

Thrombotic thrombocytopenic purpura in a patient with systemic lupus erythematosus¹

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A case is presented of a 38-year-old woman who had been diagnosed ten years earlier as having systemic lupus erythematosus (SLE). She presented with classical signs and symptoms of thrombotic thrombocytopenic purpura (TTP). Plasmapheresis and prednisone treatment resulted in a complete remission. Possible associations with connective tissue diseases are reviewed.

Index terms: Lupus erythematosus, systemic •
Thrombocytopenia

Cleve Clin Q 52:409-415, Fall 1985

Thrombotic thrombocytopenic purpura (TTP) is an uncommon disorder that classically presents with a pentad of clinical findings including fever, renal insufficiency, fluctuating neurological status, thrombocytopenia, and microangiopathic hemolytic anemia.¹⁻³

Since the original description by Moschowitz in 1924, over 500 cases of TTP have been documented in the literature.⁴ Despite the recognition of consistent pathologic features, the etiology and true pathophysiology of this disorder remain undefined.

We report a case of TTP developing in a

patient with systemic lupus erythematosus (SLE). The presentation, pathophysiology, and treatment of TTP are discussed.

Case report

The patient was a 38-year-old woman with a history of SLE who was referred to the Cleveland Clinic for evaluation of anemia.

Two weeks prior to admission, she had experienced fever, chills, and general malaise. She was treated with a single injection of penicillin. Symptoms resolved but recurred ten days later. At that time, she presented to another institution, where laboratory tests revealed a hemoglobin level of 5.0 mg/dl. Progressive alteration of mental status was also noted, and she was transferred to the Cleveland Clinic for further evaluation.

On admission, physical examination revealed a confused, normally developed female. The blood pressure was 140/80 without orthostatic change, pulse 90 beats per minute, respirations 18 per minute, and temperature 38.7° C (oral). Petechiae were present on the lower extremities and oral mucous membranes. The neck was supple. The lungs were clear. Heart sounds were normal. The spleen was not palpable. Joint deformity, effusion, and synovial thickening were not present. Neurologic evaluation revealed lethargy and disorientation to person, time, and situation. Focal findings were absent. Past medical history included SLE that had been diagnosed in 1974. At the time of diagnosis, the patient had had low-grade fever, patchy alopecia, malar rash, photosensitivity, and bilateral wrist pain/swelling. The sedimentation rate was 75, antinuclear factor test (ANA) 1:80, the LE test was positive, and the Coombs test was negative. Skin biopsy revealed hyperkeratosis, follicular plugging, and loss of dermal appendages. She was treated with prednisone and the symptoms resolved with the exception of intermittent joint stiffness.

Laboratory findings on admission included the following: hemoglobin 5.5 g/dl, hematocrit 18.2 mg/dl, white blood

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0009-8787/85/03/0409/07/\$2.75/0

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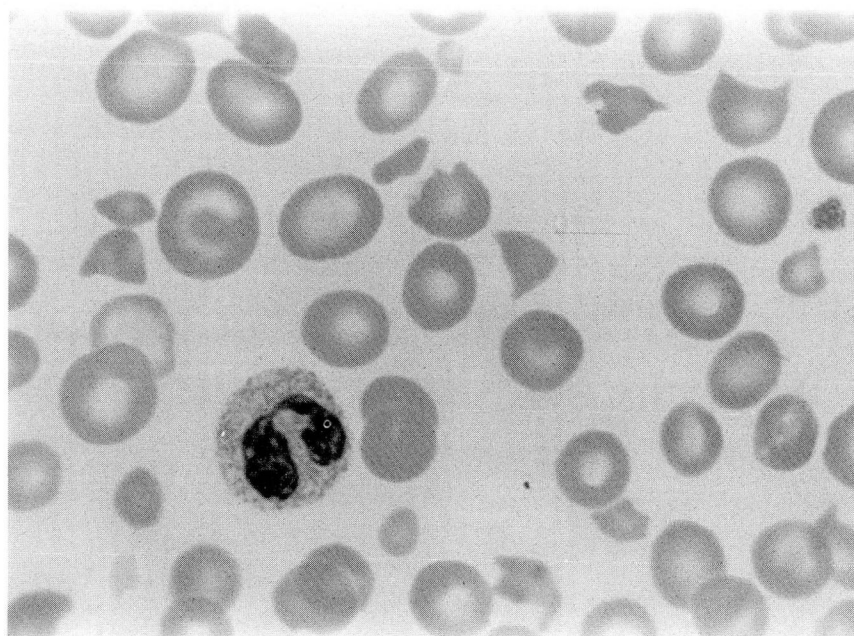


