THROMBOTIC THROMBOCYTOPENIC PURPURA
Hemorrhagic Diathesis with Generalized Platelet Thromboses*

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Thrombocytic purpura is a syndrome of relatively common occurrence. However, thrombocytic purpura associated with multiple platelet thrombi is sufficiently rare to warrant the report of an additional case and a detailed study of the clinical and pathologic picture. We have been able to find only eleven previous cases1-9 reported in the literature.

REPORT OF CASE

An 11 year old white female entered the hospital because of weakness, fever and hemorrhagic tendency. Two weeks prior to admission, the patient had an upper respiratory infection with a low grade fever. She seemed to recover after 3 days, but 1 week later she was extremely tired and listless. However, she continued to attend school despite a slightly elevated temperature. There was loss of appetite and weight loss of two pounds. At the same time, the patient noted many black and blue spots on the extremities. She had never had such spots before. Her dietary history was excellent. Simultaneously with the occurrence of the ecchymoses the patient felt nauseated, but did not vomit. There was no change in bowel habits and no gross blood was noted in the urine or feces. With the exception of aspirin, no drugs had been taken. Poliomyelitis was the only significant disease in the past history.

Physical examination revealed a pale, acutely ill white female. Temperature 100 to 101° F.; respiration 28, pulse 108. There were numerous petechiae and ecchymoses over the trunk and extremities. There was no jaundice, retinal hemorrhage, nosebleeds, cyanosis or bleeding from the gums. Aside from several pea-sized firm cervical lymph nodes, no lymphadenopathy was found. The lungs were clear, the heart was not enlarged. There was a grade 1 systolic murmur over the base. The liver was enlarged, the edge palpable two fingers below the costal margin in the mid-clavicular line; it was slightly tender on pressure. The lower pole of the spleen was palpable two fingers below the costal margin. Extremities: no ankle jerk on the right side (old poliomyelitis); otherwise no pathology of the nervous system. The patient was well oriented and quiet.

Laboratory findings: Bacteriologic examinations: Three blood cultures were negative. Urine: specific gravity 1.025, albumen 2 plus, sugar negative, bilirubin negative, urobilinogen increased; sediment 3 R.B.C./H.P.F., no casts. Serum bilirubin 1.9 mg. per cent. Blood: hemoglobin 7.0 Gm. (42 per cent). R.B.C. 2,740,000, W.B.C. 5,330, platelets: 21,000, reticulocytes 4.5 per cent. Sedimentation rate: 39 mm. uncorrected (micro method). Blood smear: marked anisocytosis and poikilocytosis of the red cells, no spherocytosis, increased polychromatophilia. White cells: polynuclear segmented 60 per cent, nonsegmented 5 per cent, lymphocytes 18 per cent, monocytes 7 per cent, no toxic granulation of the granulocytes, 3 nucleated oxyphilic red corpuscles per 100 white cells. Tourniquet test 4 plus. Bleeding time more than 10 minutes. Clotting time (Lee and White) 4 minutes. Prothrombin time 101 per cent.

The child's course was progressively downhill. The temperature fluctuated between 101 and 106.4, terminally. The pulse was always rapid. On the third day the patient suddenly became incoherent, complained of dizziness and had paresthesias in all extremities; these abnormalities disappeared after a few
hours. Two days later she was very restless, had severe frontal headaches and later was confused and disoriented. On the sixth day after admission, the patient lapsed into coma and died. A blood examination on the third day showed the following findings: Hgb 5.1 Gm. (33 per cent), R.B.C. 1.87 M., W.B.C. 9900, platelets 6000, hematocrit 17 per cent, color index 0.88, M.C.V. 91 cu. micra, reticulocytes 15 per cent. Differential count: polynuclear granulocytes: segmented 38 per cent, nonsegmented 6 per cent,
cytes, which were definitely increased in number, were normal in appearance. No signs of increased or decreased platelet production by these giant cells were demonstrable. The differential count of the bone marrow cells (1000 cells counted) was: megakaryocytes 1 per cent, histiocytes (reticulum cells) 1.5 per cent, proerythroblasts 0.3 per cent, basophilic erythroblasts 4.2 per cent, polychromatophilic erythro-

