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Thrombotic Thrombocytopenic Purpura: Combined Treatment with Plasmapheresis and Antiplatelet Agents

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Seven of eight patients with thrombotic thrombocytopenic purpura who were treated with both exchange plasmapheresis and antiplatelet agents (aspirin and dipyridamole) achieved complete remission. The eighth patient appeared to fail on this regimen but responded to corticosteroids and splenectomy. A ninth patient attained full remission after therapy with only aspirin and dipyridamole. The antiplatelet agents appeared to play an important role in the response of four patients. Eight patients received maintenance aspirin and dipyridamole. This maintenance therapy may have prevented relapses of thrombotic thrombocytopenic purpura in some patients as evidence of active, subclinical disease persisted for many weeks in most patients. Treatment with maintenance antiplatelet agents was discontinued in five patients after 7 to 18 months and no patient has relapsed. An effective therapeutic regimen for thrombotic thrombocytopenic purpura would include initial therapy with exchange plasmapheresis, aspirin, and dipyridamole and maintenance therapy with antiplatelet agents.

THROMBOTIC THROMBOCYTOPENIC purpura is characterized by thrombocytopenic purpura, microangiopathic hemolytic anemia, fluctuating neurologic abnormalities, renal disease, and fever (1). The diagnosis can be confirmed pathologically by the demonstration of subendothelial and intraluminal deposits of "hyaline" material in arterioles and capillaries (1, 2). Electron microscopic studies have shown the occluding "hyaline" material to be composed of platelet aggregates and small amounts of intermixed fibrin (3-5). Kinetic studies of thrombotic thrombocytopenic purpura have shown a decreased platelet survival, presumably due to platelet consumption in the occluding platelet thrombi, and a normal fibrinogen turnover (6). Coagulation studies usually fail to show evidence of disseminated intravascular coagulation (2-4). Based on these pathologic, kinetic, and hemostatic studies, abnormal platelet aggregation, either as a primary event or secondary to vascular injury, appears to play a central role in the pathogenesis of thrombotic thrombocytopenic purpura.

When untreated, the syndrome almost invariably follows a rapidly progressive and fatal course, with an 80% mortality rate within 3 months of diagnosis (1). Multiple therapeutic regimens have been used in an attempt to modify this poor prognosis but most approaches have been unsatisfactory. Only occasional remissions have been achieved with corticosteroids (1); splenectomy (1, 7); corticosteroids and splenectomy (8-10); corticosteroids and dextran (2); and corticosteroids, splenectomy, and dextran (11). Moreover, although the number of failures with these regimens is unknown, it probably has been very high (1, 12, 13).

Recent reports have described encouraging responses to whole blood exchange transfusion (12, 14), exchange plasmapheresis (13, 15, 16), and plasma transfusion (17, 18). The remissions attained with these treatment modalities suggest that replacement of a deficient plasma factor most likely reverses the abnormal platelet aggregation in thrombotic thrombocytic purpura, although removal of a toxic factor or platelet aggregating factor is another possibility (12, 13, 17). Furthermore, previous reports have supported the therapeutic effectiveness of antiplatelet agents (19), although failures with these drugs also have occurred (3).

The present report describes eight patients with throm-

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Table 1. Clinical Findings in Thrombotic Thrombocytopenic Purpura

Patient	Age/Sex	Fever	Purpura	Stupor/Coma	Seizure*	Paralysis†	Aphasia
	yr						
1	62/F	+	+	+	+	+	0
2	39/F	+	+	+	+	0	0
3	27/M	+	+	+	0	+	+
4	63/F	+	+	+	+	+	+
5	20/M	+	+	0	0	+	0
6	31/M	+	+	0	0	0	0
7	68/F	+	+	0	+	+	+
8	46/M	+	+	0	0	0	+
9	56/F	+	+	+	0	0	0

* Major motor.
† Paralysis or paresis of the extremities or cranial nerves.

botic thrombocytopenic purpura treated with a combination of exchange plasmapheresis and antiplatelet agents and one patient treated with only antiplatelet agents. With this combined therapeutic approach, we attempted to improve the remission rate and prolong the duration of remission.