Fig. 1. Peripheral blood smear, pretreatment. (Wright stain $\times 900$)

count (WBC) $16.0 \times 10^9/l$, platelets $16.0 \times 10^9/l$, reticulocyte count 15%, total bilirubin 3.1 mg/dl, blood urea nitrogen (BUN) 24 mg/dl, creatinine 1.5 mg/dl, prothrombin time (PT) 14 seconds (control 12 seconds), activated partial thromboplastin time (PTT) 27 seconds (normal 21–31 seconds), Westergren sedimentation rate (WSR) 35, Coombs test negative, and lactate dehydrogenase (LDH) 1965 U/ml. Antinuclear antibodies were not detected. C3, C4, CH50, C1q, and cryoglobulins were within normal limits. Urinalysis revealed many red blood cells and 3–5 granular casts/HPF. Red blood cell casts were not observed. Cultures of blood, cerebrospinal fluid, sputum, and urine were negative. A chest radiograph, electrocardiogram, and CT scan of the head were normal.

The peripheral blood smear showed pronounced red blood cell fragmentation, schistocytes, spherocytes, nucleated red blood cells, and decreased platelets (Fig. 1). Bone marrow aspiration and biopsy showed marked erythroid hyperplasia, increased megakaryocytes, and normal granulocyte appearance and maturation. Microthrombi were not observed.

A diagnosis of thrombotic thrombocytopenic purpura was made, and the patient was treated with 80 mg of prednisone per day. She also underwent daily membrane plasmapheresis with exchanges of 1,200 to 2,800 ml of fresh frozen plasma. After five days of treatment, her mental status returned to normal. She became afebrile, and the platelet count rose to greater than 100×10^9 per liter. Review of the peripheral smear revealed a significant decrease in red blood cell fragmentation (Fig. 2).

The patient was discharged and treated with 40 mg of prednisone per day; this dose was slowly tapered off over a two-month period. She continued to do well six months after her initial presentation.

Discussion

Thrombotic thrombocytopenia purpura (TTP) is an uncommon disorder that may present at any time between infancy and old age. The majority of cases, however, occur within the second and third decades of life. The incidence is highest among Caucasian females.

The presenting symptoms are nonspecific and include malaise, fatigue, fever, nausea, vomiting, abdominal pain, diarrhea, anorexia, headache, mental confusion, arthralgias, myalgias, chest pain, and dark urine.⁵

Clinical manifestations involve the skin and mucous membranes, resulting in petechiae, purpura, ecchymosis, epistaxis, and, on rare occasions, hemoptysis. Other bleeding abnormalities include hematuria, melena, hematochezia, hematemesis, as well as conjunctival and retinal hemorrhage.

Neurologic findings are both transient and recurrent. Altered mental status, muscle weakness, hemiplegia, paresthesias, aphasia, seizures, vertigo, and syncope are common.

Renal manifestations are variable, ranging from microscopic hematuria to acute renal failure. Other findings include gross hematuria, proteinuria, and cylindruria. Red blood cell casts are occasionally present.

