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Splenectomy in relapsing and plasma-refractory acquired thrombotic thrombocytopenic purpura

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A B S T R A C T

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 2 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.

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Thrombotic thrombocytopenic purpura (TTP) is a rare disorder, its annual incidence being about 3.7 cases per 10^6 individuals,[1] possibly with slight increase in recent years.[2] 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.[3] 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,[4,5] now denoted as ADAMTS (A disintegrin and metalloprotease with thrombospondin type 1 domains)-13.[6–9] 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 pathophysiologic hallmark of TTP.[10] ADAMTS-13 deficiency occurs in a constitutional[11,12] and an acquired form.[4,5,13] Hereditary TTP, due to compound heterozygous or homozygous mutations in the *ADAMTS13* gene[14–16] resulting in a congenital deficiency of ADAMTS-13 activity, often presents with a chronic relapsing course.[11] In patients with the acquired form, the lack of ADAMTS-13 activity is most often caused by inhibitory autoantibodies.[4,5]

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%.[2,17–19] However, about 35-50% of patients surviving an acute bout of TTP will relapse after an initial response to PE,[20–22] 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

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

Patient	Gender, Age	Acute TTP bouts	Clinical presentation	Laboratory findings: Hb g/L	Schist	Plt $\times 10^9$/L	LDH U/L	Urea mmol/L	AD-13 %	Inhibitor	Treatment
1	M, 33	Initial (d1)	flu-like symptoms, intermitting headaches, confusion, several transient ischemic attacks	93	+++	17	5935	6.3	< 5	present	PE, FFP infusion between PE, CS, Vincristine
		1. relapse (d 221)	fatigue, general illness	126	++	10	1518	7.2	< 5	present	PE, FFP infusion between PE, CS, Vincristine
		2. relapse (d 330)	fatigue, general illness	161	++	26	958	6.8	< 5	present	PE, FFP infusion between PE, CS, Vincristine, Splenectomy (d 365)
2	M, 17	Initial (d1)	fever, jaundice, exercise-induced dyspnea	46	+++	8	2655	6.0	< 5	present	PE, CS, Vincristine Splenectomy (d 29)
3	F, 65	Initial (d1)	fatigue, nausea	43	++	5	4554	39.6	< 5	present	PE, CS
		1. relapse (d 209)	fatigue, arthralgia	73	++	13	2931	6.2	15	not detectable	PE, FFP infusion between PE, CS Splenectomy (d 228)

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 – 380×10^9/L; LDH: < 480 U/L; Urea: 2.9 – 7.7 mmol/L.

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) and suffered from several transient ischemic attacks (left-sided homonymous hemianopsia, paresis of the left arm and dysarthria).[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

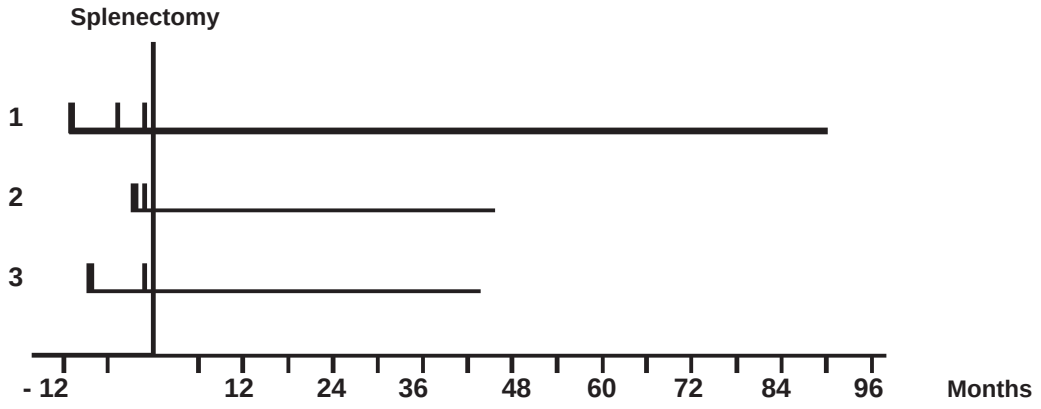

Figure 1. Time course of acute TTP episodes (|) before and after splenectomy in three patients.

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

autoantibodies. Astonishingly, however, at relapse ADAMTS-13 activity in patient #3 was only moderately reduced (15%) to a level not specific for classical TTP.[4,23] 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 patients and edited the manuscript; BL: planned the study, 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