Materials and Methods

Nine patients with thrombotic thrombocytopenic purpura who were admitted to hospitals in the Hartford, Connecticut, area between May 1976 and April 1979 were studied. In all patients the diagnosis was based on classic clinical and laboratory findings (1). Eight patients were treated with exchange plasmapheresis and antiplatelet agents and one patient with antiplatelet agents alone. Other therapy included corticosteroids in seven patients and splenectomy in two.

Exchange plasmapheresis was performed with a Haemonetics Model 30 continuous-flow blood cell separator (Haemonetics Corporation, Natick, Massachusetts) through catheters placed in the antecubital or femoral veins. Acid citrate dextrose and citrated phosphate dextrose were used as anticoagulants. For each plasmapheresis a total of 1500 to 4400 mL was withdrawn, depending on technical factors and blood flow rates. In exchange, ABO-, Rh-matched, fresh frozen plasma was reinfused in approximately equal quantity. Occasionally, supplemental platelet, whole blood, or packed erythrocyte transfusions were given as required by the patients. In Patient 2 a larger quantity of plasma was withdrawn than was reinfused in order to improve the patient's congestive cardiac failure. In all patients the procedure required only 2 to 4 hours and was well tolerated without side effects. In our group of patients, the plasmaphereses were given on a daily or every-other-day regimen and a total of three to 10 plasmaphereses were performed over a period of 4 to 30 days.

Antiplatelet agent therapy consisted of daily acetylsalicylic acid (aspirin), 600 to 2400 mg, and dipyridamole (Persantine), 200 to 600 mg, in divided doses. These agents were started 1 to 16 days after the diagnosis of thrombotic thrombocytopenic purpura was established and usually concomitantly with the plasmapheresis. The antiplatelet agents were then continued as maintenance therapy in eight patients.

Case Reports

Tables 1 to 4 present the relevant clinical findings, admission laboratory data, pathology, treatment, and time for resolution of clinical and laboratory abnormalities in the nine patients with thrombotic thrombocytopenic purpura. The diagnosis was based on the classic findings of thrombocytopenic purpura, microangiopathic hemolytic anemia, renal disease, and fever in all nine and neurologic abnormalities in eight patients (1). A remission was defined as an initial resolution of the thrombocytopenia, neurologic abnormalities, and fever and a later disappearance of the microangiopathic hemolytic anemia and renal abnormalities.

PATIENT 1

A woman was admitted to a neighboring hospital on 11 April 1978 with a 2-week history of malaise, fever, and vomiting. On

Table 2. Admission Laboratory Data and Pathology in Thrombotic Thrombocytopenic Purpura*

Patient	Hematocrit	Platelets	Reticulocytes	MAHA	Creatinine	Urine		Biopsy
						Protein	RBC/hpf	
	%	$\times 10^3/mm^3$	%		*mg/dL*			
1	29	21	2.5	4+	1.0	2+	>25	Spleen†
2	14	10	9.4	4+	1.5	3+	20	Not done
3	30	3	6.1	3+	1.6	4+	10–20	Gum†
4	31	8	9.7	4+	0.9	0	>25	Gum†
5	34	1	4.8	4+	1.0	3+	15	Gum‡
6	29	13	13.0	3+	0.9	2+	20	Spleen‡
7	28	5	5.0	3+	1.6	3+	20–30	Not done
8	21	5	10.0	1+	1.0	0	10–20	Gum‡
9	18	60	7.2	4+	3.2	4+	25	Skin†

* MAHA = peripheral blood microangiopathic erythrocyte changes (graded 0 to 4+ based on the number of schistocytes per 100 erythrocytes: >20, 4+; >15, 3+; >10, 2+; >5, 1+; 0, 0+); RBC = red blood cells; hpf = high power field.
† Diagnostic.
‡ Nondiagnostic.