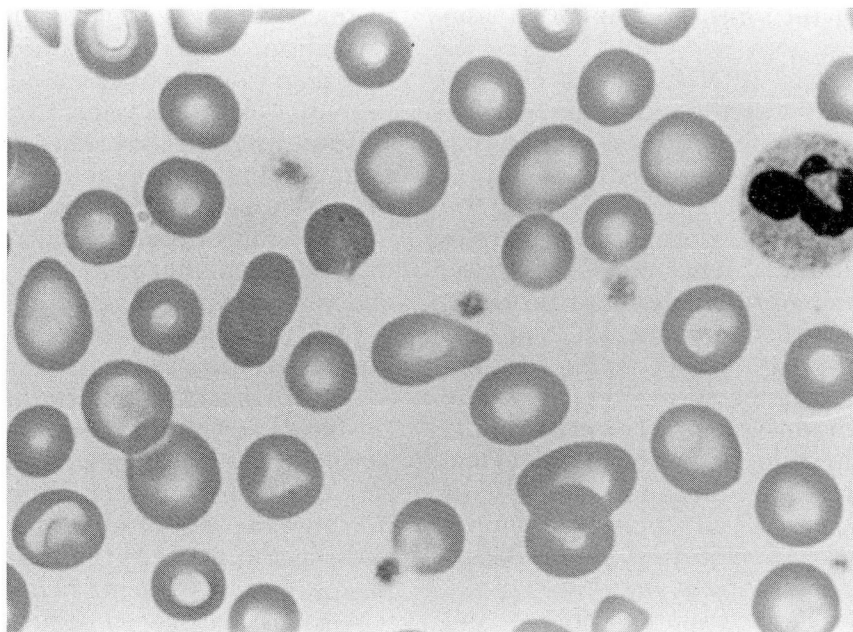


Fig. 2. Peripheral blood smear, posttreatment. (Wright stain $\times 900$)

Cardiac involvement is frequent. Myocardial infarction, congestive heart failure, nonbacterial thrombotic endocarditis, and dysrhythmias may occur.⁶ Sudden death has been reported.⁷

Numerous laboratory abnormalities have been described. Microangiopathic hemolytic anemia with pronounced red blood cell fragmentation is present in an overwhelming majority of patients. Reticulocytosis, leukocytosis, and paucity of circulating platelets are also observed. Polychromatophilia and basophilic stippling are present, and nucleated red blood cells may be numerous. Bone marrow aspirates routinely reveal hypercellularity with erythroid hyperplasia and an increased number of megakaryocytes. Leukocyte morphology is frequently shifted toward immaturity. Direct and indirect antiglobulin tests are negative. Serum bilirubin and lactate dehydrogenase (LDH) levels are elevated, reflecting the degree of hemolysis. Coagulation parameters, including prothrombin time, activated partial thromboplastin time, and thrombin time, are normal. The bleeding time is prolonged. Fibrinogen levels are normal and evidence of fibrin degradation is lacking.

Serum complement levels are normal and circulating immune complexes are rarely documented. Antinuclear antibodies are occasionally detected.

The pathologic features of TTP consist of widespread intravascular thrombi involving the capillaries and arterioles of the heart, brain, kidneys, spleen, pancreas, bone marrow, adrenals, pituitary, thymus, thyroid, and gastrointestinal tract. The liver and lung parenchyma is relatively spared. Diffuse tissue necrosis is not observed. Focal ischemic changes with and without hemorrhagic lesions are described. Originally thought to be composed of agglutinated red blood cells,⁴ the thrombi are now known to consist of platelet-fibrin aggregates with varying degrees of organization.⁸⁻¹⁰ Immunohistochemical and ultrastructural studies have revealed subendothelial and intramural fibrin deposits, which may extend to the luminal surface with subsequent platelet adhesion, aggregation, and thrombus formation.^{11,12} A wide variation and endothelial cell swelling are present. Evidence of an inflammatory process within the vessel wall is not encountered.

Pathophysiology and etiology

An endothelial cell insult within the microvascular system is the likely initial event in TTP. Physiologic as well as aberrant fibrin synthesis and deposition may ensue, thereby creating a nidus for fibrinous extension and platelet aggregation. Endothelial cell function is adversely af-

fects, particularly the synthesis and metabolism of prostaglandins.

