CLINICAL VIGNETTE

Cancer-Related Microangiopathic Hemolytic Anemia

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Case Report

A 64 year-old woman with a history of metastatic lobular breast cancer presented with progressive shortness of breath and was hospitalized for severe anemia and thrombocytopenia. Initial laboratory evaluation revealed her hemoglobin (HGB) was 6.4 g/dL and platelet count 52,000/μL. Reticulocyte count was 16%, lactate dehydrogenase 402 U/L, haptoglobin <15 mg/dL, and direct antigen test negative. PT was 11.6 sec, PTT 32 sec, fibrinogen 263 mg/dL, and D dimer 18,000 ng/mL. Examination of her peripheral blood smear identified on average 5 schistocytes per high power field.

She was diagnosed with metastatic lobular breast cancer to her colon 4 years prior. Her cancer was estrogen receptor and progesterone receptor positive, HER-2 unamplified. She was treated with multiple lines of hormone therapy, targeted therapy, and chemotherapy throughout the 4 years. By the time she presented with severe anemia and thrombocytopenia, her cancer was present in her bones, bone marrow, liver, bowels, and peritoneum. Her last line of chemotherapy was eribulin, on which her cancer had progressed.

The patient was diagnosed with cancer-related microangiopathic hemolytic anemia (MAHA). She was transfused packed red blood cells (PRBCs) but her hemoglobin continued to drop after each temporary rise. She required 2 Units of PRBCs every few days to maintain her HGB above 7 g/dL. She was started on capecitabine chemotherapy with a gradual improvement in her transfusion requirements, eventually becoming transfusion independent after 2 months of capecitabine. Imaging also revealed improvement in her sites of cancer. She maintained this response for 1 year until her cancer radiographically progressed and she developed a recurrence of MAHA, requiring PRBC transfusions again.

Discussion

The term microangiopathic hemolytic anemia (MAHA) was first used in 1962 to describe hemolytic anemias associated with schistocytes (red blood cell fragments) caused by shearing in small vessels. Brain et al proposed the phenomenon was due to a mechanical effect of lesions in the vessels against the red blood cells, rather than a chemical effect.[1] In cases of thrombotic thrombocytopenic purpura (TTP), thrombi in the capillaries and arterioles were believed to be the culprit. In MAHA related to cancer, tumor emboli in the vessels or direct vessel invasion by tumor were suspected.

Since initial description, cancer-related MAHA (CR-MAHA) has been studied by other groups and is now understood in more detail.[2,3] CR-MAHA typically presents with acute onset anemia and thrombocytopenia. The anemia is characterized by evidence of intravascular hemolysis (increased reticulocyte count and LDH; low or undetectable haptoglobin; and presence of urine hemosiderin) and schistocytes on peripheral blood smear. The anemia is typically moderate to severe in degree and responds poorly to red cell transfusions. Transfusion requirement can be as high as 2 Units of red cells per day. There can be evidence of disseminated intravascular coagulation (DIC) but not necessarily. Red blood cell fragmentation is caused by fibrin strands or intravascular tumor cells. CR-MAHA is a rare complication of metastatic cancer, but when present, occurs in the setting of disseminated cancer in the vast majority of cases. Bone marrow involvement by cancer was present in over 80% in one study.[3] The most common cancer histology is adenocarcinoma. Gastric and breast cancer are the most commonly associated cancers, but CR-MAHA is also seen with cancers of the colon, gallbladder, pancreas, prostate, lung, and unknown primaries. Though less frequent, there are reports of CR-MAHA with hematologic malignancies as well, including Hodgkin's lymphoma, angiotropic lymphoma, diffuse large B-cell lymphoma, and myeloma.

Conditions that present with MAHA are diverse and should be considered in the differential diagnosis.[4,5] Other than cancer, systemic infections (viral, bacterial, or fungal), severe hypertension (including eclampsia and HELLP syndrome), autoimmune disorders (including lupus and antiphospholipid syndrome), and transplantation (stem-cell or solid organ) are associated with MAHA. In addition, there is also a group of disorders categorized under primary thrombotic microangiopathies (TMA), that include TTP, hemolytic uremic syndrome (HUS), complement-mediated TMA, and drug-related TMA. TTP is clinically characterized by MAHA, thrombocytopenia, and evidence of organ dysfunction, including neurologic dysfunction, but rarely severe renal dysfunction. The diagnosis of TTP is supported by an ADAMTS13 level of less than 10%. Deficiency in ADAMTS13, a von Willebrand factor (vWF)-cleaving protease, leads to unusually large vWF multimers and platelet thrombi in the blood vessels. Hereditary TTP is caused by mutations in the ADAMTS13 gene and acquired TTP by autoantibodies to ADAMTS13. Hereditary TTP can manifest in adulthood, often triggered by precipitating factors such as pregnancy or surgery. Unlike TTP, HUS is characterized

predominantly by severe renal dysfunction and is due to endothelial injury from Shiga toxin produced by enteric bacteria, which can be detected in stool. Complement-mediated TMA is caused by over-activation of the alternative complement pathway leading to endothelial injury and can also be hereditary (from mutations in the complement genes, such as complement factor H) or acquired (from autoantibodies to complement). Drug-related TMA can result from a dose-related reaction (e.g. cyclosporine) or immune reaction (e.g. quinine). Chemotherapeutic drugs have been associated with either mechanisms of action.

Evaluation and management of CR-MAHA can vary depending on presentation. In our case, a patient with a known history of widely metastatic breast cancer presented with laboratory findings of MAHA. Other scenarios include patients with no known history of cancer, a prior history of cancer but considered to be disease-free, or localized active cancer. When CR-MAHA is suspected, CT imaging of the body is warranted to evaluate for metastatic disease. CR-MAHA can present with radiographically invisible cancer; when index of suspicion is high, a bone marrow biopsy should be considered and may reveal malignant involvement.[6] If MAHA is not clearly related to cancer, the differential diagnosis previously discussed should be considered. Chemotherapy-related TMA should always be on the differential if chemotherapy was recently given and appropriate drug discontinuation considered. CR-MAHA can be distinguished from TTP by an ADAMTS13 activity that is not severely low or undetectable.[6,7] Plasma exchange is very effective in the treatment of TTP but not helpful in CR-MAHA. Once the diagnosis of CR-MAHA is made, effective anti-cancer therapy should be initiated despite low blood counts if the patient is deemed an appropriate candidate. Chemotherapy can improve survival in CR-MAHA compared to no chemotherapy.[3] Regression of intravascular tumor emboli by chemotherapy is expected to reduce the MAHA process. Unfortunately, CR-MAHA has a very poor prognosis and therefore palliative care should also be considered.

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