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Case Report
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Drug-induced Thrombotic Microangiopathy During Maintenance Treatment in a Patient With Multiple Myeloma

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Multiple myeloma (MM) is still considered an incurable disorder despite the important advances in therapies in the last 10 years.[1] One of these improvements is associated with the introduction of maintenance treatment for younger patients after autologous stem cell transplantation. Lenalidomide is known to prolong progression-free survival and overall survival without any significant increase in toxicity, leading to its approval for use.[2] Other drugs, such as ixazomib, an oral proteasome inhibitor that is well tolerated and has only mild adverse effects, are being investigated for maintenance treatments.[3] Here, we describe a serious complication that could be associated with this group of drugs: a drug-induced thrombotic microangiopathy (TMA) that, although rare, can be life threatening if not diagnosed at an early stage.

TMA is clinically defined by the concurrent appearance of microangiopathic hemolytic anemia, thrombocytopenia, and organ injury caused by vascular damage that is manifested as arteriolar and capillary thrombosis. As knowledge of the pathogenesis has evolved, 9 disorders have been described and categorized as hereditary or acquired disorders. Hereditary disorders include those mediated by ADAMTS13 deficiency due to gene mutation, mutations of the complement pathway, metabolism, and coagulation. Acquired disorders include those mediated by ADAMTS13 deficiency arising from antibody inhibition, Shiga-toxin, drugs (an immune reaction or a toxic dose), and alteration of complement pathway (such as the antibody inhibition of complement factor H).[4] Below, we present a patient diagnosed with drug-mediated TMA during maintenance treatment with ixazomib.

A 55-year-old woman with a history of MM was admitted to the emergency room due to a digestive hemorrhage with significant hemodynamic and analytic repercussions. The patient had been treated as part of the Spanish Myeloma Group GEM12 clinical trial with bortezomib, lenalidomide, and dexamethasone, followed by autologous stem cell transplantation, after which she attained stringent complete remission (sCR) was achieved. She was included in another clinical trial (GEM14MAIN) for maintenance therapy with ixazomib (4 mg on days 1, 8, and 15 of 28-day cycles), lenalidomide (15 mg daily on days 1–21), and dexamethasone (20 mg on days 1–4 and 9–12) and remained in sCR after 11 months.

Upon admission to the emergency room, her initial blood analysis revealed normocytic hyperchromic anemia (hemoglobin 75 g/L) with a low reticulocyte count (25×10^9/L), and deep thrombocytopenia (1×10^9/L) with low immature platelet fraction, both suggesting a central origin. However, a blood smear was analyzed, which revealed a 12% schistocytes count. These findings, associated with renal failure (creatinine 43.4 mg/L), elevated bilirubin (12.8 mg/L), high lactate dehydrogenase (869 U/L), consumed haptoglobin, and a negative direct Coombs test, were consistent with a diagnosis of TMA.

An endoscopic investigation of the origin of the hemorrhage led to a diagnosis of erosive duodenitis. The condition was treated with proton-pump inhibitors, which resolved the bleeding.

Given the clinical suspicion of thrombotic thrombocytopenic purpura, initial management included plasma exchange therapy, with fresh-frozen plasma, and the administration of glucocorticoids 1 mg/kg per day, as well as platelet transfusion due to active bleeding. Treatment with ixazomib and lenalidomide was discontinued. Despite these measures, the thrombocytopenia persisted and the renal failure worsened, the patient requiring dialysis after 72 hours.

Screening for thrombotic thrombocytopenic purpura and hemolytic uremic syndrome included testing for ADAMTS13 activity, which had a normal level of 110%, and antibody