In TTP, prostacyclin (PGI_2) synthesis and cellular release may be markedly reduced.¹³⁻¹⁷ PGI_2 stabilizing factor (PSF) and platelet aggregating factor inhibitor (PAFI) are also reduced and, in fact, may be absent.^{18,19} The end result of the structural and functional abnormalities is platelet aggregation. Given the absence of PGI_2 activity, this process remains unrestrained and proceeds *via* platelet-released thromboxane (PGA_2), beta thromboglobulin, and lipoxigenase metabolites.²⁰ In addition, platelet aggregates trigger the coagulation cascade through activation of factors 11 and 12, thereby enhancing thrombus formation.²¹ Under normal circumstances, fibrinolysis would ensue; however, a reduction in plasminogen activator prevents clot lysis from occurring.²²⁻²⁵

TTP has been reported among siblings and concomitantly in a husband and wife.^{26,27} Cases occurring in relation to various drugs and toxins including penicillin, ampicillin, neomycin, sulfonamides, procainamide, iodine, hydantoin, oral contraceptive agents, and carbon monoxide are well described.²⁸⁻³² Infectious agents are not uncommonly implicated.³³⁻³⁶ TTP following vaccination is extremely rare.³⁷ An underlying malignancy is occasionally discovered.³⁸

There has been an increase in descriptions of TTP during pregnancy and the postpartum period.³⁹⁻⁴¹ An association with autoimmune diseases, such as rheumatoid arthritis, progressive systemic sclerosis, Sjögren's syndrome, ankylosing spondylitis, polymyositis, polyarteritis nodosa, Graves' disease, idiopathic thrombocytopenic purpura, and systemic lupus erythematosus has been observed.^{42,43}

Immune system

The association between SLE and TTP has been explored. Initial reports, presented prior to the development of clinical criteria and serologic tests currently used in making the diagnosis of SLE, were based on pathologic findings.⁴⁴⁻⁴⁷ More recent reports, which have included clinical, serologic, and pathologic information, do, however, support the association between SLE and TTP.^{48,49} A large series suggests that the association is rare, however.⁵⁰

SLE is known to predispose to thrombosis.^{51,52} Reduced PGI_2 activity has been shown.⁵³ Primary vascular changes (lupus vasculopathy) may induce

platelet adhesion, aggregation, and thrombus formation. Presence of intravascular thrombus may then cause further vascular damage, thereby perpetuating the cycle.^{54,55} The association of various immune disorders with TTP suggests that the immune system may indeed play an important pathogenic role.

Platelet-associated IgG has been described and may help explain the marked thrombocytopenia and disseminated platelet aggregation found in TTP.⁵⁶ Autoantibodies to erythrocytes and leukocytes are rare.^{57,58}

As previously stated, endothelial cell injury is the most likely initiating event in TTP. The cause of such cellular damage and its mechanism of action are unknown. Immune complex deposition may be responsible in select cases.⁵⁹ However, in the majority of patients, immune complexes are not present. Endothelial cell cytotoxicity has recently been documented.⁶⁰

Treatment

Prior to the mid-1950s, the mortality rate from TTP was approximately 90%. Since that time, it has decreased to below 50%.

Whole-blood exchange transfusions were found to be of benefit by Rubenstein et al in 1959.⁶¹ Plasma infusions have proved to be effective and may provide a factor essential for the synthesis, release, and activity of PGI_2 .^{62,63} Plasma exchange (plasmapheresis) has shown an encouraging response rate. It is postulated that factors that cause platelet aggregation (PAF) are removed, while others that prevent it (PAFI) are provided.⁶⁴⁻⁶⁶

Plasmapheresis combined with antiplatelet therapy (dextran, aspirin, dipyridamole, and oral sulfapyrazone) has been successful in treating TTP, particularly in cases of chronic recurrent TTP where continuation of antiplatelet medication may prevent relapses.⁶⁷⁻⁶⁹ Antiplatelet therapy alone may achieve a complete response, however, this is rare.^{70,71}

