Splenectomy in relapsing and plasma-refractory acquired thrombotic thrombocytopenic purpura

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Background and Objectives. Acquired thrombotic thrombocytopenic purpura (TTP) is often due to autoantibodies inhibiting ADAMTS-13 activity resulting in impaired processing of very large von Willebrand factor multimers. TTP usually presents with an acute onset and a fulminant, sometimes fatal course. With appropriate treatment including plasma exchange, and fresh frozen plasma replacement, often supplemented by immunosuppressive therapy, the acute episode generally resolves within days to weeks.

Design and Methods. We describe the clinical course of 3 patients with acquired TTP. One was refractory to PE, the other two relapsed after this treatment. All three were treated with splenectomy. ADAMTS-13 activity and inhibitor levels were monitored.

Results. ADAMTS-13 activity was initially < 5% in all 3 patients. After splenectomy the inhibitor against ADAMTS-13 disappeared rapidly in 2 patients and there was full recovery of ADAMTS-13 activity in all 3 patients.

Interpretation and Conclusions. Splenectomy, by eliminating a source of pathogenic autoantibody production, can be a successful treatment for patients with relapsing or plasma-refractory acquired TTP due to autoantibody-mediated ADAMTS-13 deficiency.

Key words: thrombotic thrombocytopenic purpura, relapse, ADAMTS-13 activity, autoantibody, splenectomy.

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder, its annual incidence being about 3.7 cases per 10^6 individuals, possibly with slight increase in recent years. It is characterized by intravascular platelet clumping resulting in thrombocytopenia and microangiopathic hemolytic anemia, often accompanied by organ dysfunction such as neurological abnormalities, renal failure and fever. In the last few years, remarkable advances in understanding the pathogenesis of TTP have been made. The condition is often associated with severe deficiency of the von Willebrand factor (VWF)-cleaving protease, now denoted as ADAMTS-13 (A disintegrin and metalloprotease with thrombospondin type 1 domains)-13. Deficiency of ADAMTS-13 prevents normal processing of very large VWF multimers, which are synthesized and secreted into plasma by endothelial cells.

It is assumed that these unusually large VWF multimers are responsible for the formation of platelet thrombi under high shear stress in the microvasculature, a pathophysiological hallmark of TTP. ADAMTS-13 deficiency occurs in a constitutional and an acquired form. Hereditary TTP, due to compound heterozygous or homozygous mutations in the ADAMTS13 gene resulting in a congenital deficiency of ADAMTS-13 activity, often presents with a chronic relapsing course. In patients with the acquired form, the lack of ADAMTS-13 activity is most often caused by inhibitory autoantibodies.

Plasma exchange (PE) with replacement of fresh-frozen plasma (FFP) is the therapy of choice in acute acquired TTP and has reduced mortality from > 90% to about 10-20%. However, about 35-50% of patients surviving an acute bout of TTP will relapse after an initial response to PE, and some are plasma-refractory or remain PE-dependent for a long time. We describe three of the five patients with acquired idiopathic TTP seen at our hospital during the last seven years; one case was plasma-refractory and the other two relapsed after PE. All three were successfully treated by splenectomy.

Design and Methods

Between January 1996 and November 1999 three adult patients, one female and
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two male Caucasians, aged 65, 33 and 17 years, respectively, presented with a first episode of classical TTP (Table 1).

All three demonstrated severe thrombocytopenic purpura and Coombs’-negative hemolytic anemia with schistocytes on the peripheral blood smear. In addition, patient 1 had neurological symptoms (headache, confusion, several transient ischemic attacks).13 Fever had preceded hospitalization in patient #2, and renal dysfunction, although not requiring hemodialysis, was present in patient #3, who had been suffering from discoid lupus erythematosus for years before presenting with TTP.

We describe the clinical management and laboratory investigations in these patients. Initially, ADAMTS-13 activity, determined by immunoblotting assay,4,13,23 was <5% and inhibitory autoantibodies were detected in all three patients. Treatment included PE, replacement of FFP, corticosteroids, and patients #1 and 2 also received vincristine (Table 1). Patient #2 was plasma-refractory, while the other two patients recovered, but relapsed seven months after disease onset. A second relapse occurred in patient #1 after another four months.

