Thrombotic thrombocytopenic purpura: successful treatment of two cases

J. Schwartz, M.D., A. Rosenberg, M.D., F.R.C.P.[C] and A. A. Cooperberg, M.D., F.A.C.P., *Montreal.*

Thrombotic thrombocytopenic purpura (TTP), originally described by Moschowitz[1] in 1925, is now widely recognized as a serious but uncommon disorder characterized by a rapid onset, fulminating course and fatal outcome, with the diagnosis being established at autopsy in most cases. Since the original description approximately 300 cases have been reported. In recent years a number of patients who have been treated with corticosteroids and splenectomy have survived.[2-13] The response to this combination therapy has been so striking that the prognosis may well have changed from one that was uniformly fatal to one with a more optimistic outlook. It is therefore important that all successfully treated cases be reported in order that the management and prognosis of this disorder may be properly assessed.

This report describes two patients with TTP who are presently alive and well after having been treated with large doses of corticosteroids and splenectomy. The diagnosis was confirmed by a gum biopsy, an unfamiliar but simple procedure that can easily be done at the bedside.

Case 1

E.H., a 52-year-old woman, was admitted to hospital with a two-week history of anorexia, nausea, vomiting and severe epigastric and right upper quadrant pain. Progressive jaundice and a low-grade fever were noted. One week prior to admission the patient had developed persistent throbbing headaches. On the day of admission she suddenly became dysarthric. There was a past history of duodenal ulcer for which she had received medical treatment.

On admission she was found to be very ill, showing marked confusion and restlessness. She was pale, with moderate icterus of skin and sclerae. Numerous petechiae and ecchymoses were scattered over the body and she continued to bleed from venipuncture sites. The blood pressure was 130/70, the pulse 150 and regular and the temperature 99.2°F. The cardiovascular and respiratory systems were normal. Examination of the abdomen revealed marked epigastric and right upper quadrant tenderness. Neither liver nor spleen could be felt. Examination of the cranial nerves was normal; the deep tendon reflexes were equal and the plantar reflexes were flexor. She was extremely dysarthric and showed lalation of a marked degree.

On admission the hemoglobin was 4.3 g.%, the hematocrit was 16%, the erythrocyte count was 1,800,000/mm.^{3} and there were 19.6% reticulocytes. The leukocyte count was 18,400/mm.^{3} with 1% myelocytes, 2% metamyelocytes, 4% stabs, 73% neutrophils, 16% lymphocytes and 4% monocytes. The platelet count was 34,000/mm.^{3} The peripheral blood smears showed a considerable degree of anisocytosis and polychromasia, as well as some spherocytes and many bizarrely shaped, contracted and distorted cells and cell fragments (Fig. 1). A bone marrow aspiration revealed a moderately hypercellular marrow with increased megakaryocytes and a normoblastic hyperplasia.

Her prothrombin time was 14 secs., the Lee White clotting time was 10 mins., the partial thromboplastin time 60 secs. and the fibrinogen 378 mg.%.

Her BUN was 43 mg.% and the serum creatinine 1.7 mg.%. There were many red blood cells in the urine, 4 to 15 leukocytes per HPF, occasional hyaline and granular casts and 3± proteinuria.

The direct Coombs' test was negative, as were tests for LE cells. The SLDH was 4050 units. The total bilirubin was 1.8 mg.% with 1.6 mg.% being unconjugated. An electrocardiogram revealed a sinus tachycardia at a rate of 150 per min. The skull films, skull echogram and a chest x-ray were all normal.

On the basis of the clinical and laboratory findings a diagnosis of thrombotic thrombocytopenic purpura was made. The patient's course is illustrated in Fig. 4. She received four units of blood during the first 48 hours in hospital which raised her hemoglobin to 12 g.%. Prednisone, 500 mg. daily, was started and 48 hours later there was marked improvement in her mental state. She was now fully aware of her surroundings and able to converse normally, although she occasionally had some difficulty in finding words. A splenectomy was performed on the sixth hospital day. Postoperatively she made rapid improvement and she was discharged from the hospital one month after admission on a daily dose of prednisone of 7.5 mg. This was gradually reduced over the next two weeks when it was discontinued. A gum biopsy performed while she was in hospital revealed typical lesions of thrombotic thrombocytopenic purpura (Fig. 3A). At the time of her discharge all abnormal cells had disappeared from the peripheral blood, and three years after operation there is no clinical evidence of her original disease.

