Plasmapheresis in the Treatment of Thrombotic Thrombocytopenic Purpura

By R. M. Bukowski, John W. King, and James S. Hewlett

Two patients with thrombotic thrombocytopenic purpura (TTP) have recovered completely after intensive plasmapheresis. The mechanisms responsible for the improvement in these instances are most likely related to the removal of an inciting or damaging agent. The possibility that this agent may be an immune complex is discussed. Plasmapheresis appears to be useful therapy for some patients with this syndrome.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) is a clinical disorder whose primary features include a microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic symptoms, and renal abnormalities. Pathologically this disorder is characterized by the presence of intravascular hyaline thrombi. These clinical and pathologic findings, however, are not pathognomonic for TTP, and have led to speculation that this disorder may be a syndrome with diverse etiologies rather than a specific disease. The therapeutic regimens employed have included high-dose corticosteroids, splenectomy, heparin, antiplatelet agents, clinical dextrans, urokinase, and whole-blood exchange transfusions.

During the past 16 yr, we have treated 15 patients with exchange transfusions, and have noted complete and lasting remissions in 9 instances. Recently Garthwaite et al. also reported remissions in 4 patients with TTP treated with exchange transfusions. The possibility that these remissions may be related to removal of soluble toxic material has led to the use of plasmapheresis in this disorder. Two patients with TTP treated with plasmapheresis form the basis of this report.

MATERIALS AND METHODS

Case 1

A 32-yr old white male had a recent history of an acute inferior myocardial infarction, and was treated with warfarin and quinidine. Six days before admission to the Cleveland Clinic Hospital, easy bleeding was noted and warfarin was stopped. Two days later, the patient had fever, chills, and lethargy and was hospitalized. A blood count revealed a hemoglobin of 8.0 g/dl and a platelet count of 15,000/cu mm. A peripheral smear showed marked red blood cell fragmentation and multiple nucleated red blood cells, compatible with a microangiopathic type of anemia. No improvement following 10 units of whole blood, 14 units of platelets, and hydrocortisone sodium succinate at a dose of 2 g daily was noted, and the patient was transferred to the Cleveland Clinic Hospital.

On admission the patient was unconscious with decerebrate posturing, minimally responsive to deep pain, and febrile with a temperature of 102°F; no movement of his right arm or leg was noted. A gingival biopsy revealed multiple fibrin thrombi in submucosal vessels. Laboratory data...
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Fig. 1. Graphic illustration of the hematologic values in case 1, demonstrating the temporal relationship of their recovery to normal following serial plasmapheresis.

on admission revealed a hemoglobin of 10.4 g/dl, reticulocyte count of 8.3%, and platelet count of 4000/cu mm. The white blood cell count was 22,500/cu mm with 24 nucleated red blood cells per 100 white blood cells. His blood urea nitrogen (BUN) was 40 mg/dl and creatinine was 2.1 mg/dl. A urinalysis revealed many red blood cells per high-power field, and 2+ proteinuria. Fibrinogen was 440 mg/dl and a direct Coombs' test was negative. Soluble fibrinogen monomer complexes (cryoprophyrin) were absent (evidence of intravascular fibrin formation and disseminated intravascular coagulation). The partial thromboplastin time was 33 sec (control 37 sec) and prothrombin time 13 sec (control 11 sec). A latex fixation titer, cold agglutinin titer, and hepatitis-associated antigen titer were negative. An anti-DNA antibody titer was 2+, (normal range 0 -4+). Total hemolytic complement was 85 mg/dl (normal range 70 -190 mg/dl).

The patient's clinical picture was consistent with TTP; dexamethasone was started at a dose of 6 mg intramuscularly every 4 hr. and serial plasmapheresis using an Aminco cell separator (American Instrument Company, Silver Springs, Md.) was begun. Subsequently, 10 plasmaphereses were performed with 3-6 units of plasma removed at each procedure and replaced by fresh frozen plasma. The patient's hematologic values during the plasmaphereses are detailed in Fig. 1. After the initial plasmapheresis, the patient was awake and able to respond to simple commands. Following six plasmaphereses his neurologic status was normal, and the dexamethasone was stopped. The morphologic appearance of his peripheral smear was normal following nine plasmaphereses. He has remained well 7 mo after the onset of his illness, and has required no further treatment.

Case 2

A 21-yr-old white woman, in the 28th week of an uneventful pregnancy, noticed increased swelling of her lower extremities, and subsequently became confused. A spontaneous abortion occurred, and she gave birth to a stillborn nonmacerated fetus. Anemia and a peripheral blood smear showing a microangiopathic hemolytic anemia were found. She was then transferred to the Cleveland Clinic Hospital for further therapy.

