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In Practice

Thrombotic Microangiopathy, Cancer, and Cancer Drugs

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Thrombotic microangiopathy (TMA) is a complication that can develop directly from certain malignancies, but more often results from anticancer therapy. Currently, the incidence of cancer drug–induced TMA during the last few decades is >15%, primarily due to the introduction of anti–vascular endothelial growth factor (VEGF) agents. It is important for clinicians to understand the potential causes of cancer drug–induced TMA to facilitate successful diagnosis and treatment. In general, cancer drug–induced TMA can be classified into 2 types. Type I cancer drug–induced TMA includes chemotherapy regimens (ie, mitomycin C) that can potentially promote long-term kidney injury, as well as increased morbidity and mortality. Type II cancer drug–induced TMA includes anti-VEGF agents that are not typically associated with cumulative dose–dependent cell damage. In addition, functional recovery of kidney function often occurs after drug interruption, assuming a type I agent was not given prior to or during therapy. There are no randomized controlled trials to provide physician guidance in the management of TMA. However, previously accumulated information and research suggest that endothelial cell damage has an underlying immunologic basis. Based on this, the emerging trend includes the use of immunosuppressive agents if a refractory or relapsing clinical course that does not respond to plasmapheresis and steroids is observed.
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CASE PRESENTATION

A 65-year-old man with a history of metastatic pancreatic cancer is referred from the oncology clinic for weakness and fatigue, epistaxis, new skin lesions over his shins, significantly elevated blood pressure (BP), and increased serum creatinine level. His medical history is significant for osteoarthritis of the knees, mild hypertension, and pancreatic malignancy initially treated with surgery and radiation. Recurrence developed with liver and peritoneal metastases. Medications include lisinopril, calcium, multivitamins, gemcitabine, capecitabine, and occasional celecoxib. Physical examination is pertinent for BP of 185/102 mm Hg, conjunctival pallor, clear lungs, S4 cardiac gallop, abdomen with ascites, purpuric skin lesions, and lower-extremity edema (1+). Laboratory tests reveal anemia and thrombocytopenia with serum creatinine level of 3.8 mg/dL (baseline, 1.1 mg/dL). Urinalysis reveals protein (2+), blood (1+), and trace leukocyte esterase. Urine microscopy demonstrates 5 to 10 dysmorphic red blood cells per high-power field and 2 to 5 granular casts per low-power field. Urine protein-creatinine ratio is 1.4. Following BP control, the patient undergoes kidney biopsy, which reveals findings consistent with thrombotic microangiopathy (TMA), most likely due to gemcitabine therapy.

INTRODUCTION

TMAs are a spectrum of disorders characterized by occlusive microvascular thrombosis, microangiopathic hemolytic anemia, thrombocytopenia, and variable and potentially fatal end-organ damage.[1] Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), the 2 idiopathic or primary forms of the syndrome, are well-known causes of TMA. However, infection, connective tissue and autoimmune diseases, bone marrow and solid-organ transplantation, pregnancy and the puerperium, exposure to toxins, radiation, vaccination, disseminated malignancy, and medications including chemotherapy are also reported to cause a secondary TMA.[2-5]

TMA is a well-described complication of both cancer and its treatment. However, in our experience, antitumor therapy appears to be a more common cause of TMA in patients with cancer. It can sometimes be difficult to establish a causal relationship between a specific chemotherapeutic agent and TMA given that malignancy itself can induce TMA. In addition, many patients are treated with multiple chemotherapeutic agents, which can lead to difficulty indicting a particular drug.[6]

TMA resulting from cancer drug exposure was characterized following the introduction of mitomycin C into the oncologic therapeutic armamentarium. As a result, physicians recognized that total cumulative dose must be limited to avoid nephrotoxicity. However, the time frame between drug administration and detectable TMA appears to be more variable, and not all cancer treatments have uniform effects on kidney function. Differences in various cancer drugs include impact of total dose, TMA severity and reversibility, and variable mortality, which are best classified into 2 categories; types I and II. Type I cancer drug–induced

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TMA includes all the chemotherapy regimens (ie, mitomycin C and gemcitabine). These agents are considered to have increased potential for long-term kidney disease, increased morbidity, and mortality. Type II cancer drug–induced TMA includes all anti–vascular endothelial growth factor (anti-VEGF) agents, which do not directly cause cell damage in a cumulative dose–dependent fashion. Supportive evidence includes the absence of the typical mitomycin C–induced cell damage with anti-VEGF agents and stability of kidney function despite long-term drug exposure, which is not observed with type I agents. Finally, recovery of kidney function is frequently (albeit not invariably) seen after type II drug interruption, assuming a type I agent was not given before or at the time of therapy.[7] Thus, it is important for clinicians to be aware of these differences to optimally manage patients who develop TMA in the setting of cancer therapy.