Case 2

C.B., an 18-year-old girl, was admitted to hospital with a two-week history of fever and bruising easily. Ten days before admission she had developed a right-sided frontal headache associated with a visual defect of the right eye, followed six days

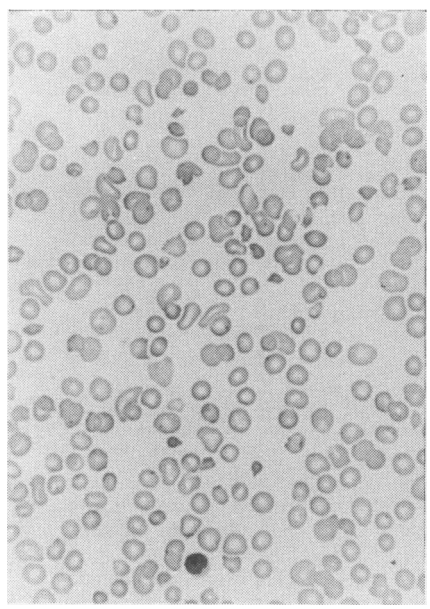

FIG. 1—Peripheral blood smear showing numerous fragmented red cells. Note absence of platelets. Wright-Giemsa stain x 500.

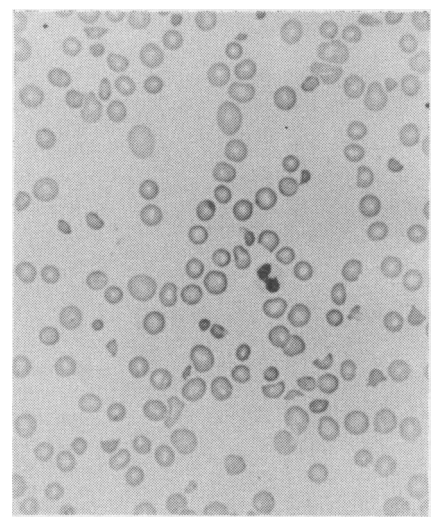

FIG. 2—Photomicrograph of peripheral blood smear showing bizarre-shaped, contracted cells and cell fragments. Wright-Giemsa stain x 500.

From the Division of Haematology, Department of Medicine, Jewish General Hospital, Montreal, Canada.
Reprint requests to: Dr. J. Schwartz, Jewish General Hospital, Department of Medicine, Division of Haematology, 3755 Côte St. Catherine Rd., Montreal 249, P.Q.

later by an episode of severe retrosternal chest pain. In addition there was some difficulty in organizing sentences and she had experienced a 15-minute episode of numbness of the right arm and hand and of the right side of the face and tongue.

On admission she was found to be very pale and slightly jaundiced. Her blood pressure was 120/60, her temperature 98°F. and her pulse 84 and regular. Several petechiae were noted on the soft palate and many scattered petechiae and a few purpuric spots on the arms and legs. Cardiovascular and respiratory systems were normal. On abdominal examination no organomegaly was found. Neurological examination disclosed no abnormality.

The hemoglobin on admission was 6 g.% and there were 31% reticulocytes. The leukocyte count was 10,000/mm.[3] with 2% myelocytes, 3% metamyelocytes, 5% stabs, 51% neutrophils, 31% lymphocytes and 8% monocytes. The platelet count was 20,000/mm.[3] Peripheral blood smears showed numerous bizarrely shaped, contracted cells and cell fragments, as well as marked anisocytosis and polychromasia (Fig. 2). Bone marrow aspiration revealed a marked normoblastic hyperplasia.

Her prothrombin time was 16.4 secs. Specific clotting studies revealed a factor V of 66%, factor VII 100%, factor X 90%, specific prothrombin 90%, plasma fibrinogen 73 mg.% and factor VIII 48%.