Table 3. Treatment of Thrombotic Thrombocytopenic Purpura

Patient	Plasmapheresis		Aspirin*	Dipyridamole*	Prednisone	Splenectomy	Ongoing Remission
	Number	Time Period					
		d		*mg/d*			*mos.*
1	5	10	1200	600	+	+	15
2	3	4	2400	400	+	0	18
3	4	5	1200	400	+	0	17
4	6	11	2400	400	+	0	13
5	7	13	2400	400	+	0	12
6	6	13	1200	200	+	+	10
7	10	30	1200	600	+	0	6
8	6	12	1200	400	0	0	4
9	0	0	2400	600	0	0	39

* Maximum dose received.

hospital day 7, a diagnosis of thrombotic thrombocytopenic purpura was made and prednisone treatment, 400 mg/d, was started (Figure 1). When the patient's condition did not improve, splenectomy was performed on day 12. Her condition remained unchanged and she was transferred to the University of Connecticut Health Center on day 18. On that day therapy with plasmapheresis and daily aspirin, 1200 mg, and dipyridamole, 600 mg, was commenced. A remission was achieved rapidly. The dose of prednisone was gradually reduced and this treatment was discontinued after 20 days. On hospital day 41 the patient was discharged on the above dosages of aspirin and dipyridamole. Two months later she inadvertently discontinued her dipyridamole treatment and a relapse occurred rapidly. Recommencement of the dipyridamole therapy, 200 mg/d, resulted in a further remission. After another year of therapy with the antiplatelet agents, the aspirin treatment was discontinued and the dipyridamole dose decreased to 100 mg daily. She currently is in full remission, receiving only the dipyridamole.

PATIENT 2

A woman was seen at another hospital on 28 January 1978 with fever and lethargy of a few days' duration. She had been receiving prednisone, 40 mg/d, for 6 months for lupus erythematosus. On the day of admission thrombotic thrombocytopenic purpura was diagnosed and the prednisone was increased to 500 mg/d. Clinical and laboratory evaluation showed no evidence of an exacerbation of the lupus erythematosus to explain the hematologic abnormalities. On hospital day 3 the patient received an infusion of 5 units of fresh frozen plasma. No response occurred, and 2 days later she was transferred to the University of Connecticut because of a further deterioration in her clinical status. On that day treatment was initiated with plasmapheresis; aspirin, 2400 mg/d; and dipyridamole, 400 mg/d. A full remission ensued. After 3 weeks the aspirin dose was decreased to 600 mg/d and the prednisone dose was reduced to 50 mg/d. The patient continued to receive the antiplatelet regimen for 12 months. Since cessation of this therapy she remains well. The prednisone dose has been decreased to 10 mg daily, and the lupus erythematosus remains inactive.

PATIENT 3

A man was admitted to New Britain General Hospital on 12 March 1978 with a week's history of a flu-like illness characterized by anorexia, fever, nausea, vomiting, and diarrhea. On that day a diagnosis of thrombotic thrombocytopenic purpura was established and prednisone treatment, 60 mg/d, was begun. On the next day treatment with dipyridamole, 100 mg/d, and aspirin, 600 mg/d, was started. When the patient failed to respond by day 5, plasmapheresis was commenced and the dose of dipyridamole was increased to 400 mg/d and the aspirin to 1200 mg/d. A full hematologic response soon followed. Five days later the dipyridamole dose was reduced to 200 mg/d. The prednisone dose was decreased and discontinued over a 2-month period. Daily therapy with aspirin, 1200 mg, and dipyridamole, 200 mg, was continued for 1 year. After discontinuation of this therapy, the patient remains in remission.

