Thrombocytic Acroangiothrombosis

Febrile Anemia, Thrombocytopenia, and Thromboses of Damaged Capillaries and Arterioles

By Hall S. Tacket, M.D., and Russell S. Jones, M.D.

Two additional cases of a syndrome characterized by arthralgia, fever, anemia, thrombocytopenia, hemorrhagic manifestations, and thromboses of arterioles and capillaries are presented. Pathologic description is given in some detail. Resemblances to certain other processes, including the rickettsial diseases, “vascular collagen” diseases and other conditions are pointed out. Deficiencies in knowledge of the entity are emphasized and a plea is made for continued efforts to define precisely the natural history of the syndrome.

In recent years a new and distinct syndrome comprising fever, arthralgia, thrombocytopenia, anemia, focal neurologic signs and hemorrhagic tendencies has been defined. Thus far the disease has been diagnosed conclusively only at autopsy. The specific pathologic changes consist of widespread thromboses in capillaries, arterioles, and occasionally in venules. These thrombi, composed of hyaline material, platelets, and proliferating endothelial cells, are associated with alterations in the vessel walls. The syndrome is a nosologic entity and has been given various designations that vary in emphasis placed upon specific clinical or histologic features: “Thrombotic thrombocytopenic purpura,” “thrombocytic acroangiothrombosis,” “generalized (or disseminated) capillary and arteriolar platelet thrombosis,” “acute febrile anemia and thrombocytopenic purpura with vasothromboses,” and “diffuse platelet thromboses with thrombocytopenia and hemolytic anemia.”1–7 The syndrome is being recognized with increasing frequency, and approximately 30 cases have now been reported in the literature since the original description by Moschcowitz1 in 1925. There have been several reviews of the reported cases, the first in 19362 and two others in 1947.3,4

Since the diagnosis can be established at the present time only by the recognition of the characteristic vascular changes at autopsy, it is obvious that the natural history of the disease is incomplete. There may be mild and transient or relapsing and chronic forms that are nonfatal. The failure of clinical recognition even of the reported severe and fatal cases is reflected in the lack of careful search for etiologic agents. Complete serologic, bacterial and animal inoculation studies have not yet been made. While the etiology is unknown and the natural history poorly defined, the syndrome is of considerable interest in its possible relationship to the rickettsial diseases, to the “vascular-collagen” group such as lupus erythematosus, polyarteritis nodosa and rheumatic fever, and to allergic phenomena in general. The difficult clinical differentiation of thrombocytic acroangiothrombosis from such diseases, and particularly from thrombocytopenic purpura, justifies dissemination of information regarding each case as it becomes recognized. Thus, the diagnosis of future cases may be more timely established and investigation of etiology and effective therapy may be stimulated.

Case Reports

Case 1. A 45 year old Negro male with a painful, inflamed, left eye was seen on Dec. 8, 1948. Weight loss of 15 pounds had occurred during the preceding three months, and weakness and pain in the hips and thighs, aggravated by activity, had been present for two months. A diagnosis of iridocyclitis was made. The patient received six intramuscular injections of 10 ml. of milk during the ensuing three weeks. Two weeks later the patient began to suffer from severe, constant, left supraorbital headache. On
Jan. 3, 19:9 he awakened with diplopia and inability to open the left eye. Physical examination disclosed ptosis of the left eyelid, slight left exotropia, and inability to move the eye upward, medially, or downward. Red blood cells numbered 4.02 million per cu. mm., white blood cells 7,550 and hemoglobin 11.5 Gm. per 100 ml. Platelets numbered 2 to 3 per oil immersion field. There were 95 per cent polymorphonuclear leukocytes, 4 per cent lymphocytes, and 1 per cent large mononuclear cells. The urine contained 2 plus albumin and innumerable leukocytes and occasional erythrocytes. Serum bilirubin was 0.3 mg. direct, 2.0 mg. total. Following cystoscopy, at which a few, small, scattered petechiae were noted in the mucosa of the bladder, massive hematuria persisted until the patient's death. Hemorrhages developed in the eye grounds and skin of the arms. On January 19, the platelets numbered 29,000 per cu. mm. (Rees-Ecker). The reticulocyte count was 12.5 per cent. The bleeding time (Ivy) was longer than 294 minutes. The clotting time was 5 minutes. No increased capillary fragility was demonstrated. Prothrombin time was 100 per cent. The bone marrow showed many mitoses in the erythroid series and many megakaryocytes. Cellular distribution was approximately normal. Fever ranging from 99 F. to 104 F. persisted throughout hospitalization. Splenectomy was done as a last resort; the patient expired 40 minutes after completion of the operation.

