Platelet Thrombosis Syndrome

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This paper reports the clinical and pathologic manifestations of seven cases of platelet thrombosis syndrome. Evidence is presented to indicate that vascular damage precedes the formation of platelet thrombi. It is suggested that the syndrome may be secondary to a variety of underlying disease entities.

The purpose of this paper is to report the clinical and pathologic manifestations of seven cases of the platelet thrombosis syndrome. In 1925 Moschowitz first described a rapidly fatal disease characterized by fever, anemia, petechiae, neurologic signs and autopsy findings of generalized capillary and arteriolar hyaline thrombi. Since then approximately 45 cases have been reported,2-20 most of them within the past 10 years. Many synonyms for the disease have been suggested, such as “thrombotic thrombocytic purpura,”11 “thrombocytic acro-angiothrombosis,”78 “thrombotic microangiopathic hemolytic anemia,”24 “disseminated arteriolar and capillary platelet thromboses,”17 and “generalized blood platelet thrombosis.”14 Much of this nomenclature is either cumbersome or suggests features of the disease that are not invariably present. We believe the term “platelet thrombosis syndrome” to be the most satisfactory until the nature of the entity is more fully elucidated.

Case Reports

Case 1. A 21 year old white male student was admitted to the Presbyterian Hospital on May 8, 1936, with a six months' history of increasing weakness and anemia following an upper respiratory infection. The only significant feature of his previous history was albuminuria for the past five years. Physical examination revealed jaundice, pallor, petechiae, retinal hemorrhages, hepatomegaly, blood pressure 150/76, and temperature of 100 F. Hemoglobin was 25 per cent, red blood cells 1 million, reticulocytes 43 per cent; anisocytosis, poikilocytosis, and polychromatophilia were present. Red blood cell fragility began at 0.425 and was complete at 0.350. White blood cells numbered 3400 (neutrophils 49, lymphocytes 32, monocytes 8, eosinophils 2, basophils 2, and myelocytes 6). Platelets numbered 9,000.* Capillary fragility was 30 cm. Hg. Bleeding time was 7 to 40 minutes. Coagulation time was 3.5 minutes. Urine showed 3 plus albuminuria, occasional red blood cells, white blood cells and casts. Nonprotein nitrogen was 48. Serum bilirubin (indirect) was 4 mg. per 100 cc. Serum proteins were 6.1 Gm. per 100 cc. (albumin 4.2, globulin 1.9). Bone marrow aspiration revealed hyperplasia with prevalence of erythroblasts in all stages.

Throughout the three month hospital stay the anemia proved refractory to multiple transfusions, iron and liver therapy. On August 1, 1936, the red blood cells were 1.66 million, serum bilirubin was 11.3 mg. per 100 cc. and blood urea nitrogen 73 mg. per 100 cc. The patient died with a terminal septicemia from an abscess in the buttock. The gross findings at autopsy revealed ascites, hydropericardium, bilateral hydrothorax, splenomegaly (500 Gm.), hepatomegaly (2000 Gm.), scattered petechial hemorrhages, abscesses of buttock, abscesses of heart, adrenal, kidney and prostate, infarct of spleen, a chronic gastric ulcer, edema of the lungs, and a vegetation on the aortic valve.

Case 2.† A 44 year old white male iron-worker was admitted to the hospital on Nov. 12, 1937, with a history of exposure to lead. For the preceding three weeks he had complained of severe headaches, weakness, tinnitus, deafness in the right ear and epigastric distress following meals. On the day before admission he had a transitory episode of aphasia. Physical examination revealed pallor, mental confusion and a right facial weakness, blood pressure 130/90, and temperature 99 to 100 F. Hemoglobin was 42 per cent, red blood cells 2 million with anisoctyosis, poikilocytosis and marked basophilic stippling; reticulocytes were 19 per cent. Erythrocyte sedimentation rate was 38. White blood cells numbered 11,300 (neutrophils 78, eosinophils 5, basophils 3, monocytes 8 and lymphocytes 6). Platelets numbered 46,000. Red blood cell fragility began

* The direct method of counting platelets was used on all occasions.
† Cases 1 and 2 have been reported briefly by I. Gore.

