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SHORT COMMUNICATION

Fatal Thrombotic Thrombocytopenic Purpura in a Psoriasis Patient Treated with Ustekinumab and Methotrexate

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Thrombotic thrombocytopenic purpura (TTP) is a rare disorder first described by Moschowitz in 1924 (1). Diagnosis is based on a symptoms pentad including thrombocytopenia, microangiopathic haemolytic anaemia, neurological abnormalities, fever and renal failure. However, only 40% of patients will manifest all 5 of the signs and symptoms (2, 3). TTP results from an excessive systemic platelet aggregation caused by the accumulation of unfolded high molecular weight von Willebrand factor (VWF) multimers in plasma. This failure to degrade the endothelium derived hyper-reactive VWF multimers into less adhesive forms is related to a severe deficiency in ADAMTS13 (A Disintegrin And Metalloproteinase with Thrombo-Spondin-1 like motifs), a protease specifically involved in this process (4). Severe ADAMTS13 deficiency results from biallelic mutations of the encoding gene in hereditary forms, or from polyclonal autoantibodies in acquired forms secondary to other clinical conditions, drugs or immune-mediated inflammatory disease (5). Common medications that cause TTP include quinine, chemotherapeutic agents, calcineurin inhibitors, oral contraceptives and platelet inhibitors (ticlopidine and clopidogrel). Acute TTP was mostly fatal until introduction of plasma therapy in the 1970s and patients died from systemic thrombotic microangiopathy (TMA) that caused cerebral and myocardial infarctions and renal failure (2,3). Prompt diagnosis is important because TTP with severe ADAMTS13 deficiency (<5%) has a good response to plasma exchange with relatively low mortality rate (8–19%).

Biological therapies are specially designed to block specific molecular steps in the pathogenesis of psoriasis and have been demonstrated to be an effective treatment in moderate to severe chronic plaque psoriasis. One of these drugs, efalizumab, has been previously reported as a potential precipitating factor for TTP (6). More recently, ustekinumab, a monoclonal antibody, which binds both interleukin (IL)-12 and IL23, was also considered as a potential secondary cause of TPP in a case report (7). Here we report a new case of TTP (without purpuric skin lesions) in association with ustekinumab used for psoriasis treatment.

CASE REPORT

A 36-year-old man with a past medical history of psoriasis for 15 years underwent several previous systemic treatments for psoriasis, including methotrexate (MTX) and cyclosporine and different anti-TNF agents including infliximab and adalimumab. In April 2013, combined treatment with MTX (Methoject® (Nordic Pharma, France) 15 mg/week) and ustekinumab (Stelara®(Janssen-Cilag, Issy-les-Moulineaux, France) 45 mg/12 weeks) injections was started. An excellent clinical response was obtained with a significant reduction of Psoriasis Area and Severity Index (PASI) and improvement of his quality of life. In April 2014, a systematic full blood count showed a low haemoglobin concentration (8.2 g/dl), a severe decrease of platelet count (10,000/mm^3), and an increase of lactate deshydrogenase (LDH) level (632 Ul/l; normal < 430 UI/l). Haptoglobine was undetectable and reticulocyte increased to 220,000 /mm^3 (normal 20,000–100,000). The peripheral blood film demonstrated fragmented red cells (7%) and the direct antibody test was negative. On physical examination, he was afebrile with a good general health status. His cardiovascular, pulmonary, abdominal and neurological examinations were all normal. His skin examination demonstrated residual psoriatic plaques which covered less than 2% of the total body surface. Bone marrow aspiration did not show any sign of MTX-induced bone marrow toxicity. Full body CT scan was normal. HIV, Hepatitis B and C antibodies were negative as were antinuclear and antiphospholipid antibodies.

