Thrombotic thrombocytopenic purpura complicating interferon therapy in chronic C hepatitis

Purpura thrombotique thrombocytopénique compliquant un traitement par interféron au cours d’une hépatite C chronique

Introduction

Thrombotic thrombocytopenic purpura is characterized by the systemic deposition of platelet thrombi with abundant von Willebrand factor (vWF) in the arterioles and capillaries. Recently, vWF cleaving protease (ADAMTS-13) activity was found to be severely deficient in hereditary and acquired idiopathic thrombotic thrombocytopenic purpura [1]. We report the case of a patient who developed thrombotic thrombocytopenic purpura during interferon therapy for chronic hepatitis C with a severe deficiency of ADAMTS-13 related to the ADAMTS-13 autoantibody.

Observation

In October 2004, a 51 year-old woman was admitted for evaluation of purpura, fever, thrombocytopenia (6 G/L), and regenerative anemia (5.6 g/dL). After erythrocyte and platelet transfusions, she had a seizure and was transferred to our department for evaluation for thrombotic thrombocytopenic purpura. The patient had genotype 1b chronic hepatitis C diagnosed eight years before. She had been treated with interferon-α (3 MU three times weekly) for six months in 1996, then interferon-α plus ribavirin (1000 mg daily) until 1998. She was again treated in 2000 with combination interferon-α, ribavirin and amantadine for one year. Hepatitis C virus was not cleared and in 2002 a liver biopsy showed extensive fibrosis (F3 according to Metavir score) leading to maintenance therapy in 2002 a liver biopsy showed extensive fibrosis (F3 according to Metavir score) leading to maintenance therapy for six months in 1996, then interferon-α plus ribavirin (3 MU three times weekly) until 1998. She was again treated in 2000 with combination interferon-α, ribavirin and amantadine for one year. Hepatitis C virus was not cleared and in 2002 a liver biopsy showed extensive fibrosis (F3 according to Metavir score) leading to maintenance therapy for chronic hepatitis C with a severe deficiency of ADAMTS-13 related to the ADAMTS-13 autoantibody.

Discussion

Side-effects of interferon are not uncommon and include exacerbation of pre-existing autoimmune disorders or the de novo induction of autoimmunity [2]. These effects are distinct from the autoimmunity associated with chronic hepatitis C, which interferon may help. In this patient, it is debatable whether hepatitis C virus or interferon therapy induced thrombotic microangiopathy [3—7]. As hepatitis C virus infection was not complicated by advanced cirrhosis, we believe that the transient ADAMTS-13 deficiency observed in our patient was not related to liver failure but to the presence of anti-ADAMTS-13 antibodies. The presence of auto-antibodies is common in patients with hepatitis C virus and the presence of the ADAMTS-13 antibody may be another autoantibody in these patients. We recently detected anti-ADAMTS-13 antibodies in three out of six untreated patients with hepatitis C virus-related cryoglobulinemia with no significant decrease in ADAMTS-13 activity (unpublished personal data). Furthermore, Yagita et al. recently reported a case of thrombotic thrombocytopenic purpura with a severe ADAMTS-13 deficiency associated with the presence of its inhibitor in a patient with hepatitis C virus end-stage cirrhosis, not treated by interferon [5]. However, in our patient the disappearance of the inhibitor linked to normalization of ADAMTS-13 activity immediately after pegylated interferon withdrawal and plasma exchanges without relapse after 36 months of follow-up, despite persistent hepatitis C infection, does not support the role of the hepatitis C virus alone in the development of thrombotic thrombocytopenic purpura. These results suggest that the onset of thrombotic microangiopathy in this patient might be due to interferon therapy. Interferon-associated thrombotic thrombocytopenic purpura has been rarely reported, mainly in patients with chronic myeloid leukaemia [3]. Only six cases of thrombotic thrombocytopenic purpura in patients with hepatitis C have been published after administration of interferon [3,5—7]. The hallmark of these cases was the unusually high cumulative dose of interferon the patients had received. It has been suggested that interferon could damage microvascular endothelial cells through induction of apoptosis or antibodies, such as anticardiolipin or anti-ADAMTS-13 antibodies [3,6]. In our patient, the diagnosis of
Interferon-induced thrombotic thrombocytopenic purpura was supported by the high cumulated dose of interferon, the presence of the ADAMTS-13 inhibitor at the onset of thrombotic thrombocytopenic purpura, and the recovery after interferon withdrawal despite persistent hepatitis C virus infection.

During interferon treatment for chronic hepatitis C, thrombocytopenia can be due to myelosuppression or induction of autoimmune thrombocytopenic purpura. However, thrombotic thrombocytopenic purpura, whose prognosis is vital and which requires a specific therapy, should be considered. Because acquired ADAMTS-13 inhibitors may develop as autoantibodies in interferon-α-treated patients with chronic viral hepatitis C, thrombocytopenia during interferon therapy could justify screening for schistocytes particularly in patients with cirrhosis and a pre-existing ADAMTS-13 deficiency. Serial determination of ADAMTS-13 activity and its inhibitor may provide useful information for the diagnosis and treatment of interferon-associated thrombotic thrombocytopenic purpura, as well as its pathogenesis.

Références


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