![Liver showing thrombosed vessels (Magn. 170X)](image)

D. Heart. Artery occluded by large thrombus (Magn. 170X)

blasts 31.2 per cent, orthochromatic erythroblasts 31 per cent, myeloblasts 3.6 per cent, promyelocytes 2.7 per cent, neutrophil myelocytes 11.5 per cent, metamyelocytes 0.6 per cent, band forms 1.8 per cent, polymorphs 3.6 per cent, eosinophilic polymorphs and myelocytes 4 per cent, lymphocytes 3 per cent.

*Postmortem Report:* (Only the essential changes are given.) Gross findings: The skin was extremely pale and numerous areas of hemorrhages were present. The heart weighed 120 Gm. The epicardium
showed several petechial hemorrhages. The myocardium, especially that of the right ventricle, was mottled with pin-point and larger red spots. Small yellowish brown discolorations, measuring about 4-6 mm. in greatest dimension, were found in close association with the red areas. The liver weighed 850 Gm. The edges of the liver were rounded. The cut surface was a light yellowish brown and dry. The spleen weighed 110 Gm. It was quite soft. The cut section was dark red with faint trabecular outlines. The follicles were prominent. Both kidneys weighed 260 Gm. Their surface was mottled with a large number of tiny reddish dots, causing a fleabitten appearance. Some of the mesenteric and periarterial lymph nodes were enlarged, soft and of a purplish red color. On sectioning, prominent follicles were noted. The brain disclosed two areas of subdural hemorrhage, one over the right postcentral gyrus and the other just beneath the tentorium, each measuring 2 by 2 cm. The right cerebral peduncle was the seat of an area of hemorrhage, measuring about 1 mm. in diameter.

Microscopic findings: Heart: Innumerable thrombi were seen throughout the sections. They were located in the capillaries, arterioles, and in smaller arteries. The thrombi consisted mainly of thrombocytes and some fibrin. Red blood corpuscles were not present in these thrombi. There were numerous foci of hemorrhages and early necrosis of heart muscle fibers located mainly in the neighborhood of the thrombosed vessels. In the papillary muscles the thrombi were especially numerous. Similar thrombi were seen in the lung, accompanied by small infarcts. Many capillaries were plugged with multinucleated cells resembling megakaryocytes. The liver also disclosed platelet thrombi. Here they were only found in the arterioles, while portal and central veins were free. A considerable amount of round cell infiltration was present in the perportal spaces. Platelet thrombi were also noted in the spleen, kidneys, urinary bladder, suprarenals, pancreas, and brain. The general architecture of the lymph nodes was well preserved. Numerous arterioles and capillaries were thrombosed. Patchy areas of hemorrhage and a distinct hyperplasia of the reticulo-endothelial cells were noted throughout the sections. Within the bone marrow there was marked increase of all cellular elements, particularly of the megakaryocytes. A few small thrombosed capillaries were also encountered.

DISCUSSION

In comparing the clinical and histologic features of our case with those of the 11 previously reported ones almost identical clinical and pathologic findings are encountered. From this it is quite obvious that we are dealing with a definite disease entity. However, most of the authors describing this disorder emphasize the hist-
Toologic pattern, but pay relatively little attention to the clinical aspects. In this study we wish to stress the clinical picture and its differential diagnosis. Only if the disease can be recognized ante mortem will an appropriate study of the pathogenic mechanisms become possible.

