CASE SERIES

Splenectomy: Does it still play a role in the management of thrombotic thrombocytopenic purpura?

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Background: Plasma exchange is first-line therapy for patients with thrombotic thrombocytopenic purpura (TTP). Splenectomy is often indicated for patients with relapsing or refractory disease. Concerns exist about its efficacy and safety in these patients. We describe a series of patients whose TTP was treated with laparoscopic splenectomy. We also reviewed the literature in order to describe the use and safety of splenectomy for refractory or relapsing TTP.

Methods: We reviewed the charts of consecutive patients with TTP referred for splenectomy and searched MEDLINE for studies describing outcomes following splenectomy for relapsing or refractory TTP.

Results: In all, 5 patients were referred for relapsing TTP and underwent uneventful laparoscopic splenectomy. All 5 were in remission after more than 40 months of follow-up. We found 18 studies (87 patients) reporting the results of splenectomy for relapsing TTP and 15 studies (74 patients) involving patients who underwent splenectomy for refractory TTP. The aggregate complication (6% v. 10%) and mortality rates (1.2% v. 5%) were lower for patients who received treatment for relapsing versus refractory TTP. The rate of postsplenectomy relapse among patients with relapsing disease was 17%, whereas the nonresponse rate was 8% for patients with refractory TTP. There were no complications among the 22 laparoscopic cases reported.

Conclusion: Although the data supporting splenectomy for treatment of TTP are limited to case series with no control groups, they suggest that splenectomy is an option for patients with refractory or relapsing disease. When performed laparoscopically in patients with relapsing disease, splenectomy is associated with minimal morbidity and mortality.

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder characterized by thrombocytopenia, microangiopathic hemolytic anemia and, less commonly, renal dysfunction, neurologic impairment and fever.[1] Plasma exchange is the first-line therapy for patients with TTP.[2] However, 20%–30% of patients are either resistant to plasma exchange or have repeated relapses requiring frequent plasma exchange therapy to maintain remission.[2–4] Treatment options for these patients include immunosuppressant medications or splenectomy. The role of splenectomy remains controversial, with a recent review on TTP indicating that the benefit of splenectomy is uncertain.[1] In this article, we describe a series of consecutive patients who underwent laparoscopic splenectomy for TTP. We also conducted a review of the literature to determine the efficacy and safety of splenectomy for patients with TTP.

Methods

Patients

We reviewed the charts of 5 consecutive patients referred to a single surgeon for laparoscopic splenectomy for TTP between September 2004 and January

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2005. The criteria used to diagnose TTP were the presence of thrombocytopenia (platelet count < $150 \times 10^3/\mu L$), microangiopathic hemolytic anemia (schistocytes on a peripheral blood smear with elevated lactate dehydrogenase) and the absence of any other identifiable cause.[1]

All 5 patients initially underwent plasma exchange and were subsequently referred for splenectomy because of relapsing disease requiring ongoing plasma exchange and/or immunosuppressive therapy. The surgical outcomes including method of surgery (laparoscopic or open), estimated intraoperative blood loss, length of stay in hospital, blood transfusions, operating time and complications were recorded. Operating time was taken from the intraoperative record and represents the time between the first skin incision and skin closure. We obtained estimated blood loss from the surgeon's operative notes. All patients were seen 1 month after splenectomy by the operating surgeon, and any postoperative complications were noted. We considered the postoperative period to extend from the time of surgery to 30 days after the procedure.

Outcomes related to TTP included the time between diagnosis and splenectomy, previous therapy and relapse rate following splenectomy. We defined remission as the maintenance of a normal platelet count (> $150 \times 10^3/\mu L$) and the absence of hemolytic anemia without immunosuppressive medication or plasma exchange. We defined patients with relapsing disease as those who went into remission following plasma exchange and then relapsed and required further therapy; in contrast, patients with refractory disease failed to respond to plasma exchange and underwent splenectomy during the acute phase of their disease.[5] Although our clinical experience deals solely with patients with relapsing disease, we reviewed the literature for both relapsing and refractory TTP.

Operative technique

All procedures were carried out by a single surgeon, and all patients received vaccinations against pneumococcus and *Hemophilus influenzae* at least 1 week before surgery. A single dose of prophylactic intravenous antibiotic was administered before surgery, and lower extremity sequential compression devices were used to minimize the risk of deep venous thrombosis.