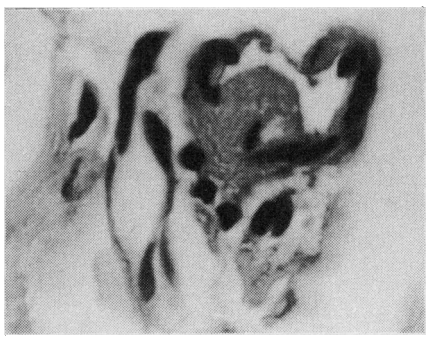

FIG. 3a—Photomicrograph of the gum biopsy from Case 1 showing "fibrinoid" material within the wall of the arteriole protruding into the lumen of the vessel. Hematoxylin-phloxine-saffron stain x 1250

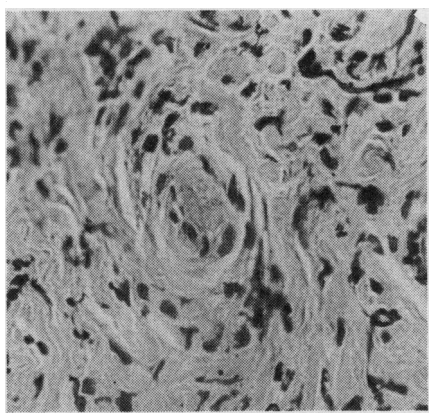

FIG. 3b—Gum biopsy from Case 2 showing fibrin and platelet thrombus. Hematoxylin-phloxine-saffron stain x 500.

The euglobulin lysis time was two hrs., 20 mins. Urinalysis showed a specific gravity of 1.014, a trace of protein, 10 to 15 red blood cells and 15 to 20 leukocytes per HPF. Her BUN was 31 mg.% and the creatinine 1 mg.%.

Direct Coombs' test was negative as were LE cell tests. The SLDH was 1640 units while the bilirubin was 5.3 mg.%, 4.7 mg.% being unconjugated.

A gum biopsy performed on the second hospital day confirmed the clinical diagnosis of thrombotic thrombocytopenic purpura (Fig. 3B). The patient had been started on prednisone 50 mg. daily on admission. This was increased to 500 mg. daily by the third day. She began to feel subjectively better although her hemolytic anemia and thrombocytopenia persisted. Her course in hospital is illustrated in Fig. 5. Because of a great deal of epigastric distress steroids were reduced. On the seventh hospital day an exchange transfusion was performed at which the patient received eight units of fresh blood. On the 11th hospital day a splenectomy was performed which was followed by a fair amount of postoperative oozing over the next 12 hours. The platelet count did not return to normal until the 11th postoperative day. The patient was discharged on the 27th hos-

pital day when she was receiving prednisone 10 mg. daily but after a few days this medication was stopped. The abnormal red cells gradually disappeared from the peripheral blood. A repeat gum biopsy two years after the original episode failed to reveal any lesions of thrombotic thrombocytopenic purpura. She is presently well and has no clinical or laboratory evidence of her disease.

Table I
Therapy in thrombotic thrombocytopenic purpura

Treatment	Number of long-term survivors	References
Steroids	3	15, 33, 34
Steroids and splenectomy	21	2-13
Steroids, splenectomy and heparin	2	19, 21
Steroids and testosterone	1	33
Steroids, testosterone and exchange transfusion	1	32
Steroids and dextran	1	30
Steroids and heparin	1	17
Steroids, heparin and magnesium	1	18
Heparin, dextran and magnesium	1	20

Discussion

In 1947, Singer, Bornstein and Wile[14] reviewed the 11 cases of TTP that had been reported since 1925, all of which were diagnosed only after postmortem examination. From their findings they established the clinical and laboratory criteria by which the diagnosis could be made during life. Typically the condition presents as an acute syndrome consisting of severe thrombocytopenic purpura, hemolytic anemia, a leukemoid reaction, fever, bizarre neurological manifestations and renal disease. More recently the changes in red blood cell morphology, similar to those seen in microangiopathic hemolytic anemia, have also been emphasized. In the majority of patients today the diagnosis can be made from the above clinical features. Many attempts have been made to confirm the diagnosis by the histological demonstration of the typical vascular lesion. However, skin and muscle biopsy, lymph node biopsy, and bone marrow sections have given variable results.[15] Because gum biopsy is a relatively simple procedure which can be performed at the bedside, it was selected for these cases. The typical lesions were evident in both specimens.