PATIENT 4

A woman was seen at a community hospital on 26 June 1978 with fever and confusion of 2 days' duration. Thrombotic thrombocytopenic purpura was diagnosed on the day of admission and the patient received transfusions of platelets, packed

Table 4. Time for Resolution of Abnormalities in Thrombotic Thrombocytopenic Purpura after Initiation of Plasmapheresis and Antiplatelet Agents*

Patient	Platelets ($\times 10^3$/mm^3)		Neurologic Findings	Anemia	Reticulocytosis	MAHA*
	>50	>150				
	←	*d*	→	←	*wks*	→
1	2	3	5	3	2	48†
2	9	17	6	17	12	10
3	4	9	7	11	40	6
4	3	13	3	3	3	10
5	4	16	‡	3	3	10
6	2	3†	None	1†	10†	24†
7	31	34	3	16	16	15
8	2	3	3	8	6	8
9	—	2	3	17	12	12

* Criteria for resolution of abnormalities: platelet count, >150,000/mm^3; neurologic findings, total disappearance; anemia, hematocrit >40% in men and >36% in women; reticulocytosis, <2%; and MAHA (peripheral blood microangiopathic erythrocyte changes), 0+.
† After splenectomy.
‡ Resolved before admission.

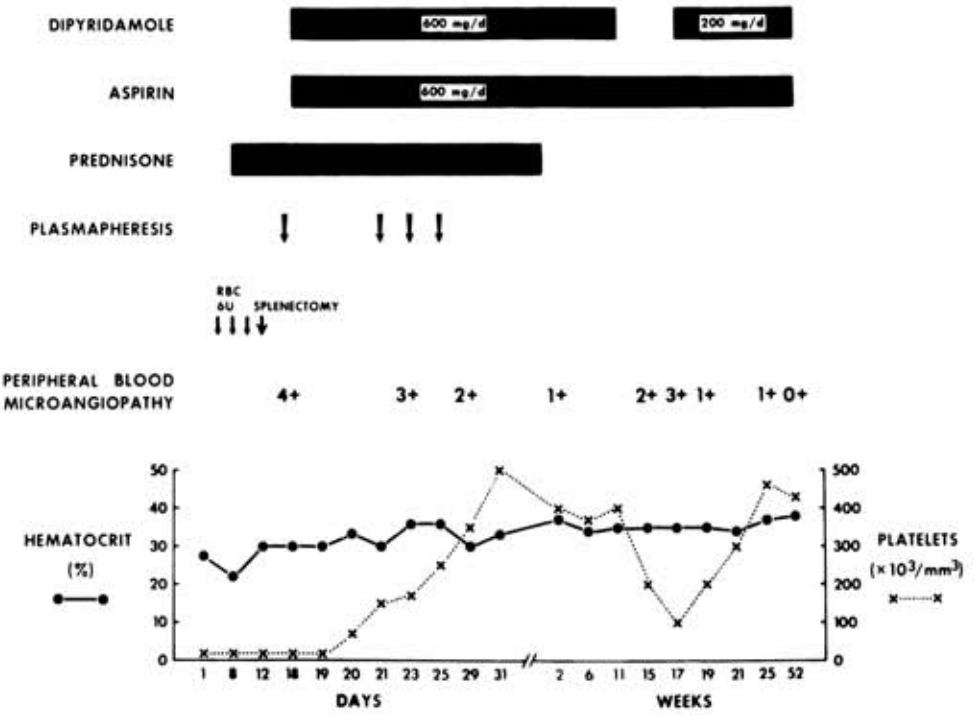

Figure 1. The hematologic course of Patient 1 during therapy with plasmapheresis and antiplatelet agents. MAHA = microangiopathic erythrocyte changes in the peripheral blood (*see* Table 2 for grading).

erythrocytes and fresh frozen plasma (8 units) over the next 2 days. When no clinical improvement occurred by day 4, she was transferred to Hartford Hospital, and therapy was started with plasmapheresis and prednisone, 60 mg/d. She received three plasmapheresis over a 5-day period. The platelet count initially rose from 8 000/mm³ to 135 000/mm³ during those 5 days. However, in spite of three further plasmapheresis, the platelet count progressively decreased to 50 000/mm³ by hospital day 11 and remained at that level for the next 3 days. On day 14 treatment with daily aspirin, 2400 mg, and dipyridamole, 400 mg, was begun and the plasmapheresis continued. A rapid remission followed, and the patient continued to receive the same regimen of aspirin and dipyridamole for 7 months. Treatment with the antiplatelet agents was stopped, and full remission continues.