**Terminology.** In order to make a clinical diagnosis of this disease it is imperative that the diagnostician consider this rare disorder when confronted with a syndrome of thrombocytopenic purpura. A glance at the list of references will demonstrate that no distinctive name has been attached to this disorder until now. The term "generalized arteriolar and capillary platelet thrombosis" is too long and cumbersome for practical use. We suggest the name "thrombotic thrombocytopenic purpura" for this syndrome, using the word "thrombotic" in the sense of "caused by thrombosis." The name also emphasizes the most plausible theory of the pathogenic mechanism responsible for the thrombocytopenia, namely the disappearance of the platelets from the circulation due to the formation of myriads of platelet thrombi.

**Race, Age and Sex.** The cases of "thrombotic purpura" reported thus far occurred in both whites and Negroes. The age of the patients varied from 9-66 years. Of the 12 reported cases (including our own) 3 were observed in children under 16. The disease seems to occur more frequently in females than in males, although the number of observations is too small for any definite conclusions. At present the ratio is 5:1 for the preponderance in females.

**Symptomatology.** The symptomatology of "thrombotic purpura" can be divided into 2 groups of manifestations. The first, which may be found in any of the thrombocytopenic purpuras, comprises petechiae and ecchymoses, epistaxis, melena, hematuria, and the laboratory findings of diminished number of platelets, prolonged bleeding time, positive tourniquet test, and poor clot retraction. The second group contains the features which may make the clinical diagnosis possible and will therefore be described in detail.

**Onset and Prodromal Symptoms.** "Thrombotic purpura" is an acute illness. Most patients give the history of an upper respiratory infection a few days or weeks prior to the appearance of the purpuric manifestations. Malaise, generalized aches and pains, arthralgia, throbbing headaches, and dizziness may be noted. There may be nausea and vomiting. Slight jaundice, the development of petechiae, and progressive pallor often bring the patient to the physician. At this time there is almost always fever of 100-102°F.

**Physical Examination** may now show the following abnormalities:

- **Skin:** There are numerous painless petechiae and ecchymoses. Some observers have noted a peculiar brownish "café au lait" color.

- **Pallor:** Anemia is a constant and conspicuous feature. The severity of the anemia is out of proportion to any loss of blood which may have been observed. Sometimes the anemia may precede the external manifestations of the bleeding tendency due possibly to a hemolytic process.

- **Jaundice and Hepato-Splenomegaly:** Manifest or latent icterus is a constant finding; the jaundice is always slight and of the acholuric or retention type. In one half
the cases the liver and spleen are palpable. This hepato-splenomegaly (always of moderate degree) may be of great importance for the differential diagnosis.

Mental and Neurological Manifestations: Almost all cases develop mental symptoms in the course of the disease. There is restlessness, confusion, irritability, incoherent screaming, muttering delirium, and stupor. These symptoms may be transitory, followed by lucid intervals. Convulsions are not infrequently seen. Besides these general symptoms of cerebral involvement, some cases show definite signs of focal lesions: facial weakness, hemiplegia, aphasia, dysphagia, apraxia, etc. Significantly, however, even these organic signs are often of a transient nature and thus differ fundamentally from the cerebral involvement (hemorrhage into the brain) seen in the other varieties of thrombocytopenic purpura in which this waxing and waning of signs is not observed. Rarely does the disorder begin with neurologic manifestations and is then followed by the other symptoms.8

Fever: Fever is almost always present. It is usually moderate in degree (100-102°F.) but terminal hyperpyrexia of 106-107°F. is not unusual. This elevation of temperature throughout the course of the disease is of diagnostic significance, as in "essential" thrombocytopenic purpura fever is usually lacking or slight.

Cardiovascular System: Acceleration of the pulse is noted in relation to the fever and anemia. Systolic murmurs over the base of the heart are common. Only in two cases was a "thrombotic nonbacterial endocarditis" observed.9 The blood pressure is not altered by the disease.

