**Brief Review**

**Overlapping Features of Thrombotic Thrombocytopenic Purpura and Systemic Lupus Erythematosus**

*James N. George, MD, Sara K. Vesely, PhD, and Judith A. James, MD, PhD*

Although thrombotic thrombocytopenic purpura (TTP) and systemic lupus erythematosus (SLE) are distinct entities, they may appear as overlapping clinical syndromes from multiple perspectives: pathogenesis, patient demographics, clinical features, and management (Table). Our interest in the similarities of these two syndromes began with our experience that patients may be diagnosed with TTP following an established SLE diagnosis and also that patients may develop SLE following recovery from an episode of TTP. To extend our observations, we systematically reviewed all published reports describing patients who had been diagnosed with both TTP and SLE and identified 87 patients. Although one of the disorders, TTP or SLE, may merely mimic the other, in some patients, there is serologic as well as clinical evidence to support the diagnosis of both TTP and SLE.

For our comparison of these two syndromes in this review, we have restricted our discussion of TTP to the subset of patients who have an acquired severe deficiency of ADAMTS 13 (4 disintegrin and metalloprotease with thrombospondin-1-like repeats), a von Willebrand factor (VWF)-cleaving protease. The acquired severe ADAMTS 13 deficiency is typically described as less than 5% activity, caused by an autoantibody that inhibits protease function. Although patients with severe ADAMTS 13 deficiency are a minority of all patients who are clinically diagnosed with TTP, they have the most clearly documented diagnosis, as well as an established autoimmune etiology. Similarly, we have restricted our discussion of SLE to patients who fulfill current classification, meeting at least 4 of 11 American College of Rheumatology (ACR) SLE criteria.

**Incidence**

The incidence of these syndromes is similar (Table). The incidence in the region of the Oklahoma TTP-HUS Registry for all patients who are clinically diagnosed with TTP is 11.3 per 10^5 population per year, but the incidence of patients with acquired severe ADAMTS13 deficiency is only 1.7 per 10^5 population per year. The incidence of SLE is 2.4 per 10^5 population per year.

The six-fold difference between the incidence for all patients who are clinically diagnosed with TTP and the incidence for patients with acquired severe ADAMTS13 deficiency emphasizes the broad clinical spectrum of patients who are initially diagnosed with TTP. Etiologies of TTP other than acquired severe ADAMTS13 deficiency include drug-induced syndromes, most commonly caused by quinine-dependent antibodies and Shiga toxin, resulting from enterohemorrhagic infection with *E. coli* O157:H7. In addition, some patients with clinically diagnosed TTP are subsequently recognized to have an alternative disorder that mimicked the presenting clinical features of TTP, such as severe preeclampsia, malignant hypertension, a systemic infection, or occult malignancy. Finally, some patients in the Oklahoma TTP-HUS Registry have had an established SLE diagnosis; we describe these patients as having both SLE and TTP, but we recognize that accurate diagnosis of these patients is difficult.

**Patient Demographics**

The typical age, race, and gender are nearly the same for both TTP and SLE (Table). In both syndromes, most patients are young women and the relative incidence is increased among blacks. This remarkable similarity suggests common features of pathogenesis.

**Pathogenesis**

A severe deficiency of ADAMTS13 activity can be associated with the accumulation of unusually large multimers of VWF that have increased platelet aggregating potential; these large VWF molecules are assumed to cause the disseminated microvascular platelet-rich thrombi that are characteristic of TTP. Observations in transgenic mice suggest that absent ADAMTS13 is a strong risk factor for TTP rather than a stand-alone etiology; these mice do not develop a TTP phenotype unless they are exposed to an additional prothrombotic stimulus. This suggests that patients could have severe ADAMTS13 deficiency caused by autoantibodies before the development of overt TTP. The phenomenon of pathologic autoantibodies preceding clinically apparent illness has been recognized in SLE and has been described as a crescendo of autoimmunity, beginning with the benign appearance of autoantibodies, progressing to pathologic autoantibodies and finally to clinical illness. Documentation of anti-ADAMTS13 autoantibodies in patients with SLE and
Table. The overlapping syndromes of thrombotic thrombocytopenic purpura (TTP) and systemic lupus erythematosus (SLE)"

