The Role of Splenectomy in Multimodality Treatment of Thrombotic Thrombocytopenic Purpura

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Current treatment modalities for thrombotic thrombocytopenic purpura (TTP) include plasmapheresis (PP), splenectomy, steroids, dextran, other antiplatelet agents, and vinca alkaloids. Prior to the development of PP and use of multimodality treatment for TTP, mortality rates exceeded 50%. This report reviews 11 patients treated for TTP, demonstrates the successful use of splenectomy as salvage therapy, and defines our indications for splenectomy in the treatment of this disorder. Ten of 11 patients were initially treated with PP; three responded completely and one died of fulminant disease. Six patients had a transient partial response to plasmapheresis and were subsequently treated with splenectomy, steroids, and dextran-70. Initial plasmapheresis resulted in improvement in laboratory values and clinical status in those patients requiring splenectomy. Durable remission (6–48 months) was achieved in 91% of patients with minimal morbidity.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) is a life-threatening microangiopathic disorder that presents clinically with thrombocytopenia, purpura, hemolytic anemia, fluctuating neurologic symptoms, fever, and renal insufficiency. The pathogenesis of the disease is unclear, but an interaction between platelets and endothelial cells resulting in vaso-occlusion by platelet aggregates is central to the process. Untreated, the mortality is 80 to 90%.[1] Use of splenectomy as a major treatment modality has been a subject of controversy since it was employed in 1927.[2] Steroids and splenectomy were first combined in the treatment of TTP in 1957.[3] This regimen remained the treatment of choice for the ensuing 20 years with response rates of about 50%.[4,5] Cuttner has advocated the addition of medium molecular weight dextran to this regimen and has reported a remission rate of 87% using splenectomy, steroids, and dextran 70.[6] Bukowski and co-workers[5] reviewed the literature and reported a 74% survival rate using a similar regimen. Since its introduction in 1977, plasmapheresis has proven to be highly effective when used as the initial treatment modality with response rates of 54% to 82%.[5,7]

The pathophysiology of TTP remains elusive. Reported responses to plasmapheresis suggest that either a platelet aggregating factor is removed or an inhibitor of aggregation is being replaced in the transfused plasma. The purpose of this report is to delineate the role of splenectomy in the multimodality treatment of TTP. Aggressive sequential application of plasmapheresis and splenectomy can now afford cure to most TTP patients with minimum morbidity and mortality rates.

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Materials and Methods

Eleven patients with TTP were treated at the University of California San Francisco between December 1979 and August 1984. Plasmapheresis was performed through Scribner shunts using an IBM 2997 continuous flow cell separator. In each treatment, 5000 ml (4000–6000 ml) of plasma was removed and replaced with frozen plasma. Plasmapheresis was repeated daily until response was established or failure was evident. Complete response was defined as achievement of a sustained platelet count of 150,000 without further treatment or transfusion. Patients underwent splenectomy when plasmapheresis failed to improve hematologic values after 5 days, or when TTP disease activity (evident initially as thrombocytopenia) recurred after an initial response despite continuation or reinstitution of plasmapheresis. Patients who had splenectomy also received methylprednisolone (100–200 mg/day intravenously) and dextran-70 (250–500 ml q 12 hrs). Duration of treatment with steroids and dextran ranged from 7 to 20 days; these agents were terminated when complete response was evident or when further plasmapheresis was required. Postplasmapheresis adjunctive therapy with vincristine, aspirin, or dipyridamole was used *ad hoc* per physician preference as indicated in Table 1.

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Results

Clinical characteristics and initial symptoms for the total patient group are summarized in Table 2. There were no obvious differences in clinical presentation between those patients who were managed successfully with plasmapheresis alone and those patients who proceeded to splenectomy, steroids, and dextran. One of the splenectomy patients (No. 1) had the rare chronic relapsing form of the disease while the rest had the more common acute form of TTP.