On admission the patient was acutely ill, lethargic, and confused, with a temperature of 100°F. Laboratory data revealed a hemoglobin of 6.5 g/dl, reticulocyte count of 30%, and platelet count of 10,000/cu mm. The white blood cell count was 20,700/cu mm, with 16 nucleated red blood cells per 100 white blood cells. The peripheral blood smear demonstrated marked fragmentation of red blood cells. Her BUN was 49 mg/dl and creatinine was 1.7 mg/dl. A urinalysis revealed many red blood cells and 2+ proteinuria. Fibrinogen level was 290 mg/dl, cryoprophyrin was absent, partial thromboplastin time was 30 sec (control 38 sec), and prothrombin time was 12 sec (control 11 sec). A lupus erythematosus preparation was negative, antinuclear factor titer 0, and a direct Coombs' test negative. A gingival biopsy was normal.

In view of the clinical picture and lack of evidence of intravascular coagulation, it was felt the
patient had TTP rather than a complication of pregnancy, such as intravascular coagulation in the setting of a miscarriage. Two whole-blood exchange transfusions were performed by a previously reported method. Following the second exchange transfusion, her hematologic values and her neurologic status were normal. Serial hematologic values are illustrated in Fig. 2. At the time of discharge from the hospital, her hemoglobin was 12.3 g/dl, platelet count 140,000/cu mm, reticulocyte count 4%, and peripheral smear normal.

One month after the last exchange transfusion, a repeat blood count disclosed her hemoglobin to be 9.2 g/dl, platelet count 55,000/cu mm, and reticulocyte count 15.6%; fragmented red blood cells were noted on the peripheral smear. Despite the absence of clinical signs, it was believed that her peripheral blood was consistent with an early recurrence of TTP, and the patient was started on intermittent plasmapheresis. During the next 30 days, 10 plasmaphereses were performed. Following the last plasmapheresis, the patient’s hemoglobin was 10.9 g/dl, platelet count 245,000/cu mm, white blood cell count 5,000/cu mm, and reticulocytes 4.3%. The peripheral smear was again normal, with no evidence of red cell fragmentation. The patient was last seen 5 mo after her last plasmapheresis; she remained asymptomatic, and her blood count was normal.

Methods

Plasmapheresis was carried out on the Aminco continuous-flow blood cell separator through catheters placed in the antecubital veins. During each procedure, 5000 units of heparin were administered. At each plasmapheresis 2-3 liters of plasma were exchanged for fresh frozen ABO and Rh compatible plasma. The procedure was extremely simple and required approximately 2-3 hr to exchange the desired amount of plasma.

RESULTS AND DISCUSSION

Our experience with exchange transfusions in TTP indicates that approximately 60% of these patients may achieve remission with this form of treatment. The mode of action of exchange transfusions is unknown, but may be related to removal of a circulating toxic substance. It seems unlikely that the mechanism of action is related to replacement of depleted clotting factors, since the majority of patients responding to exchange transfusions have demonstrated no evidence of disseminated intravascular coagulation. Recent speculation that the pathogenesis of some cases of TTP may involve soluble immune com-
plexes\textsuperscript{9,12} and our experience with exchange transfusions has led to our use of plasmapheresis in this syndrome.

The present paper describes two patients with TTP who demonstrated apparent responses to plasmapheresis. The first patient received dexamethasone in addition to intermittent plasmapheresis. However, in view of the poor response to steroids in this disease, and the fact that one patient was getting rapidly worse after 5 days on steroids, which were then rapidly tapered, it seemed unlikely that this alone was responsible for the induced remission. The second patient was treated after an initial relapse following whole-blood transfusions, and received no corticosteroids during the period of plasmapheresis. Both patients received small amounts of heparin during the procedure; however, the dose was low, and in the absence of demonstrable disseminated intravascular coagulation in either patient, it was unlikely that this was responsible for the remissions. No antiplatelet agents were administered to either patient.

Plasmapheresis has been reported to remove circulating antibody or immune complexes in a wide variety of immunologic disorders such as Goodpasture syndrome\textsuperscript{13} and systemic lupus erythematosus.\textsuperscript{14} Whether the mode of action of exchange transfusions and plasmapheresis in patients with TTP is analogous to this is unknown, but if immune complexes do play a role in some instances, this seems a plausible explanation.

Indirect evidence that immune complexes can produce a TTP-like syndrome includes the occurrence of TTP in patients with systemic lupus erythematosus.\textsuperscript{15} Immunofluorescent studies by Mant et al.\textsuperscript{16} have demonstrated IgM and complement in the vascular lesions of TTP. Additionally, decreased levels of plasma C3 in 5 of 10 patients with either TTP or the hemolytic uremic syndrome have been reported.\textsuperscript{17} If the antigenic stimulus in TTP is self-limited, and antibody production is not sustained, repeated plasmapheresis may be able to remove effectively circulating immune complexes. No phenomena associated with immune complexes were found in our patients; however, this does not exclude their presence. The possibility that the improvement noted in these two patients was secondary to removal of circulating toxic substances other than immune complexes cannot be excluded.

The exact value of plasmapheresis compared to exchange transfusions in this syndrome is unknown. Plasmapheresis appears to be a simpler method of therapy and does not require large amounts of fresh whole blood as do exchange transfusions. Most importantly, the successful use of plasmapheresis in this syndrome has perhaps supplied further insight into the pathophysiology of TTP. Since TTP is a complex syndrome, it is possible plasmapheresis may not be effective in all instances.

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