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at 0.450 and was complete at 0.30. Bleeding time was two minutes, clotting time 4 minutes, 45 seconds. Capillary fragility test was normal. Serum proteins were 6.9 Gm. per 100 cc. (albumin 3.7, globulin 3.2). Nonprotein nitrogen was 33. Serum bilirubin was 2.5 mg. per 100 cc. The Kline test was negative. The cerebrospinal fluid was normal. Urine contained a trace of albumin and many red cells.

A few days after admission petechiae and scleral icterus were noted. He finally became comatose with occasional tonic and clonic convulsions. The icterus failed to respond to transfusions, and bleeding from the gums, hematuria and temperature of 104 F. were present. He expired five days after admission. Gross findings at autopsy revealed scattered petechial hemorrhages, edema of the lungs, a spleen of 280 Gm., a liver of 1800 Gm., and a chronic gastric ulcer. Chemical analyses revealed excessive amounts of lead in viscera and bones.

Case 4. A 32 year old white housewife was admitted to the hospital on Oct. 27, 1940, with a history of transient rash on the hands two months previously. Four days before admission she developed severe epigastric pain, weakness and petechiae of the skin; these symptoms had persisted. She was mildly disoriented on the day of admission. Physical examination revealed pallor, petechiae, scleral icterus, blood pressure 105/80 and temperature of 101.6 F. During the examination she became unconscious and had a convulsion. Hemoglobin was 7 Gm. per 100 cc., red blood cells 2.15 million; anisocytosis, poikilocytosis, polychromatophilia and nucleated red cells were present. White blood cells numbered 21,640 (neutrophils 77, lymphocytes 20, myelocytes 2). Platelets numbered 50,000. Nonprotein nitrogen was 39. Serum bilirubin was 4.8 mg. per 100 cc. The Kline test was negative. The urine contained albumin and red cells.

The patient never regained consciousness and died four hours after admission. Gross findings at autopsy revealed scattered petechial hemorrhages, a spleen of 140 Gm., a liver of 1420 Gm., and two acute ulcerations of the stomach.

Case 5. A 40 year old white housewife was admitted to the hospital on Apr. 4, 1947, with a ten weeks' history of weakness and nausea. More recently she had experienced severe headaches and mental confusion. Physical examination revealed slight icterus, retinal hemorrhages, blood pressure 100/60 and temperature of 100 F. Hemoglobin was 7.3 Gm. per 100 cc. and red blood cells numbered 2.25 million with anisocytosis, poikilocytosis and basophilic stippling. White blood cells numbered 6,500 (neutrophils 57 and lymphocytes 43); there were 4 nucleated red blood cells per 100 white blood cells. Reticulocytes were 10 per cent. The cephalin flocculation was 4 plus, the thymol turbidity 3 plus. Red blood cell fragility began at 0.60 and was complete at 0.325. Serum icteric index was 9 units. Serum bilirubin was 1 mg. per 100 cc. There were no isoagglutinins at 37 C. Platelets numbered 10,000. The Kline test was negative. No anti-Rh agglutinins were demonstrable; there were questionable blocking antibodies (repeated). The urine contained albumin and red cells.

Soon after admission, aphasia, mental confusion and severe weakness of the extremities were prominent features. The hemoglobin fell to 4.6 Gm. per 100 cc.; the white count rose to 11,500 (neutrophils 79, lymphocytes 20, and monocytes 1). Despite multiple blood transfusions, folic acid and liver extract, the anemia remained refractory and she died four weeks after admission. The gross findings at autopsy revealed many scattered petechial hemorrhages and splenomegaly (320 Gm.).