Glucocorticoids, while commonly combined with other therapeutic modalities, are moderately effective as single agents when used in pharmacologic doses.^{72,73}

In the past, splenectomy was used early in the course of treatment for TTP. The occurrence of TTP in a patient with a previous splenectomy strengthens the current trend to perform splenectomy only if other therapies have failed.⁷⁴

Despite the theoretical potential for prostacy-

clin infusion, responses have not been encouraging.^{75,76} Vincristine has been used with success,⁷⁷ however, cyclophosphamide, nitrogen mustard, 6-mercaptopurine, and azathioprine have not been effective. Methods such as hemodialysis and streptokinase infusion are of little value in treating the primary disorder. Heparin infusion is likewise ineffective with the exception of treating TTP complicated by venous thrombosis, pulmonary embolism, or disseminated intravascular coagulation (DIC). Agents such as thromboxane synthetase inhibitors await clinical evaluation.

Summary

TTP is an unusual syndrome characterized by a pentad of clinical findings, which include fever, renal insufficiency, changing neurologic status, thrombocytopenia, and microangiopathic hemolytic anemia. Pathologic features are classic for this disorder and include diffuse platelet-fibrin thrombi within arterioles and capillaries. An association between autoimmune disorders and TTP exists, although the underlying mechanisms require further definition. Our patient was diagnosed as having SLE ten years prior to the development of TTP. At the time TTP was diagnosed, there were no clinical or serologic findings to support active lupus. Further, there was no evidence of vasculitis or circulating immune complexes. Despite these facts, it seems unlikely that the association between SLE and TTP is one of mere chance. The recognition of decreased PGI₂ activity in SLE suggests that autoantibodies directed not only against PGI₂ but PGI₂ stabilizing factor, platelet aggregating factor inhibitor, and conceivably endothelial cells as well may be present, thereby predisposing such individuals to the development of TTP. Further, the recent description of enhanced synthesis of high-molecular-weight von Willebrand factor multimers in inflammatory disorders and their role in platelet aggregation may prove to be a significant correlate.⁷⁸ Many questions remain regarding the etiology, course, and therapy in TTP.

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References

1. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura. *Medicine* 1966; **45**:139-155.
2. Brain MC, Neame PB. Thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. *Semin Thromb Hemostas* 1982; **8**:186-197.
3. Machin SJ. Thrombotic thrombocytopenic purpura. *Br J Haematol* 1984; **56**:191-197.
4. Moschcowitz E. An acute febrile pleiochromatic anemia with hyaline thrombosis of the terminal arterioles and capillaries. *Arch Intern Med* 1925; **36**:89-93.
5. Ridolfi RL, Bell WR. Thrombotic thrombocytopenic purpura. *Medicine* 1981; **60**:413-428.
6. Ridolfi RL, Hutchins GM, Bell WR. The heart and cardiac conduction system in thrombotic thrombocytopenic purpura. *Ann Intern Med* 1979; **91**:357-363.
7. Geisinger KR, Solomon AR. Sudden cardiac death in thrombotic thrombocytopenic purpura. *Arch Pathol Lab* 1979; **103**:599-600.
8. Baehr G, Klemperer P, Schiffrin A. Acute febrile anemia and thrombotic thrombocytopenic purpura with diffuse platelet thromboses of capillaries and arterioles. *Trans Assoc Am Physicians* 1936; **51**:43-58.
9. Altschule MD. A rare type of acute thrombotic thrombocytopenic purpura. *N Engl J Med* 1942; **227**:447-479.
10. Gore I. Disseminated arteriolar and capillary platelet thrombosis. *Am J Pathol* 1950; **26**:155-175.
11. Craig JM, Gitlin D. The nature of the hyaline thrombi in thrombotic thrombocytopenic purpura. *Am J Pathol* 1957; **33**:251-258.
12. Feldman JD, Mardiney MR, Unanue ER, Cutting H. The vascular pathology of thrombotic thrombocytopenic purpura. *Lab Invest* 1966; **15**:927-946.
13. Moncada S, Vane JR. Arachidonic acid metabolites and their interactions between platelets and blood-vessel walls. *N Engl J Med* 1979; **300**:1142-1147.
14. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 1976; **263**:663-665.
15. MacIntyre DE, Pearson JD, Gordon JL. Localisation and stimulation of prostacyclin production in vascular cells. *Nature* 1978; **271**:549-551.
16. Remuzzi G, Marchesi D, Misiani R, Mecca G, de Gaetano G, Donati MB. Familial deficiency of a plasma factor stimulating vascular prostacyclin activity. *Thromb Res* 1979; **16**:517-525.
17. Machin SJ, McVerry BA, Parry H, Marrow WJW. A plasma factor inhibiting prostacyclin-like activity in thrombotic thrombocytopenic purpura. *Acta Haematol* 1982; **67**:8-12.
18. Wu KK, Hall ER, Papp A. Prostacyclin stabilizing factor deficiency in thrombotic thrombocytopenic purpura. *Lancet* 1982; **1**:460-461.
19. Lian ECY, Mui PTK, Siddiqui FA, Chiu AYY, Chiu LLS. Properties and identification of a plasma factor which inhibits the platelet aggregation induced by TTP plasma. *Thromb Haemost* 1983; **50**:101.
20. Nalbandian RM, Henry RL. A proposed comprehensive pathophysiology of thrombotic thrombocytopenic purpura with implicit novel tests and therapies. *Semin Thromb Hemostas* 1980; **6**:356-390.
21. Walsh PN. Platelet coagulant activities and hemostasis. *Blood* 1974; **43**:597-605.

