LEUKEMIC CELLULAR THROMBI IN PULMONARY BLOOD VESSELS

Subleukemic Myelogenous Leukemia Following Chloramphenicol-induced Aplastic Anemia

JOHN S. MEYER, MD,* AND MICHAEL BOXER, MD†

After an 8-year period of aplastic anemia following chloramphenicol therapy, a 39-year-old woman developed subleukemic acute myelogenous leukemia, and she died with Pseudomonas sepsis 18 months later. Autopsy demonstrated leukemic cellular thrombi that partially or completely occluded many small pulmonary arteries, arterioles, and small veins. Scattered among the leukemic cells in the thrombi were hemosiderotic histiocytes reflecting transfusional hemosiderosis. The staining characteristics, esterase activity, and electron microscopic appearances of the cellular thrombi confirmed their myeloid leukemic nature. The leukemic cells were cemented together by fibrin. We propose that the leukemic cells produced procoagulants that initiated coagulation on their surfaces, and that the leukemic thrombi are the morphological counterpart of a local accelerated intravascular coagulopathy. The possible clinical significance of pulmonary leukemic thrombi is discussed.

THE TERM "LEUKEMIC THROMBUS" HAS BEEN used to describe aggregates of leukemic cells that occur in pulmonary alveolar capillaries when the white blood cell count has been very high.[1,16] Fibrin has not been described in these cellular aggregates, and no one has demonstrated that thrombosis plays a role in their formation or that the leukemic cells are fixed in place like the neoplastic cells of a carcinomatous throbus. True thrombi are not often present in the pulmonary arteries of autopsied leukemic patients, and evidence that leukemic cells instigate thrombosis in pulmonary vessels is lacking for ordinary forms of leukemia.[12,17,22,30] Even in the promyelocytic variant, in which intravascular coagulation often plays a prominent role, the lungs usually are free of thrombi,[27] Those fibrin-containing thrombi that have been reported have not contained appreciable numbers of leukemic cells.[4,26,27]

We describe here what we believe is the first reported instance of true leukemic cell thrombi in the pulmonary blood vessels and discuss the significance of the finding. We will present evidence that the leukemic thrombi may have resulted from release of procoagulants by the leukemic cells.

CASE REPORT

B.M., a 30-year-old Caucasian woman, was admitted to The Jewish Hospital of St. Louis in August 1962, for evaluation of weakness and easy bruising. Six months previously, following a cesarean section, she developed a urinary tract infection which was successfully treated with chloramphenicol (3.5 g over a 6-day period). She was pale and had small petechiae over the oral mucous membranes and several ecchymotic areas over the legs and arms. The heart and lungs were normal. The splenic tip was palpable on deep inspiration. Lymph nodes were not enlarged. The urine was normal, the hematocrit was 13% with a hemoglobin of 3.6 g/100 ml, and the white cell count was 1,859/mm^3 with 4% band forms, 21% neutrophils, and 75% lymphocytes. The platelet count was 3,000/mm and the reticu-

From the Department of Pathology and Medicine, Washington University School of Medicine, and The Jewish Hospital, St. Louis, Mo.

* Assistant Professor of Pathology, Washington University School of Medicine, St. Louis, Mo., and Associate Pathologist, Department of Pathology and Laboratory Medicine, The Jewish Hospital of St. Louis.

† Assistant in Medicine, Washington University School of Medicine, and Department of Medicine, The Jewish Hospital of St. Louis.

Ann Ainsworth, MD, performed the autopsy. The electron microscopy was done in the Department of Pathology, John Cochran Veterans Administration Hospital, St. Louis, Mo.

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Address for reprints: John S. Meyer, MD, The Jewish Hospital of St. Louis, 216 South Kingshighway, St. Louis, Mo. 63110.

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locyte count was 1%. Clot retraction was incomplete after 24 hours. Prothrombin and partial thromboplastin time were normal. Bone marrow aspiration showed a hypocellular marrow, and a diagnosis of aplastic anemia was made. She received seven 500-ml units of whole blood and was sent home with a prescription for prednisone 5 mg three times a day, and a hematinic containing intrinsic factor, cobalamin, iron, ascorbic acid, and folic acid.

Over the next 15 months, she received transfusions totaling 23.5 liters of whole blood in order to maintain her hematocrit between 30 and 40%. During this period, multiple episodes of purpura developed, and her spleen was always palpable on deep inspiration. She continued to take prednisone and the hematinic and also received periodic vitamin B injections. Bone marrow aspirations performed 2 and 6 months after the diagnosis had been established revealed moderately cellular marrows with a maturation arrest of the granulocytic series and normal proportions of erythroid and myeloid cells and megakaryocytes. During this period, she developed herpes zoster ophthalmicus which eventually resulted in enucleation of the left eye after five attempts at corneal transplantation.

