Thrombotic Thrombocytopenic Purpura (TTP) and Splenectomy:

A Current Appraisal

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Thrombotic thrombocytopenic purpura (TTP) is a disease process characterized by microangiopathic anemia, fever, neurologic manifestations, renal abnormalities, and thrombocytopenia. These clinical findings are caused by vascular occlusions of the microcirculation. At present the utilization of splenectomy, in the treatment of this illness, remains a highly controversial subject. However, review of the literature reveals that 70% of the long term survivors of TTP had undergone splenectomy. This report presents five patients with TTP, four of whom had been splenectomized. Long term survival (greater than one year) was achieved in three individuals. It is recommended that splenectomy be considered as part of the initial management of all patients with TTP, in addition to high dose corticosteroids and antiplatelet drugs.

IT HAS BEEN OVER A HALF CENTURY since Moschcowitz first described "an acute pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries,"[9] which Singer later termed thrombotic thrombocytopenic purpura (TTP).[13] The clinical manifestations of this illness are due to vascular occlusions of the microcirculation causing a pentad of findings: microangiopathic anemia, fever, neurologic manifestations, renal abnormalities and thrombocytopenia. Although once considered a relatively rare problem there are now approximately 400 case reports, and TTP has assumed the status of a well recognized disease complex.

Removal of the spleen is considered one of the major therapeutic modalities available for the treatment of this illness. Although the first successful splenectomy for TTP was reported in 1951,[8] it was not until 1957 that a sustained remission, utilizing the dual therapeutic approach of high dose corticosteroids and splenic removal, was achieved.[11] During the subsequent two decades many additional forms of therapy have been utilized including; antimetabolites, antiplatelet drugs, heparin, streptokinase, exchange transfusions, and hemo- and peritoneal dialysis.

This report will present five patients diagnosed as having TTP. Four of these individuals underwent splenectomy, one died seven days following surgery, and three are alive and well, without recurrence after one to five years of follow-up. The one patient who had no operative intervention also expired.

Case Reports†

Case 1 (G.M. #498259). A 32-year-old white woman had complained of cardiac palpitations, fatigue and headaches for a two week period. She was admitted to the university hospital for work-up and diagnosis of anemia and thrombocytopenia. On physical examination she was noted to be moderately obese, with scattered ecchymotic areas on her trunk although the remainder of the examination was unremarkable. At that time the hemoglobin was 7.6 mg/100 ml with a hematocrit of 24%. The white blood cell (WBC) count was 4,600/mm^3, and the reticulocyte measurement was 15%. The admission platelet count was 15,000/mm^3. Peripheral blood smear demonstrated anisocytosis and schistocytes. Serum electrolytes were within normal limits as were the blood urea nitrogen (BUN), serum creatinine and serum bilirubin. Urinalysis revealed three red blood cells (RBC) and 6–10 WBCs per high powered field, and a 1+ proteinuria. Bone marrow aspiration showed hyperplasia with increased numbers of megakaryocytes.

A diagnosis of TTP was made and high dose corticosteroid treatment was begun. However, the platelet count continued to drop, and emergency splenectomy was performed. Postoperatively the platelet count began to rise immediately, and at time of discharge (14 days following admission) it was 640,000/mm^3.

The patient has remained asymptomatic, and without evidence of recurrence 5 years later. Pathological examination of the spleen was consistent with the diagnosis of TTP.

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Case 2 (V.S. #514791). A 56-year-old white woman was transferred from an affiliated hospital for evaluation of a comatose state present for 48 hours. Three weeks prior to transfer she had developed severe chest pain with dizziness and bilateral upper extremity numbness. Two weeks following this episode she was admitted to a local hospital because of confusion, dysarthria, facial asymmetry, generalized weakness and parethesia of the right upper extremity. The patient showed progressive aphasia culminating in the comatose state. Laboratory findings revealed a hematocrit of 22%, and a platelet count of 3000/mm^3.

On transfer to the university hospital both heart rate and blood pressure were within normal limits, but Cheyne-Stokes respirations were evident as well as ecchymotic areas over all extremities. She was febrile (100.2), with no response to painful stimuli. The liver and spleen were not palpable.