22. Kwaan HC. The pathogenesis of thrombotic thrombocytopenic purpura. *Semin Thromb Hemostas* 1979; **5**:184-198.
23. Kwaan HC, Suwanwela N. Inhibitors of fibrinolysis in platelets in polycythemia vera and thrombocytosis. *Br J Haematol* 1971; **21**:313-322.
24. Eckert H, Friedlander I, Hardisty RM. The role of platelets in fibrinolysis. *Br J Haematol* 1970; **18**:575-584.
25. Johnson SA, Schneider CL. The existence of antifibrinolytic activity in platelets. *Science* 1953; **117**:229-230.
26. Norkin SA, Freedman HH, Evans GW. Thrombotic thrombocytopenic purpura in siblings. *Am J Med* 1967; **43**:294-303.
27. Watson CG, Cooper WM. Thrombotic thrombocytopenic purpura: Concomitant occurrence in husband and wife. *JAMA* 1971; **215**:1821-1822.
28. Cuttner J. Thrombotic thrombocytopenic purpura. A ten-year experience. *Blood* 1980; **56**:302-306.
29. Ahmed F, Sumalnop V, Spain DM, Tobin MS. Thrombotic thrombocytopenic purpura during penicillamine therapy. *Arch Intern Med* 1978; **138**:1292-1293.
30. Parker JC, Barrett DA. Microangiopathic hemolysis and thrombocytopenia related to penicillin drugs. *Arch Intern Med* 1971; **127**:474-477.
31. Hirsh LF. Vasculitis, thrombotic thrombocytopenic purpura, and stroke after aneurysm surgery. *Surg Neurol* 1982; **17**:426-428.
32. Kennedy SS, Zacharski LR, Beck JR. Thrombotic thrombocytopenic purpura: Analysis of 48 unselected cases. *Semin Thromb Hemostas* 1980; **6**:341-349.
33. Wasserstein R, Hill G, Goldfarb S, Goldberg M. Recurrent thrombotic thrombocytopenic purpura after viral infection. *Arch Intern Med* 1981; **141**:685-687.
34. Bayer AS, Theofilopoulos AN, Eisenberg R, Friedman SG, Guze LB. Thrombotic thrombocytopenic purpura-like syndrome associated with infective endocarditis. *JAMA* 1977; **238**:408-410.
35. Mettler NE. Isolation of a microtubule from patients with hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura and from mites in the United States. *N Engl J Med* 1969; **281**:1023-1027.
36. Reynolds PM, Jackson JM, Brine JAS, Vivian AB. Thrombotic thrombocytopenic purpura—remission following splenectomy. *Am J Med* 1976; **61**:439-447.
37. Brown RC, Blecher TE, French EA, Toghil PJ. Thrombotic thrombocytopenic purpura after influenza vaccination. *Br Med J* 1973; **2**:303.
38. Castleman B, McNeely BU. Case records of the Massachusetts General Hospital. *N Engl J Med* 1968; **278**:1336-1344.
39. Barrett C, Marshall JR. Thrombotic thrombocytopenic purpura. *Obstet Gynecol* 1975; **46**:231-234.
40. May HV, Harbert GM, Thornton WN. Thrombotic thrombocytopenic purpura associated with pregnancy. *Am J Obstet Gynecol* 1976; **126**:452-458.
41. Piver MS, Lisker SA, Rowan M, Weber LL, Brody JI, Beizer LH. Thrombotic thrombocytopenic purpura during pregnancy. *Am J Obstet Gynecol* 1968; **100**:302-304.
42. Neame PB. Immunologic and other factors in thrombotic thrombocytopenic purpura (TTP). *Semin Thromb Hemostas* 1980; **6**:416-429.
43. Dunea G, Muehrcke RC, Nakamoto S, Schwartz FD. Thrombotic thrombocytopenic purpura with acute anuric renal failure. *Am J Med* 1966; **41**:1000-1006.