Three of eleven patients experienced complete remission to plasmapheresis alone (patients 9–11). The only death during treatment occurred in a patient who had a partial response to plasmapheresis followed by relapse and death (patient 8). Six patients (55% of our TTP population) failed plasmapheresis and subsequently were treated with splenectomy, steroids, and dextran (patients 1–6). One patient was treated with the splenectomy, steroid, and dextran regimen prior to transfer to our institution for plasmapheresis (patient 7). Although four of these seven patients required plasmapheresis postsplenectomy (patients 4–7), complete remission was ultimately achieved in all seven. The patients that required splenectomy benefited from initial plasmapheresis therapy in that they were better operative candidates (Table 3). Four of six showed significant clinical improvement in neurologic deficits and all six had improved laboratory parameters prior to splenectomy. The mean time interval between admission to hospital and surgery was 12 days (range, 7–27); between the last plasmapheresis and splenectomy the mean interval was 14.6 hours (1–27 hours). Other agents including vincristine, antiplatelet drugs, and steroids were often combined with plasmapheresis as indicated in Table 1; the influence of these agents (if any) was impossible to assess.

Surgical blood loss ranged from 50 ml to 1100 ml and transfusion requirements during surgery were lower than during initial plasmapheresis (Table 4). Three of seven

TABLE 1. *Treatment and Follow-up in Eleven Patients Treated for TTP*

Patient Number	Major Treatment Sequence 1	2	3	Other Treatments	Duration of Follow-up (months)	Status
1	PP	SSD		A, D	6	NED
2	PP	SSD		A, D, V	12	NED
3	PP	SSD		A, D	13	NED
4	PP	SSD	PP	A, D, V	11	NED
5	PP	SSD	PP	A, D, V	14	NED
6	PP	SSD	PP	V	8	NED*
7	SSD	PP			29	NED
8	PP			V, S		E
9	PP			D, S	36	NED
10	PP			V, S	48	NED
11	PP				39	NED

* Died of unrelated causes 8 months after treatment with no evidence of disease.

PP, plasmapheresis; SSD, splenectomy, steroids, dextran-70; A, aspirin; D, dipyridamole; V, vincristine; S, steroids alone.

NED, no evidence of disease; and E, expired.

TABLE 2. *Clinical Characteristics and Diagnostic Criteria in Eleven Patients Treated for TTP*

Patient Number	Age (Years)	Sex	Race	Diagnostic* Criteria T	A	F	N	R	Clinical Presentation
1	28	F	C	+	+	−	+	+	Headache, purpura, paralysis
2	49	F	C	+	+	−	+	+	Headache, abdominal pain and distension, purpura, abdominal paresthesia, aphasia
3	55	F	B	+	+	+	+	+	Anorexia, hemiparesis, paresthesia, purpura, aphasia, paresthesia
4	51	M	B	+	+	+	+	+	Vertigo, emesis, GI bleed, coma, hemiparesis, seizure
5	62	F	B	+	+	+	+	−	Lethargy, abdominal pain, hemianopsia, hemiparesis
6	59	F	B	+	+	+	+	+	Hematemesis, stupor
7	51	F	C	+	+	−	+	+	Headache, paresthesia
8	55	F	O	+	+	+	+	−	Coma, purpura
9	55	M	C	+	+	+	+	+	Fatigue, abdominal pain, hematuria, purpura, aphasia, paresthesia
10	31	F	B	+	+	+	+	+	Lethargy, purpura, aphasia
11	31	M	C	+	+	−	+	+	Headache, lethargy, vomiting, abdominal pain, icterus

* Diagnostic criteria: T = thrombocytopenia (platelet count < 50 × 10^3/mm^3); A = anemia (hematocrit < 30%); F = fever (T > 38 C); N = neurologic deficit; and R = renal impairment (new elevation in serum creatinine > 2.0 mg/dl, proteinuria or microscopic hematuria).