PATIENT 5

A man was admitted to Hartford Hospital on 27 July 1978 with hematuria, purpura, and upper-extremity weakness for 2 days' duration. He was receiving prednisone, 40 mg/d, for ulcerative colitis, which was inactive at the time of admission. On the day of admission, a diagnosis of thrombotic thrombocytopenic purpura was made and therapy was initiated with plasmapheresis and daily aspirin, 2400 mg, dipyridamole, 200 mg, and prednisone, 80 mg. An initial rise in the platelet count from 1 000/mm³ to 110 000/mm³ occurred over 6 days but was followed by a rapid decline to 30 000/mm³ by day 9. On day 13 the dipyridamole dose was increased to 400 mg/d and a seventh plasmapheresis was performed. A full remission quickly ensued. For 10 months after the diagnosis, the patient remained on a daily regimen of aspirin, 2400 mg, and dipyridamole, 400 mg, with the prednisone dose decreased gradually to 5 mg. During the subsequent 2 months the dipyridamole dose was decreased to 100 mg daily and the aspirin and prednisone treatment was discontinued. The patient currently remains in a full remission on dipyridamole therapy only.

PATIENT 6

A man presented to Hartford Hospital on 1 September 1978 with nausea, dizziness, hematuria and petechiae, of 5 days' duration. On that day thrombotic thrombocytopenic purpura was diagnosed and treatment with daily dipyridamole, 200 mg, and prednisone, 60 mg, was started. On the next day plasmapheresis was begun. The platelet count increased from 13 000/mm³ to 97 000/mm³ in 3 days. However, it subsequently decreased to 20 000/mm³ by hospital day 7 and remained at that level. On day 18, aspirin, 1200 mg/d, was added but no additional plasmapheresis was given. When no further improvement occurred by day 25, a splenectomy was done and treatment with the antiplatelet agents was discontinued. A rapid remission resulted. The prednisone dose was rapidly reduced and discontinued. The patient is presently in good health receiving no medications.

PATIENT 7

A woman was admitted to the University of Connecticut on 20 January 1979 with the acute onset of aphasia after a week of an upper respiratory tract illness. On hospital day 4 a diagnosis of thrombotic thrombocytopenic purpura was made. Therapy was initiated with plasmapheresis; aspirin, 1200 mg/d; dipyridamole, 600 mg/d; and prednisone, 40 mg/d. A hematologic response did not occur until 30 days later. During that time the patient received 10 plasmapheresis in addition to the antiplatelet agents and prednisone. However, during these 30 days, the patient's clinical course was complicated by moderate azotemia and two episodes of bacteremia. On day 45 the patient was discharged receiving daily aspirin, 600 mg; dipyridamole, 600 mg; and prednisone, 10 mg. Three and one half months later the dipyridamole dose was reduced to 300 mg daily; and after 7 months, treatment with all antiplatelet agents was discontinued. A full hematologic remission continues.

PATIENT 8

A man was admitted to Hartford Hospital on 10 April 1979 with the acute onset of abdominal pain, aphasia, and purpura. Two years previously he had received a course of methimazole (Tapazole) for Grave's disease; but this disorder was inactive at the time of admission. On the day of admission a diagnosis of thrombotic thrombocytopenic purpura was made, and treatment was started with daily aspirin, 1200 mg, and dipyridamole, 400 mg. On the next day plasmapheresis was initiated. By hospital day 4, the platelet count was normal and the patient's neurologic abnormalities resolved. He achieved a full remission and was discharged on the above dosages of aspirin and dipyridamole, which he continues to take.