Thrombocytopenia in TTP is a constant finding, most platelet counts being below 100,000/mm.[3] Examination of bone marrow smears reveals normal or increased numbers of megakaryocytes, some with absence of platelet budding. The thrombocytopenia as well as the favourable response to heparin therapy in several patients[16-21] suggest that the clinical manifestations are due to widespread intravascular thrombosis. Whether this process really occurs remains highly debatable. There have been several reports of patients with normal fibrinogen levels or prothrombin times,[22-28] but specific studies to confirm the presence of diffuse intravascular coagulation (DIC) have been rare. Lerner, Rapaport and Meltzer[29] have reported a case of TTP in which systematic serial clotting studies were normal, and they concluded that there was no evidence to support the hypothesis of primary DIC in this disease. However, evidence for a consumptive coagulopathy was present in our second case. The thrombocytopenia and low levels of factors V, VIII and fibrinogen are all consistent with this diagnosis. (Unfortunately, fibrin split products were not determined.)

The therapy of TTP has in the past been generally unsatisfactory, as is apparent from the many and varied

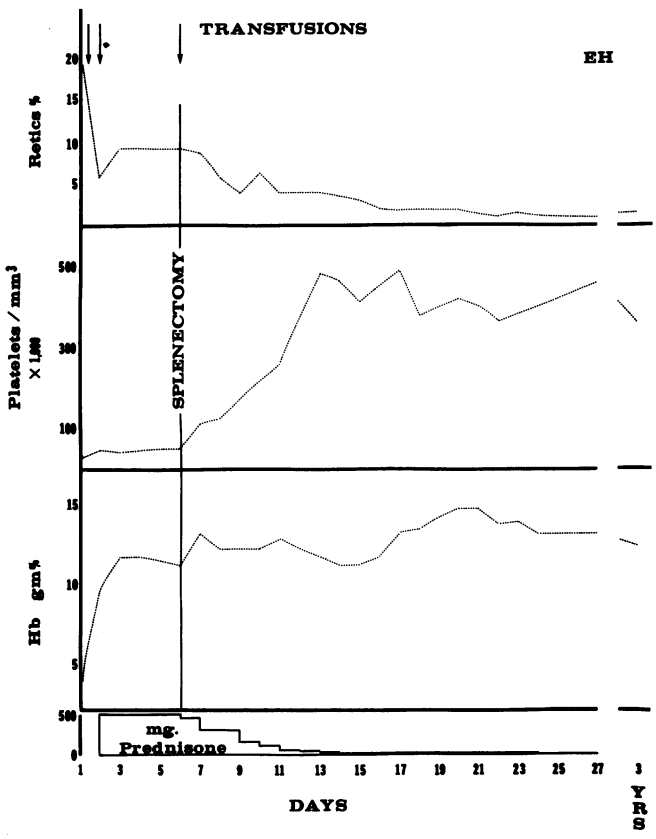

FIG. 4—Hemoglobin, reticulocytes and platelets in a patient with thrombotic thrombocytopenic purpura. Note the rapid rise in platelets after splenectomy.