44. Gitlow S, Goldmark C. Generalized capillary and arteriolar thrombosis. *Ann Intern Med* 1939; **13**:1046-1067.
45. Beigelman PM. Variants of the platelet thrombosis syndrome and their relationship to disseminated lupus. *Arch Pathol* 1951; **51**:213-233.
46. Laszlo MH, Alvarez A, Feldman F. The association of thrombotic thrombocytopenic purpura and disseminated lupus erythematosus. *Ann Intern Med* 1955; **42**:1308-1320.
47. Levine S, Shearn MA. Thrombotic thrombocytopenic purpura and systemic lupus erythematosus. *Arch Intern Med* 1964; **113**:826-836.
48. Dekker A, O'Brien ME, Cammarata RJ. The association of thrombotic thrombocytopenic purpura with systemic lupus erythematosus. *Am J Med Sci* 1974; **267**:243-249.
49. Siegel BM, Friedman IA, Kessler S, Schwartz SO. Thrombohemolytic thrombocytopenic purpura and lupus erythematosus. *Ann Intern Med* 1957; **47**:1022-1029.
50. Fernandez-Herlihy L. Systemic lupus erythematosus. A clinical and prognostic analysis of 120 cases. *Lahey Clin Found Bull* 1972; **21**:49-62.
51. Hamilton CR, Tumulty PA. Thrombosis of renal veins and inferior vena cava complicating lupus nephritis. *JAMA* 1968; **206**:2315-2317.
52. Mueh JR, Herbst KD, Rapaport SI. Thrombosis in patients with lupus anticoagulant. *Ann Intern Med* 1980; **92**:156-159.
53. McVerry BA, Machin SJ, Parry H, Goldstone AH. Reduced prostacyclin activity in systemic lupus erythematosus. *Ann Rheum Dis* 1980; **39**:524-525.
54. Neame PB, Lechago T, Ling ET, Koval A. Thrombotic thrombocytopenic purpura: Report of a case with disseminated intravascular platelet aggregation. *Blood* 1973; **42**:805-814.
55. Neame PB, Hirsh J, Browman G, et al. Thrombotic thrombocytopenic purpura: A syndrome of intravascular platelet consumption. *Can Med Assoc J* 1976; **114**:1108-1112.
56. Morrison J, McMillan R. Elevated platelet-associated IgG in thrombotic thrombocytopenic purpura. *JAMA* 1977; **238**:1944-1945.
57. Fagiolo E. Thrombotic thrombocytopenic purpura with autoimmune pancytopenia. *Acta Haemat* 1974; **52**:356-361.
58. Bukowski MJ, Koblenzer PJ. Thrombotic thrombocytopenic purpura: Report of a case with unusual features of hypofibrinogenemia and leukopenia. *J Pediatr* 1962; **60**:84-90.
59. Mant MJ, Cauchi MN, Medley G. Thrombotic thrombocytopenic purpura. Report of a case with possible immune etiology. *Blood* 1972; **40**:416-421.
60. Wall RT, Harker LA. The endothelium and thrombosis. *Ann Rev Med* 1980; **31**:361-371.
61. Rubenstein MA, Kagan BM, MacGillviray MH, Merlis R, Sacks H. Unusual remission in a case of thrombotic thrombocytopenic purpura syndrome following fresh blood exchange transfusion. *Ann Intern Med* 1959; **51**:1409-1419.
62. Byrnes JJ. Plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *Semin Thromb Hemostas* 1981; **7**:9-14.
63. Bateman SM, Hilgard P, Gordon-Smith EC. Thrombotic thrombocytopenic purpura: A possible plasma factor deficiency. *Br J Haematol* 1979; **43**:498-499.
64. Bukowski RM, Hewlett JS, Reimer RR, et al. Therapy of thrombotic thrombocytopenic purpura: An overview. *Semin Thromb Hemostas* 1981; **7**:1-8.
65. Bukowski RM, King JW, Hewlett JS. Plasmapheresis in the

