Thrombotic Thrombocytopenic Purpura: A Ten-Year Experience

By Janet Cuttner

Splenectomy, corticosteroids, and antiplatelet agents have improved survival in thrombotic thrombocytopenic purpura (TTP). In 1974 we reported the successful treatment in 5 of 6 patients using splenectomy, corticosteroids, and average molecular weight dextran. This report describes a 10-yr experience with TTP at Mount Sinai Hospital (MSH). Twenty patients with TTP were seen. Possible inciting factors included pregnancy, oral contraceptives, and surgery. Splenectomy was performed in 18 patients and typical findings of TTP were found in 14 (78%). Fifteen patients were treated with splenectomy, corticosteroids, and average molecular weight dextran. Two of the 15 patients received, in addition, ASA and dipyridamole and a third received only dipyridamole. Thirteen of the 15 (87%) have survived and remain disease-free.

IN 1974 we reported six patients with thrombotic thrombocytopenic purpura (TTP) treated with splenectomy, corticosteroids, and average molecular weight dextran.[1] Five of the six survived this highly fatal disease. All patients had the classical pentad of findings originally described by Moschowitz, namely, a hemolytic anemia, thrombocytopenia, fever, renal disease, and fluctuating neurologic findings.[2] Subsequently, seven more patients were treated in a like manner with equally good results. The first patient we reported was admitted to Mount Sinai Hospital (MSH) in 1969. We analyzed all patients admitted to MSH with the diagnosis of TTP for the 10-yr period 1969 through 1979. There were 18 patients admitted to MSH during this 10-yr period and follow-up data were obtained on all but 2 of the patients. Two patients have been included who were part of our original report and on whom we have all the data, including follow-up, but were not treated at MSH.

MATERIALS AND METHODS

The charts of all patients admitted to MSH with the diagnosis of thrombotic thrombocytopenic purpura during the years 1969 through 1979 were reviewed. No patients were excluded. Thirteen of the patients have been seen by the author. The initial blood counts, urinalyses, blood clotting studies, and presenting neurologic findings were examined. In addition, possible etiologic factors such as drugs were looked for. Eighteen patients have undergone splenectomy. In 3 cases where questionable findings of TTP were reported, the sections were reviewed by an attending pathologist who confirmed the diagnosis by histopathology and by demonstrating fibrin deposition in small vessels. Thirteen patients responded and were discharged. Eleven of the 13 were contacted about their current medical status. Two survivors are lost to follow-up.

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RESULTS

From 1969 to 1979, 18 patients were admitted to Mount Sinai Hospital with TTP. We report two additional patients; one seen in consultation by the author and the other in whom extensive telephone consultation was held. Both of these patients were part of our original report.[1]

Table 1 shows the initial laboratory findings at diagnosis. Eighteen of 20 (90%) patients were anemic (hemoglobin less than 10 g/dl). Eighteen of 20 (90%) patients had an initial platelet count less than 50,000/μl. Nineteen of 20 patients (95%) had red cell fragmentation. The single "exception" was a patient in whom this finding was not reported and the peripheral smear could not be obtained for review. Seventeen patients had elevated reticulocyte counts. Two patients with low reticulocyte counts (2%–3%) had elevated counts on subsequent days, and one patient (no. 9) was reported as having elevated reticulocytes but an exact number wasn't reported. All 3 of these patients had a negative Coomb's test and negative Lupus Erythematosis (LE) preps.

Table 2 shows the neurologic findings at diagnosis. The most common neurologic finding was an organic mental syndrome found in half of the patients. Paresis was also a common presentation, occurring in 45% of patients. Thirty percent of patients had headache and/or aphasia. Table 3 shows the initial coagulation values. Six patients had a 2–3-sec prolongation of the prothrombin time (PT). Five patients had a shortened partial thromboplastin time (PTT).

Table 4 shows the pathologic findings. Eighteen patients underwent a splenectomy. Seven patients died and 3 were autopsied. Fourteen of 19 patients (74%) showed typical findings of TTP in the spleen. Widespread organ involvement was seen in the 3 autopsied patients. Three of 3 patients had extensive intravascular thrombi in the heart. In 2 of the 3, an acute myocardial infarction was felt to be a significant contributing factor to the cause of death.