G.I. and G.U. tracts: Vomiting and nausea are frequent. Melena is occasionally present. Hematuria is a constant finding but usually only discovered on microscopic examination. Smoky urine was seen in only 2 cases.9

Laboratory Findings: Bacteriological studies of the blood have not given any results. The urine almost always shows moderate albuminuria and micro-hematuria. There is no bilirubin present, but urobilinogen is markedly increased. Examination of the blood shows a varying degree of anemia of the normochromic normocytic variety. Hemoglobin values of 5 or even 3 grams are common. There is marked reticulocytosis but no spherocytosis, and the hypotonic saline fragility is unaltered. Nucleated red cells are a common finding in the peripheral blood, sometimes as many as 55 per 100 white cells being seen.2 The serum bilirubin is moderately elevated. Studies of the hemolytic index11 have not yet been performed. According to these criteria the anemia may well be classified as of the hemolytic type.

The white blood cells are at first moderately increased in number with a slight shift to the left. Later on a myeloid reaction may be seen (in half of the cases). The immature cells in the peripheral blood are myeloblasts, promyelocytes and myelocytes. This leukemoid picture is of great significance in the differential diagnosis; it may be only transient as in our cases, and may therefore be easily missed. When the disease is suspected, daily examination of blood smears may be a very valuable procedure.

Platelets are very much diminished or absent, the bleeding time is often prolonged, the tourniquet test positive, and clot retraction poor.

Only a few bone marrow studies by sternal puncture have been reported. They
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usually show an erythroid hyperplasia and a normal or slightly increased number of megakaryocytes. In our case the number of megakaryocytes was definitely increased. The giant cell pattern seemed to be a normal one; unfortunately no quantitative studies using the method of Limarzi and Schleicher were performed.12

Table 1 lists the essential findings in the 12 observations available.

In summary then the clinical picture of "thrombotic thrombocytopenic purpura" is that of an acute febrile illness characterized by a severe anemia out of proportion to any observed blood loss, mild acholic jaundice, hepatosplenomegaly in half of the reported cases, bizarre and intermittent mental and neurological symptoms and signs of a transient nature and a leukemoid reaction in the peripheral blood, besides the hemorrhagic manifestations commonly seen in thrombocytopenic purpura.

DIFFERENTIAL DIAGNOSIS

With the clinical picture of purpura, determination of the platelet count will readily demonstrate whether the presenting syndrome belongs to the thrombocytopenic or nonthrombocytopenic variety. If a diminution of platelets establishes the diagnosis of the former, the possibility of "thrombotic purpura" should be considered.

An entirely satisfactory and generally accepted classification of the various thrombocytopenic syndromes is not available at the present time because of our very incomplete knowledge of the pathogenic mechanisms involved. If one accepts the theory that the megakaryocytes of the bone marrow produce the platelets13 15 one must also accept the concept that their production and release are likewise controlled by various metabolites or hormones. The existence of a splenic inhibitor of the marrow has recently been demonstrated.14 21 The role of such a "splenic hormone" has, however, not yet been sufficiently studied in the various types of purpuras. Although it may be premature to base any classification of the thrombocytopenic syndromes on our present knowledge of functional principles, such a correlation is attempted in this paper. The following types of thrombocytopenic purpura may be distinguished:

1. Diminution of platelet production caused by aplasia or hypoplasia of the megakaryocytic apparatus. This is seen in the aplastic anemias of the "idiopathic" or of the symptomatic type (osteosclerotic anemia, effect of benzol or gold salts, x-rays, radium, etc.). In these conditions there is anemia, leukopenia, and thrombocytopenia, the marrow is empty, and the course of the disease is usually a chronic one. Histologically the few remaining megakaryocytes appear to be normal.15

2. Diminution of platelet production due to interference by "foreign" cells. To this group belong the diseases in which one can demonstrate an "invasion" of the bone marrow by foreign cells. (Gaucher cells, cancer or sarcoma metastases, myeloma cells, etc.). The disorders which show a proliferation of the immature white cells, i.e. the acute and chronic leukemias, also fall into this group. Severe hyperplasia of the erythroid apparatus is sometimes also accompanied by thrombocytopenic purpura, as in severe pernicious anemia or in primary hypochromic anemia. There may be either mechanical interference or a metabolic disturbance. The antipermi-
### Table 1.—Clinical Manifestations in Cases Observed