Pathologic Findings

The only important gross changes were hemorrhages in the brain, gastrointestinal tract and urinary tract. The vascular changes were most prominent in the adrenal glands, myocardium, spleen, brain, kidneys and urinary bladder.

The brain presented several 3 mm. areas of hemorrhage in the brain substance. Mircoscopically, granular and hyaline masses occluded the lumens of small veins, arterioles, and capillaries, most frequently in the cerebral cortex. Proliferation of the endothelium not only accompanied these thrombi, but often occurred where no thrombi were present.

Microscopic changes in the small vessels of the myocardium were marked. In the capillaries endothelial proliferation was prominent, while in arterioles and venules the smooth muscle cells of the media were also of increased prominence. Between the enlarged and proliferated medial and endothelial cells, there were zones of vacuolization and granular homogeneous material which appeared to project into the lumen, raising the endothelium above it. Less frequent than these changes were granular, eosinophilic thrombi in the vessel lumens. These thrombi were usually attached to one portion of the wall, leaving a crescentic portion of the lumen unoccluded. Some of these intraluminal masses contained huge and bizarre nuclei, either the aggregation of several nuclei or a single nucleus. Several small vascular lesions were older than others, for partial organization by fibroblastic cells and collagen fibers had already occurred. Occasionally, the adventitial connective tissue contained a few mononuclear leukocytes and some macrophages laden with ochre-colored pigment.

Many of the pulmonary capillaries and several small pulmonary arteries contained finely granular thrombi with the previously described alterations in their walls. The same vascular changes were present in the spleen and liver. The adrenal glands were the sites of the most extensive vascular changes. These changes, similar to those already described in the myocardium, extended only a short distance into the cortex, leaving the sinusoids of the inner zones intact. The arterioles to the renal glomeruli, those among the convoluted tubules of the cortex and about the pericyveal tissue occasionally showed areas of vascular change similar to that described in other organs. The characteristic mural and luminal changes were seen in the mucosa and muscularis of the urinary bladder, associated with hemorrhage and moderate numbers of mononuclear leukocytes in the adjacent connective tissue.

The bone marrow presented a few vessels with the characteristic vascular changes. The megakaryocytes were present in the usual number and possessed the usual morphologic features. Other cells of the bone marrow showed no significant changes.

Case 2. R. L. L., a 54 year old white man, had had cavitary pulmonary tuberculosis during the four years prior to his terminal episode. In May, 1951, he began to complain of malaise, weakness, and mild headache. Three days later he was found lying in bed with motor aphasia. He became semicomatose and had a slight convulsion followed by vomiting. Fever ranged between 100 and 104 F. (rectal). The urine contained 2 to 4 plus albumin and few to many casts and erythrocytes. Blood nonprotein nitrogen ranged from 53 to 65 mg. and creatinine from 3.4 to 3.8 mg. per 100 ml. The cerebrospinal fluid was normal. The red blood cell count ranged between 2.86 million and 1.93 million per cu. mm., the hemoglobin between 8.5 and "less than 7.5" Gm. per 100 ml., the white blood cell count between 8,400 and 6,900 per cu. mm. with polymorphonuclear leukocytes between 66 and 57 per cent, lymphocytes from 22 to 27 per cent, monocytes from 3 to 13 per cent, and eosinophils from 3 to 9 per cent. There was no estimation of the number of platelets. Bleeding time was 6 minutes, 35 seconds, coagulation time 7 minutes, 20 seconds. No acid-fast bacilli were found on direct smear of the sputum. Death occurred within a week following progressively deepening coma.