Table 5 shows possible inciting factors along with the age and sex of the patients. Fourteen patients were

Table 1. Laboratory Findings at Diagnosis

	Hemoglobin (gm/dl)	Platelets/μl	Reticulocytes (%)	Red Cell Fragmentation*	Red Cells in Urine†	Coomb's Test‡	BUN (mg/dl)	Bilirubin (mg/dl)
1.	7.2	20,000	11	+++	+	Neg	40	3.0
2.	7.2	18,000	18	+++	0	Neg	20	1.5
3.	7.2	22,000	10	+++	+	Neg	26	1.1
4.	9.5	12,000	9.5	++	+	Neg	9	2.5
5.	7.3	9,000	5	++	+	NR	15	3.1
6.	11.0	33,000	2.6	++	+	Neg	29	1.0
7.	7.2	14,000	8.3	++	+	Neg	72	1.6
8.	10.0	40,000	5.6	++	+	Neg	23	3.4
9.	9.0	30,000	NR	++	+	Neg	35	NR
10.	6.4	19,000	18.1	++	+	Neg	31	2.9
11.	6.8	18,000	6.0	++	+	Neg	19	1.5
12.	9.5	30,000	5.2	++	+	NR	37	2.9
13.	7.2	22,000	5.2	++	+	Neg	15	2.2
14.	8.8	66,000	8.5	NR	+	NR	11	1.2
15.	4.0	10,000	7.1	+	+	NR	60	3.9
16.	8.0	70,000	5.1	+	+	NR	23	2.4
17.	9.2	24,000	6.6	+++	+	Neg	27	3.3
18.	6.1	21,000	20.1	++	+	Neg	15	4.5
19.	5.5	4,000	2.3	+++	+	Neg	20	2.6
20.	8.7	13,000	8.8	++	+	Neg	21	3.8

*Red cell fragmentation: +++, marked; ++, moderate; +, mild.
†Red cells in urine: +, present; 0, absent.
‡Coomb's test: Neg, negative; NR, not reported.

female (70%) with ages ranging from 17 to 70, with a mean of 39.3 yr. Four patients were taking oral contraceptives, one patient was in her ninth month of pregnancy, and one patient became ill after a therapeutic abortion. Five patients had taken antibiotics, viz., tetracycline in 3, ampicillin in 2, and 1 patient had taken penicillin. In 2 patients, TTP occurred following a surgical procedure such as hysterectomy.

Table 6 shows the results of therapy. Three patients did not respond to their first treatment and were then treated successfully with splenectomy, corticosteroids,

Table 2. Neurologic Findings at Diagnosis

	OMS*	Paresis	Head-ache	Aphasia	Slurred Speech	Ver-tigo	Seiz-ures	Other†
1.		+	+					
2.			+	+	+			
3.	+					+		
4.	+	+			+			
5.	+	+		+				
6.		+		+				
7.	+							
8.	+			+	+			
9.	+							
10.		+	+	+				
11.			+	+				
12.	+							
13.	+	+						
14.								
15.		+						NM
16.	+	+						
17.	+	+					+	
18.			+			+	+	
19.			+			+		BV
20.			+	+				

*OMS, organic mental syndrome.
†Other: NM, numbness of mouth; BV, blurred vision.

Table 3. Initial Coagulation Values

	PT*		PTT†		Fibrinogen (mg/dl)	FDP‡
	Patient	Control	Patient	Control		
1.	16.4	14	44.5	52	275	0
2.	14	13	55	50	175	
3.	14.5	12	42	36	205	0
4.	12	12	51.2	52	300	
5.	13.8	13			460	0
6.	13	13	30		400	+
7.	14	14	40	60	275	
8.	15	14	36	37	400	
9.	—		—		—	
10.	16	13.4	47	55	200	Trace
11.	13	13	55	53	275	0
12.	14.8	12.4	31	—	380	0
13.	16	13.6	42	52	315	
14.	16	12	68	54	380	
15.	12.3	12	42.6	39.5	228	+
16.	13.2	12.4	51.2	51	410	
17.	12.6	14	53	54	200	
18.	10.2	11.2	45	48	250	0
19.	12.5	11	48	48	250	
20.	11.1	11.3	48	48	250	

*PT, Prothrombin time in seconds.
†PTT, Partial thromboplastin time in seconds.
‡FDP, Fibrin degradation products (thrombo Wellcotest).

