Relapsing thrombotic thrombocytopenic purpura with low ADAMTS13 antigen levels: An indication for splenectomy?

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Abstract

With more recent modalities of immunosuppression, splenectomy is now rarely considered in refractory/relapsed thrombotic thrombocytopenic purpura (TTP). However, the surgical approach had shown convincing evidences of high efficacy in the pre-rituximab era and therefore may still represent a lifesaving option in selected challenging cases. To define the characteristics of subjects who may benefit from splenectomy may ease clinical decision making. In this paper we describe the clinical and laboratory data of 2 multiple relapsing TTP cases who successfully underwent splenectomy in the pre-rituximab era. Whereas high anti-ADAMTS13 antibody titre and low ADAMTS13 activity never correlated with remission and relapse, a drop in the ADAMTS13 antigen level was always associated with the acute phase, whereas levels consistently returned to normal following splenectomy, heralding long term remission. Splenectomy may therefore be considered in refractory TTP cases associated with increased ADAMTS13 antigen clearance, irrespective of persistence of inhibitory antibodies.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy characterized by haemolytic anaemia, severe thrombocytopenia, and organ ischemia triggered by disseminated microvascular platelet rich-thrombi. The presence of a severe deficiency of ADAMTS13 activity (<10%) is considered diagnostic for TTP.[1] A severe functional ADAMTS13 deficiency causes the accumulation of ultra-large VWF multimers, leading to the formation of platelet-rich microthrombi within small arterioles.

Plasma exchange (PEX) and corticosteroids are the mainstays of treatment of acquired TTP in the acute phase. In subjects who fail to respond to PEX and corticosteroids and in relapsing TTP, rituximab is now considered standard of care. In TTP patients who are still refractory to PEX and rituximab, the best approach is unknown and recommendations are based on small case series and anecdotal evidence. Among these, splenectomy can be considered.[1]

The choice and the timeframe for considering splenectomy in TTP can be challenging if one considers the high surgical risk and the sometimes very unstable clinical setting of acute TTP. Therefore, it would be of utmost help to define whether a specific subset of subjects may benefit from splenectomy to achieve stable remission. We present two cases of relapsed/refractory TTP who successfully underwent splenectomy which was followed by durable remission.

Materials and Methods

ADAMTS13 quantitation was performed as previously described.[2] Platelet poor plasma (PPP) was prepared by a centrifugation at 2000 g for 15 min. The plasma was aliquoted and frozen at -80°C until assayed. ADAMTS13 activity was measured by the fluorescence resonance energy transfer assay (FRETS-VWF73). Anti-ADAMTS13 IgG and ADAMTS13 antigen were measured using the ADAMTS13-INH ELISA kit and ADAMTS13 ELISA kit (Technoclone, Wien, Austria), respectively, according to manufacturer's instructions. ADAMTS13 autoantibodies' inhibitory activity was determined by 50: 50 mixing of heated patients' plasma (56 C for 30 min) with normal human plasma (NHP); residual ADAMTS13 activity was then assayed by FRETS-VWF73.

An inhibitor was judged to be present if the ADAMTS13 activity of pooled normal plasma (PNP) was reduced by more than 50%. We performed sequencing of the ADAMTS13 gene (29 exons and ~50 bases of flanking noncoding sequence) as previously described.[2]

Case Report #1

In 1996, a 28-yr-old HIV-negative woman presented with headache, confusion, anaemia and thrombocytopenia (10×10^9/L). Biochemical evidences of haemolysis with schistocytes were noted. Reduced ADAMTS13 activity and the presence of ADAMTS13 inhibitory antibodies were consistent with acquired TTP (Table 1). From 2001 to 2005, three relapses were documented, all successfully treated with PEX and steroids. Complete resolution of clinical symptoms, recovery of thrombocytopenia and full resolution of haemolytic anaemia followed treatment in all episodes. Following resolution of relapse, the patient agreed to proceed to splenectomy, which was performed in 2005, with an unremarkable post-surgical clinical course. She is currently in remission at 13 years follow up. As shown in Table 1, ADAMTS13 antigen levels were always below 0.5 IU/mL on TTP recurrence, whereas it returned to close to normal values during remission periods. On the contrary, anti-ADAMTS13 antibodies and ADAMTS13 activity did not correlate with remission as we always found very high antibody levels (>120 UI/mL) and severe reduction of ADAMTS13 activity (<5%). As ADAMTS13 antigen levels in this patient did not completely recover during remission phases, we performed sequence analysis of the *ADAMTS13* gene

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locus. The analysis identified 4 amino acid changes previously described, R7W (signal peptide), Q448E (cysteine-rich domain), P618A (spacer domain) and A732V (thrombospondin type 1 repeat -2), all in heterozygous form.[3] As previously shown, it is possible that coexistence of these heterozygous mutations may be responsible for the slight reduction in baseline antigen level in our patient, without a significant impact on ADAMTS13 function.