The patients were placed in the right lateral decubitus position. The operating room table was flexed to expose the area between the left costal margin and the iliac crest. Intra-abdominal access was obtained through 3 ports (two 5-mm and one 10-mm) placed along the costal margin. A pneumoperitoneum was achieved to 15 mm Hg, and the surgeon examined the patient's abdomen for the presence of accessory spleens using a 30° laparoscope. The surgeon mobilized the spleen from the colon and its lateral attachments using a harmonic scalpel (Ethicon). The upper pole of the spleen was freed and the short gastrics divided by the harmonic scalpel. The surgeon then rotated the spleen laterally to expose the hilum, and the hilar vessels were divided using a vascular endostapler. The spleen was then placed in an impermeable retrieval bag and morcellated for removal. The splenic bed was irrigated, and the facial openings of the port sites were closed.

Literature review

We searched MEDLINE (Mar. 25, 2009) for articles pertaining to splenectomy for treatment of TTP using a combination of the medical subject heading (MeSH) terms "splenectomy" and "thrombotic thrombocytopenic purpura." We also enlisted the aid of a health sciences librarian who expanded our initial search by using the following keyword search string: (splenectom*[tw] OR "spleen removal"[tw] OR "removal of spleen"[tw]) AND (Moschcowitz disease[tw] OR Moschkowitz disease[tw] OR TTP[tw] OR thrombotic thrombocytopenic purpura[tw] OR Upshaw-Schulman syndrome[tw]) AND (in process[sb] OR publisher[sb]).

We reviewed the titles and abstracts of identified articles, and we obtained the full-text versions of the relevant articles. We also searched the reference lists of these articles to identify additional articles. We included only articles that reported outcomes following splenectomy for patients who had initially received plasma exchange but either relapsed or failed to respond and subsequently underwent splenectomy. We excluded articles published before 1977 because this was the year that plasma exchange was first advocated as first-line treatment for TTP.[6] We also excluded articles that did not include patients with TTP, patients who underwent splenectomy or patients who underwent plasma exchange before splenectomy. We excluded duplicate publications, review articles, and case reports or papers that only included 1 patient with splenectomy in order to focus on larger patient series. We also excluded articles that did not include follow-up data or specify the length of follow-up after splenectomy.

We abstracted data from each selected article about the indication for splenectomy, laparoscopic or open surgery, complications, mortality, relapse or response of TTP after surgery and length of follow-up. We aggregated the data for complication, mortality and relapse or response rates following splenectomy using only the studies that provided the required data. We did not statistically compare outcomes between patients with refractory or relapsing disease because these represent different patient populations.

RESULTS

Patients

Five patients (3 women, 2 men, age 45–71 yr) underwent laparoscopic splenectomy for TTP during the study period

(Table 1). The diagnosis of TTP was confirmed by the presence of thrombocytopenia and microangiopathic hemolytic anemia, with all patients having schistocytes on peripheral blood smears and elevated serum lactate dehydrogenase levels before treatment. All patients underwent splenectomy for relapsing disease.

Patient 1 initially responded to plasma exchange and cyclophosphamide but relapsed 2 months after starting therapy and subsequently underwent a splenectomy. Patient 2 initially underwent plasma exchange and then relapsed 3 months following diagnosis and required monthly cyclophosphamide treatments to maintain remission. Patient 3 was initially given a combination of plasma exchange and cyclophosphamide. His disease was in remission for 2 years, but it became resistant to these treatments and he was given mycophenolate. He continued to require mycophenolate to maintain remission and underwent splenectomy 6 months later. Patient 4 was diagnosed in 1998 and responded to plasma exchange and azathioprine, which was stopped in 2002. Her disease stayed in remission until December 2004, at which point she required monthly cyclophosphamide to maintain a normal platelet count; she underwent splenectomy 1 month later. Patient 5 was initially diagnosed in 1997. Her disease initially responded to plasma exchange and was in remission until November 2004, when she required daily plasma exchange to maintain a normal platelet count; she underwent splenectomy 2 months later. All patients have completed more than 40 months of follow-up, and none of the patients have relapsed or taken immunosuppressive medications since undergoing splenectomy.

