Treatment of Thrombotic Thrombocytopenic Purpura With Antiplatelet Drugs

By Jacob Amir and Stephen Krauss

Thrombotic thrombocytopenic purpura (TTP) is a disease with an extremely high mortality rate. Many modalities of therapy have been tried with very limited success. Lately, antiplatelet drugs have been proposed in the treatment of TTP. We report a well-documented case of TTP that presented with severe hemolytic anemia, thrombocytopenia, neurologic manifestations, kidney involvement, and fever. The patient did not respond to splenectomy, corticosteroids, and heparin sodium, but she made a full recovery after antiplatelet drugs (aspirin and dipyridamole) were added to the therapeutic regimen. The coagulation studies showed thrombocytopenia, hypofibrinogenemia, and a positive protamine sulfate test, indicative of disseminated intravascular clotting. The spleen showed numerous arterioles occluded with subendothelial hyaline material. The platelet investigations during antiplatelet therapy revealed impaired platelet aggregation and clot retraction that became normal after discontinuance of the drugs. The patient has now been in full remission more than 12 mo.

Since Moschcowitz described thrombotic thrombocytopenic purpura (TTP) in 1925, more than three hundred patients have been reported. In the majority of cases, the disease has a rapid and fulminating course with a fatal outcome. Approximately 20 patients are known to be alive and clinically cured or in remission. The mortality rate is probably higher than indicated, as there is a tendency to report all survivors and to underreport fatal cases.

The etiology and exact pathophysiology of TTP are unknown. Disagreement still exists as to whether TTP represents a primary vascular disease or a disorder of coagulation.

Many forms of therapy have been used in TTP, including exchange transfusions, splenectomy alone or in combination with high doses of corticosteroids, hemodialysis and, lately, antiplatelet drugs.

We recently had the opportunity to study a patient with well-documented TTP who had a short-lived partial remission after treatment with splenectomy, heparin sodium, and high doses of corticosteroids. A complete remission was achieved after antiplatelet drugs were added to the therapeutic regimen. Our impression is that the antiplatelet drugs played a very important role in the management of that patient.
MATERIALS AND METHODS

Venous blood for coagulation and platelet studies was collected with a disposable needle and plastic syringe and was mixed with one-tenth volume of 3.8% sodium citrate solution in a plastic tube. For determination of platelet clot retraction, blood was mixed with sodium ethylenediaminetetraacetic acid (EDTA).

The following clotting studies were performed: bleeding time, clotting time, platelet count, prothrombin time, partial thromboplastin time, plasma fibrinogen, thrombin time, assay of antihemophilic factor (factor VIII), assay of proaccelerin (factor V), fibrinogen-fibrin split products, and serial dilution protamine sulfate test (SDPS).

Platelet clot retraction was performed by a modification of the method of McDonald. In brief, 10 ml of venous blood were mixed with 6 mg sodium EDTA. The platelets were separated by differential centrifugation at 4°C. The platelets were then resuspended in platelet-free plasma (prepared by blood centrifugation at 12,000 g for 30 min) to give platelet concentrations of 400, 200, 100, 50, 25, and 12.5 X 10^3 platelets per cu mm. An aliquot of 0.5 ml of platelet-free plasma was then added to 0.2 ml of each of these platelet-rich plasmas. Thrombin (0.05 ml, 50 U/ml, Parke Davis Co.) was added to initiate clot formation. The tubes were then placed in a 37°C water bath. After 10 min they were removed; the clots were separated by agitation, and the tubes were returned to the water bath for an additional 2 hr. Then the clots were gently transferred to a weighing boat, and the weight of each clot (with trapped plasma) was determined.

Platelet aggregation was performed by the method of Born, using an aggregometer (Chrono-Log Corp., Broomall, Pa.) attached to a recorder. Adenosine diphosphate (ADP) (Sigma Chemical, St. Louis, Mo.) diluted in isotonic Veronal-buffered saline (pH 7.4) was used as an aggregating agent. These studies were performed at room temperature.

A fresh 1% stock solution of protamine sulfate (Eli Lilly Co., Indianapolis, Ind.) was used in the SDPS test. Antiserum to human fibrinogen produced in rabbits (Hyland Co., Costa Mesa, Ca.) was used in the hemagglutination inhibition test for fibrinogen-fibrin split products. Polystyrene tubes (internal diameter 9 mm) were used in clotting assays. The contents of tubes were mixed by inversion over Parafilm (Marathon, American Can Co., Neenah, Wisc.). The spleen sections were stained with hematoxylin-eosin, acid hematoxylin, Alcian-Blue PAS, and Lillie's Allchrome stains.