Table 4. Pathologic Findings*

	Spleen	Heart	Adrenal	Pancreas	Liver	Kidney
1.	+					
2.	+					
3.	+					
4.	+					
5.	+	+ Acute myocardial infarction	+	+	+	+
6.	−					
7.	−†	+	+	+	+	+
8.	+					
9.						
10.	+					
11.	−					
12.	−	+ Acute myocardial infarction	+	+		
13.	+					
14.	+					
15.	+					
16.	−					
17.	+					
18.	+					
19.	+					
20.	+					

*+, Thrombi in small vessels; −, no intrvascular thrombi.
†Fibrin demonstrated in small vessels of spleen.

and average molecular weight dextran, making a total of 23 treatments. All patients received corticosteroids. Two patients received corticosteroids and heparin and died. Fifteen patients were treated with splenectomy, corticosteroids, and dextran 70. Two of these 15 patients also received dipyridamole and aspirin (ASA), and one other received dipyridamole in addition but not ASA. Thirteen of these 15 patients (87%) went into remission on this therapy. Figure 1 shows the survival duration. In nonresponding patients, the median survival was 1 wk. We were able to contact 11 of 13 survivors. All 11 remain well on no therapy. One patient (no. 13) suffered a relapse of TTP after a cholicystectomy and recovered with corticosteroids and dextran 70.

DISCUSSION

Over 400 cases of TTP have been reported since the original description by Moschowitz. The etiology is as elusive now as when originally reported. The disease can affect all ages, from children to the elderly. As pointed out by Amorosi, females are more likely to get TTP than males.[3] In our series, 70% of the patients were female. One wonders about the influence of estrogenic and progestational hormones. TTP is a known, though rare, complication of pregnancy, there being at least 22 reported cases.[4-7] In one of our cases, TTP occurred during the ninth month of pregnancy. In a second patient, the disease occurred within a few days after a therapeutic abortion. Four of our patients developed TTP while taking oral contraceptives, and we are aware of another woman who developed TTP while taking oral contraceptives.[8] Vesconi et al. reported a case of TTP that also occurred while taking oral contraceptives.[9] There are 3 reported cases of TTP occurring in members of the same family.[6,10,11] Of interest, 2 sisters developed fatal TTP during pregnancy several years apart.[6] Another report notes that 2 sisters, who lived in a two-family house, developed fatal TTP 6 mo apart.[11] Both sisters were taking oral contraceptives. Surgery appeared to be an inciting factor in one of our patients (no. 13), who developed TTP after a hysterectomy. She responded well to splenectomy, dextran, and corticosteroids. The disease recurred 4 yr later after an elective cholecystectomy and again responded to dextran and steroids. Five of our patients received antibiotics prior to development of TTP.

Eighteen patients underwent splenectomy. In 14 of 18 (78%), intravascular thrombi were seen in arterioles and capillaries. Seven patients died and 3 were autopsied. As reported by Berkowitz et al., the pancreas, adrenals, and heart were found to be very severely affected.[12] In 2 of our 3 patients, acute myocardial infarction was a contributing cause of death.

Table 5. Possible Inciting Factors

	Age	Sex	Oral Contra-ceptives	Preg-nancy	Antibio-tics*	Other Drugs	Other†
1.	35	M					
2.	17	M					
3.	52	F					
4.	29	F		+			
5.	40	F	+				
6.	68	M					
7.	70	F					
8.	56	F					
9.	32	F			Tetra		Colitis
10.	21	F	+		Flagyl		
11.	25	F	+		Flagyl	Haldol	
12.	46	M			Ampi		Choli
13.	51	F			Tetra Ampi		Hyster
14.	37	F					AHA
15.	36	F			Tetra Amph		
16.	45	M					
17.	26	F		+	Penic		
18.	18	M					
19.	24	F	+				
20.	58	F					

*Tetra, tetracycline; Ampi, ampicillin; Amph, oral amphotericin; Penic, penicillin.
†Choli, cholicystectomy; Hyster, hysterectomy; AHA, daughter died of autoimmune hemolytic anemia.