Laboratory findings were a hemoglobin of 6.1 mg/100 ml, and a hematocrit of 18%. White blood cell count was 10,900/mm^3, with a reticulocyte count of 9.2%. The platelets numbered 3,000/mm^3. Peripheral blood smear demonstrated schistocytes. Serum electrolytes were within normal limits although the BUN was 22 mg/100 ml and serum creatinine was 1.4 mg/100 ml. Total serum bilirubin was 4.0 mg/100 ml with a direct reacting fraction of 1.7 mg/100 ml. Urinalysis revealed numerous RBCs per high powered field, granular casts and 4+ proteinuria.

Preliminary diagnosis of TTP was made in addition to central nervous system lupus erythematosus. Treatment utilizing high dose corticosteroids and heparin was begun, but there was no improvement. Peritoneal dialysis was also instituted, again without benefit. The downhill course continued in spite of treatment, and she expired one week following admission. Consent for postmortem examination was not obtained.

Case 3 (B.T. #524168). A 35-year-old white woman, previously healthy, was referred from another hospital where she had presented 24 hours earlier with complaints of disorientations, fever and headache. On admission she was agitated and dysarthric. There was a moderate tachycardia with a fever of 101°. The patient was obese with multiple petechiae on the upper extremities. The liver and spleen were not palpable.

Laboratory examinations revealed a hemoglobin of 7.5 g/100 ml, and a hematocrit of 20%. The WBC count was 21,800/mm^3, with a platelet measurement of 2,000/mm^3. Peripheral blood smear showed poikilocytosis, schistocytes and tear drop forms. The serum electrolytes and BUN and serum creatinine were within normal limits. Total serum bilirubin was 2.7 mg/100 ml, with a direct reacting fraction of 1.2 mg/100 ml. There was a 2+ proteinuria on urinalysis.

A diagnosis of TTP was made, and treatment with aspirin suppositories, dipyridamole and methyprednisolone was begun. The morning following admission the neurological evaluation had worsened, and an emergency splenectomy was performed. Postoperatively she developed a retroperitoneal hematoma requiring 32 units of whole blood transfusion. Because of continued thrombocytopenia and a rapidly deteriorating neurological status it was decided to perform hemodialysis. The patient's clinical condition never improved with the highest platelet count being 30,000/mm^3. Seven days following admission she suffered a cardiac arrest and expired. Postmortem examination was denied by the family.

Pathological examination of the spleen showed the small trabecular arteries and arterioles to have a substantial subendothelial deposit of eosinophilic material which was PAS positive. This was felt to be consistent with the diagnosis of TTP.

Case 4 (S.C. #542863). A 40-year-old white man, in previous good health, was evaluated for hematuria and easy bruisability of two weeks duration. Physical examination revealed a well developed individual with numerous ecchymoses over his trunk and extremities. The liver was palpable 4 cm below the right subcostal margin, but the spleen was nonpalpable. Remainder of the physical examination, including the neurologic status, was within normal limits.

Laboratory data showed a hemoglobin of 10.3 mg/100 ml, and a hematocrit of 32%. The WBC count was 12,500/mm^3 with a reticulocyte measurement of 30%. Platelets were 27,000/mm^3. Peripheral blood smear demonstrated aniso- and poikilocytosis with occasional schistocytes. The serum electrolytes were within normal limits, but the BUN was 21 mg/100 ml, and the serum creatinine was 1.2 mg/100 ml. Urinalysis showed 5–10 RBCs per high powered field, numerous hyaline and granular casts and a 2+ proteinuria. Bone marrow aspiration revealed reactive hyperplasia with increased megakaryocytes.

The presumed diagnosis was TTP, and treatment was begun using high dose corticosteroids. Within 48 hours of admission the patient experienced a transient aphasia and right upper extremity weakness. Because of the deteriorating neurological status an emergency splenectomy was performed. Postoperatively he did well with resolution of the neurological deficits, and an increase in the number of platelets. On the fourteenth postoperative day he became febrile, and a diagnosis of left subphrenic abscess was made. This was drained although a small pancreatic fistula soon became evident. Total parenteral nutrition was started, and once the pancreatic drainage had substantially decreased an elemental diet was begun. The patient was discharged one month following admission with complete resolution of the TTP. Two year follow-up has shown the patient to remain in good health. Pathological examination of the spleen revealed severe congestion with occasional subendothelial deposits in the arterioles felt to be consistent with TTP.

Case 5 (W.P. #553440). A 26-year-old white man was treated at an affiliated hospital for fever, generalized urticarial rash and pharyngitis. Two days following this therapy he noticed the onset of darkened urine, and petechial eruptions on the extremities. One week later he was admitted to the same hospital after having been involved in an automobile accident in which he apparently had a loss of consciousness and question of seizure-like activity. He was placed on steroids, but within six hours of admission had a grand mal seizure, and was transferred to the university hospital with a presumptive diagnosis of TTP.

