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Volume 37 | Number 1 Article 9

3-1989

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Van Slyck, Ellis J.; Raman, Sundara B. K.; and Janakiraman, Nalini (1989) "Primary Fibrinolysis in Acute Monocytic Leukemia," *Henry Ford Hospital Medical Journal* : Vol. 37 : No. 1 , 33-36.
Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol37/iss1/9

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Primary Fibrinolysis in Acute Monocytic Leukemia

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We present the case of a young man with acute monocytic leukemia (French-American-British classification:M5) and systemic hyperfibrinolysis with severe bleeding. Although fibrinolysis is usually mild and secondary to disseminated intravascular coagulation, its role as a primary and dominant factor in rare cases of leukemia warrants that its presence be sought as a cause of abnormal bleeding. Decreased serum plasminogen and increased serum plasmin determined by synthetic substrate assay and a negative protamine paracoagulation test are crucial findings. Use of high-dose epsilon-aminocaproic acid was effective in treating this complication. A transient increase in fibrinolytic activity coincident with the early effect of antileukemic treatment suggested that plasminogen activator and/or fibrinolytic protease substances were released from leukemic cells. Fibrinolytic activity subsequently disappeared with reduction in the population of leukemic cells. (Henry Ford Hosp Med J 1989;37:33-6)

Although thrombocytopenia is the abnormality associated with clinical bleeding in the majority of patients with acute leukemia (1), other disorders of coagulation are the principal culprits in some cases (2-6). The frequency of disseminated intravascular coagulation (DIC) in acute promyelocytic leukemia (French-American-British [FAB] classification:M3) is so well known that most clinicians treat patients thus afflicted with prophylactic heparin before initiating antileukemic chemotherapy (7-9). In a smaller number of cases of acute nonlymphocytic leukemia of all FAB types, the presence of DIC with or without secondary fibrinolysis has been described (10-15). Instances of apparent primary fibrinolysis, though rare, have been reported (16-19), although never previously in acute monocytic leukemia (FAB:M5). We report such a case and note some important diagnostic and therapeutic considerations.

Case Report

A 30-year-old carpenter came to the Emergency Room of Henry Ford Hospital on June 2, 1980, with atypical substernal pain. He was admitted with a possible myocardial infarction. Physical examination disclosed no abnormalities. The following day the substernal pain spontaneously disappeared, and subsequent studies failed to implicate any cardiac disease. However, WBC count was noted to be 13.2×10^9/L (13,200/μL) with 0.17 (17%) polys, 0.38 (38%) lymphocytes, 0.05 (5%) monocytes, 0.05 (5%) metamyelocytes, 0.23 (23%) myelocytes, 0.02 (2%) promyelocytes, and 0.10 (10%) blasts. The hemoglobin was 144 g/L (14.4 g%), hematocrit 0.42 (42 vol%), and the platelet count 161×10^9/L (161,000/μL).

A bone marrow examination showed overall cellularity of 90% with a myeloid-to-erythroid ratio of 10:1. It was infiltrated by sheets of blasts which were large with sizable spongy nuclei and multiple nucleoli (Fig 1). The cytoplasm of the blasts was abundant, blue, and occasionally vacuolated. Granulocytes were noted to be hypogranular. Special stains showed a strongly positive reaction to nonspecific esterase in most of the blasts. The Sudan Black B, specific esterase, periodic acid-Schiff, and toluidine blue stains showed nongranulocytic and nonlymphocytic reaction patterns. A diagnosis of acute monocytic leukemia (FAB:M5) was made. The patient was treated with doxorubicin 60 mg/M^2, vincristine 2 mg, cytosine arabinoside 200 mg/M^2 days 1-7, and prednisone 100 mg days 1-5 (ADOAP). Bone marrow examination on the eighth day showed 15% cellularity with no blasts present. On July 3rd, he had recovered from this induction course; his marrow was 70% cellular and in complete remission. The patient then received three courses of consolidation treatment with ADOAP followed by monthly maintenance with vincristine, cytosine arabinoside, and prednisone. He remained in remission through March 4, 1981 (eight months).

On April 22, 1981, the patient returned with gross hematuria of two days' duration. He had also recently noted bruises on the anterior thighs and had experienced epistaxis and bleeding gums. The physical examination confirmed abnormal bruising. The urine was grossly bloody. Laboratory studies showed a hemoglobin of 162 g/L (16.2 g%), WBC count of 24×10^9/L (24,000/μL) with 0.12 (12%) blasts. The platelet count was 192×10^9/L (192,000/μL). Bone marrow examination