Case 6. A 44 year old Mexican man was admitted to the hospital on May 10, 1952, with a long and complex history of variable neuromuscular complaints over the preceding seven years. One year ago his blood pressure began to rise and reached 200/100. Three months ago he became staxic, with vertigo, headaches, nausea and vomiting, diplopia and
anesthesia of the left side of his face. Physical examination revealed flaccidity of the extremities, ataxia, dysarthria and hypertensive retinopathy, apical murmur suggestive of Austin-Flint, blood pressure 200/100 and temperature of 99.2 F. Hemoglobin was 14 Gm. per 100 cc. The erythrocytes sedimentation rate was 75 mm. in 1 hour. White blood cells numbered 7,100 (neutrophils 68 and lymphocytes 25). The urine contained 4 plus albumin and 10 to 15 red blood cells and 20 to 30 white blood cells per high power field. Nonprotein nitrogen was 61 mg. per 100 cc. The cephalin flocculation was negative. Serum proteins were 6.8 Gm. per 100 cc. (albumin 3.5, globulin 3.3). The cerebrospinal fluid was normal.

He deteriorated rapidly with rise in temperature, aphasia and stupor, and expired May 18, 1952. The gross findings at autopsy revealed vegetations of the mitral and aortic valves, a spleen weighing 110 Gm., a liver weighing 1900 Gm., each kidney weighing 170 Gm., finely granular, mottled and hemorrhagic, and cerebral petechiae.

Case 7. A 37 year old housewife was admitted to the hospital on Aug. 6, 1952, with a three months' history of progressively severe headaches, vertigo and diplopia. Two days before admission she experienced two brief convulsive episodes and had been disoriented and restless since. Physical examination revealed scattered petechiae, retinal hemorrhages, blood pressure 200/150 and temperature of 102 F. Hemoglobin was 8.7 Gm. per 100 cc. and red blood cells numbered 3,27 million. Red blood cell fragility began at 0.44 and was complete at 0.30. The erythrocyte sedimentation rate was 83. Platelets numbered 24,000. White blood cells numbered 8,400 (neutrophils 94 and lymphocytes 6). Later the white blood cells numbered 35,000 (neutrophils 97 and lymphocytes 3). Nonprotein nitrogen was 31 mg. per 100 cc. Prothrombin time was 22.4 seconds. The Coombs test was negative. Serum bilirubin was 0.3 mg. per 100 cc. The urine contained albumin and red cells.

Massive hematuria commenced soon after admission. An electrocardiogram revealed recent myocardial damage. Her condition rapidly deteriorated, with further convulsive episodes, and she expired on Aug. 10, 1952. The gross findings at autopsy revealed hypertrophy of the left ventricle, focal myocardial infarct, vegetations on the mitral valve, splenomegaly (380 Gm.) with scattered infarcts, hepatomegaly (2200 Gm.), hemorrhagic kidneys and hemorrhagic cystitis.

**SUMMARY OF CLINICAL FEATURES**

The average age of these patients was 33 years. There appeared to be no obvious sex or racial predilection. The average duration of the entire illness was 17 weeks; occasionally, however, vague prodromal symptoms were present for several weeks before the onset of the acute illness. Case 1 had an unusually long illness lasting nine months; case 6 presents difficulty in differentiating the lengthy history of neuromuscular disorders from the more recent central nervous system disease.

