platelet infusion causes deterioration of the clinical condition of TMA due to occlusive thrombosis in many organs (15).

In summary, we encountered a patient with RRMS who developed TMA following eight years of IFN-β1b therapy. After discontinuation of the medication and initiation of antihypertensive treatment, the patient rapidly improved. The new onset of hypertension or headache requires careful attention in cases of long-term administration of IFN-β1b. Routine monitoring of blood pressure and hematological tests may help detect TMA early in patients treated with IFN-β1b.

The authors state that they have no Conflict of Interest (COI).

References

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med **371**: 654-666, 2014.
2. Vosoughi R, Marriott JJ. Thrombotic microangiopathy in Interferon Beta treated multiple sclerosis patients: review of literature and report of two new cases. Mult Scler Relat Disord **3**: 321-325, 2014.
3. Nishio H, Tsukamoto T, Matsubara T, Okada Y, Takahashi R, Yanagita M. Thrombotic microangiopathy caused by interferon beta-1b for multiple sclerosis: a case report. CEN Case Rep **5**: 179-183, 2016.
4. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med **358**: 1129-1136, 2008.
5. Goldberg RJ, Nakagawa T, Johnson RJ, Thurman JM. The role of endothelial cell injury in thrombotic microangiopathy. Am J Kidney Dis **56**: 1168-1174, 2010.
6. Kumpfel T, Then Bergh F, Pollmacher T, Holsboer F, Trenkwalder C. Acute effects of interferon beta-1a on plasma cytokine levels in patients with MS. Neurology **55**: 1231-1233, 2000.
7. Takano S, Ishikawa E, Matsuda M, Yamamoto T, Matsumura A. Interferon-beta inhibits glioma angiogenesis through downregulation of vascular endothelial growth factor and upregulation of interferon inducible protein 10. Int J Oncol **45**: 1837-1846, 2014.
8. Zheng H, Qian J, Carbone CJ, Leu NA, Baker DP, Fuchs SY. Vascular endothelial growth factor-induced elimination of the type 1 interferon receptor is required for efficient angiogenesis. Blood **118**: 4003-4006, 2011.
9. Ito Y, Arahata Y, Goto Y, et al. Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. AJNR Am J Neuroradiol **19**: 415-417, 1998.
10. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. AJNR Am J Neuroradiol **23**: 1038-1048, 2002.
11. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apher **31**: 149-162, 2016.
12. Kavanagh D, McGlasson S, Jury A, et al. Type I interferon causes thrombotic microangiopathy by a dose-dependent toxic effect on the microvasculature. Blood **128**: 2824-2833, 2016.
13. Kundra A, Wang JC. Interferon induced thrombotic microangiopathy (TMA): analysis and concise review. Crit Rev Oncol Hematol **112**: 103-112, 2017.

14. El-Bietar J, Warren M, Dandoy C, et al. Histologic features of intestinal thrombotic microangiopathy in pediatric and young adult patients after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **21**: 1994-2001, 2015.

15. Harkness DR, Byrnes JJ, Lian EC, Williams WD, Hensley GT. Hazard of platelet transfusion in thrombotic thrombocytopenic purpura. JAMA **246**: 1931-1933, 1981.