Pathologic Findings

The significant gross changes consisted of splenomegaly, cardiomegaly, petechial hemorrhages over the extremities, epicardium, and gastrointestinal tract, and pulmonary tuberculosis. The vascular
Fig. 1. Legend on facing page.
wall changes and "hyaline" thromboses were most marked in the myocardium, kidneys, adrenal glands, posterior lobe of the pituitary, and pancreas. The brain showed the same vascular wall changes, and granular and hyaline thrombi in the arterioles and capillaries as were noted in the first case. There was considerable involvement of the small vessels of the posterior lobe of the pituitary. The heart was soft and pale with scattered petechial hemorrhages throughout its substance and over its surface. Microsections showed disruption of the vessel walls by vacuolization and granular material with occlusion of the lumina partially or completely by "hyaline" masses containing variable numbers of endothelial or fibroblastic cells. A few of these thrombi appeared older than others, being replaced by older fibroblasts and collagen. About such vessels a moderate number of mononuclear leukocytes with basophilic cytoplasm was present. A number of capillaries showed marked proliferation, of endothelium without luminal masses.

Scattered caseomalous lesions were present throughout both upper lobes of the lung and groups of tubercles were present in the apical portions of both lower lobes. No vascular changes consistent with aeroangiothrombosis were found in the pulmonary tissue either about or away from the sites of the tuberculous lesions. Some arterioles of the spleen, pancreas and retroperitoneal lymph nodes showed the characteristic mural and luminal changes. Changes in the adrenal vessels were less marked than in the previous case. Many small arteries, arterioles, and capillaries of the kidneys showed the mural and luminal changes. A few hyaline thrombi were seen in the capillary tufts. The parietal epithelial cells of Bowman's capsule were of increased prominence.

Discussion

Clinical and Laboratory Findings. The characteristic listlessness and malaise of this syndrome were not as outstanding in the first patient as in the second. Central nervous manifestations in our patients were less prominent than in many of the previously reported cases. The only neurologic lesion demonstrated involved the left third cranial nerve. The frontal headache in the first case could have been due to either irido-cyclitis or intracranial vascular disease. Hepatosplenomegaly was not observed in the first patient and was slight in the second. The febrile course is characteristic of thrombocytopenic aeroangiothrombosis. Purpura was outstanding in both patients. The persistence and unusual severity of the hematuria in the first case finally led to splenectomy as the therapeutic procedure of last resort.

The laboratory findings, most complete in case 1, were typical: the severe anemia, the prolonged bleeding time and normal clotting time, the thrombocytopenia, the hyperplastic bone marrow, and mild elevation of serum bilirubin. The negative tourniquet test, however, in our first case is contrary to the observation of this test in the majority of other reported cases.

Clinically, thrombocytopenic aeroangiothrombosis is most readily mistaken for idiopathic thrombocytopenic purpura. The following features may be more outstanding in thrombocytopenic aeroangiothrombosis than in idiopathic thrombocytopenic purpura: (1) splenomegaly, (2) jaundice, (3) fever, (4) prodromal symptoms of weakness, malaise, and joint pains, (5) focal

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**Fig. 1.** Examples of mural and luminal changes in thrombocytopenic aeroangiothrombosis.

A. Arteriole in the adrenal capsule shows marked changes in its wall and obliteration of most of its lumen. Masson stain × 225

B. Myocardial capillary with small thrombus partially covered by endothelial cells. Hematoxylin and eosin × 535

C. Small artery in myocardium with focal vacuolization of media and some increase in the subintimal tissue. Hematoxylin and eosin × 535

D. Branching epicardial vessel with thrombus containing endothelial cells, collagen and reticulin fibers interspersed among amorphous material (a) "fibrinoid" changes, (b) at point of branching, and loosely aggregated particles, apparently platelets (e). Masson × 460

E. Small artery with interrupted elastica interna and a lumen distended and occluded by endothelial and fibroblastic cells, collagen, reticulin and amorphous material. This represents an older, and more marked process than that in D. The thrombotic mass is undergoing healing. "Fibrinoid" changes—i.e., the reddish staining with fragmentation of collagen with Masson stain—was present in the adjoining tissue. Combined connective tissue stain (elastic, reticulin and collagen) × 535

F. The elastica interna of the lower arteriole is almost intact while that of the upper arteriole is no longer visible. There are some medial changes and moderate subintimal increase in both arterioles. This subintimal and luminal material is Schiff-positive and the reticulin fibers are of increased distinctness. Orcein-silver stain for elastin and reticulin × 535
neurologic signs rather than massive cerebral hemorrhages, (6) transient leukemoid blood picture, (7) anemia disproportionate to observed blood loss, and (8) frequent association with sensitivity phenomena. While these findings lead one to suspect thrombocytic acroangiothrombosis in a patient with purpura and thrombocytopenia, the syndrome cannot be positively diagnosed at the present time without the histologic demonstration of widespread thrombosis of the arterioles and capillaries in association with changes in the walls of these vessels.