<table>
<thead>
<tr>
<th>No. of Case</th>
<th>Name of Author</th>
<th>Race</th>
<th>Age</th>
<th>Sex</th>
<th>Prodromal Symptoms</th>
<th>Hemorrhagic Manifest (Petechiae, Ecchymoses)</th>
<th>Pallor</th>
<th>Jaundice</th>
<th>Hemanagia</th>
<th>Splenomegaly</th>
<th>Mental and Neurological Manifestations</th>
<th>Fever 101°-104°F</th>
<th>G.I. Symptoms</th>
<th>Hematuria</th>
<th>Severe Anemia</th>
<th>Leukemoid Reaction</th>
<th>Thrombocytopenia</th>
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<tbody>
<tr>
<td>1</td>
<td>Moschcowitz</td>
<td>White</td>
<td>16</td>
<td>F</td>
<td>weakness, arthralgia</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>absent</td>
<td>absent</td>
<td>absent  pareis of left facial, paralysis, coma</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>2</td>
<td>White</td>
<td>White</td>
<td>91</td>
<td>F</td>
<td>listless, pale, headache</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>absent</td>
<td>absent  clonic twitching, vertigo, headache, irrationality muttering delirium, stupor terminal right hemiplegia, com</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>3</td>
<td>Baehr, Klemperer, and Schifrin</td>
<td>White</td>
<td>18</td>
<td>F</td>
<td>brownish pallor, weakness, vertigo, headache</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>absent</td>
<td>absent</td>
<td>absent  clonic twitching, vertigo, headache, irrationality muttering delirium, stupor terminal right hemiplegia, com</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
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<tr>
<td>4</td>
<td>White</td>
<td>White</td>
<td>22</td>
<td>F</td>
<td>not reported</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>absent</td>
<td>absent</td>
<td>absent  clonic twitching, vertigo, headache, irrationality muttering delirium, stupor terminal right hemiplegia, com</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>5</td>
<td>White</td>
<td>White</td>
<td>48</td>
<td>F</td>
<td>arthralgia, upper respiratory infection</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>absent</td>
<td>absent</td>
<td>absent  right hemiplegia</td>
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<td>vomiting</td>
<td>present</td>
<td>not reported</td>
<td>not reported</td>
<td>present</td>
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<tr>
<td>6</td>
<td>Gitlow &amp; Goldmark</td>
<td>White</td>
<td>18</td>
<td>F</td>
<td>upper respiratory infection, malaise, vomiting</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>absent</td>
<td>absent</td>
<td>absent  right hemiplegia</td>
<td>present</td>
<td>vomiting</td>
<td>present</td>
<td>not reported</td>
<td>not reported</td>
<td>present</td>
</tr>
<tr>
<td>7</td>
<td>Altschule</td>
<td>White</td>
<td>50</td>
<td>F</td>
<td>malaise, abdominal pains, fatigue, arthralgia</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present  headaches, dizziness, confusion, restlessness, delirium convulsions, coma</td>
<td>present</td>
<td>vomiting, meleina</td>
<td>present</td>
<td>not reported</td>
<td>not reported</td>
<td>present</td>
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<tr>
<td>8</td>
<td>Bernheim</td>
<td>White</td>
<td>33</td>
<td>F</td>
<td>weakness, throbbing headaches</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>absent</td>
<td>absent</td>
<td>absent  restlessness, delirium convulsions, coma</td>
<td>present</td>
<td>anorexia</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>9</td>
<td>Trobaugh et al.</td>
<td>White</td>
<td>24</td>
<td>M</td>
<td>upper respiratory infection, malaise, aphasia, begin with neurologic changes</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>absent</td>
<td>present</td>
<td>absent  restlessness, delirium convulsions, coma</td>
<td>present</td>
<td>vomiting</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>not observed</td>
</tr>
<tr>
<td>10</td>
<td>Carter</td>
<td>Negro</td>
<td>66</td>
<td>M</td>
<td>aphasia, begin with neurologic changes but thrombocytopenia</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>absent  delirium, disorientation, spastic pariesis</td>
<td>present</td>
<td>vomiting</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>11</td>
<td>Engel, Scheinker &amp; Humphrey</td>
<td>Negro</td>
<td>15</td>
<td>F</td>
<td>upper respiratory infection, vomiting, headache weakness, upper respiratory infection</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present  delirium, disorientation, spastic pariesis</td>
<td>present</td>
<td>vomiting</td>
<td>present</td>
<td>present</td>
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<td>present</td>
</tr>
<tr>
<td>12</td>
<td>Own case</td>
<td>White</td>
<td>11</td>
<td>F</td>
<td>upper respiratory infection</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present  delirium, disorientation, spastic pariesis</td>
<td>present</td>
<td>vomiting</td>
<td>present</td>
<td>present</td>
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</tr>
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</table>
cious principle appears to have a definite effect on the megakaryocytes. Administration of liver produces an increase in platelets in pernicious anemia which precedes the elevation of the reticulocyte count in the peripheral blood. In all these disorders the diagnosis can usually be made without great difficulty from the bone marrow smear. Histologically the megakaryocytes appear to be normal.