PATIENT 9

A woman was admitted to the University of Connecticut on 26 May 1976 with a week's history of nausea, vomiting, diarrhea, and abdominal cramps. A diagnosis of thrombotic throm-

bocytopenic purpura was made, and therapy with daily aspirin, 2400 mg, and dipyridamole, 600 mg, was begun. A full remission followed. Attempts to discontinue the therapy after 11 months were unsuccessful because of the patient's psychological dependence. However, over the next 7 months, the doses were slowly reduced and the drug treatment eventually discontinued. The patient's disease currently remains in complete remission.

Results

Clinical and laboratory findings are shown in Tables 1 and 2. Patients 1, 3, 7 and 8 had a viral-like prodromal illness. All nine patients had fever (38 to 39.5 °C) and purpura. Eight had severe neurologic deficits, including depressed levels of consciousness, major motor seizures, paralysis or paresis of the extremities or cranial nerves, and aphasia. Anemia with a characteristic peripheral blood microangiopathic picture was present in all cases. The platelet count was below 60 000/mm^3 in all nine patients and less than 20 000/mm^3 in seven. Coagulation profiles, including a prothrombin time, activated partial thromboplastin time, thrombin time, and fibrinogen level, were normal in the nine cases. In only Patients 1 and 6 were the fibrinogen-fibrin degradation products elevated to a level of 10 and 80 μg/dL (normal, less than 10), respectively. An abnormal urine sediment was present in all patients, but azotemia (serum creatinine 4.0 to 7.0 mg/dL) occurred in only three. A histologic diagnosis of thrombotic thrombocytopenic purpura was made in four patients by biopsy of the gingiva, skin, or spleen.

Viral serologic studies were done for Patients 3 and 9. Patient 3 had a 16-fold increase in complement fixation titers for herpes simplex virus during a 2-week observation period: 13 March, negative; 20 March, 1/8; and 27 March, 1/32. The titers for eleven other respiratory, encephalitic, and exanthematous viruses showed no sequential changes. Serologic studies for Patient 9 showed no increase in any viral titers. No specialized immunologic studies were performed on any patients.

With the therapeutic regimens shown in Table 3, a full hematologic remission of the thrombotic thrombocytopenic purpura was achieved in all patients. A remission was determined by a resolution of the fever, neurological findings and renal abnormalities and by a return to normal of the platelet count, hematocrit, and peripheral blood microangiopathic erythrocyte changes. Although the treatment was not uniform, seven of eight patients appeared to respond to the combination of plasmapheresis and antiplatelet agents, one (Patient 9) to antiplatelet agents alone, and one (Patient 6) to corticosteroids and splenectomy. Seven patients treated with plasmapheresis and antiplatelet agents also received corticosteroids whereas the eighth (Patient 8) did not. However, Patients 2 and 5 developed thrombotic thrombocytopenic purpura while receiving prednisone, 40 mg/d, for other disorders. Moreover, Patients 2, 4, and 6 appeared refractory to corticosteroid therapy and Patient 1 was refractory to corticosteroids and splenectomy. In addition, Patients 2 and 4 failed to respond to short trials of fresh frozen plasma infusion whereas a subsequent course of therapy with plasmapheresis and antiplatelet agents was effective.

The antiplatelet agents appeared to play an important role in the therapeutic response of four patients (Patients 1, 4, 5 and 9). A full remission of the thrombotic thrombocytopenic purpura was achieved with antiplatelet therapy alone in Patient 9. A complete response was attained in Patient 4 only after antiplatelet agents were added to the plasmapheresis. In addition, as shown in Figure 1, Patient 1 relapsed when dipyridamole treatment was discontinued after 3 months of an apparent remission. However, reinstitution of the dipyridamole reestablished a persistent remission. Also, a remission was achieved in Patient 5 only after his daily dipyridamole dosage was increased from 200 to 400 mg, suggesting that a minimum adequate dosage of dipyridamole was required for an initial response of thrombotic thrombocytopenic purpura in this patient. Finally, although Patient 6 appeared to respond to corticosteroids and splenectomy, his "refractoriness" to plasmapheresis and antiplatelet agents may have been due to a failure to receive both aspirin and dipyridamole combined with plasmapheresis or to an adequate dose of dipyridamole (200 mg/d). In fact, he did show an initial, but unsustained, response to plasmapheresis.

