CLINICAL VIGNETTE

Ramucirumab and the Risk of Thrombotic Microangiopathy

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Case Presentation

A 69-year-old male with a history of chronic hypertension and stage IV esophageal adenocarcinoma presented with dyspnea, oral mucosal bleeding, and bloody diarrhea. Regarding oncological history, the patient had initially been treated with carboplatin and paclitaxel followed by radiation and capecitabine. On surveillance imaging, there was progression of disease burden, and paclitaxel and ramucirumab was initiated. The shortness of breath and dyspnea progressively worsened over the preceding five weeks. During this time, his hypertension became uncontrolled with systolic blood pressures greater than 180 mm Hg despite compliance with antihypertensive medications. Four days prior to presentation, he began to experience oral mucosal bleeding and bloody diarrhea, prompting an outpatient visit with hematology/oncology. His physical exam was notable for a temperature of 36.9°C, pulse of 88 beats per minute, respiratory rate of 22 breaths per minute, and blood pressure of 186/87 mm Hg. He was in mild respiratory distress with accessory muscle use and crackles to mid lungs bilaterally. There was also bilateral 2+ pitting edema in the lower extremities. The patient appeared pale with fresh blood in oropharynx oozing from the gums. Digital rectal exam was positive for stools stained with bright red blood.

Laboratory data was significant for platelets (13 x 10^9/L), a negative direct antiglobulin test, lactate dehydrogenase 1075 U/L (high), and haptoglobin <8 mg/dL (low). Due to concerns for acute hemolysis and need for transfusion, the patient was sent to the hospital for admission.

Admission, laboratory results included white blood cell count of 11.5 x 10^9/L, hemoglobin 9.5 g/dL, platelets 47 x 10^9/L, absolute reticulocyte count 0.2066 x 10^{12}/L (low), blood urea nitrogen 30 mg/dL, creatinine 0.81 mg/dL, total bilirubin 3.3 mg/dL (direct bilirubin 0.4 mg/dL, indirect bilirubin 2.9 mg/dL), B-type natriuretic peptide 731 pg/mL (high).

Patient's dyspnea was attributed to a new diagnosis of acute diastolic congestive heart failure exacerbation in the setting of hypertensive urgency and volume overload due to total parenteral nutrition administration in addition to acute hemolysis. Blood pressure was aggressively managed as well with furosemide diuresis, which led to improvement in edema, though he remained mildly dyspneic.

Due to ongoing hemolysis despite transfusions, a decision was made to proceed with empiric plasma exchange. Patient underwent four cycles of plasma exchange in addition to four doses of 40mg dexamethasone intravenously without significant improvement in his hemolytic markers. Additional admission laboratory resulted including disintegrin and metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS13) 20.8% (low). Stool testing including shigatoxin was negative. With this information, leading diagnosis at this time was hemolysis secondary to either malignancy versus drug induced with his recent initiation of ramucirumab. The patient underwent left iliac crest bone marrow biopsy and flow cytometry in which showed no evidence of malignancy. Based on his laboratory and pathology findings in addition to refractory treatment response, he was diagnosed with drug induced thrombotic microangiopathy (DITMA) related to ramucirumab and continued with supportive measures including three units of platelet transfusions throughout his hospitalization.

The patient was discharged home on hospital day eleven after there was no further evidence of active hemolysis or dependence on blood product transfusions. Outpatient labs one week post-discharge revealed stable hemoglobin and platelet counts. Given the concern for DITMA, oncology discontinued ramucirumab. He remains on paclitaxel.

Discussion

Thrombotic microangiopathy (TMA) is a condition which is best characterized as small vessel injury due to platelet microthrombi. The formation of the platelet microthrombi may precipitate organ damage (renal, neurologic, or cardiac), and results in microangiopathic hemolytic anemia as well as thrombocytopenia. The classical finding of schistocytes on the peripheral blood smear is the hallmark of TMA diagnosis. The TMA diagnosis could be primary or be secondary to systemic conditions such as malignancies, infections, malignant hypertension, or result from pregnancy related complications such as pre-eclampsia. The primary TMA conditions are characterized by ADAMTS13 deficiency which classically results in thrombotic thrombocytopenia (TTP) and the shigatoxin exposure, the culprit of hemolytic uremic syndrome (HUS). Interestingly, some TMA instances may be drug induced (DITMA). DITMA is an acquired form of TMA, and may result from a dose-dependent drug toxicity (type I) or drug related immune-mediated and not dose-dependent mechanisms (type II). Quinine is the most common cause of DITMA (immune-mediated) but many different drugs including

vaccines, beverages and herbal remedies are also associated with TMA.[1,2]

DITMA is a rare disorder characterized by the presence of schistocytes on the peripheral blood smear, hemolytic anemia, renal injury and thrombocytopenia. The mechanism of the DITMA is either immune-mediated or direct-dose-dependent drug toxicity.[3-5] DITMA may be predominantly associated with hematologic hallmarks of classical TMA or the emphasis may be on the renal toxicity. The latter is well described with vascular endothelial growth factor (VEGF) inhibitors. These agents can trigger DITMA by inhibiting VEGF[6] which in turn may lead to the injury of the renal podocytes. However, the VEGF inhibition appears to be one of the several mechanisms of DITMA induced renal toxicity.[7]

Ramucirumab is a recombinant monoclonal antibody that targets the vascular endothelial growth factor receptor 2. This in turn results in the reduction of the tumor vascularity and ultimately tumor growth.[8,9] Ramucirumab is used in the treatment of various malignancies including but not limited to colorectal cancers, gastric cancer, hepatocellular carcinoma, and metastatic Non-small cell lung cancer.[10] Our review of the literature yielded only one case report of ramucirumab induced TMA.[11] This case of ramucirumab associated TMA appeared to be renally limited and occurred immediately after a prior bevacizumab therapy.

It is important to note that the VEGF signaling pathway (VSP) inhibitors such as ramucirumab are associated both with hypertension, proteinuria and renal injury. An intact VEGF pathway is crucial in maintaining a healthy renal function. DITMA is a well described complication of the VSP inhibitors. Reports of both bevacizumab and VEGF-trap associated DITMA are common. However, it is interesting to point out that in about 50% of patients with biopsy-proven renal TMA due to VSP inhibitors, no apparent hematologic manifestations are noted.[6,12]

The exact mechanism of ramucirumab-induced TMA remains elusive and may be reminiscent to that of VSP inhibitors. However, the lack of a mechanistic explanation of DITMA is common in our literature. The patient in this case report seemed to have hematologic predominant TMA as an overt renal injury could not be readily documented. Hence, we believe that ramucirumab associated TMA may mechanistically transcend the well-established VSP inhibitory properties. This is because TMA emanating solely from the VSP pathway inhibition is invariably associated with renal toxicity.

The management of the DITMA remains challenging, but the standard of care demands an immediate withdrawal of the offending drug and the institution of standard supportive measures. However, plasma exchange may be appropriate if the diagnosis of DITMA is uncertain. In addition, anti-complement therapy is appropriate in cases of progressive renal disease.[13,14] The prognosis of DITMA is variable and across available therapeutic measures recovery may be slow and incomplete.[15]

This is the first case report of ramucirumab-induced TMA in a patient with metastatic esophageal adenocarcinoma. More specifically, our goal is to raise the clinical awareness of a case of ramucirumab associated TMA independent of prior bevacizumab exposure. Such awareness is crucial as the use of the ramucirumab continues to steadily increase in the oncologic arena.

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