Thrombotic Microangiopathy in a Patient Treated With Gemcitabine
Sowmya Nanjappa, MBBS, MD, Vivek Singh, MBBS, Shyam Uttamchandani, MD, and Smitha Pabbathi, MD

Summary: Thrombotic microangiopathy syndromes consist of a collection of disorders with a varied etiology that share common clinical and pathological features. Although thrombotic microangiopathy is rare, it is associated with significant morbidity and mortality. Without early recognition and intervention, the prognosis of the disease is poor. This report illustrates the case of a 56-year-old man with advanced-stage metastatic pancreatic cancer who presented with hemolytic uremic syndrome associated with gemcitabine use. His condition was managed with eculizumab, a monoclonal antibody, although he was dependent on dialysis. This report reflects the importance of considering thrombotic microangiopathy syndromes in the differential diagnosis, because many malignancies and use of chemotherapeutic agents can trigger hemolytic uremic syndrome.

Introduction
Thrombotic microangiopathy (TMA) syndromes consist of a collection of disorders with a varied etiology that share common clinical and pathological features. The classification of TMA syndromes has been revised over time.1 It now includes disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 (ADAMTS13), deficiency-mediated TMA and complement-mediated TMA.1 These 2 entities include thrombotic thrombocytopenic purpura (TTP) and primary hemolytic uremic syndrome (HUS), respectively.1 Secondary HUS, which historically included TMA disorders caused by infection, drug use, pregnancy, or autoimmune-related diseases, is now classified according to underlying etiology.1,2

The prognosis for such disorders is poor. More than 65% of cases progress to end-stage renal disease or death within 1 year of diagnosis.2,3 However, treatment options do exist for HUS based on the underlying etiology of the disorder, and significant improvements have been made following the approval of eculizumab, a terminal complement inhibitor, by the US Food and Drug Administration in 2011.2,4,5

The following is a case report of HUS triggered by gemcitabine use for the treatment of advanced-stage metastatic pancreatic cancer.

Case Report
A 56-year-old man with stage IV metastatic pancreatic cancer presented with fatigue. He denied fever, nausea, vomiting, diarrhea, confusion, or headache. Eight days prior to his presentation, he received chemotherapy with gemcitabine and paclitaxel. He denied any ill contacts or recent travel. He had not consumed any quinine or tonic water.

Laboratory studies were obtained. Significant values included a hemoglobin level of 4.8 g/dL and a platelet count of 34,000/µL. His blood urea nitrogen level was 79 mg/dL and his creatinine (Cr) level was 3.9 mg/dL. Urine analysis showed 6 to 10 white blood cells, more than than 100 red blood cells (RBCs), trace bacteria, 11 to 30 hyaline casts, and a protein level of 300 mg/dL. His lactate dehydrogenase (LDH) level was 925 U/L. Peripheral smear showed schistocytes. His C3 and C4 levels were 76 and 6, respectively. Antinuclear antibody and antineutrophil cytoplasmic antibody studies were negative. An ADAMTS13 level was 37%. A clinical diagnosis of secondary HUS was made.

Plasmapheresis was initiated. After 8 daily sessions, his platelet count improved to 141,000/µL and his LDH level improved to 345 U/L. However, his renal function continued to worsen (Cr 5.3 mg/dL), so hemodialysis was initiated. After plasmapheresis was discontinued, his platelet count, LDH, and Cr levels continued to worsen (90,000/µL, 101 U/L, and 4.1 mg/dL, respectively); therefore, he was started on eculizumab on hospital day 11. After 1 week of eculizumab therapy, his platelet count was 75,000/µL, his LDH level was 437 U/L, and his Cr level was 5.0 mg/dL. His platelet count continued to slowly improve, his LDH level eventually stabilized, and he no longer required plasmapheresis.

The patient had a prolonged hospital course of 21 days and was discharged with plans to continue
hemodialysis and weekly eculizumab infusions as an outpatient for 4 weeks and then twice per month for a total of 11 treatments. His platelet count and LDH and hemoglobin levels remained stable for approximately 4 months. However, the patient’s clinical condition began to rapidly deteriorate as his alkaline phosphatase and bilirubin levels increased. In addition, his level of cancer antigen 19-9 marker increased by more than 20,000 U/L in 2 weeks. Due to concern of disease progression and rapidly developing liver failure, the patient was enrolled in hospice care.

Discussion

TMA syndromes are characterized by common clinical and pathological features. Clinical features include microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and target organ damage. MAHA is characterized by a negative result on a Coombs test, reflecting nonimmune hemolysis, and the presence of schistocytes, which arise because of RBC fragmentation secondary to the shearing of RBCs from blood flow past an occluded microcirculation. Thrombocytopenia develops because platelets are consumed within microscopic thrombi. Pathological features include vascular thrombosis with corresponding endothelial damage.

The differential diagnosis for patients presenting with a TMA syndrome includes the following:

- HUS
- TTP
- Scleroderma renal crisis
- Disseminated intravascular coagulation
- Antiphospholipid antibody syndrome
- Malignant hypertension
- Drug-induced toxicity (commonly cyclosporine, clopidogrel, quinine)

The patient in this case report had no evidence of TTP, scleroderma renal crisis, disseminated intravascular coagulation, antiphospholipid antibody syndrome, malignant hypertension, and was not taking cyclosporine, clopidogrel, or quinine. Therefore, a clinical diagnosis of HUS/TTP was made.