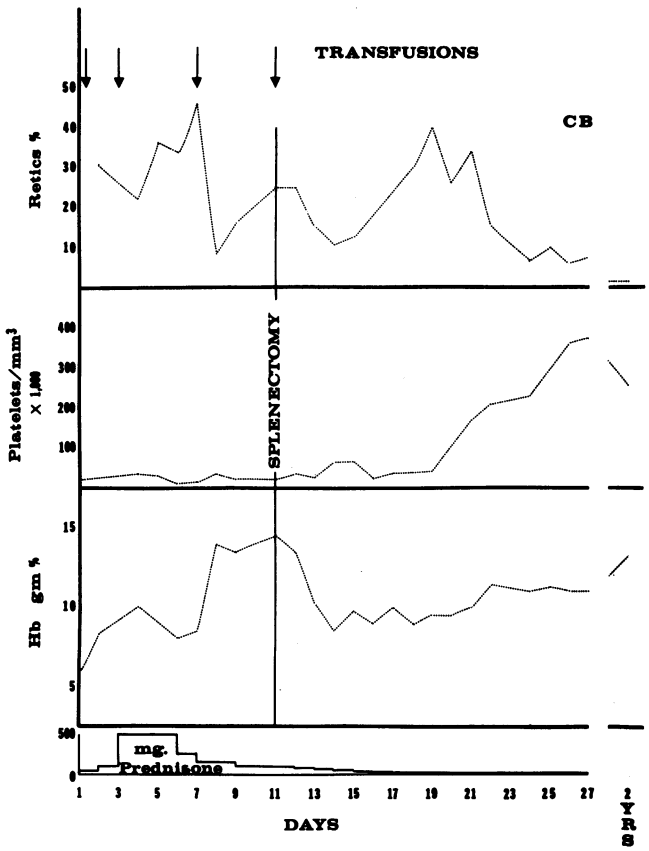

FIG. 5—Hemoglobin, reticulocytes and platelet values. There is a delay in the rise of the platelet count until the 9th postoperative day.

forms of treatment attempted. These have included exchange transfusion,[30-31] heparin,[16-21] steroids,[15, 32, 33] splenectomy,[34, 35] and the combination of the last two measures, large doses of corticosteroids being followed as soon as possible by splenectomy.[2-13] Amorosi and Ultmann,[15] in their review of 271 cases, reported only 13 patients with classical TTP who responded to therapy and were apparently alive and well. Of these, seven had been treated with a combination of corticosteroids and splenectomy.[2-6] Since that time additional cases have been reported, bringing the total number of survivors to 32 (Table I), of whom 23 have been treated by this combined therapy.[7-13, 18, 20]

In many cases large doses of steroids were given early in the course of the disease with only a slight or incomplete response until the splenectomy was performed, after which a dramatic remission occurred. In others, as in our second case, improvement was delayed. In one case[20] heparin was administered after the patient failed to respond; the subsequent improvement was attributed solely to the heparin and not to the previously administered corticosteroids and splenectomy.

Because TTP in the majority of cases runs a fulminant course with death occurring rapidly, it is imperative that therapy be instituted as soon as the clinical diagnosis has been made. It would seem that the use of large doses of steroids followed by splenectomy as rapidly as possible provides the best chance of a cure. In those instances where splenectomy does not induce a rapid and dramatic remission, heparin therapy may then be of additional value.

Despite the recently improved outlook the prognosis must remain guarded, since some patients do relapse and die after being in remission for many months.

