CLINICAL VIGNETTE

New Onset Jaundice and Thrombotic Microangiopathic Hemolytic Anemia in a Multiple Myeloma Patient

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A 38-year-old male with a diagnosis of IgG Kappa Multiple Myeloma presented with relapsed disease. He had received Cycle 1, Day 1 of salvage treatment with carfilzomib, dexamethasone and daratumumab and developed jaundice with hemolysis two days later.

His past Oncologic History is reviewed briefly. He initially presented eight years previously with severe back pain, renal insufficiency and anemia. Laboratory studies revealed an elevated total protein of 17.4 gm/dL with an albumin of 1.7 gm/dL. Serum Protein and Immuno-Electrophoresis was significant for a Monoclonal IgG Kappa protein 7.8 g/dL. Bone marrow biopsy revealed a hyper-cellular marrow with plasmacytosis of 80 %. He was diagnosed with Durle-Salmon Stage IIIB IgG Kappa Multiple Myeloma with IGHv rearrangement. He received induction therapy with lenalidomide, bortezomid and dexamethasone, plus zoledronic acid with minimal response. He then received VRD-PACE with very good partial response. He subsequently underwent high dose chemotherapy and autologous bone barrow transplant (BMT) with complete remission. He did well for five years before developing rising M protein, and new bone disease in his right acetabulum. He was treated with daratumumab, lenolidomide and dexamethasone. PET/CT 10 months later revealed complete resolution of his FDG avid disease in the right acetabulum.

Two years later, the patient was found to have progressive disease in the left femur. Laboratory studies revealed a normal CBC and normal comprehensive metabolic panel, including normal kidney function.

He received Cycle 1 Day 1 of daratumumab, carlfilzomib and dexamethasone but developed jaundice and presented to the Emergency Department. ED evaluation included a normal WBC and Hgb but a low platelet count of 31k. He had new onset renal insufficiency with a BUN of 33 mg/dL and Creatinine of 1.23 mg/dL. Other labs included elevated total bilirubin of 9.9 mg/dL and elevated LDH of 1581 U/L. Haptoglobin was low, < 8 mg/dL. Urine analysis showed 3+ blood. His DAT was Negative. He was hydrated and sent home for an outpatient evaluation at another Oncology practice. He subsequently presented to our practice and was sent back for admission and further evaluation.

On admission his peripheral smear revealed 1 + shistocytes. Repeat labs confirmed a Coombs negative Hemolytic Anemia and persistent thrombocytopenia. Microangiopathic hemolytic anemia (MAHA) was diagnosed with a differential of thrombotic microangiopathic hemolytic anemia (TMA) versus thrombotic thrombocytopenia purpura. (TTP) An ADAMTS13 was sent off. We calculated his PLASMIC score which was low risk for TTP. He was given supportive care with hydration and monitored with labs. Therapeutic plasma exchange (TPE) was discussed but did not became necessary. He was discharged home after 5 days with daily labs and management as an outpatient.

Microangiopathic Hemolytic Anemia (MAHA) is a descriptive term for Non-Immune Hemolysis or Coombs Negative Hemolysis. Intravascular red blood cell fragmentation produces schistocytes on the peripheral smear.

Thrombotic Microangiopathic hemolytic Anemia (TMA) describes a process that leads to microvascular thrombosis. It is commonly suspected in patients presenting with microangiopathic hemolytic anemia and thrombocytopenia. Patients with TMA can be critically ill, so rapid and accurate identification of the underlying etiology is essential. Due to better insights into pathophysiology and causes of TMA, we can now categorize TMA's as Thrombotic thrombocytopenia purpura TTP, postinfectious (mainly Shiga toxin-producing Escherichia coli-induced) TMA associated with coexisting conditions such as transplantation or drugs or Atypical HUS, Complement associated HUS with or without genetic abnormalities.[1]

