Rituximab Treatment of Thrombotic Thrombocytopenic Purpura in the Setting of Connective Tissue Disease

TIMOTHY B. NIEWOLD, DEBORAH ALPERT, CARLA R. SCANZELLO, and STEPHEN A. PAGET

**ABSTRACT.** Thrombotic thrombocytopenic purpura (TTP) causes significant morbidity and mortality, and may be associated with connective tissue diseases (CTD). Some cases are refractory to plasma exchange and require immunosuppressive therapy. We describe 2 patients with CTD who had refractory TTP treated successfully with rituximab. Both patients also developed heparin-induced thrombocytopenia (HIT). The propensity of a patient with a CTD to develop autoantibodies to ADAMTS-13 and platelets likely explains the association of such a disease with TTP and HIT. Rituximab should be considered in this complex clinical setting, because it may decrease the production of multiple pathogenic autoantibodies.

**Key Indexing Terms:**

- THROMBOTIC THROMBOCYTOPENIC PURPURA
- CONNECTIVE TISSUE DISEASES
- MONOCLONAL ANTIBODIES
- SYSTEMIC LUPUS ERYTHEMATOSUS
- HEPARIN

Thrombotic thrombocytopenic purpura (TTP) is a clinical syndrome characterized by a classical pentad of thrombocytopenia, microangiopathic hemolytic anemia, renal failure, fever, and neurologic symptoms. Abnormally large von Willebrand multimers that can induce platelet aggregation and thrombosis are present in the plasma of patients with TTP. Von Willebrand multimers are normally cleaved by the metalloproteinase ADAMTS-13. Mutations in the ADAMTS-13 gene can cause familial TTP, and in sporadic cases acquired antibody inhibitors of the metalloproteinase have been demonstrated. TTP is associated with a number of connective tissue diseases (CTD), including systemic lupus erythematosus, dermatomyositis, scleroderma, and others. An increased disease-related propensity to form autoantibodies to ADAMTS-13 may explain this association. Rituximab has been used to treat refractory sporadic TTP, as well as various autoimmune diseases. We describe 2 cases of TTP associated with CTD that were treated successfully with rituximab. Interestingly, both patients also developed heparin-induced thrombocytopenia (HIT). To our knowledge, this is the first report of rituximab therapy for TTP associated with CTD, as well as the first report of HIT in the setting of TTP.

**CASE REPORTS**

**Case 1.** A 69-year-old woman presented with a 6-week history of shortness of breath, symmetric proximal weakness, and polyarthritis of the metacarpophalangeal and proximal interphalangeal joints. Platelet count, creatinine, and urinalysis were normal. Erythrocyte sedimentation rate (ESR) was 107 mm/h (normal ≤ 27 mm/h), rheumatoid factor was 116 IU/ml (≤ 20 IU/ml), creatine kinase (CK) was 505 U/l (30-135 U/l), and an antinuclear antibody (ANA) test was positive at a titer of 1:2560. Anti-Smith, anti-Ro, anti-La, anti-RNP, anti-dsDNA, anti-IgG, and cryoglobulins were all negative, and thyroid studies were normal. Chest computerized tomography suggested interstitial lung disease, and electromyography was compatible with inflammatory muscle disease. She was diagnosed with an overlap CTD. She improved with intravenous methylprednisolone, and was discharged.

Three days later she was readmitted with fever, acute renal failure, thrombocytopenia, and schistocytes on peripheral blood smear. Coagulation studies were normal. She was diagnosed with TTP and treated with plasma exchange, high dose intravenous methylprednisolone, and hemodialysis. Initially she improved; however, 5 days later her TTP recurred despite daily plasma exchange. She was given 2 doses of rituximab 375 mg/m² intravenously weekly for refractory TTP. She improved, and plasma exchange was discontinued. At this time, ADAMTS-13 activity was decreased to 31% (normal ≥ 67%) but no inhibitor was present.

She later had recurrent thrombocytopenia without hemolysis, accompanied by an intravenous catheter-related thrombosis. She had been receiving heparin, anti-platelet factor 4/heparin (anti-PF4) antibodies were positive, and she was diagnosed with HIT. Her platelet count improved taking lepirudin. She remained hemodialysis-dependent, and eventually died of line-related sepsis.