CHEMOTHERAPY-INDUCED TMA: DIAGNOSIS, PATHOPHYSIOLOGY, AND TRIGGERING FACTORS

Vascular injury as a result of chemotherapy is reported with increasing frequency.[8] Although a variety of clinical disorders are described, the most devastating is TMA, a term originally proposed by Symmers.[9] A sudden decrease in hemoglobin level, acute kidney injury (AKI), uncontrolled hypertension, and thrombocytopenia should alert clinicians of the possibility of TMA. When TMA is suspected, evidence supporting a microangiopathic process (schizocytes and elevated lactate dehydrogenase level) should be sought. However, kidney-limited TMA is not an unusual finding, particularly with exposure to anti-VEGF agents (type II cancer drug–induced TMA), in which significant kidney damage without detectable extrarenal or hematologic manifestations may be seen. The National Cancer Institute grading scale according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 guidelines for TMA are summarized in Box 1.[10]

TMA has been observed with a number of cancer-treating agents. The syndrome more closely resembles HUS with more severe kidney injury than TTP, which usually develops within weeks to months after drug exposure. Diagnosis of TMA may be delayed when bone marrow depression–induced thrombocytopenia related to chemotherapy is initially suspected. The most common clinical scenario is slowly progressive kidney failure, new or exacerbated hypertension, and relatively bland urine sediment, often occurring in the absence of clinically apparent tumor. The pathologic features characterizing TMA are vascular damage manifested by arteriolar and glomerular capillary thrombosis with abnormalities in the endothelium and vessel wall, including thickened capillary walls, occlusion of vascular lumens, fibrin deposition, and endothelial separation, with expansion of the subendothelial zone (Fig 1).

Box 1. NCI Grading Scale of TMA[10]

Definition of TMA: Presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.
Grade 1: Evidence of RBC destruction (schistocytosis) without clinical consequences
Grade 2: -
Grade 3: Laboratory findings with clinical consequences (eg, decreased kidney function, petechiae)
Grade 4: Life-threatening consequences, (eg, CNS hemorrhage or thrombosis/embolism or kidney failure)
Grade 5: Death

Abbreviations: CNS, central nervous system; NCI, National Cancer Institute; RBC, red blood cells; TMA, thrombotic microangiopathy.

Drug-related endothelial injury is presumed to be the initiating event. However, it has been proposed that von Willebrand factor multimers may be involved in the pathogenesis of intravascular platelet clumping. von Willebrand factor is synthesized in endothelial cells and then amassed into larger multimers, which are known as unusually large von Willebrand factor. After this, the factor is quickly broken down in the circulation into the normal size range of von Willebrand factor multimers by a specific von Willebrand factor–cleaving protease, which is called ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13).[11]

Approximately 50% of patients with atypical HUS[12] have genetic abnormalities in their complement cascade. To date, 6 unique mutations in genes

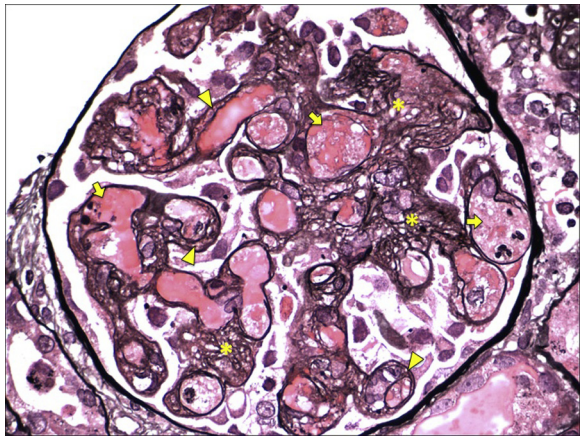

Figure 1. The glomerulus shows endothelial denudation, mesangiolysis (asterisks), red blood cell congestion (arrows), and glomerular basement membrane duplication (arrowheads) in this example of thrombotic microangiopathy. (Jones methenamine silver stain; original magnification, ×3,600.) Reproduced from Perazella with permission of ASN/CJASN.