Fever, in the 99 to 102 F. range, was a constant feature. Hemorrhagic manifestations, noted in five cases consisted of purpura, retinal hemorrhages, hematuria or bleeding gums and epistaxis. In cases 4 and 6 no hemorrhagic manifestations were present; in case 4 no thrombocytopenia was detected; and in case 6 platelet counts were not performed. Pallor, weakness and easy fatigability were notable in the five cases with severe anemia, four of whom were jaundiced. Six patients had neurologic findings such as headaches, drowsiness, mental confusion, convulsions, focal paresthesia and paresis. In cases 6 and 7 hypertension was marked but, apparently, preceded evidence of the final illness, at least in case 6. Laboratory examinations revealed a severe normochromic anemia in five cases and minimal anemia in cases 4 and 6. Anisocytosis, poikilocytosis, reticulocytosis, and nucleated red cells were frequently present. Serum bilirubin levels were elevated in four cases. Coomb's test was negative in case 7, but blocking antibodies were questionable in case 5. Red blood cell fragility studies were normal in four cases examined. Elevation of the erythrocyte sedimentation rate was a common finding. There was a leukocytosis with a "left shift" in four cases; in case 1, however, persistent leukopenia with "left shift" was present. A severe thrombocytopenia was present in five cases; a platelet count was not performed on case 6. Of unusual interest is the fact that platelet counts in case 4 were repeatedly within normal range with an unexplained transient prolongation of prothrombin times. The Kline or Wassermann test was negative in all cases. Positive cephalin flocculation and thymol turbidity tests were found in two of three cases examined. The blood proteins were estimated in four cases, hypergammaglobulinemia being present in two (the cephalin flocculation and thymol turbidity tests were negative in one, and not performed in the other). Of the four patients
without concomitant renal disease, two had increased nonprotein nitrogen blood levels and hematuria. Of the three cases with concomitant renal disease, two had elevated nonprotein nitrogen blood levels; all three had albumin and red cells in the urine. The cerebrospinal fluid of three patients was normal. Electrocardiographic studies were performed on three cases and evidence of acute myocardial damage was found in two.

**Summary of Postmortem Findings**

Significant gross findings were scant. Occasional areas of hemorrhage, vegetations on the heart valves, focal areas of visceral necrosis, particularly in the brain, and splenomegaly were the only gross features that could be related specifically to the syndrome.

Microscopically, the most characteristic finding was the widespread presence of hyaline thrombi in the small arteries, arterioles, and capillaries. (See fig. 1.) These platelet thrombi were present in the kidneys and myocardium in all cases. Involvement of these organs was usually widespread. Markedly dilated, thin-walled vessels containing thrombi were characteristically seen in these two organs. (See fig. 2.) On the basis of serial sections in cases studied by Orbison these dilated vessels were considered to be aneurysmal dilatations and were regarded as evidence for primary vascular damage. In the myocardium many arterioles and capillaries were filled with platelet thrombi in various stages of organization. These were often associated with minimal to abundant endothelial proliferation. (See fig. 3.) In adjacent areas, the myocardium exhibited foci of necrosis and fibrosis. In addition to the myocardial changes, hyaline thrombi were found on the aortic and mitral valves in three cases. These vegetations differed in no respect from the usual picture of thromboendocarditis. Bacteria were not present, and there was no associated inflammatory process. There was eosinophilic degeneration of the valve substance adjacent to the thrombi. (See fig. 4.) It appeared that this eosinophilic degenerated material was extending from the valve surface. Others have reported similar findings on the heart valves.
In the kidneys, the cortical vessels were commonly the site of platelet thrombi formation. Especially affected were the afferent arterioles with occasional extension of the process into the glomerular tufts. Foci of cortical hemorrhage with red blood cells filling the tubules were occasionally observed. In one case, intercapillary glomerular nephritis was present. What the relationship is between the glomerular nephritis and this syndrome is not clear. Two other cases with marked hypertension had advanced arteriolar nephrosclerosis. Endothelial proliferation in the glomerular tufts was present in still another case. In none of the postmortem material was there anything suggestive of the changes seen in lupus erythematosus.

Brain examinations were performed in three cases, but the presence of neurologic manifestations in all but one of the seven patients would indicate that the brain was involved to the same degree as the kidneys and the heart. The brains that were examined contained widespread involvement of numerous vessels with
platelet thrombi. As in the other sites, endothelial proliferation was present. (See fig. 5.) In one case where the lesions were most widespread, there were numerous gross areas of encepalomalacia. Vessels in the pia arachnoid were similarly involved.