In November 1963, 15 months after diagnosis, her peripheral blood counts returned to normal. The hematocrit ranged from 35 to 42%, the white cell count ranged between 3,000 and 4,800/mm^3, and the platelet count stabilized at 210,000/mm^3. She received no further therapy other than the hematinic, isoniazid, vitamin B_{12}, and prednisone for the next 75 months. In March 1970, her hematocrit fell to 19%, and the white cell count was 2,100/mm^3. A bone marrow aspiration showed a profusion of young reticulum cells and forms suggesting monoblasts or stem cells. An acid hemolysis (Ham) test showed no excess hemolysis. During the next 18 months, she received 57 units of buffy-coat poor packed red blood cells. Her course was complicated by a staphylococcal septicemia from an intravenous catheter, and she developed dysfunctional uterine bleeding that was successfully treated by radiation castration. Oral candidiasis and spontaneous hemorrhages into the thighs occurred. Her medications during this period included nystatin, isoniazid, prednisone, and androgens.

Three days prior to her final admission in September 1971, she became febrile, and her level of consciousness began to deteriorate. She was hospitalized with a temperature of 103.8F, pulse 144, respiratory rate 28/min., and blood pressure 100/70mm Hg. She was responsive only to deep pain. Her skin was deeply bronzed. There was no papilledema and no palpable adenopathy. Her lungs were clear, and the liver was palpable 10 cm below the right costal margin. The hematocrit was 12.6%, the hemoglobin was 4.6 g/100 ml, and the white cell count was 1,400/mm% with 30% blast cells. A platelet count was 4,000/mm^3. The prothrombin concentration was 31.5% of control, and the whole blood partial thromboplastin time was 65 sec. (control 40 sec.). The blood serum levels of urea, glucose, and electrolytes were normal. A chest roentgenogram revealed multiple ill-defined densities throughout both lung fields suggestive of multiple pulmonary abscesses. She was treated with cephalothin and gentamicin intravenously, pharmacologic dosages of corticosteroids, and three units of buffy-coat poor blood. *Pseudomonas aeruginosa* grew from blood cultures. Her temperature rose to 105.2F, blood pressure became unrecordable, pulse rose to 160 and respirations to 60/min., and she died 42 hours after admission.

MATERIALS AND METHODS

An autopsy was performed 5 hours after death, and tissues were fixed in 4% formaldehyde buffered to *p*H 7.0 with phosphates. Sections were cut at 5 μ from paraffin-embedded blocks for light microscopy and were stained with hematoxylin and eosin, Giemsa, PAS. Turnbull's Prussian blue stain for hemosiderin, Verhoeff's elastic tissue stain, and Leder's naphthol AS-D chloroacetate esterase stain.[18] The esterase stain was controlled by substituting $NaNO_3$ for $NaNO_2$ (negative reaction), and with sections containing mast cells (positive reaction) and pulmonary arterial breast carcinoma thrombi (negative reaction). Following formalin fixation, we selected blocks of small pulmonary blood vessels from wet lung tissue with aid of a hand lens for electron microscopy. These blocks were post-fixed in glutaraldehyde and osmium tetroxide, dehydrated in ethanol, and embedded in epoxy resin. Thin sections mounted on copper grids were stained with uranyl acetate and lead citrate.

POSTMORTEM OBSERVATIONS

Gross examination: The body was well nourished. The skin was bronzed, and numerous ecchymotic lesions, some with bullous centers, were present. The serous cavities contained small effusions. The heart weighed 250 g and showed no abnormal pigmentation. The lungs weighed 800 g and contained scattered

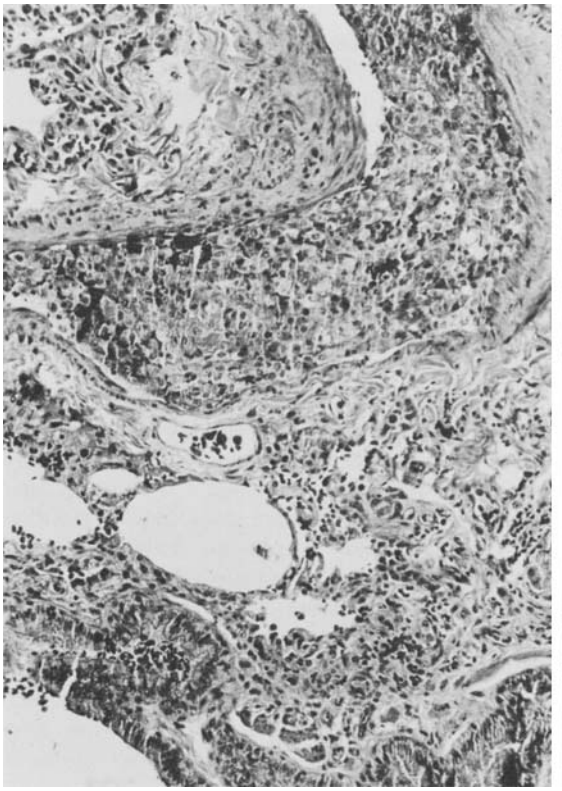
hemorrhagic nodules 0.5 to 1.5 cm in diameter. No thrombi, webs, or bands were present in the pulmonary arteries. The liver weighed 1,850 g and was brownish-yellow with a normal lobular pattern. The spleen weighed 320 g and was brownish. Lymph nodes and pancreas were brown and not enlarged. The kidneys weighed 130 and 150 g, and their architectural markings were normal. The adrenal glands were atrophic (total weight 16 g). The bone marrow of vertebrae and femoral shaft had a cellular, brown appearance. The prosector noted no significant changes in the other organs.