Severe hemolytic anemia of the acquired type with thrombocytopenia is unusual. In nocturnal hemoglobinuria (Marchiafava-Micheli syndrome) diminution of platelets is frequently seen but not accompanied by purpuric manifestations. The chronic character of the disease, the hemoglobinuria, and the nocturnal rhythm are sufficiently distinct features.

3. Inhibition of release of the platelets. To this group belong the cases of thrombocytopenic purpura which have been classified as "Werlhof's disease" or "essential purpura." Recent investigations have demonstrated that this syndrome is caused by an inhibitory influence of a "splenic hormone" on the bone marrow. The number of megakaryocytes is increased but they show great diminution in platelet production, following splenectomy the production of platelets from the megakaryocytes often becomes demonstrable to an extreme degree. This "splenic inhibition" syndrome may be present in an acute or chronic form. In the acute type, which is of special interest in the differential diagnosis of "thrombotic purpura," fever is absent or slight, and when present is caused by secondary infection. Anemia is present only in proportion to the blood loss. Neurologic manifestations occur but are caused by gross hemorrhage into the brain and are not of an intermittent type. Hepatomegaly is not seen and splenomegaly is a rare finding. Leukemoid reactions are rarely encountered.

Splenic inhibition may also occur symptomatically in liver cirrhosis, in congestive splenomegaly and in Felty's syndrome, but the clinical picture in these latter disorders is usually of such a nature that it does not resemble "thrombotic purpura." The megakaryocyte pattern in the symptomatic splenic inhibition may be the same as in Werlhof's disease or may be a normal one. Further extensive marrow studies in these disorders are indicated.

4. Allergic purpura. The fourth group comprises the cases of allergic thrombocytopenic purpura which may be caused by allergy to drugs (sedormid, quinine, sulfa compounds, etc.), to food stuffs, or to bacteria or viruses. The point of attack of the pathogenic mechanism operating in this group is not clear. Schwartz has recently pointed out that in such cases there is a considerable increase of the eosinophils in the marrow even in the absence of eosinophilia in the peripheral blood. No such increase has been observed in "thrombotic purpura." Furthermore, the course of the allergic purpuras is never as stormy or rapid as in the thrombotic variety.

