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Perspective

Thrombotic Microangiopathy: A Multidisciplinary Team Approach

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Thrombotic microangiopathy (TMA) is characterized by the presence of microangiopathic hemolytic anemia and thrombocytopenia along with organ dysfunction, and pathologically, by the presence of microthrombi in multiple microvascular beds. Delays in diagnosis and initiation of therapy are common due to the low incidence, variable presentation, and poor awareness of these diseases, underscoring the need for interdisciplinary approaches to clinical care for TMA. We describe a new approach to improve clinical management via a TMA team that originally stemmed from an Affinity Research Collaborative team focused on thrombosis and hemostasis. The TMA team consists of clinical faculty from different disciplines who together are charged with the responsibility to quickly analyze clinical presentations, guide laboratory testing, and streamline prompt institution of treatment. The TMA team also includes faculty members from a broad range of disciplines collaborating to elucidate the pathogenesis of TMA. To this end, a clinical database and biorepository have been constructed. TMA leaders educate front-line providers from other departments through presentations in various forums across multiple specialties. Facilitated by an Affinity Research Collaborative mechanism, we describe an interdisciplinary team dedicated to improving both clinical care and translational research in TMA. *Am J Kidney Dis.* 70(5):715-721. © *2017 by the National Kidney Foundation, Inc.*

INDEX WORDS: Thrombotic microangiopathy (TMA); multidisciplinary team; complement-mediated hemolytic uremic syndrome (CM-HUS); thrombotic thrombocytopenic purpura (TTP); clinical care; rare disorder; translational research; nephrology; hematology.

Development of a Thrombotic Microangiopathy Team

Rationale

Thrombotic microangiopathy (TMA) is a rare life-threatening condition characterized by the widespread formation of microthrombi, resulting in multiorgan failure in its severe and disseminated form.[1,2] TMA is identified by laboratory abnormalities such as thrombocytopenia, microangiopathic hemolytic anemia, and decreased glomerular filtration rate, and clinically, by end-organ injury primarily affecting the kidneys and central nervous system.[2,3] Pulmonary, cardiac, and gastrointestinal manifestations are also common in severe TMA.[4] Classically, microangiopathic hemolytic anemia presents with elevated lactate dehydrogenase concentration, low haptoglobin concentration, negative direct antiglobulin (Coombs) test, and the presence of schistocytes in the peripheral-blood smear.[5] However, these tests can be insensitive to early detection of TMA and discrepant results may confuse the picture. Some guidelines no longer require all parameters to be present to diagnose TMA.[6-9]

TMA comprises multiple acquired and hereditary conditions, including thrombotic thrombocytopenic purpura, Shiga toxin–mediated and complement-mediated hemolytic uremic syndrome (CM-HUS), and drug-induced TMA, among others (Box 1).[1,2] The pathophysiologic processes leading to some TMA syndromes are relatively well understood. For example, acquired thrombotic thrombocytopenic purpura results from reduced ADAMTS13 (von Willebrand factor protease) activity secondary to an acquired inhibitor in the more common sporadic (nonhereditary) form.[10] Shiga toxin mediates HUS and mutations in the complement system mediate CM-HUS.[1] Moreover, many conditions (Box 2) mimic the laboratory abnormalities of TMA, resulting in delay in the diagnosis and treatment for the underlying cause.

Early detection and diagnosis of TMA are essential to improve clinical outcomes. A delay in the diagnosis and treatment of the cause of TMA may result in irreversible end-organ damage, including kidney failure, stroke, and cardiac dysfunction. As an example, untreated CM-HUS is associated with a 50% risk for end-stage renal disease and a 25% mortality rate.[2] In CM-HUS, these outcomes are

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Box 1. Classification of Primary TMA

Thrombotic thrombocytopenic purpura
- Hereditary
- Acquired (inhibitory autoantibody)

Shiga toxin–mediated HUS
- *Shigella dysenteriae*
- *Escherichia coli*, serotypes O157:H7 and O104:H4