References

1. Moschowitz E: Acute febrile pleiochromic anemia with hyaline thrombosis of terminal arterioles and capillaries. *Arch Intern Med* 36: 89, 1925
2. Shapiro HD, Doktor D, Churg J: Thrombotic thrombocytopenic purpura. Report of a case with remission after splenectomy and steroid therapy. *Ann Intern Med* 47: 582, 1957
3. Rodriguez HF, Babb DF, Pérez-Santiago E, et al: Thrombotic thrombocytopenic purpura: Remission after splenectomy. *N Engl J Med* 257: 983, 1957
4. Panayotopoulos E, Zurukzpolu E: Purpura thrombotique thrombocytopenique (étude d'un cas atypique se trouvant en régression après splénectomie). *Sang* 30: 847, 1959
5. Dorantes S, Soto R, Esparza H, et al: Thrombotic thrombocytopenic purpura: Spontaneous remission and remission concurrent with splenectomy and administration of ACTH, steroids and quinacrine. *Bol Med Hosp Infant (Mex)* 17: 199, 1966
6. Hill JM, Loeb E: Massive hormone therapy and splenectomy in acute thrombotic thrombocytopenic purpura; report of three cases with one eight year cure. *JAMA* 173: 778, 1960
7. Taub RN, Rodriguez-Erdmann F, Dameshek W: Intravascular coagulation, Shwartzmann reaction and the pathogenesis of thrombotic thrombocytopenic purpura. *Blood* 24: 775, 1964
8. Casale LA: Thrombotic thrombocytopenic purpura: Report of a case and review of 157 cases. *Hawaii Med J* 25: 93, 1956
9. Distenfeld A, Oppenheim E: The treatment of acute thrombotic thrombocytopenic purpura with corticosteroids and splenectomy. *Ann Intern Med* 65: 245, 1966
10. Moorhead JF: Thrombotic thrombocytopenic purpura recovery after splenectomy. *Arch Intern Med* 117: 284, 1966
11. Hill JB, Cooper WM: Thrombotic thrombocytopenic purpura: Treatment with corticosteroids and splenectomy. *Arch Intern Med* 122: 353, 1968
12. Bernard RP, Bauman AW, Schwartz SI: Splenectomy for thrombotic thrombocytopenic purpura. *Ann Surg* 169: 616, 1969
13. Scharoff JR, Serlin N, Atamer MA: Thrombotic thrombocytopenic purpura: Report of a case treated with splenectomy and steroids. *Acta Haematol* 41: 180, 1969
14. Singer K, Bornstein FP, Wile SA: Thrombotic thrombocytopenic purpura. Hemorrhagic diathesis with generalized platelet thromboses. *Blood* 6: 542, 1947
15. Amorosi EL, Ultmann JE: Thrombotic thrombocytopenic purpura: Report of 16 cases and a review of the literature. *Medicine* 45: 139, 1966
16. Bernstock L, Hirson C: Thrombotic thrombocytopenic purpura: Remission on treatment with heparin. *Lancet* 1: 28, 1960
17. Allanby KD, Huntsman RG, Sacker LS: Thrombotic microangiopathy. Recovery of a case after heparin and magnesium therapy. *Lancet* 1: 237, 1966
18. Rodriguez-Erdmann F, Rubin AD, Dameshek W: Heparin in thrombotic microangiopathy. *Lancet* 1: 1033, 1966
19. Carmichael DS, Medley DRK: Heparin in thrombotic microangiopathy. *Lancet* 1: 1421, 1966
20. Richardson JH, Smith BT: Thrombotic thrombocytopenic purpura. Survival in pregnancy with heparin sodium therapy *JAMA* 203: 518, 1968
21. Bernstock L, Hirson C: Heparin in thrombotic microangiopathy. *Lancet* 2: 281, 1966
22. Bornstein B, Boss JH, Gasper J, et al: Thrombotic thrombocytopenic purpura: Report of a case presenting as a chronic neurological disorder and characterized by unusual histological findings. *J Clin Pathol* 13: 124, 1960
23. Finestone AJ, Lawrence JW: Thrombotic thrombocytopenic purpura. Intestinal hemorrhage as a cardinal manifestation. *Arch Intern Med* 107: 750, 1961
24. Brown J, Taylor RF: Thrombotic thrombocytopenic purpura. *Can Med Assoc J* 89: 613, 1963
25. Kennedy A: Thrombotic thrombocytopenic purpura. *Can Med Assoc J* 91: 450, 1964
26. Antes EH: Thrombotic thrombocytopenic purpura: A review of the literature with report of a case. *Ann Intern Med* 48: 512, 1958
27. McCormack P, O'Brien DJ, Oliver RAM: Two cases of thrombohemolytic thrombocytopenic purpura associated with changes in red cell morphology. *J Clin Pathol* 16: 436, 1963
28. Green MA, Rosenthal S: Generalized blood platelet thrombosis. Report of three cases with necropsy findings. *Mt. Sinai Hosp J* 16: 110, 1949
29. Lerner RG, Rapaport SI, Meltzer J: Thrombotic thrombocytopenic purpura: Serial clotting studies, relation to the generalized Shwartzman reaction and remission after adrenal steroids and dextran therapy. *Ann Intern Med* 66: 1180, 1967
30. Wile SA, Sturgeon P: Thrombotic thrombocytopenic purpura: Review of the subject with a report of three cases in children. *Pediatrics* 17: 882, 1956
31. Rubinstein MA, Kegan BM, MacGillviray MH, et al: Unusual remission in a case of thrombotic thrombocytopenic purpura syndrome following fresh blood exchange transfusions. *Ann Intern Med* 51: 1409, 1959
32. Burke HA Jr, Hartmann RC: Thrombotic thrombocytopenic purpura: Two patients with remission associated with the use of large amounts of steroids. *Arch Intern Med* 103: 105, 1959
33. Robinson MJ, Orchard NP, Eden AR: Thrombotic microangiopathic hemolytic anemia. *Arch Dis Child* 33: 520, 1958
34. Friedberg CK, Gross L: Non-bacterial thrombotic endocarditis associated with acute thrombocytopenic purpura. *Arch Intern Med* 58: 641, 1936
35. Meacham GC, Orbison JL, Heinle RW, et al: Thrombotic thrombocytopenic purpura: A disseminated disease of arterioles. *Blood* 6: 706, 1951.