Table 4 summarizes the timing of clinical and laboratory improvement after the initiation of treatment with plasmapheresis and antiplatelet agents. The platelet count increased to above 50 000/mm^3 within 2 to 7 days in seven of eight patients. In Patient 7 the rise was delayed for 31 days. In all patients a normal platelet count was attained within 2 to 34 days. The rise in platelet count was slowest in the two patients (Patients 2 and 7) with moderate azotemia (serum creatinine, 6.8 and 7.0 mg/dL), which may have depressed bone marrow activity. A total resolution of neurologic abnormalities in our patients occurred within 3 to 7 days, although dramatic improvements were noted in some patients several hours after initiating the plasmapheresis. The fever disappeared in all patients within the first week of hospitalization and was apparently unrelated to treatment or to the resolution of other clinical and laboratory abnormalities. Finally, as noted in Table 4, anemia, reticulocytosis, and peripheral blood microangiopathic changes persisted for 10 to 40 weeks in most patients.

All nine patients are currently in full remission 4 to 39 months after the diagnosis of thrombotic thrombocytopenic purpura (Table 3). Maintenance antiplatelet therapy (aspirin and dipyridamole) was continued in all patients except Patient 6. Treatment with these agents was discontinued in five patients (Patients 2 to 4, 6 and 7) after 7 to 18 months of maintenance therapy and no patient has relapsed subsequently. The other three patients (Patients 1, 5, and 8) continue to receive the antiplatelet therapy, although in reduced dosages in Patients 1 and 5, after 4 to 15 months.

Discussion

In this series a complete remission was achieved in all nine patients with thrombotic thrombocytopenic purpura. This response appeared to be attained in seven of eight patients with plasmapheresis and antiplatelet agents, in one with antiplatelet agents alone, and in one with corticosteroids and splenectomy after a probable failure with plasmapheresis and antiplatelet agents.

Prior reports have established the effectiveness of exchange plasmapheresis (13, 15, 16) and whole blood exchange transfusion (12, 14) in the treatment of thrombotic thrombocytopenic purpura. The rapid clinical and laboratory response previously reported with these regimens also was observed in some patients in our series. In our series the rapid clearing of severe neurologic abnormalities and a rapid rise in the platelet count were the most dramatic responses seen. However, unlike other reports of therapy with plasmapheresis and whole blood exchange transfusion, a rise in the platelet count above 50 000/mm^3 was delayed beyond 48 hours in many of our patients. Since these patients still achieved a remission, a failure of the platelet count to increase above 50 000/mm^3 within 48 hours of therapy does not necessarily indicate a poor prognosis, as suggested previously (12). In two of our patients, azotemia may have contributed to a delayed hematologic response. Two patients demonstrated a response to plasmapheresis after failure of fresh frozen plasma infusion, similar to what was observed in a prior report (15). Possibly a longer trial of plasma infusion may have been effective. However, for patients with congestive cardiac failure or renal failure, plasmapheresis would be the preferred treatment because it allows removal of excess plasma volume, as in one of our patients, whereas plasma transfusion therapy could be dangerous in these situations.

A role for antiplatelet agents in the therapy of thrombotic thrombocytopenic purpura has been proposed (6, 19-23). However, to our knowledge, Patient 9 is only the second reported patient with thrombotic thrombocytopenic purpura to achieve a remission with only antiplatelet agents (24). In addition, in four patients in this series antiplatelet agents appeared to play a major role in initiating and maintaining a remission of the thrombotic thrombocytopenic purpura. As in prior reports dipyridamole, 400 to 600 mg/d, with aspirin appeared to be an effective antiplatelet regimen (19-21). In addition, a minimum dipyridamole dose of 400 mg/d may be necessary to initiate a remission in some cases of thrombotic thrombocytopenic purpura, as suggested by our Patient 5 and previous reports (20, 23).