Microscopic findings including histochemistry: The skin and lungs showed numerous necrotizing lesions in which bacilli had infiltrated the walls of blood vessels, and *P. aeruginosa* was cultured from the blood and lungs. The reticuloendothelial cells of the liver, spleen, bone marrow and lymph nodes contained large amounts of hemosiderin, and hemosiderin was also abundant in the parenchymal cell cytoplasm of the liver, renal tubules, pancreatic acini and islets, zona glomerulosa of the adrenal glands, and thyroid gland. Hemosiderin was not present in the myocardium, and the pattern of its distribution was typical of advanced hemosiderosis occurring in patients with aplastic anemia who have received a great many blood transfusions.[7,25] Neither the liver nor the spleen showed fibrosis.

Hematopoietic cells and fat cells each occupied about 50% of the volume of the bone marrow of the ribs, vertebral bodies, and the femoral shaft. Although the cellularity was within normal limits for the first two sites, the femoral shaft marrow was undoubtedly hypercellular. The hematopoietic cells in the marrow consisted chiefly of primitive myeloid cells with round or oval nuclei, one or more prominent nucleoli, and small to moderate amounts of cytoplasm. Very few erythroid precursors and megakaryocytes were present. The marrow was not fibrotic. Naphthol AS-D chloroacetate esterase stains showed strong to moderate staining of many primitive cells of the bone marrow as well as the more mature myeloid cells. Hemosiderin-containing cells were uniformly esterase-negative. The red pulp of the spleen contained moderate numbers of primitive, esterase-positive leukemic cells, and similar cells were scattered in the sinuses of lymph nodes and adrenal medullae. Sinusoidal lining cells of the spleen and lymph nodes were esterase-negative. The liver did not contain a leukemic infiltrate.

The most striking finding was partial or complete occlusion of many small pulmonary arteries, arterioles and small veins by aggregates of cells resembling immature myeloid cells of the bone marrow (Figs. 1–3). These cells were packed in tight clumps and adhered to the vascular walls. Hemosiderin-containing histiocytes were mingled with them. Most myeloid cells in the pulmonary vessels were immature, but a few metamyelocytes and segmented granulocytes were present. The immature cells had round or oval nuclei, dispersed chromatin, and one or more nucleoli. Many of the immature cells, as well as the more mature granulocytes, showed a strongly positive esterase reaction (Figs. 2, 3). The proportion of esterase-positive cells in the pulmonary vascular deposits was approximately the same as in the femoral bone marrow. Hemosiderin-containing cells were consistently esterase-negative in both locations. Giemsa stains showed that the cells within the pulmonary blood vessels were more sparsely granulated than those of the bone marrow, although occasional well-granulated neutrophilic and very rare eosinophilic and basophilic cells were present in the pulmonary vessels. Small arteries showed fibrous intimal thickening where the leukemic cells were attached to their walls. We identified some vessels containing leukemic thrombi as veins because of position (far removed from bronchi or bronchioles) and chiefly collagenous, thin walls without well-defined inner and outer elastic lamellae, despite external diameters up to 2 mm (Fig. 3).

Electron microscopic observations: Primitive cells consistent with myeloblasts or promyelocytes, more mature myeloid cells of the neutrophilic series, and hemosiderin-containing histiocytes comprised the great majority of cells within the pulmonary vascular thrombi (Figs. 4, 5). Rare lymphocytoid cells were also seen. The primitive cells classified as myeloblasts contained nuclei with finely dispersed chromatin, and a prominent nucleolus was seen in some. We found occasional examples of nuclear membrane loops (cytoplasmic intranuclear protrusions) like those reported previously in leukemic myeloblasts.[2,5,31] The cytoplasm contained scattered round of oval mitochondria that often had clear centers. A few profiles of rough endoplasmic reticulum cisternae filled with finely granular, moderately electron-dense material were present.