A diagnosis of TTP was based on fragmented red cells (schizocytes) in the blood smear (reflecting hemolysis) and was confirmed by low level of ADAMTS13 activity (< 5%) and an elevated rate anti-ADAMTS13 antibody (> 100 Ul/dl; normal < 12 UI/dl). Daily plasma exchange was immediately started with standard 50 ml/kg (weight was 76 kg with approximately 4 l exchange per treatment) and prednisone (1 mg/kg/day). On day 5, platelet count increased to 164,000/mm^3 and LDH level was normal. However, on day 7, platelet count decreased to 41,000/mm^3 while LDH level increased to 648 U/l. The platelet count continued to decrease and anti-CD20 monoclonal antibody (Rituximab®, 375 mg/m^2) was then introduced on days 8 and 11 in addition to plasma exchange. On day 12, platelet count was 5,000/mm^3 and our patient developed transitory neurological symptoms with left hemiparesis. CT scan of the brain did not show any intracerebral haemorrhage. On day 13, plasma exchange was increased to 8 l/day and prednisone to 2 mg/kg/day leading to an increase of platelet count to 38,000/mm^3. Unfortunately, clinical status of our patient deteriorated rapidly with generalised seizures and multiple organ failure. The patient died on day 14 after his admission.

DISCUSSION

In this report, we present a second case of TTP occurring in a psoriasis patient treated with ustekinumab (7). This monoclonal antibody binds to the p40 subunit of IL-12 and IL-23, key cytokines in the pathogenesis

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of psoriasis (8). Studies have not only shown clinical benefit in the management of psoriasis, but also a lack of long-term toxicity (9).

Secondary drug-induced TTP have already been reported (3, 5). The severe deficiency of ADAMTS-13 activity induced by drugs is thought to be due to the formation of immune complexes, the induction of inhibitors, and also by direct endothelial damage. To our knowledge, only 2 case of TTP induced by monoclonal antibodies have been described in psoriasis patients (6, 7). The exact mechanisms involved are unknown and several hypotheses have been raised. First, the formation of immune complexes against ADAMTS-13 as a result of treatment with efalizumab, has been suggested as the mechanism of development of TTP (6). Ustekinumab may have induced immune dysregulation by neutralisation of proinflammatory cytokines and disruption of T-regulatory cell pathways leading to ADAMTS13 auto-antibody formation (7). However, in our observation, less antibodies formation should be expected through the concomitant treatment with MTX. MTX, indeed has been shown to reduce the immunogenicity in response to monoclonal antibody therapies in chronic inflammatory diseases (10, 11). The mechanism whereby MTX acts on the immune response has not been fully demonstrated; however, suppression of early T- and B-cell expansion may be responsible for modulation of the immune response (12).

Second, the possibility of a predisposing autoimmunity against ADAMTS13 associated with psoriasis should be suspected. There is indeed evidence for an association between psoriasis and autoimmune diseases (13). In a retrospective cohort study conducted in 25,341 patients with 2 or more diagnosis codes for any psoriatic disease, the authors found 14 autoimmune diseases significantly associated except immune thrombocytopenia purpura and haemolytic anaemia. But to our knowledge, TTP was never demonstrated to be significantly associated with psoriasis. However, it was remarkable to notice in our observation the presence of anti-ADAMTS13 antibodies (20 UI/dl) with normal ADAMTS13 activity at least one year (March 2013) before the introduction of ustekinumab and MTX. The possibility of a predisposing secondary acquired ADAMTS13 deficiency can thus not be excluded in our patient. In this case, ustekinumab would have precipitated a severe deficiency of ADAMTS13 through the induction of additional antibodies against ADAMTS13.

We do not have any explanation for the fatal outcome of our patient, except the initial severity of TTP as defined by Coppo et al. (14). The prognostic score recently validated to identify at diagnosis patients at risk of fatal TTP (15) was indeed not filled in our observation.

In conclusion, this case report suggests that ustekinumab can be considered as a potential secondary cause of TTP. However, we cannot exclude the possibility that our patient experienced the idiopathic form of the disease. Although exceptional, the patient's fatal clinical course should alert physicians to the rare occurrence of TTP if their patients treated with ustekinumab develop thrombocytopenia associated with haemolytic anaemia while using this effective therapy.

The authors declare no conflict of interest.

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