Table 2 summarizes the operative outcomes. The operative time ranged from 65 to 130 minutes. All patients had normal preoperative platelet counts. There were no conversions to open surgery or complications, and none of the patients required blood products during the perioperative period. Most patients stayed in hospital for less than 24 hours. The pathology specimens of all patients revealed hemophagocytosis and cellular congestion consistent with enhanced immune activity. Only 1 patient had evidence of microvascular thrombi. The patients in our series were all undergoing treatment and had relatively stable disease at the time of surgery; this likely explains the lack of thrombi seen in most patients. A lack of thrombi among resected spleens was also reported in a large series of TTP patients who underwent splenectomy, with only 2 of 33 patients having arteriolar thrombi.[5]

Table 1. Characteristics of patients who underwent splenectomy for thrombotic thrombocytopenic purpura

Patient	Age*	Sex	Time from diagnosis to splenectomy, mo.	Indication for splenectomy	Post-splenectomy relapse	Follow-up, mo.
1	71	M	3	Relapse	0	41
2	46	F	9	Relapse	0	43
3	45	M	35	Relapse	0	48
4	63	F	73	Relapse	0	43
5	53	F	92	Relapse	0	40

F = female; M = male.
*Age at time of splenectomy.

Literature review

We identified 272 articles in our search. We excluded 51 articles published before 1977, 29 articles that did not include patients with TTP, 33 that did not include patients who underwent splenectomy and 22 that did not include patients who underwent plasma exchange before splenectomy. We excluded 3 duplicate publications, 41 review articles, 55 case reports or articles with only 1 patient, and 13 articles that did not include follow-up data or specify the length of follow-up after splenectomy. In total, 25 studies met our inclusion criteria and were included in our review.

Overall, there were 18 studies that reported the outcomes of 87 patients who underwent splenectomy for relapsing TTP (Table 3), and there were 15 studies that reported the outcomes of 74 patients who underwent splenectomy for refractory TTP (Table 4). Although we excluded case reports, both Wells and colleagues[8] (Table 3) and Kremer Hovinga and colleagues[21] (Table 4) are listed as having 1 patient; however, each of these studies included a total of 3 patients. We separated these patients into different tables according to the indication for splenectomy.

The overall mortality (1.2% v. 5%) and complication rates (6% v. 10%) were lower for patients who underwent splenectomy for relapsing TTP compared with refractory TTP. However, the relapse rate following splenectomy was higher for patients with relapsing disease (17% v. 8%). The follow-up times varied greatly between studies, with the mean follow-up ranging from 7 to 147 months.

Discussion

The role of splenectomy in the care of patients with TTP has evolved. Initially, splenectomy in combination with corticosteroids was considered to be first-line therapy for TTP.[30–32] This approach often led to response rates of

Table 2. Operative outcomes of patients who underwent splenectomy for thrombotic thrombocytopenic purpura

Patient	Preoperative platelet count, $\times 10^3/\mu L$	OR time, min	EBL, mL	Transfusions	Complications	Length of stay, d
1	244	130	50	0	0	1
2	270	65	30	0	0	1
3	143	80	50	0	0	2
4	220	75	80	0	0	1
5	199	80	50	0	0	1

EBL = estimated blood loss; OR = operating room.

around 50%[31–34] and had a mortality rate of up to 40%,[31,32,34] with many patients dying of recurrent or persistent TTP. With the advent of plasma exchange, first advocated by Bukowski in 1977,[6] the prognosis for patients with TTP has improved, with remission rates of 70%–80%.[2,3] In the era of plasma exchange, splenectomy remains a controversial option for patients with relapsing or refractory TTP. Rice[35] argues against the use of splenectomy for TTP by pointing out that many patients with relapsing disease will go into spontaneous remission regardless of therapy and that relapses are often mild and successfully treated with plasma exchange. Hayward and colleagues[26] describe 4 such patients who went into spontaneous remission without any therapy.

Although spontaneous recovery has been described, most patients who relapse require ongoing plasma exchange or immunosuppressant medication to maintain remission. In our series of 5 patients, all initially responded to plasma exchange but relapsed and required further immunosuppressive medications (cyclophosphamide, mycophenolate, azathioprine) in addition to plasma exchange to maintain remission. All 5 underwent uneventful laparoscopic splenectomy, and all remain disease-free with more than 40 months follow-up. The benefits of splenectomy for preventing relapses are evident among the 18 studies found in the literature, with an aggregate rate of relapse of only 17% following splenectomy (Table 3). A similar trend can be seen in studies that compared presplenectomy relapse rates to postsplenectomy relapse rates,[5,12,19] with the largest study of 24 patients showing a decrease in relapse rate from 0.74 relapses/patient-year to 0.10 relapses/patient-year after splenectomy.[5]