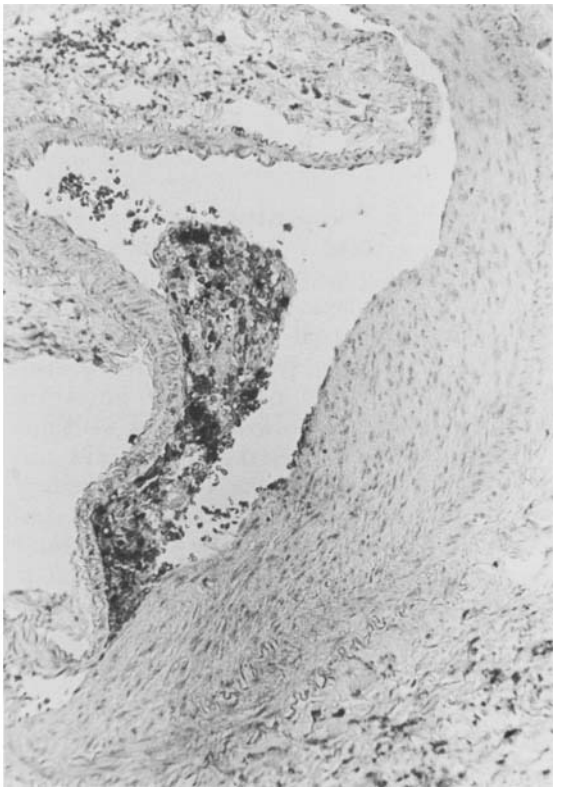


FIG. 1 *(left)*. Pulmonary artery (top) is occluded by a mass of leukemic cells (leukemic thrombus). At the bottom is a bronchiole (H and E, ×115).

FIG. 2 *(right)*. Pulmonary artery contains mural leukemic thrombus that only partially occludes lumen. Black granules in photograph represent orange esterase reaction product in thrombus. Note fibrous intimal thickening (naphthol AS-D chloroacetate esterase stain, ×115).

These cells contained variable numbers of cytoplasmic granules of two types known to exist in leukemic myeloblasts and promyelocytes.[2,5,31] One sort of granule (type A) was spherical, relatively large (up to 0.7 μ), and filled with moderately electron-dense granular of flocculent material. The other form of granule (type B) tended to be smaller (0.1–0.6 μ), often elongated, and was uniformly electron-dense. Distinct limiting membranes surrounded both types of granules. Intermediate forms containing both relatively electron-dense and electron-lucent areas were also present. The type B granules were more numerous than the type A granules. We identified juxtanuclear Golgi complexes in a few primitive myeloid cells. Glycogen particles were absent, but this is explicable as a result of postmortem glycolysis. Hemosiderin and ferritin were not present.

More mature granulocytes typical of neutrophilic myelocytes, metamyelocytes, and segmented granulocytes were identified in small numbers. These cells contained large numbers of the same types of granules noted in the more immature myeloid cells, with a relative preponderance of type A granules in segmented neutrophils.

Histiocytes contained elongated or indented nuclei with dispersed chromatin, and the distinguishing cytoplasmic features of markedly electron-dense, finely granular inclusions of hemosiderin and scattered tetrapolar ferritin molecules[29] (Fig. 6).

Electron-dense wisps of fibrin, with typical periodicity of about 200 Å, were present in narrow interstices between the myeloid and histiocytic cells of the leukemic thrombi (Fig. 7), and occasional erythrocytes were trapped in the thrombi. Walls of blood vessels containing the leukemic thrombi appeared intact, and endothelium separated the thrombi from the vascular basement membranes (Fig. 8). We did not note fibrin between the leukemic cells and the endothelium. However, we can not be sure that foci of endothelial damage

and fibrin deposits in contiguity with vascular walls were actually present but were not included in the sample of tissue studied by electron microscopy.

DISCUSSION

We interpret the patient's illness as chloramphenicol-induced hypoplastic anemia with eventual development of acute myelogenous leukemia. The diagnosis of acute myelogenous leukemia is supported by the presence of circulating blast cells, profound thrombocytopenia, and increased numbers of immature cells in the bone marrow associated with virtual disappearance of erythropoietic cells and megakaryocytes during the terminal period, and by the infiltrates of esterase-positive, immature, granulated cells in the spleen, lymph nodes , and pulmonary capillaries observed at autopsy. Hypoplastic anemia following chloramphenicol therapy is a well-established entity with reported incidences of 1/15,000 to 1/300,000, but cases of leukemia evolving from chloramphenicol-induced hypoplastic anemia are very rare.[14] Nevertheless, transition to acute myelogenous leukemia has been described.[6,8,10] The mechanism whereby chloramphenicol damages the marrow is not clear, although it is known to inhibit protein synhesis by binding to the 50-S ribosomes.[36] Dameshek proposed that the transition from marrow hypoplasia to leukemia might represent the emergence of a cell line genetically distinct from the chloramphenicol-damaged line.[9]