Complement-mediated TMA[a]
- Loss-of-function mutations: CFH, CFI, MCP, thrombomodulin, and CFHRs
- Gain-of-function mutations: CFB, C3

Drug-induced TMA
- Quinine, gemcitabine, quetiapine, mitomycin, cyclosporine, tacrolimus, sirolimus, opioids, others[b]

Metabolism-mediated TMA
- Mutations affecting cobalamin (vitamin B_{12}) metabolism

Coagulation-mediated TMA
- DGKE, thrombomodulin and plasminogen mutations

Abbreviations: CFB, complement factor B; CFH, complement factor H; CFHR, complement factor H–related proteins; CFI, complement factor I; DGKE, diacylglycerol kinase epsilon; MCP, membrane cofactor protein; TMA, thrombotic microangiopathy.

[a]All have acquired and hereditary forms.

[b]For a detailed review of agents associated with TMA, see reviews by George and Nester,[1] 2014, and Noris and Remuzzi,[2] 2009.

Box 2. Causes of Secondary Thrombotic Microangiopathy

Pregnancy
- HELLP syndrome, preeclampsia

Hypertension
- Malignant hypertension

Infectious
- Bacterial: infective endocarditis, pneumococcal, rickettsia, brucella, borrelia
- Viral: HIV, CMV, HBV, HCV, influenza A, parvovirus B19, EBV, dengue
- Fungal: aspergillus, blastomyces, *Candida* spp, *Cryptococcus* spp
- Parasitic: *Babesia* spp, *Plasmodium falciparum*

Malignancy
- Breast, ovarian, gastric, colorectal, lung, pancreatic, lymphoma, myelodysplastic syndrome

Autoimmune disorders
- SLE, antiphospholipid antibody syndrome, scleroderma, dermatomyositis

Transplantation
- Allogeneic bone marrow transplantation, solid-organ transplantation

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HELLP, hemolysis, elevated liver function test, low platelet; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

significantly improved by the early administration of complement inhibitor therapies.[11,12]

Adding to the difficulty in rapidly diagnosing the cause of TMA is the long-standing approach of relying on hematology or nephrology consultants working independently, and sometimes with limited communication between them. Additionally, these 2 specialties are focused on their specialty-specific differential diagnoses, leading to a narrower vision of the full clinical picture. Moreover, individual consultants have varying degrees of experience with diagnosing and managing specific TMA causes, which may lead to errors in management. Therefore, new approaches to uncommon and high-mortality illnesses such as TMA are needed to improve clinical outcomes.[9]

Goals of a TMA Team

In response to the need to facilitate more rapid diagnosis and institution of TMA therapy, we created a multidisciplinary TMA team composed of individuals with an interest and expertise in managing this rare disorder. The active participation of clinicians with our department's Thrombosis and Hemostasis Affinity Research Collaborative (ARC) facilitated creation of the TMA team. As we published earlier,[13] an ARC consists of investigators from different disciplines with a shared interest in a biomedical problem with the ultimate goal of improving clinical care. The TMA team is designed to address 3 major goals. First, we aimed to improve clinical outcomes through rapid diagnosis and treatment, with a goal to improve patient morbidity and mortality and decrease inpatient length of stay and health care delivery costs. Second, we aimed to educate a wide range of front-line clinicians to increase awareness of TMA. Finally, we aimed to develop research on the pathogenesis of TMA. Our team represents a novel model of a multidisciplinary assembly in the inpatient and outpatient settings for the management of a rare disorder such as TMA. In order to bring together the relevant disciplines needed to diagnose and treat TMA, we sought an interdisciplinary paradigm to address the unmet clinical need of a rare disorder such as HUS, with an estimated incidence of 4 to 6 per million.[2]

In the current article, we describe our approach and the role of the TMA team in increasing TMA awareness throughout the hospital, facilitating the early diagnosis of TMA and early treatment implementation directed at the underlying condition. We also describe how such an effort can result in a better understanding of this complex condition by enhancing research.

Clinical Aspects of the TMA Team

The first step toward our goal has been to determine the scope of TMA expertise in the team. To