Cancer-Associated Thrombotic Microangiopathy in a Patient with Metastatic Esophageal Adenocarcinoma

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The patient is a 65-year-old female with metastatic esophageal adenocarcinoma to lymph nodes and liver. She received multiple cycles of FOLFOX, followed by ramucirumab/paclitaxel, and most recently, on a clinical trial with combination of an icos agonist with a PD-1 inhibitor, status post 2 doses. She began noticing scleral icterus two weeks later and was admitted to the hospital 21-days after her second dose of these agents with symptomatic hypotension and hypoxemia. The initial evaluation confirmed jaundice and hepatomegaly, and laboratory data demonstrated normocytic anemia (hemoglobin 5.8), thrombocytopenia (platelets 39), elevated LDH (> 7000), indirect hyperbilirubinemia, reticulocyte count of 14 and reticulocyte index of 7, suggestive of a hemolytic process. DAT negative. ADAMTS13 activity was low at 56% (normal value: ≥ 70). Presumed to have developed an immune-related hemolytic anemia, T-cell mediated, she was promptly initiated on methylprednisolone 1 mg/kg IV every 12 hours, along with best supportive care. She continued to rapidly decline with tachypnea, tachycardia, hypoxemia, and hepatomegaly, and did not respond to treatments including transfusion of 4 units of packed red blood cells, steroids, and best supportive measures. She developed frank hypoxemic respiratory failure necessitating high flow oxygen, and elevated troponins as a result of the supply-demand mismatch secondary to the acute anemia. The blood smear showed anisopoikilocytosis, many spherocytes, and schistocytes, teardrop forms, nucleated RBCs, burr cells, bands, metamyelocytes; no blasts and no hypo or hypersegmented neutrophils were seen. These findings were consistent with Thrombotic microangiopathy (TMA). Her condition continued to deteriorate despite maximum efforts. Goals of care and code status were revisited, opting for comfort measures and no further escalation of therapies. Patient succumbed five days after admission. The autopsy demonstrated "metastatic adenocarcinoma involving small vessels" in multiple organs including heart, lungs, liver, spleen, lymph nodes, pancreas, adrenals, small and large bowel, kidneys, uterus, and vagina. Bone marrow was hypercellular with trilineage hematopoiesis and hemosiderin-laden macrophages.

DISCUSSION

The Thrombotic microangiopathy (TMA) syndromes are a group of disorders, extraordinarily diverse, united by common, defining clinical and pathological features [1].

The clinical features of TMA include microangiopathic hemolytic anemia, thrombocytopenia, and organ injury. The clinical criterion reflects intravascular hemolysis: schistocytes, increased LDH, decreased haptoglobin, negative Coombs, anemia, thrombocytopenia, and organ injury, with or without kidney failure [1,2]. Thrombocytopenia, schistocytosis, and elevated levels of LDH are enough to form a diagnosis in clinical practice.

The majority of cases are idiopathic, but several etiologies have been recognized, including drugs, and cytotoxic chemotherapies, such as gemcitabine, carboplatin, cisplatin, bleomycin, and a vinca alkaloid [3-8]. TMA induced by the use of an icos agonist in combination with a PD-1 inhibitor has not been described [9], and was not the cause of TMA in this case, as confirmed by autopsy findings. Severe immune-related adverse events (irAEs) remain rare (approximately 10% of cases under monotherapy), but they can become life-threatening if not anticipated and managed appropriately [10].

TMA may also be caused by the underlying malignancy itself [11], as confirmed in this case. TMA in the cancer patient shares the pathogenic microvascular occlusive lesion and many clinical manifestations as the classical TMA observed in non-cancer patients, with several subsets seen, including a microangiopathic hemolytic anemia in advanced cancer, chemotherapeutic drug-associated microangiopathy and those seen in the transplant setting [2,12]. However, the prognosis is less favorable. Clinicians should be aware of cancer-associated TMA due to its potentially lethal evolution [12,13].

KEYWORDS

cancer-associated thrombotic microangiopathy, hemolytic anemia

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