TABLE 3. *Clinical and Laboratory Response to Plasmapheresis in Patients Requiring Splenectomy*

Patient Number	Platelet Count (× 10^3/mm^3)			Reticulocytes (% RBCS)		LDH (IU/DL)		Neurol. Status*	No. PP Treatments	
	Pre-PP	Max.	Pre-OP	Pre-PP	Pre-OP	Pre-PP	Pre-OP		Pre-OP	Post-OP
1	39	110	30	6.1	4.8	305	211	S	5	0
2	6	80	12	13	6	1400	500	S	7	0
3	30	300	80	9	2	408	284	PR	15	0
4	4	92	19	2	4	1500	154	CR	7	14
5	19	240	12	10	1	1205	338	PR	7	7
6	10	192	32	5	5	2500	133	CR	6	6

* After initial PP.
S, stable; CR, complete response; and PR, partial response.
PP, plasmapheresis.

patients required no postoperative transfusions. Major hemorrhage due to ruptured ovarian cysts accounted for the large number of transfusions administered to patient no. 2; she required emergency oophorectomy 5 days after the splenectomy. Patients who responded promptly to plasmapheresis (patients 8–11) had much lower transfusion requirements than those who ultimately required splenectomy.

Treatment-related morbidity included one episode of pulmonary edema after plasmapheresis, one sterile wound hematoma, and one case of postoperative pneumonia. Of the 10 patients who survived treatment, nine were disease-free at last follow-up (6–48 months; median, 13 months). One patient died an accidental death without further evidence of TTP.

Discussion

The development of more effective therapies has dramatically improved the prognosis for patients with TTP. Since the pathogenic mechanisms in TTP have not been defined, all treatments are empiric. The multimodality therapies currently employed are combinations of individual modalities with some demonstrated efficacy. The earliest treatments successfully employed were splenectomy and steroids. Employed alone, neither is very effective. However, combined treatment with splenectomy and steroids has yielded an overall complete response rate of 53%.[5] When dextran-70 was added to this combination, a response rate of 87% was reported;[6] however, this high response rate has not been reproduced by other investigators. The observation that some patients develop transient remission following blood transfusions or infusions of fresh plasma[8] led to trials of exchange transfusion and, more recently, plasmapheresis with frozen plasma replacement. Plasmapheresis is now the initial therapy of choice for TTP in many centers; response rates range from 54% to 82%.[5,7] The role of antiplatelet drugs remains unclear. Since they are most often used in combination with plasmapheresis or splenectomy, their true impact in these patients is difficult to assess.[9] Vincristine has also been reported to have activity in a small series of patients with TTP.[10]

TABLE 4. *Transfusion Requirements in 11 Patients Treated for TTP*

Patient Number	Surgical Blood Loss (ml)	Transfusions (Units)					
		Initial PP		Operative		Post-up	
		PRBC	PLT	PRBC	PLT	PRBC	PLT
1	600	6	0	1	10	0	0
2	150	2	20	0	10	11*	20
3	200	2	0	0	0	0	0
4	50	4	20	1	10	6	100
5	300	2	0	0	10	0	0
6	1100	8	40	3	0	4	20
7	250	NA	NA	1	0	0	28
8	NA	0	0	NA	NA	NA	NA
9	NA	0	0	NA	NA	NA	NA
10	NA	0	0	NA	NA	NA	NA
11	NA	5	0	NA	NA	NA	NA

NA = not applicable.
* Postoperative transfusion requirements secondary to hemorrhage from ruptured ovarian cysts.

We initially treat all patients with plasmapheresis. Those that fail this initial therapy then proceed to splenectomy, steroids and dextran-70. Further plasmapheresis, vincristine, and antiplatelet drugs are used as adjunctive therapy for patients who do not respond promptly to splenectomy. Our 91% durable remission rate with this treatment sequence is among the best reported in the literature. Although the number of complete responses we achieved with plasmapheresis alone (3/10) is somewhat lower than that found by other investigators, an additional four patients responded to plasmapheresis following splenectomy. Of the seven patients treated with splenectomy, steroids, and dextran, three responded completely while the remaining four required further plasmapheresis to achieve remission. Our 40% (3/7) immediate response rate to this regimen is much lower than the 87% rate reported by Cuttner et al.[6] Although our initial response rates to treatment with either plasmapheresis or the Cuttner reg-