Case Report #2

Patient 2 is a 30-yr-old HIV-negative woman who presented in 1994 with visual scotoma, low grade fever and headache. Thrombocytopenia (15×10^9/L), anaemia with schistocytes and biochemical evidences of haemolysis were present, a clinical picture strongly consistent with TTP. The patient was started on corticosteroids and PEX with fresh frozen plasma replacement, with progressive resolution of symptoms and platelet count normalization.

From 1995 to 2006, eight episodes all with characteristics suggesting recurrence of TTP were diagnosed. In all cases she received PEX and steroids, with recovery. As in case 1, ADAMTS13 activity and ADAMTS13 inhibitory antibodies showed a stable profile of reduction and high titre persistence, with levels of <5% and >120 IU/mL, respectively (Table 1), whereas a reduction and normalization of the antigen level was consistently correlated with acute episodes and periods of remission, respectively (Table 1). In 2006, the patient underwent splenectomy with no complications. In July 2007 an isolated episode of thrombocytopenia with mild haemolytic anaemia, consistent with mild TTP relapse, was rapidly resolved after a short course of PEX. From that episode onward, the patient always showed stable remission at follow up.

Discussion

Most TTP subjects show response to upfront treatment including PEX and corticosteroids. However, a significant number of patients are refractory to first line treatment and will require further interventions, like rituximab or more intense immunosuppression. In very select and refractory cases, splenectomy can still be considered in light of the previously reported high relapse-free survival rate.[4]

Multiple mechanisms can explain the pathogenic effect of anti-ADAMTS13 antibodies in TTP. These antibodies may function as protease inhibitors by occupying functionally relevant epitopes in the molecule. Alternatively, ADAMTS13 function could be compromised also by clearance of antibody-ADAMTS-13 complexes from the circulation.[5,6] The latter mechanism is particularly relevant as it has been recently reported that a low ADAMTS13 antigen level is associated with the highest mortality for TTP, synergistically with the anti-ADAMTS13 IgG antibody titre.[7]

The clearance of IgG-containing immune complexes (ICs) is known to occur primarily in the liver, both through Fc receptor-dependent and independent mechanisms.[8] However, the spleen has also been implicated in the clearance of ICs in some studies, and the size and type of IC may influence the relative contribution of different clearance mechanisms.[9]

The response rate of refractory TTP to splenectomy has been evaluated only in a limited number of cases in the published literature. A literature review describing 74 cases of refractory TTP reported a 90% success rate.[10] A significant high rate of complications has been noted, more often in subjects who failed to show TTP response.

It has been proposed that splenectomy may be beneficial in TTP by removing a large reservoir of B lymphocytes producing the pathogenic autoantibodies.[4] However, our data do not support the hypothesis that response to splenectomy depends on disappearance or, at least, reduction of anti-ADAMTS13 antibody titre. In fact, both patients showed post-splenectomy persistence of high autoantibody titres and very low ADAMTS13 activity but normalization of ADAMTS13 antigen level.

Conclusions

Although the risks of the surgical procedure and the long-term risk of infections must be weighed against the potential benefits, and newer modalities of immunosuppression be considered, our experience suggests that, by removing a major site of clearance of opsonized ADAMTS13, splenectomy could be considered in those refractory TTP subjects who relapse and have concomitant low ADAMTS13 antigen levels.

Table 1. Laboratory values at different timepoints of the disease.

Patients, stage	Year	Acute (A) or Remission (R)*	Platelets ×109/L (range)°	ADAMTS13 activity % (n.v.65-130)	IgG-ADAMTS13 inhibitor UI/mL (n.v.<17)	BU/mL	ADAMTS13 antigen° UI/mL (n.v.0.6-1.6)
Patient 1	1996	A	10	<5	N.A.	>1	NA
Pre-splenectomy	2000	R	287	<5	>120	NA	0.50
	2001	A	13	<5	>120	>1	0.2
	2002	A	48	<5	>120	>1	0.2
	2004	R	336	<5	>120	>1	0.50
	2005	A	23	<5	>120	>1	0.08
Patient 1 Post-splenectomy	2006-2018	R	276-405	<5	>120	>1	0.50-0.55
Patient 2	1994-2006	A	7-41	<5	>120	>1	0.06-0.3
Pre-splenectomy	(9 episodes)						
	2005-2006	R	198-290	<5	>120	>1	0.7-0.9
Patient 2	2006	R	371	<5	>120		0.7
Post-splenectomy	2007	A	88	<5	>120	>1	0.4
	2008-2018	R	186-339	<5	>120		0.7-1

NA, not available; NV, normal value; BU, Bethesda Units. *Acute episodes were always associated with laboratory data consistent with haemolytic anaemia. °Ranges are provided when multiple episodes were considered. Normal values were considered levels of ADAMTS13 activity and antigen measured in 50 control patients

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