CASE REPORT

R.F., a 17-yr-old black female student, was admitted to a local hospital because of weakness. Her past, social, and family histories were unremarkable. The examination revealed severe anemia and thrombocytopenia. She was treated with iron and blood transfusions. The patient did not respond to treatment; her condition deteriorated over the next 3 days, and she was referred to the University of Tennessee Memorial Research Center and Hospital.

On admission, the patient, a well-developed well-nourished pale black woman, appeared to be acutely ill. She was stuporous and incoherent. The blood pressure was 112/78 mm Hg, the pulse rate was 120 beats/min, and the temperature was 103°F. Petechiae and ecchymoses were present over the trunk and extremities. Neither lymphadenopathy nor hepatosplenomegaly was found. The patient was unable to move her right hand and leg. A Babinski sign was elicited bilaterally. Eye ground hemorrhages were present without papilledema.

The laboratory data were: hemoglobin 6.9 g/100 ml, hematocrit 21%, reticulocytes 35%, white cell count 13,600/cu mm with 41% neutrophils, 44% lymphocytes, 10% stab cells, and 5% metamyelocytes. The peripheral smear showed severe poikilocytosis, anisocytosis, schistocytes, helmet cells, and macrocytes with polychromatophilia. Basophilic stippling was striking, and Howell-Jolly bodies were frequent. Many orthochromatic normoblasts were seen. The platelet count was 7000/cu mm. The bone marrow aspiration revealed increased megakaryocytes and erythroid hyperplasia. Urinalysis showed 2+ protein and 15–25 white blood cells, 10–20 red blood cells, and 3–4 granular casts per high power field.
THROMBOTIC THROMBOCYTOPENIC PURPURA

The blood urea nitrogen (BUN) was 41 mg; plasma bilirubin was 3.8 mg with the unconjugated fraction 2.4 mg, the total plasma protein was 7.2 g with albumin 3.4 g/100 ml. The lactic dehydrogenase (LDH) was 600 mU/ml (normal value 100-200 mU/ml). The bleeding time was 15 min, the Lee-White clotting time was 9 min, the prothrombin time was 15.3 sec (control 10.8 sec), the partial thromboplastin time was 90 sec (control 65 sec), the thrombin time was 44 sec (control 30 sec), the fibrinogen was 60 mg/100 ml, the fibrinogen degradation products were 25 µg (normal less than 8 µg), the serial dilution protamine sulfate test (SDPS) was positive in all four dilutions, factor VIII was 30%, and factor V was 40%. The spinal fluid was clear, no cells were seen, the protein was 32 mg/100 ml, and the sugar was 85 mg/100 ml. The Coombs’ test and the lupus erythematosus (LE) preparation were negative. The haptoglobin was 30 mg/100 ml, and the plasma hemoglobin was 72 mg/100 ml. The chest film was normal.

On the basis of the above-mentioned clinical and laboratory manifestations, the diagnosis of TTP was made. An emergency splenectomy was performed, and the patient was started on heparin sodium (1500 U/hr given by continuous infusion) and hydrocortisone, 100 mg given intravenously every 6 hr (Fig. 1). The spleen weighed 135 g and histologically showed hyaline occlusions of the small arterioles and capillaries. These occlusions stained bright orange in the Liliie-Allochrome strain indicating the presence of fibrin. They failed to react with the Aacman-Blue reagent for acid mucopolysaccharides. On the day of splenectomy and 24 hr postoperatively, the patient appeared more alert; she could recognize her relatives and could move her right hand and leg. The platelet count rose to 100,000/cu mm. The heparin sodium maintained the Lee-White clotting time between 17 and 20 min.

On the second postoperative day, the patient suddenly became restless, disoriented, paranoid, and hallucinatory. Neurologic examination revealed paresis of the right arm. The platelets dropped to 60,000/cu mm, and the reticulocytes rose to 20%. Treatment with heparin sodium and corticosteroids was continued, and because of the continued anemia 15 U of blood were administered during the next 5 days. On the sixth postoperative day, right leg paresis was evident. At that point, aspirin (900 mg every 6 hr) was added to the therapeutic regimen. In 24 hr, a dramatic improvement was noted. The patient became lucid, and the right-sided paresis disappeared. Concomitantly with the neurologic improvement, her hematologic status began to improve with a steady rise in platelet count and hematocrit and a fall in reticulocyte count. Two days later dipyridamole was added, 100 mg every 6 hr. The heparin sodium was discontinued on the seventh postoperative day. The corticosteroids were gradually tapered off. Platelet studies performed 7 days after initiation of antiplatelet therapy showed 400,000 platelets per cu mm with impaired platelet aggregation to ADP. Platelet clot retraction was also abnormal. The antiplatelet therapy was continued for 16 days. The patient had an intraperitoneal abscess that necessitated laparotomy for drainage on the 30th postoperative day. The surgical procedure was uneventful. A muscle biopsy taken at that occasion did not show any arteriolar or capillary occlusions. Platelet aggregation and clot retraction were examined 30 days after discontinuation of the antiplatelet drugs and were found to be normal. The patient was discharged and has been followed as an outpatient for the past 12 mo and is completely asymptomatic. The blood counts and coagulation parameters are all in the normal range.