There were only 5 complications among the 87 patients who underwent splenectomy for relapsing disease (Table 3), with only 1 requiring a repeat laparotomy for bleeding. One patient in this group died; this patient relapsed shortly after splenectomy and died of TTP-related complications. No complications were reported among the 22 laparoscopic cases. In comparison with patients who underwent splenectomy for relapsing TTP, the mortality and morbidity of patients who underwent splenectomy for refractory TTP was higher. Among the 74 patients described in the literature, there were 4 deaths and 7 complications (Table 4). At least 2 of the deaths resulted from progression of TTP that was refractory to all treatment modalities.

It is important to note that patients who undergo treat-

Table 3. Studies involving patients who underwent splenectomy for relapsing thrombotic thrombocytopenic purpura

Study	No. of patients	Surgical method	No. (%)			Follow-up, mean (range), mo.*	Comment
			Deaths	Complications	Postsplenectomy relapses		
Liu et al.[7]	2	Open	0	1 (50)	0	7, 7	Complication: postoperative hemorrhage requiring a repeat laparotomy
Wells et al.[8]	1	Open	0	0	0	30	
Eldor et al.[9]	2	Open	0	0	0	28, 35	
Onundarson et al.[4]	6	Open	0	1 (17)	0	42 (11–68)	Complication: incisional hematoma
Hoffkes et al.[10]	2	Open	0	0	0	24, 24	
Veltman et al.[11]	5	Open	0	0	0	39 (9–62)	
Crowther et al.[12]	6	Open	0	0	2 (33)	45 (10–96)	
Rund et al.[13]	2	Open	0	0	0	10, 52	
de la Rubia et al.[14]	2	Laparoscopic	0	0	1 (50)	11, 26	
Schwartz et al.[15]	6	Laparoscopic	0	0	0	32 (19–54)	
Wichmann et al.[16]	2	Laparoscopic	0	0	0	11, 32	
Modic et al.[17]	2	Laparoscopic	0	0	0	5, 13	
Essien et al.[18]	2	Laparoscopic	0	0	0	16, 19	
Aqui et al.[19]	8	Open	1 (12.5)	0	4 (50)	21 (1–67)	One patient died from relapsing TTP 2 days after splenectomy
Zomas et al.[20]	5	Open	0	0	0	13‡	
Kremer Hovinga et al.[21]	2	Not reported	0	0	0	44, 91	
Kappers-Klunne[5]	24	Open†	0	3 (12.5)	6 (25)	111 (9–230)	Complications: 1 wound infection, 1 subphrenic abscess and 1 pancreatic injury with fluid collection
Outschoorn and Ferber[22]	3	Not reported	0	0	2 (66)	43 (2–80)	
Present study	5	Laparoscopic	0	0	0	43 (40–48)	
Total	87		1 (1.2)	5 (6)	15 (17)		

TTP = thrombotic thrombocytopenia purpura.
*Or the number of months in studies with 1 or 2 patients.
†Includes 3 laparoscopic cases.
‡Median follow-up.

ment for refractory TTP are at greater risk of complications and death following splenectomy. This increased risk likely results from the inability to preoperatively optimize the patient's blood counts because they are resistant to plasma exchange. This also highlights the importance of optimizing the blood counts of patients with TTP who respond to plasma exchange preoperatively so that splenectomy can be carried out with minimal morbidity and mortality. The proportion of patients whose disease relapsed or persisted following splenectomy was greater for patients with relapsing TTP than for those with refractory TTP (17% v. 8%). The prognosis of patients whose disease relapses or persists following splenectomy is worse for those with refractory disease. Of the 15 recurrences following splenectomy in patients with relapsing disease, all but one successfully underwent repeat plasma exchange and achieved remission. Patients with refractory TTP whose disease persists following splenectomy fare worse, with only 1 of 6 patients recovering with additional therapy and 3 of 6 patients dying of progressive disease.