Next in frequency of involvement were the pancreas, adrenals, spleen, and gastrointestinal tract (six out of seven cases). However, the number of vessels implicated was considerably less than in the previously mentioned sites. There were numerous thrombi in the adrenals, limited almost entirely to the vessels immediately beneath the capsule. (See fig. 6.) Occasionally vessels outside of the capsule contained thrombi. Focal hemorrhages were present. In the pancreas, the involvement was diffuse and generally located in those vessels in the interlobular connective tissue. No secondary changes were present in the pancreas. In the spleen, only few vessels were involved. Splenomegaly was present in four cases. There was considerable congestion and in two cases there were splenic infarcts. There was no

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**Fig. 6.** Photomicrograph (hematoxylin and eosin, X 250) showing adrenal cortex with thrombi in capillaries just beneath the capsule.

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**Fig. 7.** Photomicrograph (hematoxylin and eosin, X 250) of large pulmonary vessel with small hyaline thrombi attached to intimal surface.

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**Fig. 8.** Photomicrograph (hematoxylin and eosin, X 250) of vessel in myocardium with prethrombotic lesion and superimposed endothelial proliferation.
concentric perivascular fibrous proliferation. Megakaryocytes were infrequent.

In the gastrointestinal tract, the vessels in the submucosa were the ones usually containing thrombi. Foci of hemorrhage were observed. Three cases revealed gastric ulcers (two chronic and one acute). It is possible that the development of these ulcers was related to the vascular occlusions.

Particularly significant was the limited involvement of the lungs and liver. Of the major organs, these were the least frequently involved, and when thrombi were present, it was only in an occasional vessel. In the liver, the usual site was the vessels in the portal region, whereas in the lung there was no characteristic site. The involvement of one vessel in the lung was of considerable interest. It was a considerably larger vessel than those usually seen with platelet thrombi. Attached to its intimal surface at several separate points were small hyaline thrombotic masses. (See fig. 7.) The lumen was not obliterated. This type of involvement would tend to support the view that the vascular change is primary. Megakaryocytes were present in the lungs in three cases.

Other sites in which vessels contained thrombi were the thyroid, pituitary, gall-bladder, larynx, diaphragm, urinary bladder, peripheral nerves, tonsils, and striated muscle. It is interesting that striated muscle has only been rarely implicated.

The bone marrow in all cases was uniformly hyperplastic. Abundant megakaryocytes were found and the changes in the marrow were considered consistent with those seen characteristically in secondary anemia. The vessels in the marrow did not contain hyaline thrombi.

A careful search was made for the prethrombotic vascular changes described by Gore.17 In several instances, these changes were unmistakably identified (fig. 8) and would support the thesis that vascular changes precede the formation of the thrombi. The widespread nature of the process without marked localization to those areas most susceptible to stagnation of the circulation has already been referred to as an argument against this syndrome originating primarily as an intraluminal phenomenon.

**Discussion**

The etiology of the entity is unknown. It is not even clear whether this condition can be regarded as a primary one or secondary to a variety of underlying diseases. The present evidence supports the view that the thrombi follow vascular damage and is in keeping with the observation of similar changes in known hypersensitive reactions. Platelet thrombi associated with vascular damage have been observed in fatal cases of drug sensitivity reactions.10, 11 Four of the cases in this study had associated processes which could have produced vascular damage (lead poisoning, glomerulonephritis, and malignant hypertension). In other reports, platelet thromboses have been seen in lupus erythematosus and polyarteritis.31, 32 On occasion, platelet thrombi are seen in the myocardial arterioles in rheumatic heart disease. Thus, it is entirely possible that this syndrome is not a primary and independent disease.

**Summary**

1. The clinical and necropsy findings in seven cases of "platelet thrombosis syndrome" have been presented.
2. The findings of this study favor the view that vascular damage precedes the thrombus formation.
3. The view is presented that this syndrome may be entirely secondary to a variety of underlying disease entities.

**Sumario Español**

En este trabajo se informan las manifestaciones clínicas y patológicas en siete casos del síndrome de trombosis de plaquetas. Se presenta evidencia que indica que el daño vascular precede la formación del trombo de plaquetas. Se sugiere que el síndrome puede ser secundario a una variedad de enfermedades subyacentes.

**References**


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