1. Torok TJ, Holman RC, Chorba TL. Increasing mortality from thrombotic thrombocytopenic purpura in the United States-analysis of national mortality data, 1968-1991. Am J Hematol 1995; 50:84-90.
2. Rock GA. Management of thrombotic thrombocytopenic purpura. Br J Haematol 2000;109:496-507.
3. Moake JL. Thrombotic microangiopathies. N Engl J Med 2002;347:589-600.
4. Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med 1998;339:1578-84.
5. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 1998;339:1585-94.
6. Fujikawa K, Suzuki H, McMullen B, Chung D. Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family. Blood 2001;98:1662-6.
7. Gerritsen HE, Robles R, Lämmle B, Furlan M. Partial amino acid sequence of purified von Willebrand factor-cleaving protease. Blood 2001;98: 1654-61.
8. Zheng X, Chung D, Takayama TK, Majerus EM, Sadler JE, Fujikawa K. Structure of von Willebrand factor-cleaving protease (ADAMTS13), a metalloprotease involved in thrombotic thrombocytopenic purpura. J Biol Chem 2001;276:41059-63.
9. Soejima K, Mimura N, Hirashima M, Maeda H, Hamamoto T, Nakagaki T, et al. A novel human metalloprotease synthesized in the liver and secreted into the blood: possibly, the von Willebrand factor-cleaving protease? J Biochem (Tokyo) 2001;130:475-80.
10. Moake JL, Rudy CK, Troll JH, Weinstein MJ, Colannino NM, Azocar J, et al. Unusually large plasma factor VIII:von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. N Engl J Med 1982; 307:1432-5.
11. Furlan M, Lämmle B. Aetiology and pathogenesis of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. Best Pract Res Clin Haematol 2001; 14:437-54.
12. Allford SL, Harrison P, Lawrie AS, Liesner R, MacKie IJ, Machin SJ. Von Willebrand factor-cleaving protease activity in congenital thrombotic thrombocytopenic purpura. Br J Haematol 2000; 111:1215-22.
13. Furlan M, Robles R, Solenthaler M, Lämmle B. Acquired deficiency of von Willebrand factor-cleaving protease in a patient with thrombotic thrombocytopenic purpura. Blood 1998;91: 2839-46.
14. Levy GG, Nichols WC, Lian EC, Foroud T, McClintick JN, McGee BM, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature 2001;413: 488-94.
15. Kokame K, Matsumoto M, Soejima K, Yagi H, Ishizashi H, Funato M, et al. Mutations and common polymorphisms in ADAMTS13 gene responsible for von Willebrand factor-cleaving protease activity. Proc Natl Acad Sci U S A 2002; 99:11902-7.
16. Schneppenheim R, Budde U, Oyen F, Angerhaus D, Aumann V, Drewke E, et al. Von Willebrand factor cleaving protease and ADAMTS13 mutations in childhood TTP. Blood 2003;101:1845-50.
17. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med 1991;325:393-7.
18. Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. N Engl J Med 1991; 325:398-403.
19. George JN. How I treat patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Blood 2000; 96:1223-9.
20. Shumak KH, Rock GA, Nair RC. Late relapses in patients successfully treated for thrombotic thrombocytopenic purpura. Canadian Apheresis Group. Ann Intern Med 1995;122:569-72.
21. Kappers-Klunne MC, van der Meulen JH, Holdrinet RS, van der Meer J, Wijermans PW, Brand A. Thrombotic thrombocytopenic purpura in 13 Dutch centres: treatment and longterm follow-up. Ned Tijdschr Geneeskd 1997;141: 1192-6.
22. Vesely SK, George JN, Lämmle B, Studt JD, Alberio L, El-Harake MA, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood 2003;102:60-68.
23. Bianchi V, Robles R, Alberio L, Furlan M, Lämmle B. Von Willebrand factor-cleaving protease (ADAMTS13) in thrombocytopenic disorders: a severely deficient activity is specific for thrombotic thrombocytopenic purpura. Blood 2002;100: 710-3.
24. Gutterman LA, Kloster B, Tsai HM. Rituximab therapy for refractory thrombotic thrombocytopenic purpura. Blood Cells Mol Dis 2002;28:385-91.
25. Chemnitz J, Draube A, Scheid C, Staib P, Schulz A, Diehl V, et al. Successful treatment of severe thrombotic thrombocytopenic purpura with the monoclonal antibody rituximab. Am J Hema-

tol 2002; 71:105-8.
26. Zheng X, Pallera AM, Goodnough LT, Sadler JE, Blinder MA. Remission of chronic thrombotic thrombocytopenic purpura after treatment with cyclophosphamide and rituximab. Ann Intern Med 2003;138:105-8.
27. Tsai HM, Shulman K. Rituximab induces remission of cerebral ischemia caused by thrombotic thrombocytopenic purpura. Eur J Haematol 2003; 70:183-5.
28. Cuttner J. Thrombotic thrombocytopenic purpura: a ten-year experience. Blood 1980;56:302-6.
29. Schneider PA, Rayner AA, Linker CA, Schuman MA, Liu ET, Hohn DC. The role of splenectomy in multimodality treatment of thrombotic thrombocytopenic purpura. Ann Surg 1985;202:318-22.
30. Onundarson PT, Rowe JM, Heal JM, Francis CW. Response to plasma exchange and splenectomy in thrombotic thrombocytopenic purpura. A 10-year experience at a single institution. Arch Intern Med 1992;152:791-6.
31. Veltman GA, Brand A, Leeksma OC, ten Bosch GJ, van Krieken JH, Briet E. The role of splenectomy in the treatment of relapsing thrombotic thrombocytopenic purpura. Ann Hematol 1995;70: 231-6.
32. Crowther MA, Heddle N, Hayward CP, Warkentin T, Kelton JG. Splenectomy done during hematologic remission to prevent relapse in patients with thrombotic thrombocytopenic purpura. Ann Intern Med 1996;125:294-6.
33. Eldor A. Thrombotic thrombocytopenic purpura: diagnosis, pathogenesis and modern therapy. Baillière's Clin Haematol 1998;11:475-95.
34. Schwartz J, Eldor A, Szold A. Laparoscopic splenectomy in patients with refractory or relapsing thrombotic thrombocytopenic purpura. Arch Surg 2001;136: 1236-8; discussion 1239.
35. Aqui NA, Stein SH, Konkle BA, Abrams CS, Strobl FJ. Role of splenectomy in patients with refractory or relapsed thrombotic thrombocytopenic purpura. J Clin Apheresis 2003;18:51-4.