In our patient, the major differential diagnosis was between TTP and TMA associated with drugs. TTP results from insufficient activity of the von Willebrand factor (vWF) protease known as ADAMTS13. This protease activity cleaves ultra-large multimers of a vWF that are highly thrombogenic in the uncleaved form. When ADAMTS 13 activity is lacking, ultra-large multimers accumulate and act as a scaffold for excessive platelet aggregation, resulting in uncontrolled microvascular thrombosis and hemolysis. TTP is commonly caused by IgG autoantibodies directed against ADAMTS13. Hereditary TTP results from homozygous or compound heterozygous mutations in the ADAMTS13 gene. Current recommended treatment for TTP is therapeutic plasma exchange and

immunosuppressive therapy, aimed at reducing the concentration of autoantibodies and restoring ADAMTS 13 activity.[1]

Thrombotic Microangiopathy can be associated with coexisting disease and or drugs. Various conditions have been described as potential triggers for TMA, including viral infections, malignancies and hematopoietic and solid organ transplantation. Both therapeutic and recreational drugs have been implicated in TMA. In many cases of drug-induced TMA, the TMA will resolve on discontinuation of the offending drug.

Our patient had new onset jaundice, with evidence of hemolysis including elevated total bilirubin, elevated LDH and low haptoglobin. We initially made the diagnosis of MAHA based on the peripheral smear with 1+ schistocytes in the presence of a Coombs Negative Hemolytic Anemia. The patient was also thrombocytopenic. This was new and unlikely to results from his recent chemotherapy, due to the short time frame and TMA was diagnosed, ADAMSTS13 was ordered but results would not be available for a few days. The PLASMIC score index was calculated. This is a tool to quantify the likelihood of TTP, which may support initiation of presumptive treatment before an ADAMTS13 activity is available. It assigns points for a number of clinical features. His PLASMIC score was low risk for TTP.

Literature review revealed that proteasome inhibitors could cause TMA. Thus, a diagnosis of Drug Induced or carfilzomib induced TMA was made. Nephrology was consulted was consulted during hospitalization and therapeutic plasma exchange was discussed but not instituted. The patient remained clinically stable and asymptomatic except for some nausea and tea colored urine. During hospitalization his Hgb fell to a low of 7.5 gm/dL on Day 3. His renal function deteriorated to a BUN of 41 gm/dL and creatinine of 2.43mg/dL. However, his platelet count began to improve to 41 K (low of 10 K) and his indices of hemolysis were also improving. With informed decision making we elected to defer TPE and continued with vigorous IV hydration only. He remained in the hospital for 4 days and then was discharged on Day 5 with continued oral hydration. On Day 7 the patient was seen in the office and lab values revealed a Hgb of 9.1gm/dl and Plts of 256k. His BUN/Creatinine was 20 mg/dl and 1.31 mg/dl. His LFT's completely normalized with a Total Bili of 1.1 md/dl. His LDH had fallen to 545 Units/L. His ADAMTS 13 score resulted negative.

In summary, proteasome inhibitors are known to cause TMA but there are few published cases. The mechanisms by which TMA occurs have not been so far identified. There are few therapeutic options; supportive therapy and drug discontinuation being the most widely accepted.[2]

There are two specific case reports in the literature of Carfilzomib induced TMA in patient with Multiple Myeloma that were successfully treated with Ecluzimab. In the first case TPE was initiated on account of declining kidney function with the development of acute kidney injury Stage 3. Dialysis was necessary one day later. After six days of TPE neither LDH nor Platelets had improved and Ecluzimab was begun. In the second case, a 59-year-old IgGKappa MM patient showed late onset TMA during the fourth and last cycle of elotuzumab-KRd consolidation on a clinical trial. In both patient's plasma exchange (TPE) was initiated as soon as TMA was diagnosed. In patient # 1 dialysis became necessary. Both patients received complement inhibitor eculizumab with impressive improvement in other labs and kidney function.[3]

Our case demonstrates the complexity of making a correct diagnosis in a timely fashion and considerations involved in discussing treatment options. We made a diagnosis of TMA and attributed his hemolysis to the recently administered drug carfilzomib. We instituted supportive care with hydration and were able to defer TPE since his hemolytic indices were improving and he was clinically stable. Similarly, he did not need Ecluzimab. This patient eventually had complete recovery of his renal function, and all hemolysis indices normalized following discontinuation of carfilzomab.

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