Case report of thrombotic microangiopathy associated with subcutaneous interferon beta-1a: An emerging complication?☆

Microangiopatía trombótica asociada a interferón beta-1a subcutáneo: ¿una complicación emergente? Descripción de un caso

Dear Editor:

The term thrombotic microangiopathy (TMA) defines a series of microvascular alterations with involvement of the vascular wall. They normally present with microangiopathic haemolytic anaemia, platelet aggregation, and thrombocytopaenia. Two clinical entities have been described, depending on whether lesions are dominant at the renal or the cerebral level: haemolytic-uraemic syndrome and thrombotic thrombocytopenic purpura.[1]

Although TMA may have various aetiologies, the number of cases of drug-induced TMA in the literature has been increasing in the past few years. Drug-associated TMA can be an acute, immune-mediated disorder or the result of gradual, dose-dependent toxicity.[2]

The most frequent adverse events of interferon treatment are flu-like symptoms, asthenia, anorexia, and skin reactions. Renal adverse effects and TMA are infrequent but well-documented in the literature, and this event is more frequently associated with the use of alpha-interferons.[3,4] The literature contains anecdotal case descriptions of TMA associated with the use of interferon beta.[5–7] However, increasing numbers of TMA cases have been reported, a trend that is probably associated with a change in the formulation of subcutaneously-administered interferon beta-1a (Rebif®).[7]

We present the first case of a patient who presented TMA after 9 years of treatment with subcutaneous interferon beta.

This 36-year-old man diagnosed with relapsing-remitting multiple sclerosis had been taking interferon beta-1a (Rebif® 44) since 2004. He showed good tolerance to treatment without displaying any clinical or radiological activity since treatment onset (EDSS 1.5). His history of hypercholesterolaemia treated with gemfibrozil and bipolar disorder treated with lithium is relevant.

He was admitted due to progressive symptoms of dyspnoea in the context of heart disease with systolic dysfunction and pulmonary hypertension. While he was hospitalised, we observed persistently high blood pressure values, normocytic/normochromic anaemia (Hb 8.3 g/dL) and thrombocytopaenia (76 000/mm^3), and high LDH levels. A blood smear revealed schistocytes. No decrease in renal function was observed. We performed a complete diagnostic study which ruled out infectious, toxic, or autoimmune aetiology; TMA probably related to treatment with interferon beta was suspected. We discontinued Rebif® and started treatment with corticosteroids (mg/kg/12 h) and plasmapheresis, which progressively improved clinical and analytical parameters. The patient presented psychotic decompensation and we began dosing down the corticosteroids until they could be discontinued completely. One year after the episode that resulted in hospitalisation, the patient present arterial hypertension responding poorly to drug treatment. He is not receiving treatment for multiple sclerosis. We have not observed any new clinical exacerbations or increased lesion loads in radiology studies.

In a recently published study in the *New England Journal of Medicine*, Hunt et al.[7] exhaustively reviewed cases of TMA associated with interferon beta-1a and reported between 1998 and August 2013. In 2007, when the formulation of Rebif® changed, we observed an increase in the incidence of reported cases in European countries in which the new formulation was distributed. This rise in cases has not been associated with other formulations of Rebif® or with Avonex®, which lets us rule out a possible association between the change in formulation and the higher number of reported cases.

Our own patient, as well as the cases reviewed by Hunt et al.,[7] showed these clinical symptoms after years of well-tolerated treatment, and experienced acute, severe disease progression associated with acute arterial hypertension. TMA can have fatal consequences and lead a significant number of patients to develop chronic kidney disease and drug-resistant hypertension. Doctors must remain vigilant for signs of this entity to facilitate prompt diagnosis and treatment.

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