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Complement Regulatory Genetic Mutations in the Setting of Autoimmune Thrombotic Thrombocytopenic Purpura: A Case Series

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Abstract

Objective: To explore the benefits of adding eculizumab for the treatment of refractory autoimmune thrombotic thrombocytopenic purpura (iTTP) with complement dysregulation.

Patients and Methods: From January 1, 2014, through July 1, 2017, we identified patients with iTTP defined by ADAMTS13 (disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) levels less than 5% and the presence of ADAMTS13 inhibitor. Patients who progressed after receiving standard of care management for iTTP were subjected to a comprehensive evaluation to look for evidence of complement activation. Herein, we share our single-institute experience regarding the clinical course and treatment algorithm for 3 patients with refractory iTTP.

Results: All the patients had clinical deterioration despite treatment with plasma exchange, corticosteroids, rituximab, and vincristine, which prompted us to look for evidence of complement activation and associated genetic mutations. Complement-related genetic aberrations were present in all 3 patients, who had had different degrees of complement activation. The first 2 patients did not benefit from eculizumab when treatment was started before complete clearance of inhibitors to ADAMTS13. However, they had durable remissions when eculizumab was introduced after clearance of ADAMTS13 inhibitors. The third patient started eculizumab therapy after inhibitor levels were undetectable.

Conclusion: We found eculizumab therapy to be effective in all 3 patients. However, its efficacy was prominent only after clearance of antibodies against ADAMTS13 via therapeutic plasma exchange.

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Thrombotic microangiopathies (TMAs) are a diverse group of disorders presenting with non–immune-mediated hemolytic anemia and thrombocytopenia.[1] Treatment of the underlying cause in such cases is crucial for controlling the TMA. However, once all other causes are excluded, physicians face the diagnostic challenge of determining which one of the life-threating TMAs it is: hereditary or autoimmune thrombotic thrombocytopenic purpura (iTTP), *Escherichia coli*–induced hemolytic uremic syndrome (HUS), or atypical HUS (aHUS).

Classic HUS is caused by Shiga toxin–producing organisms; aHUS is associated with complement dysregulation due to mutations in CD46, complement factor (CF) I, CFB, complement component 3, CFH-related (CFHR) 5, CFH, and thrombomodulin or secondary to CFH autoantibodies.[2] On the other hand, TTP is characterized by congenital or autoimmune-related deficiency of the von Willebrand factor cleaving protein ADAMTS13 (disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).[3]

The case series reported herein illustrates an unusual clinical entity in 3 patients with an acute TMA syndrome with clinical and laboratory features of refractory iTTP associated with genetic mutations typically seen in aHUS as well. All the genetic mutation tests were performed by Machaon Diagnostics.

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CASE REPORTS

Patient 1

A 24-year-old African American man with Klinefelter syndrome had recently started

working at a new job in a poultry processing facility, where he was in direct contact with meat. He initially presented with bloody diarrhea, diffuse abdominal pain, and acute renal failure, with a creatinine level up to 7 mg/dL (to convert to μmol/L, multiply by 88.4). An *E coli* infection was ruled out. ADAMTS13 activity was less than 5%, with inhibitor titers of 5 Bethesda units (BU). Treatment of TTP is outlined in Figure 1. Initially, the patient had a good response to treatment, and his creatinine level improved, down to 3 mg/dL, for a few weeks only and thereafter started to climb again to the point where hemodialysis was required. As a result of the severe renal injury and lack of lasting response to therapeutic plasma exchange (TPE), corticosteroids, rituximab, cyclophosphamide, and vincristine, aHUS genetic mutation testing was performed. He was found to have a large homozygous deletion in *CFHR1* and *CFHR3* genes. Skin biopsy performed at this time showed focal C5b-9 deposition within vessels, including the superficial vascular plexus (Figure 2). Antibodies against CFH were detectable. Therefore, eculizumab treatment was added to TPE (Figure 1). We noted the inadequate response to eculizumab, without clearance of ADAMTS13 inhibitor, and so eculizumab administration was with held until serial testing showed loss of the inhibitor. Reinstitution of eculizumab after clearance of the ADAMTS13 inhibitor led to improvement in renal function such that dialysis could be stopped and he maintained his platelet count in the reference range.

Patient 2

A 35-year-old African American woman presented with slurred speech and left-sided numbness; her renal function was within the reference range. Testing revealed less than 5% ADAMTS13 activity and anti-ADAMTS13 antibody titers of 2.2 BU. Corticosteroid therapy and TPE were initiated without an adequate response. Rituximab and vincristine were added, but the response was still inadequate (Figure 1). Genetic mutation testing for complement-related genes showed multiple genetic mutations (Table). Eculizumab administration was started before clearance of ADAMTS13 inhibitor, without an adequate response to treatment. The decision was made to hold eculizumab until the ADAMTS13 inhibitor had been cleared. One year after her diagnosis, the patient continues to do well, and she receives eculizumab every 2 weeks.

Patient 3

A 64-year-old African American woman presented with mouth droop and left arm weakness. ADAMTS13 activity was less than 5%, with an inhibitor level of 1.1 BU. Renal function was mildly decreased (creatinine clearance, 30 mL/min per 1.73 m^2 [to convert to mL/s per m^2, multiply by 0.0167]). Daily TPE and corticosteroid therapy were initiated for acquired TTP. This resulted in complete clearance of the ADAMTS13 inhibitor; however, her condition continued to deteriorate and right-sided weakness, bilateral cerebral infarcts on magnetic resonance imaging, and seizure-like activity developed. Hence, complement-related genetic testing was ordered and showed a large homozygous deletion in CFHR1-CFHR3. Treatment with eculizumab was instituted, and an improvement in the platelet count was seen after the first dose (Figure 2). Six months after inititating treatment with eculizumab, treatment was discontinued. Two years later, she has not had a recurrence of her TMA. Further details about this patient can be found in a recently published report.[6] Baseline testing for CFH antibodies at diagnosis is not available. However, antibodies to CFH were undetectable during treatment with eculizumab.

DISCUSSION

Severe ADAMTS13 deficiency has been considered the unique pathognomonic event of TTP. Initially, Furlan et al[3] reported normal ADAMTS13 activity in approximately 85% of patients with HUS. The finding that patients with HUS have normal ADAMTS13 activity was classically used as the definitive criteria to differentiate patients with HUS from those with TTP. However, these findings have been challenged by reports of the coexistence of iTTP and aHUS. The first report described a patient with clinical deterioration despite TPE; a skin biopsy confirmed the presence of heavy perivascular CF depositions and triggered