<table>
<thead>
<tr>
<th></th>
<th>TTP</th>
<th>SLE</th>
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<tr>
<td>Incidence (per year)7,8</td>
<td>1.8/10^6</td>
<td>2.4/10^6</td>
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<tr>
<td>Pathogenesis</td>
<td></td>
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<tr>
<td>Occurrence of severe</td>
<td></td>
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<tr>
<td>ADAMTS13 deficiency</td>
<td>100%</td>
<td>Rarely reported</td>
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<tr>
<td>Occurrence of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>70%</td>
<td>99%25</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>10%</td>
<td>70%25</td>
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<tr>
<td>Patient demographics7,8</td>
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<tr>
<td>Peak age (years)</td>
<td>30–39</td>
<td>15–40</td>
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<tr>
<td>Race (increased incidence in blacks compared to non-blacks)</td>
<td>9-fold</td>
<td>3-fold</td>
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<td>Gender (% women)</td>
<td>74%</td>
<td>80–90%</td>
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<td>Diagnosis</td>
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<td>Microangiopathic hemolytic anemia and thrombocytopenia without an alternative etiology</td>
<td>Plasma exchange currently required; use of additional immunosuppressive agents increasing</td>
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<td>Management</td>
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<td>Chronic disease with intermittent &quot;flares&quot; of activity and major morbidity; 3-fold increased mortality compared to controls</td>
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<tr>
<td>Clinical course3,26</td>
<td></td>
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<tr>
<td>Acute episodes with 20% mortality; remissions with minor morbidity; relapses in 50%</td>
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*For this comparison, data on TTP were restricted to patients with a severe acquired deficiency of ADAMTS13 activity. Similarly, data on SLE were restricted to patients who fulfilled current classification7,16 that include meeting at least 4 of 11 American College of Rheumatology (ACR) SLE criteria.

documentation of autoantibodies that are characteristic of SLE in patients with TTP has provided evidence for a possible convergence of these syndromes.16–18

Severe ADAMTS13 deficiency caused by an inhibitor, characteristic of patients with TTP, has been reported in 3 patients with an established diagnosis of SLE.16,17 However, in a survey of 36 patients with SLE who did not have signs or symptoms of TTP, the mean ADAMTS13 activity was only slightly less than normal; none of the 36 patients had severe deficiency characteristic of TTP, and none had detectable autoantibodies identified as inhibitory activity of ADAMTS13.19

Autoantibodies characteristic of SLE have been detected in patients with acute TTP who have severe ADAMTS13 deficiency. In a cohort of 31 patients with TTP who had acquired severe ADAMTS13 deficiency, 22 (71%) patients had a positive test for antinuclear antibodies (ANA) with titers of \( \geq 1:80 \), and 3 (10%) patients had a positive test for anti-double-stranded (ds) DNA (\( \geq 100 \) IU) at the time of their initial diagnosis.18 Ten of the 22 patients with a positive test for ANA had clinical features of other autoimmune disorders: nondestructive polyarthritis, cutaneous lesions consistent with discoid lupus, and autoimmune thyroiditis associated with type I diabetes mellitus.18 One of these 10 patients fulfilled diagnostic criteria for SLE.5,6

Pathology

Although the typical pathologic lesions of SLE and TTP both primarily involve arterioles, the characteristic histologic patterns are distinct: inflammation with vasculitis in SLE and platelet-rich thrombi without overt inflammation, termed thrombotic microangiopathy, in TTP. However, thrombotic microangiopathy, the defining pathologic feature of TTP, may also occur in patients with established SLE.20 Also, patients with SLE have a high risk for arterial thrombosis, related to abnormalities of vascular endothelium.21 These observations of vascular abnormalities leading to arterial or arteriolar thrombosis in both TTP and SLE predict an overlap of the clinical features.

Diagnosis

In the era before effective treatment, TTP was characterized by a pentad of clinical features: thrombocytopenia, microangiopathic hemolytic anemia, neurologic and renal abnormalities, and fever; all of these clinical features may also be present in SLE patients.5,6,22 When plasma exchange treatment transformed TTP from a syndrome with high mortality to one in which most patients survived, urgency for treatment required more limited diagnostic criteria. Currently, only thrombotic thrombocytopenia and microangiopathic hemolytic anemia without an apparent alternative etiology are required to establish the diagnosis and initiate plasma exchange treatment.3 The combination of these nonspecific diagnostic criteria and urgency for treatment has lead to a sevenfold increase in the number of patients treated with plasma exchange for suspected TTP.23 This change in the standard of practice, with more urgent and less specific diagnoses of TTP, has inevita-
bly resulted in confusion with similar syndromes, such as SLE. The occurrence of overlapping clinical features has resulted in many patients being diagnosed with both disorders and emphasizes the dilemma faced by clinicians who care for these patients.

Management

Because of the recognition of an autoimmune etiology in some patients with TTP, immunosuppressive treatment is becoming increasingly important. Although plasma exchange remains the principal treatment for patients with TTP, high-dose steroids, cyclophosphamide, and rituximab are also used in patients with TTP, similar to their use in SLE patients.

Conclusions

Overlaps between TTP and SLE occur inpatient demographics, pathogenesis, pathology, presenting features, and management (Table). These overlapping features create a diagnostic dilemma for physicians. The appropriate resolution when confronted by a patient with clinical diagnostic criteria for both TTP and SLE may be to initiate treatment for both syndromes. A distinction between TTP and SLE may become clear when the patient has recovered from his or her critical illness. Patients with TTP typically recover without overt sequelae, while patients with SLE may have a more chronic course. However, some patients will have diagnostic criteria for both TTP and SLE; these patients emphasize the principle of overlapping autoimmune disorders and the importance of further investigation to discover common underlying disease pathways.

References