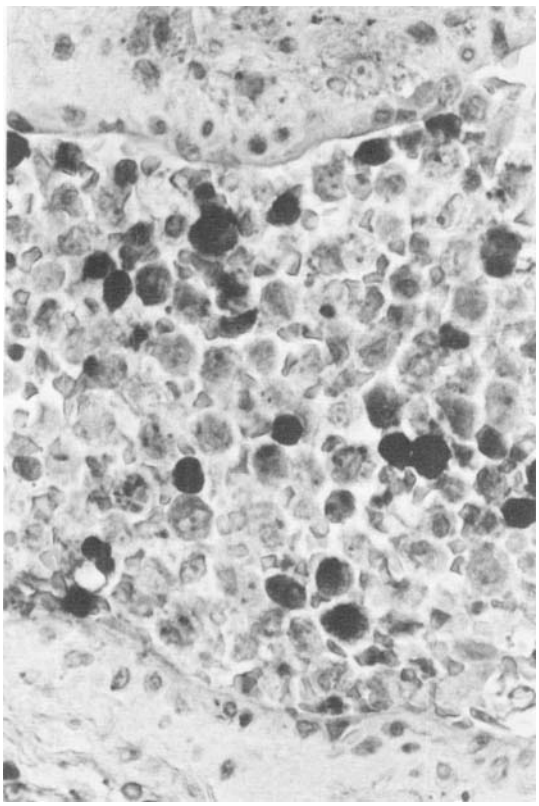


FIG. 3. Pulmonary vein occluded by leukemic thrombus. Note numerous granulocytes that are strongly esterase-positive (appear black) and nucleolated, immature granulocytes (naphthol AS-D chloroacetate esterase stain, ×420).

The participation of leukemic cells in the obstructive pulmonary vascular lesions of our patient has been established on morphological, histochemical, and ultrastructural grounds. The immature cells in the thrombi had nuclear and cytoplasmic features, including presence of Giemsa-stainable granules in some cells, consistent with those of myeloblasts and promyelocytes. The napthol AS-D chloroacetate esterase reaction was strongly positive in many of the immature cells, which is characteristic of myeloblasts and promyelocytes.[19] Electron micrographs confirmed the presence of granules in the immature cells and showed other features, including formation of nuclear envelopes, that are characteristic of immature leukemic myeloid cells.[2,4,31] These findings rule out a histiocytic or reticulum cell identity of the immature cells, even though hemosiderin-containing cells typical of histiocytes were present among them. We believe the hemosiderotic cells are not a part of the neoplastic process because they were naphthol AS-D chloroacetate esterase-negative and contained very large amounts of hemosiderin in cytophagosomes together with numerous scattered cytoplasmic ferritin molecules, while the leukemic cells lacked hemosiderin, ferritin, and cytophagosomes while having cytoplasmic granules of the neutrophilic myeloid cell types. We do not know why the hemosiderotic histiocytes accompanied the leukemic cells in the pulmonary vascular lesions. Histiocytes have not been described in intravascular pulmonary carcinomatosis or sarcomatosis,[3,15,21,24,32,33,35] nor have we been able to find them, even when stained for iron, in a case of pulmonary intravascular carcinomatosis that we recently studied. It is possible that histiocytes regularly accompany the cells growing in pulmonary blood vessels, but are readily recognizable only when they contain a hemosiderin marker.