- treatment of thrombotic thrombocytopenic purpura. *Blood* 1977; **50**:413-417.
66. Machin SJ, Defreyn G, Chamone DAF, Vermeylen J. Plasma 6-keto-PGF_{1α} levels after plasma exchange in thrombotic thrombocytopenic purpura. *Lancet* 1980; **1**:661.
67. Myers TJ, Wakem CJ, Ball ED, Tremont SJ. Thrombotic thrombocytopenic purpura: Combined treatment with plasmapheresis and antiplatelet agents. *Ann Intern Med* 1980; **92**:149-155.
68. Amorosi EL, Karparkin S. Antiplatelet treatment of thrombotic thrombocytopenic purpura. *Ann Intern Med* 1977; **86**:102-108.
69. Amir J, Krauss S. Treatment of thrombotic thrombocytopenic purpura with antiplatelet drugs. *Blood* 1973; **42**:27-33.
70. Gundlach WJ, Tarnasky R. Thrombotic thrombocytopenic purpura: Remission following treatment with aspirin and dipyridamole. *Minn Med* 1977; **60**:20-22.
71. Woodruff RK, Castaldi PA. Treatment of TTP with high-dose dipyridamole. *Blood* 1978; **52**:856.
72. Harker LA, Slichter SJ. Platelet and fibrin consumption in man. *N Engl J Med* 1972; **287**:999-1005.
73. Castleman B, McNeely BU. Case records of the Massachusetts General Hospital. *N Engl J Med* 1968; **278**:36-43.
74. Zacharski LR, Lusted D, Glick JL. Thrombotic thrombocytopenic purpura in a previously splenectomized patient. *Am J Med* 1976; **60**:1061-1063.
75. Cocchetto DM, Cook L, Cato AE, Nidel JE. Rationale and proposal for use of prostacyclin in thrombotic thrombocytopenic purpura therapy. *Semin Thromb Hemostas* 1981; **7**:43-51.
76. Hensby CN, Lewis PJ, Hilgard P, Mufti GJ, Hows J, Webster J. Prostacyclin deficiency in thrombotic thrombocytopenic purpura. *Lancet* 1979; **2**:748.
77. Gutterman L, Stevenson TD. Vincristine in the treatment of thrombotic thrombocytopenic purpura. *Blood* 1979; **54**:242.
78. Kelton JG, Moore J, Santos A, Sheridan D. Detection of a platelet-agglutinating factor in thrombotic thrombocytopenic purpura. *Ann Intern Med* 1984; **101**:589-593.