Physical examination revealed a now alert and fully responsive patient. Numerous petechiae were noted on the trunk and all extremities. The spleen was palpable 1 cm below the left subcostal margin, but the liver was nonpalpable. The remainder of the examination, including neurologic status, was within normal limits.

Laboratory data revealed a hemoglobin of 8.5 mg/100 ml, and a hematocrit of 25%. The WBC count was 12,600/mm^3 with a reticulocyte count of 14%. The platelet measurement was 17,000/mm^3. Peripheral blood smear showed polychromasia and schistocytes. Serum electrolytes, including BUN and serum creatinine, were within normal limits. There was gross hematuria and associated proteinuria in the urinalysis. Sternal marrow aspirate demonstrated a hypercellular marrow with marked megakaryocyte hyperplasia.

The patient was immediately begun on high dose corticosteroids and received platelet transfusions. On the second hospital day he had another seizure, and became unresponsive. An emergency splenectomy was performed, but the patient remained comatose. Twenty-four hours following the removal of the spleen he underwent an exchange transfusion of 7 units of whole blood. By the third postoperative day he begun to show gradual improvement in comprehension and state of alertness. The platelet count rose to 320,000/

mm^3, and the hematocrit increased to 36%. He was discharged 19 days following admission, and one year follow-up has shown no recurrence of the disease.

Pathological examination of the spleen showed small blood vessels with rare areas of subendothelial (PAS +) hyalinization. The histologic spectrum was felt to be consistent with the diagnosis of TTP.

Discussion

Although initially described in 1924,[9] and termed thrombotic thrombocytopenic purpura by Singer in 1947,[13] the number of reported cases was very small up to the early 1950's. Since that time there has been a sharp increase, and over 400 cases are presently known. A true increase in the incidence of the illness cannot be epidemiologically ruled out, but the accepted rationale is greater recognition and better reporting.

The etiology of this disease remains unknown even though its clinical presentation and subsequent course are now well documented. Among the varying etiologies which have been suggested are: allergic, autoimmune, infectious, toxic and vascular. It has also been stated that TTP is a syndrome, rather than a specific disease entity, because of the variety of presenting symptoms and signs, the overlap between this entity and the microangiopathic anemias, and the variable success of a wide range of therapeutic approaches, however, this remains to be proven. It appears to have a peak incidence in the third decade of life, with females being affected slightly more often than males.

As noted, in the five patients presented, the majority of individuals have very vague, nonspecific symptoms for a period of one to three weeks prior to development of the fulminant disease complex. The most frequently observed chief complaints were fatigue, headaches, and transient neurologic deficits.

The well known pentad of clinical findings are due to thrombotic vascular occlusions in the arterioles and capillaries of the brain, kidney, and throughout the microcirculation. These are caused by the deposition of a hyaline-like (PAS +) substance associated with local intimal proliferation, but without vasculitis. The occluding material is composed of fibrin and platelets, and this originally led investigators to believe that disseminated intravascular coagulation (DIC) was an integral part of the TTP phenomenon. It, however, has now been relegated to the role of a secondary reaction.

Approximately 50% of the patients will experience all five of the cardinal manifestations of TTP: microangiopathic anemia, fever, neurologic and renal abnormalities, and/or thrombocytopenia. However, both the anemia and the thrombocytopenic reaction are considered hallmarks of the illness, and those patients not having either of these manifestations must be considered to have a questionable diagnosis. The differential diagnosis of TTP includes: aplastic anemia, drug reaction, eclampsia, idiopathic autoimmune hemolytic anemia (IAIHA), idiopathic thrombocytopenic purpura (ITP), leukemia, paroxysmal nocturnal hemoglobinuria, periateritis nodosa, sepsis, systemic lupus erythematosus (SLE), and toxin exposure.

The laboratory findings are extremely important in establishing the final diagnosis. All bone marrow aspirates, in the cases presented, demonstrated marked hypercellularity with an increase in the number of megakaryocytes. The peripheral blood smears revealed aniso- and poikilocytosis with schistocytes. Renal manifestations ranged from minimal abnormalities to gross hematuria to 4+ proteinuria (Table 1).