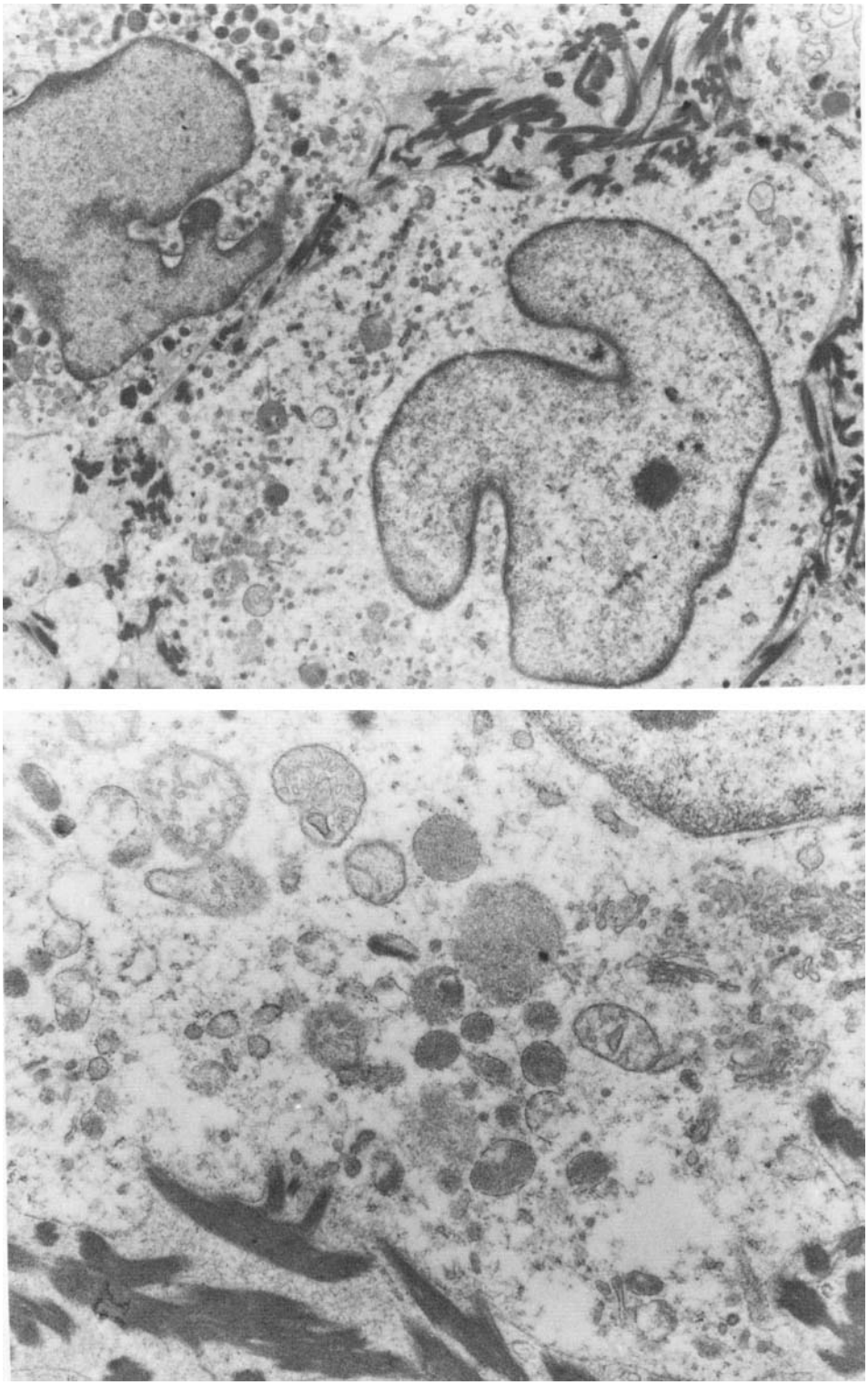


FIG. 4 *(top)*. Two immature granulocytes are separated from each other by narrow spaces containing fibrin (dark fascicles amid fine fibrils). The cell on the right contains a nucleolus, has finely dispersed chromatin, and relatively few cytoplasmic granules. The cell in the upper left is more mature and contains numerous granules of types A and B. Note intimate relationship between cell membranes and fibrin (uranyl acetate, lead citrate, ×9,000).

FIG. 5 *(bottom)*. Immature granulocyte contains juxtanuclear Golgi apparatus (upper right), mitochondria, and granules. Type A granules are relatively large and less dense than the smaller, type B granules. Fibrin is intimately associated with the cell membrane (lower margin), and extends into indentations of the cell membrane. The nucleus is immature and contains a large nucleolus (upper right) (uranyl acetate, lead citrate, ×25,000).

The pathogenesis of the leukemic thrombi in the pulmonary blood vessels invites speculation. We do not believe that they formed by trapping of leukemic cells in ordinary thrombi or emboli, because the leukemic thrombi consisted almost entirely of immature, nucleated cells with only small amounts of fibrin and few red blood cells, and the white blood cell count was never high. If leukemic cells had proliferated in and gradually replaced thromboemboli, we would expect to have found some unreplaced remnants of the thromboemboli together with pulmonary arterial webs and bands. Furthermore, the leukemic thrombi involved pulmonary veins as well as arteries. The leukemic throbi can not be bone marrow emboli because of involvement of veins and absence of lipocytes. Lipocytes were plentiful in all areas of the bone marrow that were sampled (vertebae, rib, and femoral shaft).

The presence of ultrastructually characteristic fibrin between the closely apposed cell membranes in the leukemic thrombi, the fibrous arterial intimal thickening at the sites of some lesions, and the fact that some cellular thrombi were eccentric and nonocclusive indicate that the process involved firm adherence of the cells in the manner of a tumor thrombus rather than mere impaction. The almost complete filling of narrow intercellular interstices by fibrin is consistent with antemortem coagulation rather than postmortem clotting. The cohesive aggregates of immature cells, which lack desmosomes or other forms of intercellular attachment plates, evidently were cemented together during life by the intercellular fibrin.

Until recently, granulocytes were thought to have only weak procoagulant properties. However sterile incubation of human and rabbit granulocytes results in appearance of strong