5. Infectious or toxic thrombocytopenic purpura. This type is seen occasionally but by no means regularly in infectious diseases as subacute bacterial endocarditis, typhoid fever, smallpox, infectious mononucleosis and lupus erythematosus. To this group also belongs Minot's thrombocytopenic purpura with lymphocytosis. The mechanisms causing these purpuras are unknown. S. O. Schwartz and one of us (K. S.) have recently observed a case of infectious mononucleosis with thrombo-
cytopenia in which the marrow showed a marked eosinophilia. It is therefore conceivable that an allergic mechanism may also be in operation in some of these infectious purpuras.

"Thrombotic purpura" can easily be differentiated from the first and second group. If a leukemoid picture is present, exclusion of leukemia is necessary by means of marrow studies. It can also be ruled out on clinical grounds. Thrombocytopenia is regularly found in acute leukemia which, however, shows a different blood picture (hiatus leukemicus, Naegeli). In chronic myelogenous leukemia, purpura is only seen in the last stages of the disease. Allergic purpura can also be differentiated by means of the stormy, febrile course of "thrombotic purpura" and the absence of eosinophilia in the marrow. Splenogenic "essential" purpura rarely shows the degree of anemia, fever, and the transitory neurologic and hematologic responses seen in "thrombotic purpura." The greatest differential diagnostic difficulties may be encountered in the symptomatic purpuras of the infectious or toxic type; often, however, the underlying disorder may manifest itself so obviously that the diagnosis can be established. In subacute bacterial endocarditis, for example, the blood culture, the history of a pre-existing heart disease and the type of murmurs may be of great help in the differentiation. A lymph node biopsy may also be of great diagnostic value if the characteristic histologic pattern can be found.

Although the recognition of "thrombotic purpura" is not simple, we are certain that when familiarity with this clinical picture increases, ante mortem diagnoses will certainly be made more often in the future.

PATHOLOGY AND PATHOGENESIS

The remarkable histologic pattern which is found at autopsy in the cases of "thrombotic purpura" consists of innumerable thrombotic lesions within the capillaries and the small arterioles. There is general agreement that these thrombi are composed of masses of platelets. Only a small amount of fibrin and no erythrocytes are found in the thrombi. In the capillaries of the lungs characteristic megakaryocyte thrombi may be present. This is a frequent but inconstant finding. The endothelial lining of the vessels shows proliferation of varying degree. Most observers believe that this endothelial reaction follows the formation of the thrombi and is therefore a secondary phenomenon. Altschule considered the possibility of a primary vascular disease with secondary thrombus formation. In support of the first mentioned interpretations are the observations that no evidence of endothelial damage is demonstrable in any other parts of the vascular tree where no thrombi are found, but that thrombosis may be present without any noticeable proliferation of the endothelium. In the case of Carter, however, necrosis of the capillary wall with extrusion of the thrombotic material into the adjacent tissue was seen, and Trobaugh and al. found swelling of the capillaries without thrombi. From the histologic findings it is quite obvious that the formations of the platelet thrombi take place in a succession of attacks. One is tempted to speculate whether the transitory character of some of the manifestations of "thrombotic purpura" may not be related to such paroxysms of vascular occlusion.

There is also general agreement amongst all pathologists who have studied
THROMBOTIC THROMBOCYTOPENIC PURPURA

"thrombotic purpura" that this disorder is in no way related to generalized disseminated lupus or polyarteritis. The vascular lesions in these latter diseases consist in primary alterations of the wall of the blood vessels, whereas in "thrombotic purpura" the platelet thrombi are the outstanding feature of the histologic pattern.

Baehr, Klemperer and Schifrin suggested that the myriads of platelets caught in the thrombi may account for the lack of thrombocytes in the circulating blood. The increase of the number of megakaryocytes in the bone marrow could then be explained as a compensatory reaction. This "exhaustion theory" may plausibly account for the diminution of platelets in the blood but does not satisfactorily explain the bleeding tendency. Bedson's repeatedly confirmed experiments have shown that lack of platelets produced by intravenous injection of agar or antplatelet serum does not result in purpura; however, if the capillary endothelium is damaged by means of an anti-red cell serum, hemorrhage occurs. It must therefore be assumed that such a damaging "toxic" factor is also operative in "thrombotic purpura."