Advances in the understanding of the pathogenesis of this disease have been made, although controversy still exists. Severe deficiency of a von Willebrand factor–cleaving protease, named ADAMTS-13 (A Disintegrin And Metalloprotease with ThromboSpondin type domains) has been found in patients with TTP,[21,36,37] although not all patients with TTP have severe ADAMTS deficiencies.[38,39] In a prospective study of 142 patients with TTP, Vesley and colleagues[38] identified only 18 patients (13%) with severe ADAMTS-13 deficiency. ADAMTS-13 deficiency is the result of autoantibodies that inhibit the activity of this protease which normally cleaves large von Willebrand factor multimers.[36,37] The persistence of these large multimers in the circulation results in the formation of platelet thrombi in the microvasculature leading to the clinical and pathological features of TTP. Kremer Hovinga and colleagues[21] examined the levels of ADAMTS-13 and its inhibitor in 3 patients who underwent splenectomy for refractory (n = 1) and relapsing (n = 2) TTP. All 3 patients initially had less than 5% protease activity, and all 3 patients regained full ADAMTS-13 activity following splenectomy. Interestingly, the levels of inhibiting autoantibodies disappeared rapidly in 2 of the 3 patients following splenectomy but persisted in the third patient, even though the patient remained in complete remission. ADAMTS-13 deficiency plays a role in the pathogenesis of TTP for some patients, although other

Table 4. Studies involving patients who underwent splenectomy for refractory thrombotic thrombocytopenic purpura

Study	No. of patients	Surgical method	No. (%)			Follow-up, mean (range), mo.*	Comment
			Deaths	Complications	Failure to respond to splenectomy		
Thompson and McCarthy[23]	2	Open	0	1 (50)	0	4, 8	Complication: *Staphylococcal* infection
Evans et al.[24]	2	Open	0	0	0	12, 12	
Schneider et al.[25]	6	Open	0	2 (33)	0	11 (6–14)	Complications: pneumonia and postoperative hemorrhage
Liu et al.[7]	5	Open	0	0	1 (20)	18 (8–36)	
Wells et al.[8]	2	Open	0	0	0	6, 36	
Hayward et al.[26]	13	Open	2 (15)	Not reported	0	20 (6–67)	Two deaths following splenectomy, specific cause not reported
Winslow and Nelson.[27]	6	Open	0	0	0	21 (6–38)	
Rund et al.[13]	2	Open	0	0	1 (50)	21, 86	
Mant et al.[28]	7	Open	1(14)	0	1 (14)	29 (18–37)	One patient failed to respond and died of TTP
de la Rubia et al.[14]	2	Laparoscopic	0	0	0	11, 26	
Schwartz et al.[15]	2	Laparoscopic	0	1 (50)	1 (50)	†	Complication: postoperative hematoma in splenic bed
Rosen et al.[29]	9	Laparoscopic	0	2 (22)	1 (11)	13 (1–30)	Complications: 1 diaphragmatic tear and 1 retroperitoneal hematoma
Aqui et al.[19]	6	Open	0	0	0	147 (72–176)	
Kremer Hovinga et al.[21]	1	Not reported	0	0	0	46	
Kappers-Klunne et al.[5]	9	Open‡	1 (11)	1 (11)	1 (11)	92 (28–201)	One patient did not respond and died of TTP postoperatively, 1 patient developed a pulmonary embolism postoperatively
Total	74		4 (5)	7 (10)§	6 (8)		

TTP = thrombotic thrombocytopenia purpura.
*Or the number of months in studies with 1 or 2 patients.
†Follow-up included in patients with relapsing TTP from Table 3.
‡Includes 1 laparoscopic case.
§Excludes Hayward et al.,[26] who did not report the complication rate following splenectomy.

autoimmune mechanisms are likely involved as well.

The exact role that the spleen plays in the pathogenesis of TTP is not known. The spleen is a major source of autoantibody production and antibody–antigen complex clearance. Given the autoimmune nature of this disease, the removal of this site of antibody production and/or consumption likely accounts for the beneficial effects of splenectomy. This interpretation is shared by other authors but remains speculative.[5,17,19,21]

Because of the likely role that autoantibodies play in the pathogenesis of TTP, the anti-CD20 antibody rituximab has been used to treat relapsing or refractory TTP. This antibody binds to the CD-20 antigen found on the surface of B cells and clears these cells from circulation.[40] Small case series have been published describing the benefits of rituximab, with most patients responding and achieving remission; however, long-term follow-up is lacking.[40,41] In the largest series of 25 patients who took rituximab for relapsing or refractory TTP, all patients responded and went into remission; however, the median follow-up was only 10 months.[40] Rituximab is well tolerated by most patients, but there is a risk of severe adverse effects. Millward and colleagues[42] describe the case of a patient with TTP who developed severe acute respiratory distress syndrome and heart failure following infusion with rituximab. Rituximab is an option for patients with relapsing or refractory TTP, but its precise role in the treatment of TTP remains to be determined. A randomized control trial of rituximab has been developed to address this issue.[41]