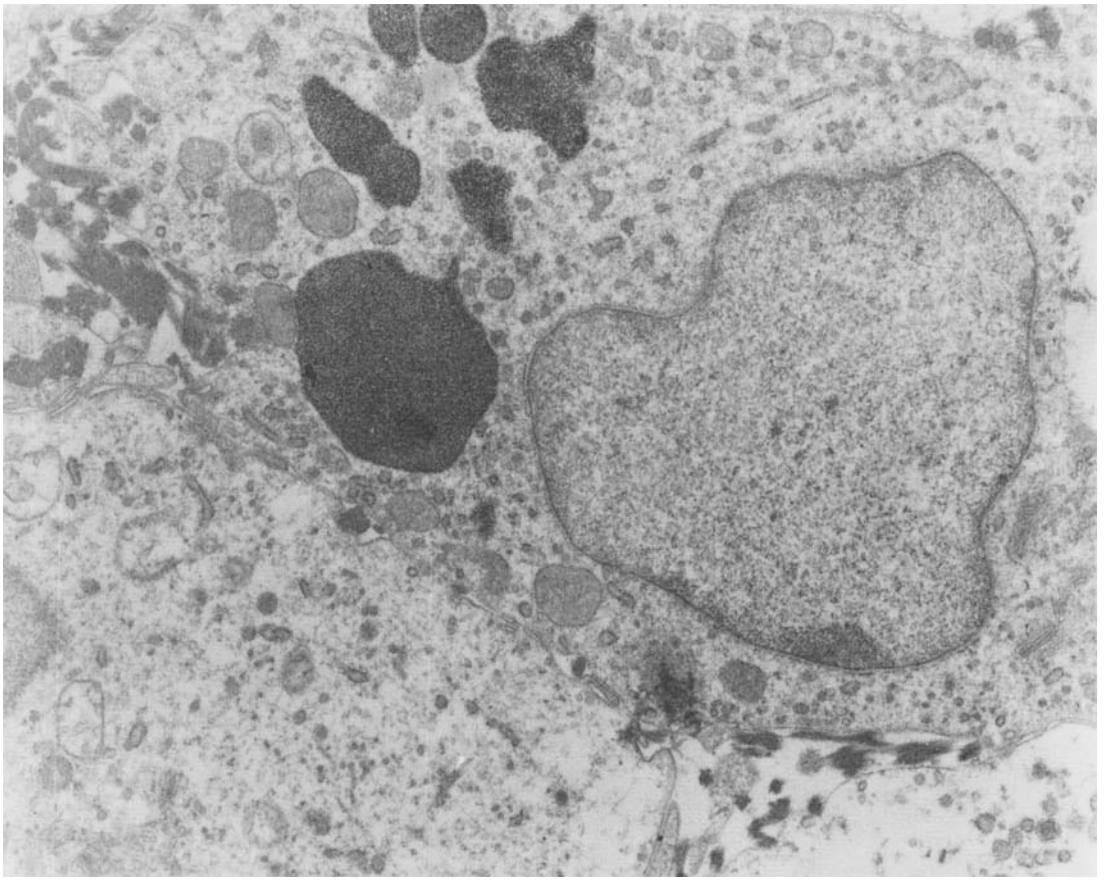


FIG. 6. Histiocyte in leukemic thrombus contains finely granular, electron-dense inclusions of hemosiderin (to left of nucleus). Fibrin is present in space separating it from an adjacent cell (upper left). Portions of two immature granulocytes are present (bottom) with fibrin in intercellular space (uranyl acetate, lead citrate, ×14,400).