Table 6. Results of Therapy

	CS* (mg)	Splenectomy	Dextran 70	Dipyridamole	ASA	Heparin	Other†	Outcome‡
1.	H-1000	+	+					CR
2.	H-1000	+	+					CR
3.	M-300	+	+					CR
4.	H-1000	+	+					CR
5.	H-1000	+	+					NRD
6.	P-60					+		NR 1st R_x
6.	M-1000	+	+					CR
7.	D-8							NRD
8.	H-500	+						NRD
9.	H-800					+		NRD
10.	H-800	+	+	+	+	+	Hemodialysis	CR
11.	H-300	+	+					CR
12.	H-400	+						NRD
13.	H-1000	+	+					CR
14.	H-400	+	+	+	+			CR
15.	M-250					+		NR 1st R_x
15.	H-250	+	+					CR
16.	H-1000	+						NRD
17.	H-800	+	+				Hemodialysis	PRD
18.	D-12			+	+		FFP Plasmapheresis	NR 1st R_x
18.	D-16	+	+					CR
19.	H-800	+	+	+				CR
20.	H-900	+	+					CR
Total	23	18	15	4	3	4		

*CS, Corticosteroids; H, hydrocortisone; M, methylprednisolone; D, dexamethasone; P, prednisone.

†FFP, Fresh-frozen plasma.

‡CR, Complete remission; NRD, no response died; PRD, partial remission died; NR, no response; 1st R_x, 1st treatment.

TTP is a highly fatal disease. Prior to the 1960s, there was a mortality of 77%. In 1976, Reynolds et al. reviewed the cases of TTP reported from 1968 to 1975, numbering 84.[13] There was a mortality of 48%, and it is probably higher, poor results tending not to be reported.

The most effective treatment reported prior to the 1960s was splenectomy and corticosteroids.[14-16] This still remains a cornerstone of the treatment. In the last 15 yr or so, antiplatelet agents have been added to corticosteroids with and without splenectomy.[1,13,17-19] There is no doubt that adding these agents has improved survival. Dipyridamole, aspirin, and dextran are the antiplatelet agents most commonly used. In the last few years, the use of exchange transfusion and plasmaphereses has been added to other therapeutic regimens with some success.[20,21]

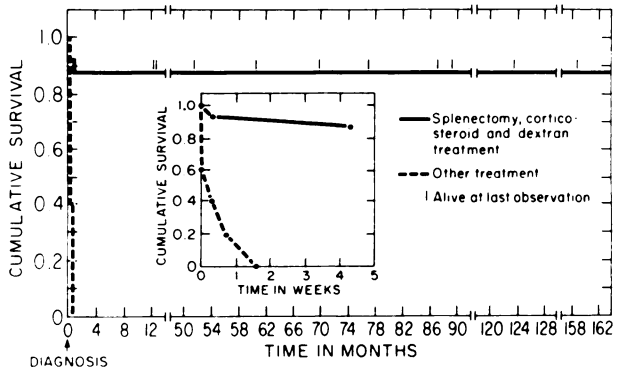

Fig. 1. Survival duration of all patients with TTP from 1969 through 1979 comparing splenectomy, corticosteroids, and dextran with other therapy. The vertical lines indicate the patient was alive at last observation.

Since this is a rare disease, no one investigator sees a large number of patients. This report of 20 patients from a single institution is one of the largest. Fifteen patients received corticosteroids, splenectomy, and average molecular weight dextran. Two patients received, in addition, dipyridamole and aspirin, and one other patient received dipyridamole. Thirteen of these 15 patients (87%) are surviving for up to 10+ yr. We have a follow-up on 11 of the 13 survivors. To the best of our knowledge, this is the best reported survival for TTP.

In our experience, splenectomy, corticosteroids in high doses, and average molecular weight dextran (dextran 70) is a highly effective treatment in TTP.

The corticosteroids should initially be given as hydrocortisone 800–1000 mg/day for 1 wk and then decreased slowly over the next week. After 2 wk, patients should be placed on prednisone 60 mg/day, which should be reduced by 5 mg every 2 wk. The dextran should be given over 30 min every 12 hr for 14 days. If the patient does not respond, then other antiplatelet agents, especially dipyridamole, should be added. If there is no response, then plasmapheresis should be performed.

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