Many of our patients had laboratory evidence of ongoing subclinical disease for 10 to 40 weeks. Moreover, one of our patients relapsed when dipyridamole treatment was discontinued after 3 months of remission. In addition, in a previously reported case of thrombotic thrombocytopenia purpura, a decreased platelet survival was demonstrated even after the resolution of peripheral blood microangiopathic changes (25). These findings suggest that the natural history of thrombotic thrombocytopenic purpura in some patients includes active, subclinical disease for weeks to months. In our series, maintenance antiplatelet agents during this time may have prevented clincial relapses, which occur frequently in some patients receiving no maintenance therapy (17).

The optimum duration of therapy with maintenance antiplatelet agents is speculative. However, a treatment period of 6 to 12 months appears rational in view of the chronicity of laboratory abnormalities seen in our patients. Currently, no relapses have occurred in five patients whose maintenance therapy was discontinued after 7 to 18 months. In addition, no toxicity was observed with chronic antiplatelet therapy.

Although corticosteroids were used in seven patients in association with plasmapheresis and antiplatelet agents, the effect of corticosteroids on the therapeutic outcome is difficult to evaluate. However, four patients appeared refractory to steroid therapy but responded to plasmapheresis and antiplatelet therapy, and two patients developed thrombotic thrombocytopenic purpura while receiving large doses of prednisone. Prior reports have suggested a similar unsatisfactory response to corticosteroids (1, 8, 12, 13). Moreover, the rationale for their occasional effectiveness is nuclear and their use may be associated with many side effects (1, 7, 8).

One patient in our series appeared to achieve a remission with corticosteroids and splenectomy. This patient failed to receive plasmapheresis combined with antiplatelet agents and possibly an optimal regimen of dipyridamole. These factors may have contributed to his apparent lack of response to plasmapheresis and antiplatelet therapy. However, occasional responses of thrombotic thrombocytopenic purpura to corticosteroids and splenectomy have occurred (1, 8, 10) and suggest a heterogeneity in the etiology (26).

Ideally, pathologic confirmation of the diagnosis would have been preferred in all patients in this series. However, the positive findings in only four of seven patients in whom biopsies were done is consistent with the frequency reported in other series (1, 27). Therefore, the diagnosis of thrombotic thrombocytopenic purpura is most often based on a complex of clinical and laboratory findings (1, 27, 28), and therapy is usually dictated by the clinical diagnosis even if biopsy findings are negative.

Two patients in the present series developed thrombotic thrombocytopenic purpura on the background of immunologic disorders: lupus erythematosus and Grave's disease. Thrombotic thrombocytopenic purpura has been associated previously with lupus erythematosus (29, 30) but not with Grave's disease or ulcerative colitis, to our knowledge. This association with immune diseases and the findings of increased platelet-associated IgG (28, 31) and immunoglobulin and complement in the vascular lesions (32) have provided indirect evidence that thrombotic thrombocytopenic purpura may be immunologically mediated (28-33). Moreover, reports of thrombotic thrombocytopenic purpura in conjunction with a prodromal viral illness or with viral infections such as coxsackie B (25), influenza (34) and possibly herpes simplex (Patient 3 in the present series) indirectly suggest an infection-triggered immune response underlying this disease (25, 33, 34).

Until the true underlying pathophysiologic mechanism(s) of thrombotic thrombocytopenic purpura is (are) determined, a definitive treatment approach cannot be established. However, our results suggest that a combination of plasmapheresis and antiplatelet agents may be effective therapy. We suggest a combined therapeutic regimen beginning on the day of diagnosis which includes [1]

exchange plasmapheresis every other day until the platelet count is normal and the patient's neurologic abnormalities resolve and [2] daily dipyridamole, 400 to 600 mg, and aspirin, 600 to 1200 mg. Maintenance treatment with antiplatelet agents then should be continued for 6 to 12 months.

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