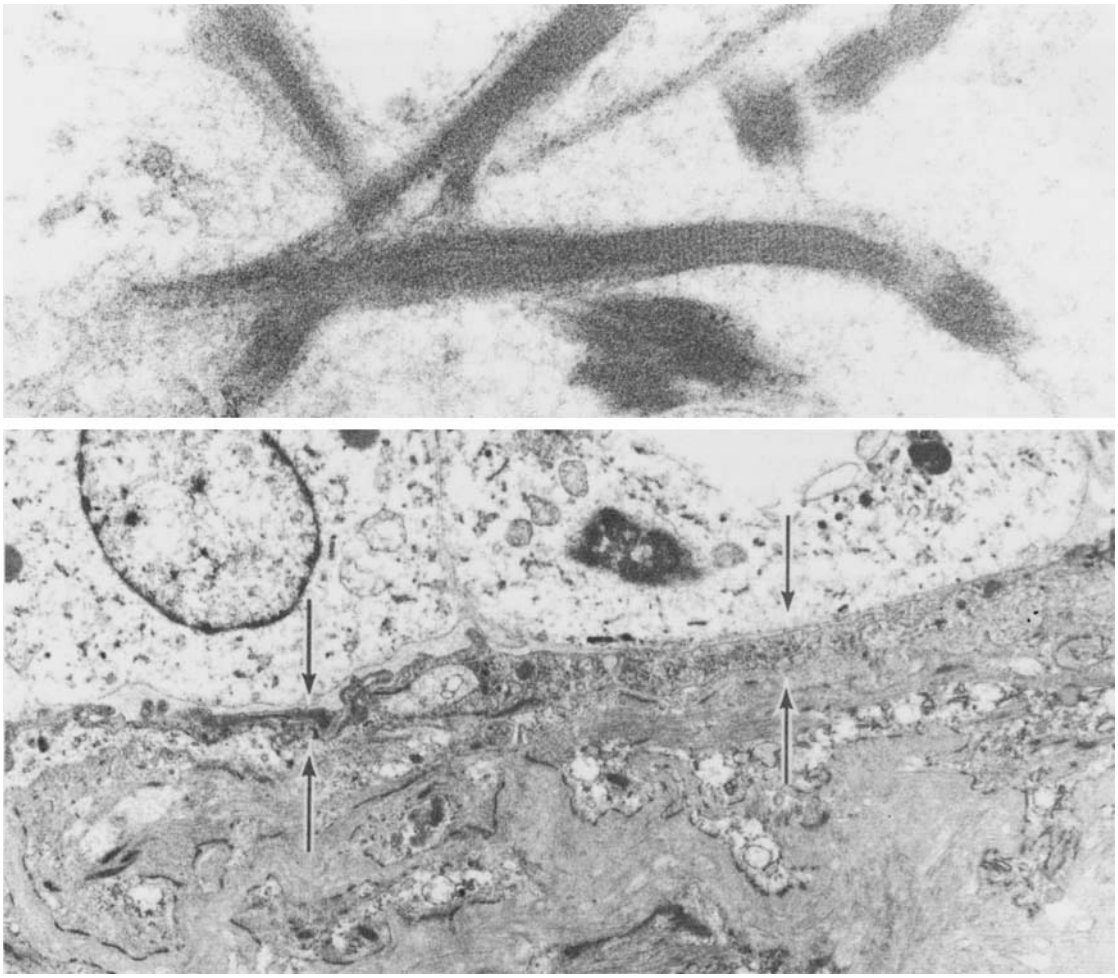


FIG. 7 *(top)*. Fibrin in intercellular space of leukemic thrombus shows typical regular periodicity of approximately 200 A (uranyl acetate, lead citrate, ×48,000).

FIG. 8 *(bottom)*. Leukemic thrombus in pulmonary vein is separated from the underlying wall of the vein by a layer of endothelium (arrows) (uranyl acetate, lead citrate, ×6,000).

procoagulant activity, mediated through activation of factor VII, and procoagulant development is enhanced by presence of endotoxin.[20,23] Gralnick et al.[11] have reported accelerated intravascular coagulation in a group of patients with acute leukemia of various types other than promyelocytic. The abnormality of coagulation caused clinical manifestations in some patients, but others had only laboratory evidence of it. The results of laboratory studies indicated that local intravascular coagulation and local, but not systemic, hyperfibrinolysis were occurring. All of these patients had elevated white blood counts with high proportions of blast cells. The leukemic pulmonary thrombi in our patient appear to be the morphological counterpart of local intravascular coagulation in which leukemic cells played a direct role. We interpret the presence of fibrin between the leukemic cells as evidence of a procoagulant effect of the leukemic cells. The absence of fibrin from the surfaces of the leukemic thrombi suggests an effect of plasmatic fibrinolysin, which evidently was unable to attack the fibrin sheltered from circulating plasma in narrow interstices between the leukemic cells. Since the leukemic thrombi appear to have antedated the terminal *Pseudomonas* septicemia, which was accompanied by prolongation of coagulation times consistent with accelerated intravascular coagulation, evidence that bacterial endotoxin initiated in their formation is lacking, although it may have contributed to their growth.

The hypercoagulative state that commonly

accompanies promyelocytic leukemia[26,27] appears to be related to the presence of azurophil granules and large, splinter-form granules demonstrated by electron microscopy.[34] Our patient did not have a predominance of promyelocytes, and we did not see splinter-form granules by electron microscopy or many azurophil granules by light microscopy of marrow films. We are unable to assign the presumed procoagulant activity in our patient's leukemic granulocytes to any cellular organelle.

The leukemic thrombi within pulmonary blood vessels are reminiscent of pulmonary intravascular carcinomatosis. Intravascular carcinomatosis of the lung is a well-recognized phenomenon, most often reported in carcinoma of the breast and stomach,[35] but particularly prone to occur as a complication of choriocarcinoma.[24] The malignant cells are commonly found in arteries, arterioles, and venules in association with fibrin and often with thrombi. Pulmonary vascular invasion appears to be a precursor of pulmonary lymphangitic carcinomatosis. Intravascular pulmonary carcinomatosis may produce enough vascular obstruction to cause cor pulmonale, but our patient had a lesser degree of vascular involvement without cor pulmonale.

True leukemic thrombi in pulmonary blood vessels could be clinically significant in three ways. First, the leukemic thrombi could represent a reservoir of neoplastic cells that would not be detectable by examination of bone marrow or blood or as enlargement of the parenchymatous viscera. Second, the leukemic thrombi might cause pulmonary infactions. Third, extensive leukemic thrombi could sufficiently obstruct the pulonary circulation to cause cor pulmonale, as in pulmonary vascular carcinomatosis.[3,35] This potential complication would have to be distinguished from the alveolar-capillary block that occasionally results from extensive non-thrombotic infiltration of alveolar septums by leukemic cells.[13,28] Although the extent of the leukemic pulmonary vascular thrombi did not reach the threshold of clinical manifestations in our patient, the condition may be regarded as a potential addition to the list of pulmonary complications of leukemia.

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