Most striking of the laboratory findings were the extremely low admission platelet counts noted in the two patients (#2 and #3) who expired. It is likely that a more advanced stage of the disease was seen at the time of initial examination. The admission platelet count might prove to be of prognostic value with regards to the ultimate outcome of the therapy. Of the long-term survivors, both in this report and the literature, the vast majority have had admission platelet counts above $10{,}000/mm^3$.[3]

Although the exact role of the spleen in TTP has not yet been demonstrated, the published reviews and the present series suggest splenomegaly to be present in approximately 20% of the individuals. Kardi has hypothesized that intrasplenic phagocytosis may be a major factor in the etiology of TTP, in that the platelets forming the vascular occlusions may have been damaged during their circulation through the splenic vasculature.[6] The different effects of splenectomy might be related to the varying times at which the procedure is performed, in relation to the course of the illness.

In a 1976 review of the TTP literature, over 340 cases were collected including at least 62 patients who had survived for three months or longer.[10] Since 1968 approximately 70% of the long-term survivors have received dual splenectomy and steroid therapy. A recent report concluded, ". . . 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 steroids followed by splenectomy, as rapidly as possible, provides the best chance of a cure. . ."[12] This statement is tempered by the fact that there still remains a substantial number of individuals who succumb even though they have re-

TABLE 1. *The Clinical and Laboratory Manifestations of TTP*

	Case #1	Case #2	Case #3	Case #4	Case #5
Hemoglobin g/100 ml	7.6	6.4	7.5	9.9	8.5
Platelets/mm³	15,000	3,000	2,000	27,000	17,000
Temperature (F°)	100	100[2]	101	98[6]	101
Urinalysis	3 RBCs 6–10 WBCs 1+ proteinuria	numerous RBCs granular casts 4+ proteinuria	2+ proteinuria	5–10 RBCs granular casts 2+ proteinuria	gross hematuria
Peripheral blood smear	anisocytosis schistocytes	schistocytes	poikilocytosis schistocytes	poikilocytosis anisocytosis schistocytes	polychromasia schistocyte
Neurological deficits	—	comatose confusion dysarthria weakness parathesia	agitation aphasia	aphasia weakness	grand-mal seizures comatose
Palpable spleen	no	no	no	no	yes
Therapeutic regimen	steroids splenectomy	steroids heparin dialysis	aspirin dipyridamole steroids dialysis splenectomy	steroids splenectomy	exchange transfusions steroids splenectomy
Outcome and follow-up	without recurrence (5 years)	expired	expired	without recurrence (2 years)	without recurrence (1 year)

ceived this combined therapeutic approach. In addition, it would be a natural consequence that the literature is positively biased in favor of the publication of successfully treated patients. Therefore, it would be presumptutous to draw any definitive conclusions concerning this mode of therapy. The recommended dosage schedule for the high dose corticosteroid preparations ranges from 100 to 2,000 mg of cortisone equivalents per day.[7] Specific protocols have included hydrocortisone (1,000–1,200 mg/day), prednisolone (320–1,000 mg/day) and prednisone (40–1,000 mg/day).[5]

In addition to splenectomy, steroids, and exchange transfusions[4] the other major therapeutic regimen, currently under investigation, is that of the antiplatelet drugs (*i.e.*, aspirin, Dextran 70 and dipyridamole). The most recent review of this form of therapy shows 18 long-term survivors, but in 11 of these splenectomy had been performed.[2] It should be noted that 6 of the 18 survivors were from reports in which the author stated quite specifically that any patient diagnosed with TTP should undergo splenectomy as part of the initial management of the illness.[5,7] Yet, the authors of the review suggest that removal of the spleen be performed only if the antiplatelet drug therapy is of no benefit. The recommended dosage schedule of the antiplatelet drugs is aspirin 600–1,200 mg/day, Dextran 500–1,000 ml/day, and dipyridamole 300–400 mg/day, all in equally divided doses.[2]

Clearly the data are not conclusive concerning any one specific type of therapy, but the fact remains that TTP runs a rapidly progressive and often fatal course. In view of the controversy surrounding the varied therapeutic modalities to treat TTP, and the published experience with this illness, it would seem most prudent for the initial management to consist of a combined approach. Once the diagnosis is made the patient should be immediately prepared for emergency splenectomy. Time is of the essence, and waiting for a deterioration in the neurologic status or a hoped for benefit of drug therapy may prove ultimately fatal to the patient. Concurrent with the preparation for emergency surgery treatment with high dose corticosteroids and antiplatelet drugs must be begun. The length of drug therapy will depend on the individual's clinical response.

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