Results

Microangiopathic hemolysis and thrombocytopenia characterized all three relapses, additional organ dysfunction was not present. At relapse, patients #1 and 3 were treated with PE and FFP replacement, additional FFP infusions between PE sessions and corticosteroids. Patient #1 also received vincristine. Inhibitory antibody titers decreased during daily PE treatment, but increased again after 6-13 days in both male patients.13 Splenectomy was performed on day 29 of the first episode in the plasma-refractory patient (patient #2) and 35 and 19 days after the last relapse in patients #1 and 3, respectively. Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B infections was performed before (patient #1) or after splenectomy (patients #2 and 3). The post-operative courses were uneventful. Daily PE was continued in patient #1 for six days postoperatively but could be

### Table 1. Characteristics of the three patients with acquired TTP at disease onset and at relapse.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender, Age, Initial</th>
<th>Acute TTP Clinical presentation</th>
<th>Hb g/L</th>
<th>Schist.</th>
<th>LDH U/L</th>
<th>Urea mmol/L</th>
<th>AD-13 %</th>
<th>Inhibitor</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 33</td>
<td>Initial (d1) flu-like symptoms, intermittent headaches, confusion, several transient ischemic attacks</td>
<td>93</td>
<td>++</td>
<td>5935</td>
<td>6.3</td>
<td>&lt; 5</td>
<td>present</td>
<td>PE, FFP infusion between PE, CS, Vincristine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. relapse (d 221) fatigue, general illness</td>
<td>126</td>
<td>++</td>
<td>1518</td>
<td>7.2</td>
<td>&lt; 5</td>
<td>present</td>
<td>PE, FFP infusion between PE, CS, Vincristine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. relapse (d 330) fatigue, general illness</td>
<td>161</td>
<td>++</td>
<td>958</td>
<td>6.8</td>
<td>&lt; 5</td>
<td>present</td>
<td>PE, FFP infusion between PE, CS, Vincristine, Splenectomy (d 365)</td>
</tr>
<tr>
<td>2</td>
<td>M, 17</td>
<td>Initial (d1) fever, jaundice, exercise-induced dyspnea</td>
<td>46</td>
<td>+++</td>
<td>2655</td>
<td>6.0</td>
<td>&lt; 5</td>
<td>present</td>
<td>PE, CS, Vincristine, Splenectomy (d 29)</td>
</tr>
<tr>
<td>3</td>
<td>F, 65</td>
<td>Initial (d1) fatigue, nausea</td>
<td>43</td>
<td>++</td>
<td>4554</td>
<td>39.6</td>
<td>&lt; 5</td>
<td>present</td>
<td>PE, CS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. relapse (d 209) fatigue, arthralgia</td>
<td>73</td>
<td>++</td>
<td>2931</td>
<td>6.2</td>
<td>15 not detectable</td>
<td>PE, FFP infusion between PE, CS, Splenectomy (d 228)</td>
<td></td>
</tr>
</tbody>
</table>

Hb: hemoglobin; Schist.: schistocytes; Plt.: platelets; LDH: lactate dehydrogenase; AD-13: ADAMTS-13 activity; inhibitor: ADAMTS-13 inhibitor; PE: plasma exchange; FFP: fresh frozen plasma; CS: corticosteroids; d: day (day 1: day of initial diagnosis). Normal range: Hb: men135 – 168 g/L; women: 121 – 154 g/L; Plt: 140 – 380x10^9/L; LDH: < 480 U/L; Urea: 2.9 – 7.7 mmol/L.
withheld in the other two. Post-operatively, thrombocytopenia resolved within one to two days, and hemoglobin levels normalized within four weeks. Corticosteroids were tapered off over a period of 5-19 weeks. After splenectomy, the inhibitor against ADAMTS-13 disappeared rapidly (patients 1 and 2), paralleled by a full recovery of ADAMTS-13 activity in all three patients. Follow-up is now 91, 46 and 44 months, respectively. None of the patients have had a relapse of TTP or serious infections so far (Figure 1). ADAMTS-13 activity has remained between 25-100% and inhibitors have not reappeared in patients #1 and 3. In patient #2, however, a strong inhibitor resulting in severe ADAMTS-13 deficiency reappeared 3.4 years after splenectomy. This patient has been closely followed during the last six months. He continues to be in clinical remission with hemoglobin concentration and platelet counts in the normal range.