Pathologic Changes. In thrombocytic acroangiothrombosis, there are changes in vessel walls as well as thromboses within the vessels. Some writers have thought that the thromboses were the initial lesions, but Altschule and later Trobough suggested the primary defect to be in the vessel wall at the arteriolarcapillary junction. Gore's reconstruction of the development of the thrombotic lesions confirms these observations and concurs with the findings in our two cases. Apparently there is an initial accumulation of vacuoles of unidentified content and granular, hyaline material in the arteriolar or capillary wall. The granular material, which stains red with the leukofuchsain, accumulates predominantly within the intima and above the elastica interna. The latter becomes fragmented and may disappear. With the continued accumulation of material, it may rupture externally, causing hemorrhage into the surrounding tissues. It also extrudes intraluminally where the material is rapidly covered by aggregates of platelets and then by endothelial and fibroblastic cells. The thrombus may propagate along the length of the vessel, which is usually quite distorted and which may present focal aneurysmal dilations. Perivascular leukocytic response is mild. There is mild “fibrinoid” alteration in portions of the vessel wall and in the perivascular connective tissue.

The older elongated fibroblasts and the collagen fibrils in some of the thrombotic lesions suggest that the lesions are of different ages, but there is no conclusive evidence that they occur in “crops.” The granular mural material and intraluminal mass is red in color with periodic leukofuchsain (Schiff) stain, orange-red with phosphotungstic acid, red with Giemsa and with hematoxylin and eosin, and red to green with Masson stain. Fat stains indicate that it has no lipid content. It is obvious that the exact nature of the material cannot be determined by these staining procedures. Many vessels showed changes in the wall without accompanying thrombi and many of the “thrombi” in our two cases actually consisted of this mural substance. Unmistakable groups of platelets and even a few leukocytes and erythrocytes were sometimes incorporated in and about these masses, however. Healing apparently occurs by the deposition of collagen and reticulin about fibroblastic and endothelial cells in the thrombus.

Pathogenesis. It is evident that definition of predisposing and inciting causes of thrombocytic acroangiothrombosis is entirely speculative. Primarily because of the lack of clinical recognition of this syndrome, complete studies in an effort to demonstrate an infectious etiologic agent have not yet been made. Exploration of relationships and similarities to other diseases gives some clues, of perhaps dubious value, to the underlying cause of the syndrome.

In common with many diseases, especially those of the vascular system such as polyarteritis nodosa, temporal arteritis, thrombangiitis obliterans, idiopathic migratory thrombophlebitis and even arteriolosclerosis, this syndrome represents an entity established by a combination of clinical and pathologic findings. Only severe and fatal cases have been recognized and recorded in the literature, and many less severe cases may remain unrecognized. Its relation to other syndromes of unknown etiology and uncertain pathogenesis remains obscure. For example, an atypical case of disseminated lupus erythematosus may present many of the features of thrombocytic acroangiothrombosis such as splenomegaly, anemia, thrombocytopenia, purpura, hematuria, arthralgia, and even arteriolar and capillary thromboses.

Purpura is generally classified by the presence or absence of an inciting agent and of thrombocytopenia. Apparently the arteriolarcapillary junction is the site of vascular rupture both in nonthrombocytopenic purpura and
in the thrombocytopenic form. This site of vascular rupture was shown by Humble to be common to a wide variety of purpuric conditions. The arteriolarcapillary junction is, also, the predominant site of vascular damage in acroangiothrombosis, suggesting a relationship between this disease and other purpuras. However, no mural damage or thrombi have been observed in cases of either secondary or primary thrombocytopenic purpura by Nickerson and Sunderland or by us in a review of autopsies of patients with thrombocytopenic purpura.

The cause for the reduction in platelets in idiopathic thrombocytopenic purpura is not conclusively established. The relative rates of intravascular accumulation and lysis of platelets are proposed by Gore as factors determining the presence or absence of the platelet thrombi in acroangiothrombosis. It is conceivable that the thrombocytopenia in both syndromes may arise from the same mechanism, and the absence of vascular thrombi in thrombocytopenic purpura may be due to preponderance of factors favoring lysis of platelets. The thrombocytopenia of thrombocytopenic acroangiothrombosis has been attributed to exhaustion of circulating platelets by the formation of platelet thrombi. Recent indications that the thrombi are composed largely of material other than platelets may require revision of this concept.