Historically, TTP and HUS syndrome were grouped together as an overlapping clinical presentation and treatment for both conditions was the same. The classic pentad for TTP/HUS is fever, MAHA, thrombocytopenia, acute kidney injury, and neurological symptoms. Neurological symptoms predominate in TTP, whereas renal insufficiency is more common in HUS. However, a full pentad of symptoms is rare because therapy is often started before the onset of full-blown disease; moreover, only MAHA and thrombocytopenia are needed to make the diagnosis and justify the initiation of therapy.

Research into the pathophysiology of the disease process has shown that TTP is distinct from HUS: Both are characterized by endothelial damage, but their underlying pathological process is different. ADAMTS13 is a protein synthesized in endothelial cells that degrades unusually large-sized von Willebrand factors into normal-sized von Willebrand factor multimers. ADAMTS13 deficiency leads to the accumulation of von Willebrand factor multimers, thereby leading to platelet aggregation and the formation of platelet thrombi. This deficiency can occur because of an immunoglobulin G antibody against ADAMTS13 or congenital deficiency in ADAMTS13 (Upshaw-Schulman syndrome).

Whereas TTP is thought to be caused by an accumulation of von Willebrand factor leading to endothelial damage, HUS is likely caused by an overactivation of the complement system. Affected individuals have a gene mutation or an antibody to certain complement proteins. A trigger event (eg, infection, malignancy, pregnancy, medication use) can lead to the uninhibited, continuous activation of an alternative complement pathway, thereby leading to the formation of the membrane attack complex. This, in turn, causes renal endothelial damage that activates the coagulation cascade and TMA. The most common genetic mutation occurs in factor H; other genetic mutations include CD46, factors I and B, complement 3, and thrombomodulin mutations. Autoantibodies can also develop, the most common of which are to factor H.

HUS can be classified as being either primary or secondary. Primary causes can arise from gene mutations or autoantibodies; gene mutations are the most common underlying etiology. Secondary causes include infection, drug-induced toxicity, pregnancy, and autoimmune disorders. Common infectious agents that cause secondary HUS include Shiga-toxin–producing Escherichia coli, which presents with a bloody diarrhea, HIV, and Streptococcus pneumoniae. The most common drugs related to secondary HUS are quinine, gemcitabine, mitomycin C, and cyclosporine. Pregnancy and autoimmune disorders causing HUS have also been reported, but they are rare.

Endothelial damage in TTP is mediated by a deficiency in ADAMTS13, whereas this damage occurs in HUS due to an overactivation of the complement system. For this reason, an ADAMTS13 level can distinguish between the 2 conditions. An ADAMTS13 level below 10% is diagnostic of TTP, whereas an ADAMTS13 level above 10% is consistent with HUS.

Treatment for HUS has historically been plasmapheresis, which involves removing antibodies and restoring normal functioning to complement proteins. Because irreversible renal lesions can occur within days, plasmapheresis must be started as soon as HUS is suspected; however, despite this, no randomized controlled trials have evaluated clinical outcomes after plasmapheresis. In general, the goals of plasmapheresis are to stabilize the hemoglobin level, normalize
the platelet count, and improve renal function. Use of maintenance plasmapheresis is based on the risk of recurrent disease and irreversible renal injury. However, plasmapheresis does not interrupt complement dysregulation, which causes target organ damage.

Eculizumab, a monoclonal antibody, acts as a terminal complement inhibitor and is a promising treatment for thrombotic microangiopathy. Legendre et al. studied eculizumab, concluding that it led to: normalized platelet counts at 1 week after the initiation of therapy in more than 50% of patients studied; the cessation of plasmapheresis in more than 80% of participants; a mean increase in estimated glomerular filtration rate of 32 mL/minute after 60 weeks; and dialysis cessation in 4 of 5 study patients. Those with less-severe disease experienced event-free survival for 12 weeks and their hematological values normalized for 4 weeks. The medication was well tolerated. More than 70% of study patients described improved quality of life; however, more than 30% developed uncontrolled hypertension.

Because eculizumab blocks the terminal complement cascade, patients receiving eculizumab are at high risk for encapsulated bacterial infection. All patients taking the drug must receive meningococcal vaccination; in addition, vaccines against *Haemophilus influenza* and *S. pneumoniae* are also recommended (especially for pediatric patients) prior to the administration of eculizumab.

Our index of suspicion for a TMA syndrome was high in our patient because he experienced acute kidney injury and had evidence of MAHA and thrombocytopenia. His condition clinically improved following plasmapheresis, but ongoing hemolysis was still observed even after plasmapheresis was discontinued. Once eculizumab therapy was started, his LDH level normalized, his hemoglobin level eventually stabilized, and his platelet count normalized. However, he did not regain enough renal function to discontinue dialysis.

**Conclusions**

Hospital-based physicians often care for patients with hematological derangements and renal insufficiency. Our case reflects the importance of considering thrombotic microangiopathy syndromes in the differential diagnosis, because many malignancies and use of chemotherapeutic agents can trigger hemolytic uremic syndrome. In addition, the timely diagnosis and initiation of therapy can alter patient outcomes, including risk of mortality and target organ damage (e.g., acute kidney injury). Following the development of an assay for disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13, thrombotic thrombocytopenic purpura can now be distinguished from hemolytic uremic syndrome, which, in turn, can make targeted therapies such as eculizumab more effective. Adhering to the guidelines for the administration of eculizumab and recognizing the adverse events of this drug are keys to help improve the prognosis of thrombotic microangiopathy, a rare yet debilitating disease.

**References**