**Discussion**

Inhibition of ADAMTS-13 activity constitutes an important factor in the pathogenesis of acute idiopathic TTP.\(^3\)-\(^5\),\(^11\),\(^13\) In the light of this pathophysiologic concept the effectiveness of PE is thought to be due to the replacement of ADAMTS-13 and concurrent elimination of inhibitory ADAMTS-13 antibodies from the patient’s circulation. Nowadays, it is estimated that 80-90% of patients with acute idiopathic TTP survive because of the effectiveness of PE.\(^2\),\(^17\)-\(^19\) PE is often used in combination with immunosuppressive treatment strategies such as corticosteroids\(^18\) or vincristine.\(^3\),\(^13\) Recently, a few patients have been treated with the monoclonal anti-CD20 antibody rituximab.\(^24\)-\(^27\) The presence of anti-ADAMTS-13 autoantibodies provides the rationale for these immunosuppressive treatment modalities.

Survivors of acute idiopathic TTP are at high risk of relapses, which occur in 35-50% of patients achieving a remission after a first bout of acute TTP.\(^20\)-\(^22\) Relapses seem to be more common in TTP patients initially displaying severe acquired ADAMTS-13 deficiency than in those without.\(^22\) Treatment as well as prevention of relapses constitute important issues in the care of TTP patients. For many years, splenectomy was performed empirically, mainly in patients with plasma-refractory or chronic relapsing courses of TTP with reported success rates in small case series of 50-100%.\(^20\),\(^21\),\(^28\)-\(^35\)

The clinical remission of the first bout of TTP in our patient #1 was associated with disappearance of ADAMTS-13 inhibiting autoantibodies and normalization of ADAMTS-13 activity.\(^13\) Reappearance of the inhibitor leading to severe ADAMTS-13 deficiency preceded clinical relapse by three months, and splenectomy led to a lasting elimination of inhibiting autoantibodies, normalization of ADAMTS-13 activity and clinical remission.\(^13\) Whereas ADAMTS-13 activity remained in the normal range in patients #1 and 3, a strong ADAMTS-13 inhibitor reappeared 3.4 years after splenectomy in patient #2. Despite severe ADAMTS-13 deficiency he has remained in clinical remission for the last 6 months, being closely followed in our outpatient clinic. This case as well as the observation of two severely ADAMTS-13 deficient asymptomatic adult siblings of patients with hereditary TTP\(^11\) suggest that, besides severe ADAMTS-13 deficiency, additional, hitherto unknown trigger(s) is (are) apparently necessary for the onset of an acute TTP episode, at least in some patients.

Our experience with splenectomy in three patients with plasma-refractory or relapsing acquired TTP suggests that the clinical effectiveness of this procedure may be due to the elimination of an important source of B-lymphocytes producing inhibitory ADAMTS-13

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**Figure 1.** Time course of acute TTP episodes (|) before and after splenectomy in three patients.
autoantibodies. Astonishingly, however, at relapse ADAMTS-13 activity in patient #3 was only moderately reduced (15%) to a level not specific for classical TTP. It may be speculated that autoantibodies interfering with ADAMTS-13 binding to microvascular endothelial cells, not detectable by our assay of ADAMTS-13 activity in plasma, caused this relapse.3

In the light of the pathophysiology outlined here, and based on several case series reported in the literature,20,21,28-35 we believe that splenectomy may be a useful treatment option in patients with relapsing or plasma-refractory acquired TTP due to severe autoantibody-mediated ADAMTS-13 deficiency. The observation in patient #2 shows that prospective studies on large numbers of patients are needed to determine whether regular measurement of ADAMTS-13 activity is a valuable laboratory tool to identify patients at high risk of relapse and to assess the impact of ADAMTS-13 inhibitory antibodies on the clinical course of patients who have survived an acute episode of TTP.

JAKH planned the study, performed laboratory assays, was responsible for patient care, searched the literature and wrote the manuscript; JDS performed laboratory assays; FDB, MS, LA, CZ, AT were all involved in patient care over several years and edited the manuscript; BMT, SF were responsible for plasma exchange therapy, cared for patients and edited the manuscript; BL planned the study; BH was responsible for patient care, helped in writing and final editing of the manuscript together with JAKH. The authors reported no potential conflicts of interest and a rate of redundant publication of < 50%.

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References