**Case 2.** A 32-year-old woman with a history of episodic TTP 2 years earlier was transferred to our hospital after suffering 2 discrete ischemic strokes in different vascular distributions. A transthoracic echocardiogram had suggested an aortic valve thrombosis and she was treated with unfractionated heparin. No arthritis, rash, or livedo reticularis was appreciated. Review of systems was positive for alopecia. She was anemic, thrombocytopenic, and had schistocytes on blood smear. Her ANA titer was elevated at 1:640, and anti-Ro was 126 U (0–49 U). Anti-La, anti-Smith, anti-rubulocleroprotein, and anti-dsDNA antibodies were negative. Cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies, anti-PF4 antibodies, anticardiolipin antibodies, and lupus anticoagulant assay were negative. Creatinine, ESR, and C3 and C4 complement levels were all normal.

She was diagnosed with SLE and probable recurrent TTP and was treated with high dose intravenous methylprednisolone and 4 days of plasma
exchange, and her platelet count increased (Table 2). She later had recurrent thrombocytopenia, increasing schistocytosis, and rising lactate dehydrogenase. Due to concern for HIT, her anticoagulant was switched to lepirudin. Anti-PF4 antibodies were newly positive. Her platelet count increased on lepirudin, however an ADAMTS-13 activity assay sent at time of her thrombocytopenia showed undetectable ADAMTS-13 activity with a high-titer inhibitor. Despite the improvement in platelet count, there was substantial laboratory evidence of ongoing immune-mediated TTP in addition to HIT. Therefore, it was felt that she required additional immunosuppression, and she was treated with rituximab 375 mg/m² intravenously. She received three additional weekly doses with sustained resolution of her thrombocytopenia.

DISCUSSION

The association of TTP with CTD has long been appreciated; however, the exact incidence is unknown. When renal biopsy samples from 257 consecutive SLE patients with renal failure were examined, microangiopathy compatible with TTP was discovered in 4 samples. The ADAMTS-13 assay is a new tool in the diagnosis of TTP, and its clinical utility is still being defined. ADAMTS-13 activity is expressed as a percentage of activity compared to normal, and an inhibitor is present if the addition of normal sera does not correct deficient activity. A study of 100 patients with TTP showed that 48% of patients had severely decreased ADAMTS-13 activity (< 10%), 24% had moderately reduced activity (10–46%), and 28% had normal activity. It is not known whether the assay is insensitive, or if patients with TTP can have truly normal ADAMTS-13 activity. Severely reduced ADAMTS-13 activity of < 10% is highly specific for TTP, and is not seen in other thrombocytopenic disorders such as sepsis and HIT.

Assessing the cause of thrombocytopenia in CTD can be challenging, because background immune-mediated thrombocytopenia is common. As illustrated by these 2 cases, a broad differential including TTP and HIT must be entertained, and these diagnoses may overlap in the same patient. Particularly in case 2, the diagnosis of recurrent TTP was uncertain, and ADAMTS-13 testing confirmed the diagnosis. In case 1 the patient had moderately reduced ADAMTS-13 activity, without a demonstrable ADAMTS-13 inhibitor. However, the test was performed following treatment with rituximab, which could have lowered the titer of an inhibitor. Decreased ADAMTS-13 activity with an inhibitor has been described in an SLE patient with TTP, and disappearance of the inhibitor correlated with clinical improvement.

In patients with CTD who frequently produce autoantibodies, it is possible that the presentation of antigens from activated platelet aggregates in TTP during exposure to heparin may lead to both anti-ADAMTS-13 and anti-PF4 antibody formation. Rituximab could work by decreasing autoantibody production; in fact rituximab has proven effective in other antibody-mediated diseases such as idiopathic thrombocytopenic purpura. We suggest that rituximab is a reasonable therapeutic option for refractory thrombotic thrombocytopenic purpura in the setting of connective tissue disease.

REFERENCES


Table 1. Laboratory data summary for Case 1.

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<th>Hospital Day</th>
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<td>7.1</td>
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Reference values: Hemoglobin: 11.7–16.0 g/dl, platelets: 160–400/μl, LDH: 96–200 U/l, anti-platelet factor 4: 0.001–0.349 U, ADAMTS-13 activity: ≥ 67%, ADAMTS-13 inhibitor: ≤ 0.4 U. ‡ Plasma exchange initiated. ‡‡ Rituxan 375 mg/m² given.

Table 2. Laboratory data summary for Case 2.

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Reference values: Hemoglobin: 11.7–16.0 g/dl, platelets: 160–400/μl, LDH: 96–200 U/l, anti-platelet factor four 0.001–0.349 U, ADAMTS-13 activity ≥ 67%, ADAMTS-13 inhibitor ≤ 0.4 U. † Hospital discharge day. * Hemoglobin drop occurred in the setting of an acute right thigh hematoma. ‡ Plasma exchange initiated. § Rituximab 375 mg/m² given. Heparin was started D6 and stopped D10.