No explanation is available for the constant presence of a very severe anemia. It is unlikely that the severe anemia is due to "hemorrhage into the tissues." The hemosiderosis of the tissues is only slight in almost all observed cases and it must therefore be inferred that the anemia is caused by intravascular destruction of the red cells.

The etiology of the disease is unknown. There is no evidence either for or against the assumption that "thrombotic purpura" is caused by some unknown type of infection. The presence of a powerful toxin could explain the hemolytic anemia, the capillary damage, and the change in the clotting mechanism which are present in this disorder. That some abnormality of the clotting mechanism is present seems very likely but no systematic studies have been performed until now. Bernheim examined cadaver blood for platelet agglutinins but was unable to demonstrate such antibodies.

Schwartzman, Klemperer and Gerber produced lesions similar to those seen in "thrombotic purpura" experimentally in animals by inducing the Schwartzman phenomenon. These findings may offer some kind of explanation of this enigmatic disease.

PROGNOSIS AND TREATMENT: FURTHER INVESTIGATIONS

Our knowledge of "thrombotic thrombocytopenic purpura" is based on cases with a fatal outcome. Whether milder, unrecognized variations of the disease exist, from which recovery is possible, is unknown. One case showed transitory improvement. Splenectomy was performed in two cases but the patients died immediately after the operation. On theoretical grounds there seems to be no indication for such an operation, as no inhibition of the marrow appears to be present. If the disease is diagnosed in vivo, treatment with heparin or dicoumarol may be indicated.

If in the future an ante mortem diagnosis of "thrombotic purpura" should be made, the following studies might be of interest.

It has been pointed out that the anemia present is of the hemolytic type; the
mechanisms involved are unknown. It may be worthwhile to look for incomplete immune bodies attached to the red cells by means of an anti-human globulin serum; this procedure has proved its value in cases of acquired hemolytic anemia. Differential fragility tests using lysolecithin and saponin as hemolytic agents may also be of interest.

Liver function tests (thymol turbidity, bromsulfphthalein) should be performed in order to determine the role which the liver plays in the pathogenesis of the icterus. It is well known that inability to remove bilirubin from the blood is one of the first signs of hepatic damage.

Assays of splenic 'hormone' may be of interest. Studies of the clotting mechanisms step by step are definitely indicated. Particular attention should be given to the newly discovered plasma factors of Owen. Quantitative evaluations of the number and type of the megakaryocytes using the technique of Limarzi and Schleicher should also prove valuable. Bacteriologic studies, particularly inoculation of animals, should be attempted.

SUMMARY

1. "Thrombotic thrombocytopenic purpura" is the name which we propose for a rare but well-defined disorder which manifests itself clinically as an acute febrile illness and which is characterized by (a) petechiae and ecchymoses, thrombocytopenia, prolonged bleeding time and poor clot retraction, (b) by a severe anemia out of proportion to any observed blood loss, (c) by mild acholic jaundice, hepatosplenomegaly, (d) by bizarre and intermittent mental and neurologic symptoms and signs, and (e) by a transient leukemoid reaction in the peripheral blood.

2. This clinical picture must be correlated with a remarkable histologic pattern, namely the presence of myriads of platelet thrombi in the small arterioles and capillaries of almost all organs of the body.

3. Eleven such cases have been described in the literature. One case of our own is added.

4. The clinical features of this disease are detailed and the differential diagnosis is discussed. It is emphasized that if the physician is familiar with this syndrome a correct clinical diagnosis may become readily possible.

REFERENCES


THROMBOTIC THROMBOCYTOPENIC PURPURA

THROMBOTIC THROMBOCYTOPENIC PURPURA: HEMORRHAGIC DIATHESIS WITH GENERALIZED PLATELET THROMBOSES

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