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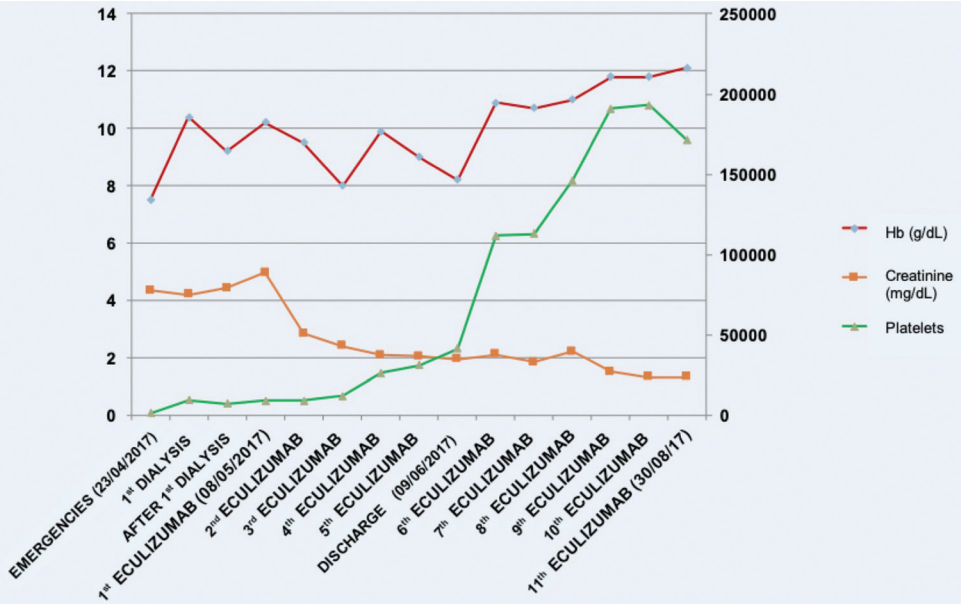

Figure 1. Improvement of creatinine, hemoglobin and platelet count after eculizumab initiation.

detection, which yielded a negative result. Serological tests for infectious diseases and a stool culture with Shiga toxin-producing *Escherichia coli* gave negative results. As active disease is known to be a cause of TMA, the MM status was re-evaluated, which confirmed the sCR.[4,5] Autoimmune studies including complement factors C3, C4, and C5 showed an abnormally low fraction of C3 and C4 and an elevated C5 fraction. Even though, classically, these findings were consistent with a diagnosis of complement-mediated hemolytic uremic syndrome; there is now evidence that C3, C5a, and C9 are not suitable for diagnosis because abnormal circulating levels are found in only around 50% of the patients.[6] We searched for possible triggers in our patient, but found only proteasome inhibitors to be a possible cause.[7–10] She was therefore diagnosed with drug-mediated TMA.

Proteasome inhibitors are known to be a cause of TMA,[7–10] but, there are few published cases. The mechanisms by which TMA occurs have not so far been identified. Some hypotheses propose that there is both immune-mediated and dose-dependent damage. One of the best-studied potential mechanisms is microvascular damage mediated by inhibition of vascular endothelium growth factor, which is essential for the functional integrity of the glomerular endothelium. There are few therapeutic options, support therapy and drug discontinuation being the most widely accepted.[4,8] In the last few years, cases of TMA not responding to standard therapy have been published, and it has been suggested that rescue treatment with eculizumab, an inhibitor of the complement alternative pathway, may be beneficial.[9,11,12]

Due to the catastrophic evolution of the disease in our patient despite support therapy, treatment with eculizumab was started. This monoclonal antibody binds with high affinity to C5 complement protein and blocks the generation of proinflammatory C5a.[13] The dose was 900 mg weekly for 4 weeks followed by maintenance therapy of 1200 mg every 2 weeks, as used for complement-mediated TMA. Renal impairment was alleviated after the first dose, and the patient achieved independence from hemodialysis after the 2nd dose. From the 6th dose onward, hemoglobin and platelet count gradually increased, achieving until normal values by the 10th administration. Figure 1 shows the evolution of hemoglobin, platelets, and creatinine after the initiation of treatment with eculizumab.

Reaching an accurate diagnosis of this case was challenging. Since the complement factors were altered, we initially concluded that the patient was suffering a complement-mediated TMA. However, literature review showing complement factor alteration is very nonspecific, and considering the negative result of genetic tests for complement mutations, and the possible association with drugs, prompted us to consider a diagnosis of drug-mediated TMA.

There is no evidence of there being an optimal time to stop therapy with eculizumab. Some studies, with a small number of patients with complement-mediated TMA, have concluded that treatment may be withdrawn from patients with a good initial response and those with mutations like CD46, who have a lower risk of recurrence.[14] There are no useful parameters in the follow-up, since the levels of C3, C5, and C9 cannot be reliably measured.[6] Given the complete response we decided to stop treatment after 11 cycles; especially since other data suggest that, should the disease recur, reintroduction of eculizumab is equally effective.[14,15] At the time of writing, the patient maintains her complete response to both MM and TMA.

Although drug-mediated TMA is a very rare condition, it is a potentially fatal disorder if therapy is not initiated early on. For this reason, prompt suspicion and diagnosis, together with the identification of a potential trigger, are keys to achieving a good outcome. Eculizumab might be an option for patients who do not respond to the initial therapy.

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