Hyaline thrombi occur in the arterioles and capillaries in many different diseases, for example, arterioloscleroser with uremia, septicemia, disseminated lupus erythematosus, and sulfonamide reactions. The wide dissemination of thrombi in arterioles and capillaries whose walls are altered assists in the morphologic distinction of thrombocytopenic acroangiothrombosis from these conditions. Among other diseases resembling thrombocytopenic acroangiothrombosis are certain rickettsial diseases. Fever, headache, mental symptoms, prostration, myocarditis, pulmonary vasculitis, petechial hemorrhages in viscera, and a purpuric rash with arteriolar necrosis and thromboses are features in common. Morphologic distinctions in epidemic typhus and Rocky Mountain spotted fever are based on the prominent perivascular leukocytic infiltration and endothelial cell damage without the occurrence of thrombi. Although in cases of scrub typhus platelet thrombi may be found in the eschar, the rash, and infrequently in the septal capillaries of the lung or the glomerular tuft capillaries of the kidney, the predominant involvement of the venules and veins, the occurrence of “typhus nodules” in the brain, and certain “allergic” responses such as fibrinoid necrosis of collagen, necrosis of lymph nodes and spleen, and a characteristic cellular infiltrate serve to differentiate the two conditions. Rickettsias may be demonstrated in the swollen endothelial cells of the altered vessels.

Toxoplasmosis in the adult may also be similar both clinically and pathologically to thrombocytopenic acroangiothrombosis. The presence of a red maculopapular skin eruption and the absence of focal neurologic signs, thrombocytopenia, and profound anemia assist in the clinical differentiation. Although uveitis may occur, the ocular lesion is usually chorioretinitis. Toxoplasma may be identified in the cutaneous papules, the cerebrospinal fluid, the bronchioles, and the myocardium. Hyaline thrombi are not prominent.

Although thrombocytopenic acroangiothrombosis resembles in several respects diseases of rickettsial or other infectious origins, there are, also, indications of a possible allergic etiology. Little is gained from grouping this syndrome as an allergic disease, for “allergy” or “hyper-sensitivity” itself is a most nebulous and poorly understood body response which has gained a false distinction through long uncritical usage. The body responds to each disease due to a known etiologic agent, including the rickettsial diseases, with some component of “allergy” and “immunity.” In Ehrlich’s case the disease seemed to follow the administration of an iodine compound. Some reported patients have had a history of sensitivity to sulfonamide drugs, and others have had urticaria. The importance of a reaction to nonspecific protein therapy, consisting of intramuscular injections of milk, in the genesis of our first case is an intriguing consideration. Such therapy could have aggravated milder lesions characterized by iridocyclitis, malaise, and arthralgia. The possibility exists that certain therapeutic measures and other
circumstances may precipitate or aggravate a nonspecific body response, resulting in the complete development of this syndrome. Thrombocytic acroangiothrombosis cannot yet be relegated to the allergic group of vascular and connective tissue responses, at least until there has been a careful search for etiologic agents.

SUMMARY

Two additional cases of a syndrome characterized by fever, anemia, hemorrhagic manifestations, central nervous symptoms, and the occurrence histologically of thrombotic occlusions of capillaries are presented. The two cases, in general, were analogous to the previously reported cases with quantitative rather than qualitative variation in symptomatology from them. The synthesis of clinical and pathologic data in these cases comprises a discrete nosologic entity. There are, however, resemblances to other processes including thrombocytic purpura, rickettsial diseases, certain allergic phenomena, and the large group of vaguely defined "vascular collagen" diseases such as disseminated lupus erythematosus and polyarteritis nodosa. Various clinical and pathologic features permit differentiation from such diseases. The cause of the condition remains obscure, although similarities with other diseases of known etiology, particularly the rickettsial group, may give some hint of the nature of the inciting agent. Sufficient investigation with respect to a possible infectious etiology has not yet been done to permit exclusion of such causation. Until all etiologic possibilities have been evaluated, categorization of the entity as a manifestation of allergy, as has been previously suggested, is not justified.

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HALL S. TACKET and RUSSELL S. JONES

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