The data supporting splenectomy for TTP are limited, being from small, single-institution case series lacking control groups. Follow-up duration is variable from study to study, with many reporting less than 3 years of follow-up data. This likely results in an underestimation of the true relapse rate following splenectomy because late recurrences can occur, with 1 patient having a recurrence 9 years after splenectomy.[12] Other therapies used in these studies also varied, with some patients undergoing splenectomy alone and others taking immunosuppressant medication before splenectomy. Given the rarity of this disease and the small number of cases reported, it is possible that authors are more likely to publish cases that have been successfully treated with splenectomy. This publication bias would lead to a further underestimation of the true relapse or nonresponse rate to splenectomy in patients with TTP and must be considered when interpreting the results of the studies presented in this article.

Despite these limitations, splenectomy remains an option for patients with refractory or relapsing TTP. When performed in patients with relapsing disease, it is associated with minimal morbidity and mortality and achieves a greater than 80% response rate. The laparoscopic approach is favoured because it is associated with fewer complications.

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References

1. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. *N Engl J Med* 2006;354:1927-35.
2. Rock GA, Shumak KH, Buskard NA, 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.
3. Bell WR, Braine HG, Ness PM, et al. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. *N Engl J Med* 1991;325:398-403.
4. Onundarson PT, Rowe JM, Heal JM, et al. 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.
5. Kappers-Klunne MC, Wijermans P, Fijnheer R, et al. Splenectomy for the treatment of thrombotic thrombocytopenic purpura. *Br J Haematol* 2005;130:768-76.
6. Bukowski RM, King JW, Hewlett JS. Plasmapheresis in the treatment of thrombotic thrombocytopenic purpura. *Blood* 1977;50:413-7.
7. Liu ET, Linker CA, Shuman MA. Management of treatment failures in thrombotic thrombocytopenic purpura. *Am J Hematol* 1986;23:347-61.
8. Wells AD, Majumdar G, Slater NG, et al. Role of splenectomy as a salvage procedure in thrombotic thrombocytopenic purpura. *Br J Surg* 1991;78:1389-90.
9. Eldor A, Moser AM, Rose M, et al. Thrombotic thrombocytopenic purpura: the Israeli experience. *Transfus Sci* 1992;13:53-7.
10. Hoffkes HG, Weber F, Uppenkamp M, et al. Recovery by splenectomy in patients with relapsed thrombotic thrombocytopenic purpura and treatment failure to plasma exchange. *Semin Thromb Hemost* 1995;21:161-5.
11. Veltman GA, Brand A, Leeksma OC, et al. The role of splenectomy in the treatment of relapsing thrombotic thrombocytopenic purpura. *Ann Hematol* 1995;70:231-6.
12. Crowther MA, Heddle N, Hayward CP, et al. Splenectomy done during hematologic remission to prevent relapse in patients with thrombotic thrombocytopenic purpura. *Ann Intern Med* 1996;125:294-6.
13. Rund D, Schaap T, Gillis S. Intensive plasmapheresis for severe thrombotic thrombocytopenic purpura: long-term clinical outcome. *J Clin Apher* 1997;12:194-5.
14. de La Rubia J, Garcia I, Jarque I, et al. Splenectomy in patients with refractory or relapsing thrombotic thrombocytopenic purpura. *Haematologica* 2000;85:440-1.
15. 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.
16. Wichmann MW, Meyer G, Hiller E, et al. Laparoscopic splenectomy in thrombotic thrombocytopenic purpura. Surgical and hematological results in 2 patients [Article in German]. *Dtsch Med Wochenschr* 2001;126:299-302.
17. Modic M, Cernelc P, Zver S. Splenectomy: The last option of immunosuppressive therapy in patients with chronic or relapsing idiopathic thrombotic thrombocytopenic purpura? *Transplant Proc* 2002;34:2953-4.
18. Essien FA, Ojeda HF, Salameh JR, et al. Laparoscopic splenectomy for chronic recurrent thrombotic thrombocytopenic purpura. *Surg Laparosc Endosc Percutan Tech* 2003;13:218-21.