RESULTS AND DISCUSSION

Thrombotic thrombocytopenic purpura is characterized by a pentad of symptoms: fever, thrombocytopenic purpura, Coombs-negative hemolytic anemia, neurologic deficits, and renal involvement.23 Schistocytes, helmet cells, and spherocytes typical of microangiopathic hemolytic anemia and leukocytosis are also found in TTP.24 Histologically, widespread hyaline occlusions of terminal arterioles and capillaries are necessary to confirm the diagnosis. In view of our patient’s clinical presentation, her hematologic findings and the histology of the spleen, she undoubtedly had TTP.
Fig. 1. Course of illness and treatment.

Controversy still exists over the pathogenesis of TTP. In 1936, Baehr et al.\textsuperscript{25} considered it to be the result of widespread platelet thrombi. Later, it was ascribed to nonspecific endothelial injury causing platelet thrombi,\textsuperscript{26} to hypereic damage to vessel walls,\textsuperscript{27} and to subendothelial deposition of an abnormal material, with associated disruption of the elastica and microaneurysm formation.\textsuperscript{28} The frequent failure of the thrombotic material to stain with conventional fibrin stains, and their common association with overlying swollen endothelial cells, has led some authors to postulate that the primary lesion of TTP relates to abnormal vascular material, presum-
ably elaborated by injured endothelial cells. Moore and Schoenberg\(^{28}\) suggested that this substance was an acid mucopolysaccharide elaborated by damaged endothelial cells. We could not demonstrate the presence of an acid mucopolysaccharide in the spleen sections of our patient. Others have had the same experience.\(^{29}\) Recent evidence, based on immunofluorescence and electron microscopic observations, indicates that the vascular deposits in TTP are comprised of fibrin.\(^{30,31}\) The failure of these deposits to stain consistently with conventional histochemical stains may be explained by the electron microscope finding of Vassalli and McCluskey\(^{32}\) that thrombi of this type are often comprised of incompletely polymerized fibrinogen that has variable staining qualities. The positive Allochrome stain in the spleen preparation of our patient indicates that the hyaline material found was fibrin.

The coagulation studies in our patient clearly indicated the presence of disseminated intravascular clotting (DIC). The thrombocytopenia, low levels of fibrinogen, low activity of factors VIII and V, high level of fibrinogen split products, and most important the positive SDPS test all give support to this diagnosis. It is very difficult to determine whether disseminated intravascular coagulation is the primary pathologic process that is responsible for fibrin deposition in the small vessels, or whether some primary damage to the vascular wall causes platelets to aggregate to the collagen of the damaged wall, thereby triggering intravascular coagulation. The study of our patient did not contribute to the elucidation of that problem. Careful scrutiny of the literature reveals that most typical patients with TTP show little or no evidence of DIC. Deykin\(^{33}\) expressed the opinion that the few patients with the classical findings of DIC together with TTP represent a different pathogenetic entity.

More than 50% of patients with TTP who had a prolonged remission were treated with splenectomy and corticosteroids.\(^{2}\) Heparin sodium has been used in TTP with variable responses. Our patient underwent splenectomy and received corticosteroids and heparin sodium. She went into a short partial remission and relapsed. Then antiplatelet drugs were added to the therapeutic regimen. In a situation like this, it is often difficult to assess the effect of any single drug. However, the dramatic improvement in clinical and laboratory findings strikingly coincided with the addition of the antiplatelet drugs to the therapeutic regimen. We have found three recent publications\(^{8,34,35}\) that reported the use of aspirin and dipyridamole in patients with TTP. Unfortunately, none of these had histologic support to the diagnosis. In all three, the addition of antiplatelet drugs to the therapeutic regimen coincided with the onset of remissions lasting from 5 wk to 8 mo. Aspirin and dipyridamole are known to inhibit platelet aggregation and adhesiveness.\(^{36,37}\) Aspirin is especially effective in preventing platelet aggregation to collagen which could be an important factor in the event that the primary pathologic process in TTP is a damage to the vessel wall.

The benignness of the antiplatelet drugs, their apparent effectiveness, and the high mortality rate encountered in TTP are all factors that recommend these drugs in the treatment of this disease.
ACKNOWLEDGMENT

We wish to thank Dr. W. Law for referring this patient to us, Dr. T. McDonald for performing the special platelet studies, and Dr. A. Kattine for performing the pathology studies.

REFERENCES

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