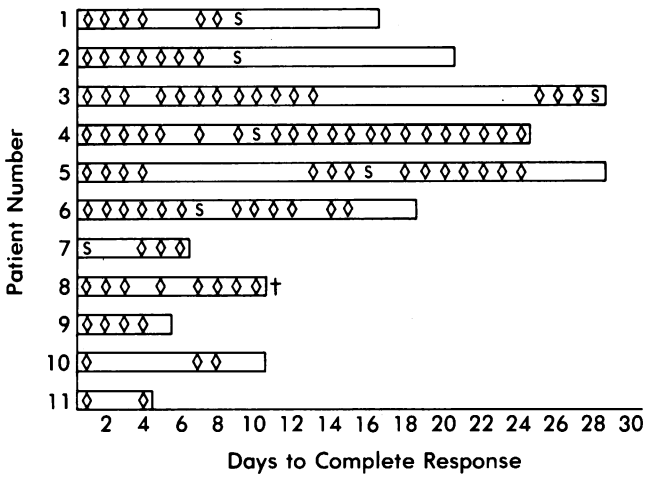

FIG. 1. Time to achievement of complete response in 11 patients with TTP. The "◇" indicates individual plasmapheresis treatments; the "S" indicates when splenectomy was performed; the "†" identifies the patient who died during treatment. Complete response was defined as a platelet count >150,000 without further treatment or transfusion.

imen are lower than in some reports, it is clear that persistent sequential use of these modalities will lead to remission in most patients (Fig. 1).

The timing of splenectomy is an issue of major importance. The single mortality in our series (patient 8) was a patient who had a dramatic response to plasmapheresis with resolution of coma and marked improvement in hematologic parameters. She then became refractory to further plasmapheresis and deteriorated rapidly. The opportunity to perform splenectomy was lost as a result of persistence with nonoperative management in the face of treatment failure. A declining platelet count during treatment with plasmapheresis uniformly indicated treatment failure in this series. Treatment failure is usually associated with rapid clinical deterioration. Once it is clear that a patient is failing plasmapheresis (*i.e.*, falling platelet count below 150 K), splenectomy should be undertaken without delay.

Although some investigators still favor initial splenectomy in treating patients with TTP,[6] these patients are frequently extremely ill at presentation and are poor surgical candidates. Significant surgical morbidity has been reported.[11-13] There are two compelling advantages to initial treatment with plasmapheresis. First, in a significant number of patients plasmapheresis alone is definitive treatment, obviating the need for splenectomy. Second, plasmapheresis will achieve initial transient response in most patients, making them better surgical candidates. It is evident that the clinical and laboratory parameters improved in most of our patients after plasmapheresis (Table 3). We believe that the low surgical morbidity in this series is attributable to preoperative preparation with plasmapheresis.

Thrombotic thrombocytopenic purpura, once a hopeless disease, is now curable in nearly all patients. Treatment should commence with high-volume plasmapheresis with frozen plasma replacement as initial therapy. Expeditious progression to splenectomy with concomitant high-dose steroids and medium molecular weight dextran should be used without delay in patients failing plasmapheresis. Some patients will require postsplenectomy plasmapheresis. Aggressive utilization of this sequential multimodality treatment regimen will lead to durable remission in most TTP patients with a low incidence of treatment-related morbidity.

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DISCUSSION

DR. EDWARD E. MASON (Iowa City, Iowa): This is an important paper for those of you who have seen these patients. There are some emergency situations in medicine, and this is certainly one of them.

At the University of Iowa there has been an understanding between the hematologist and the surgeon that when a patient with thrombotic thrombocytopenic purpura is admitted or diagnosed, the surgeon will be notified and he can follow along so that there will be as little delay as possible, if splenectomy is elected.