19. Aqui NA, Stein SH, Konkle BA, et al. Role of splenectomy in patients with refractory or relapsed thrombotic thrombocytopenic purpura. *J Clin Apher* 2003;18:51-4.
20. Zomas A, Gigantes S, Vasiloglou G, et al. Early therapeutic splenectomy may reduce morbidity and management costs in selected resistant or relapsing cases of TTP/HUS [abstract]. *J Thromb Haemost* 2003;1(Suppl):326.
21. Kremer Hovinga JA, Studt JD, Demarmels Biasiutti F, et al. Splenectomy in relapsing and plasma-refractory acquired thrombotic thrombocytopenic purpura. *Haematologica* 2004;89:320-4.
22. Outschoorn UM, Ferber A. Outcomes in the treatment of thrombotic thrombocytopenic purpura with splenectomy: a retrospective cohort study. *Am J Hematol* 2006;81:895-900.
23. Thompson HW, McCarthy LJ. Thrombotic thrombocytopenic purpura. Potential benefit of splenectomy after plasma exchange. *Arch Intern Med* 1983;143:2117-9.
24. Evans TL, Winkelstein A, Zeigler ZR, et al. Thrombotic thrombocytopenic purpura: clinical course and response to therapy in eight patients. *Am J Hematol* 1984;17:401-7.
25. Schneider PA, Rayner AA, Linker CA, et al. The role of splenectomy in multimodality treatment of thrombotic thrombocytopenic purpura. *Ann Surg* 1985;202:318-22.
26. Hayward CP, Sutton DM, Carter WH Jr., et al. Treatment outcomes in patients with adult thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Arch Intern Med* 1994;154:982-7.
27. Winslow GA, Nelson EW. Thrombotic thrombocytopenic purpura: indications for and results of splenectomy. *Am J Surg* 1995;170:558-61, discussion 561-3.
28. Mant MJ, Turner AR, Bruce D, et al. Splenectomy during partial remission in thrombotic thrombocytopenic purpura with prolonged plasma exchange dependency. *Am J Hematol* 1999;62:56-7.
29. Rosen M, Brody F, Walsh RM, et al. Outcome of laparoscopic splenectomy based on hematologic indication. *Surg Endosc* 2002;16:272-9.
30. Cuttner J. Splenectomy, steroids, and dextran 70 in thrombotic thrombocytopenic purpura. *JAMA* 1974;227:397-402.
31. Cuttner J. Thrombotic thrombocytopenic purpura: a ten-year experience. *Blood* 1980;56:302-6.
32. Rutkow IM. Thrombotic thrombocytopenic purpura (TTP) and splenectomy: a current appraisal. *Ann Surg* 1978;188:701-5.
33. Bukowski RM, Hewlett JS, Reimer RR, et al. Therapy of thrombotic thrombocytopenic purpura: an overview. *Semin Thromb Hemost* 1981; 7:1-8.
34. Bernard RP, Bauman AW, Schwartz SI. Splenectomy for thrombotic thrombocytopenic purpura. *Ann Surg* 1969;169:616-24.
35. Rice L. Splenectomy for relapsing thrombotic thrombocytopenic purpura. *Ann Intern Med* 1997;126:915.
36. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med* 1998;339:1585-94.
37. Furlan M, Robles R, Solenthaler M, et al. Acquired deficiency of von Willebrand factor-cleaving protease in a patient with thrombotic thrombocytopenic purpura. *Blood* 1998;91:2839-46.
38. Vesely SK, George JN, Lammle B, 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;102:60-8.
39. Zheng XL, Kaufman RM, Goodnough LT, et al. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. *Blood* 2004;103:4043-9.
40. Scully M, Cohen H, Cavenagh J, et al. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. *Br J Haematol* 2007;136:451-61.
41. George JN, Woodson RD, Kiss JE, et al. Rituximab therapy for thrombotic thrombocytopenic purpura: a proposed study of the Transfusion Medicine/Hemostasis Clinical Trials Network with a systematic review of rituximab therapy for immune-mediated disorders. *J Clin Apher* 2006;21:49-56.
42. Millward PM, Bandarenko N, Chang PP, et al. Cardiogenic shock complicates successful treatment of refractory thrombotic thrombocytopenia purpura with rituximab. *Transfusion* 2005;45:1481-6.

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