Submitted for publication: November 4, 1988.
Accepted for publication: January 4, 1989.
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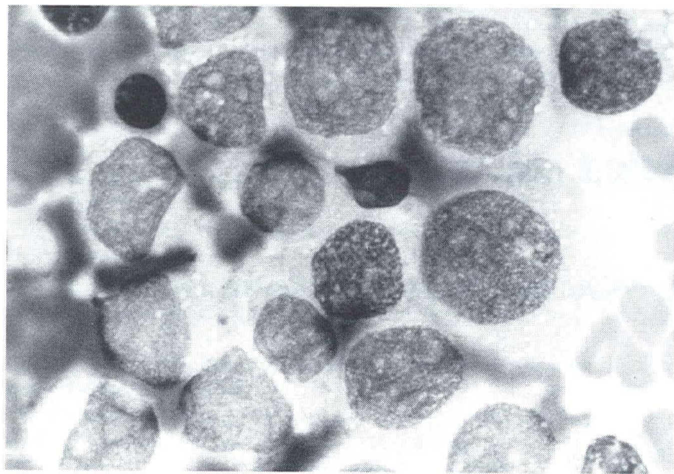

Fig 1—Bone marrow aspirate smear showing sheets of large blasts with abundant cytoplasm and sizable spongy nucleii containing several nucleoli (Leishman stain, X1000).

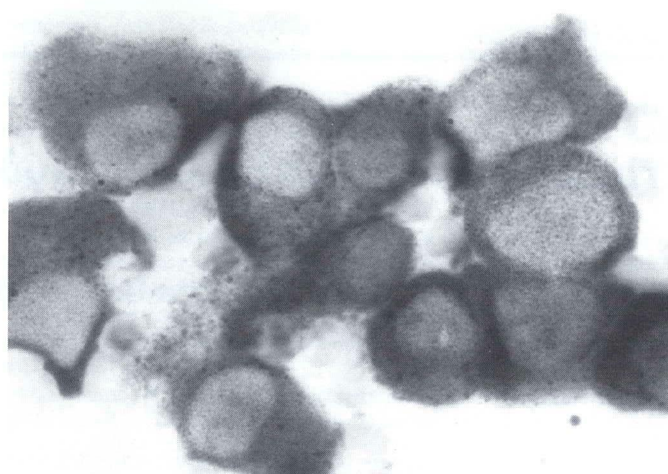

Fig 2—All leukemic blasts in this field show strong nonspecific positivity (alphanaphthol butyrate esterase, X1000).

showed marked hypercellularity with 0.892 (89.2%) large primitive stem cells. These cells again showed 94% positivity with nonspecific esterase stain and were diagnostic of acute monocytic leukemia (FAB:M5) in relapse (Fig 2).

The results of the coagulation investigation were as follows: activated partial thromboplastin time (APTT), done by modification of the method of Proctor and Rapaport (20) using automated APTT reagent (activator micronized silica) from General Diagnostics, was significantly prolonged. One stage prothrombin time (PT) done by the method of Quick (21) using Ortho Brain Thromboplastin was also prolonged. Fibrinogen measured on Lancer fibrinogen analyzer using the Lancer fibrinogen determination reagent kit was 0.4 g/L (40 mg%) (normal 1.8 to 4.1 g/L). Fibrin split products were measured by agglutination of latex particles. Initial level was 80 μg/mL (normal < 10 μg/mL) and later increased to 160 μg/mL. Factor VIII assayed by modified one stage APTT using the method of Egeberg (22) was increased to over 200% (normal 50% to 150%), and Factor V determined by the method of Stefanini (23) was slightly below normal (47%), as was Factor VII (47%), measured by the method of Owren and Aas (24). Protamine sulfate paracoagulation test (25) was consistently negative for fibrin monomers suggesting that fibrinolysis was the dominant pathologic process. Plasminogen and plasmin were assayed by using a synthetic fluorogenic substrate, D-valine-lysine-5-amidoisophthalic acid by the method of Pochron et al (26) using a fluorogenic assay (Protopath™, Dade Corporation, Miami, FL). The plasminogen level was consistently decreased, reaching levels below 1 CTAU (Committee on Thrombolytic Agents units)/mL (normal 3.1 ± 0.7 CTAU/mL). Plasmin was demonstrated in the serum before epsilon-aminocaproic acid was given, but subsequent tests were negative.

These data were interpreted as indicating the presence of primary fibrinolysis. On April 24th, epsilon-aminocaproic acid was begun initially at an oral dose of 5 g every four hours; this was subsequently changed to 1 g every hour intravenously. After 48 hours no new areas of ecchymosis were seen, and by 72 hours the hematuria was greatly improved. On this date (April 27th), antileukemic treatment with ADOAP was reinstituted, and the epsilon-aminocaproic acid was continued. An exacerbation in fibrinolysis occurred shortly after chemotherapy was started, but then strikingly improved and disappeared over the next seven days. Because of the continued presence of leukemic cells in the marrow, cytosine arabinoside was administered for an additional three days. On May 9th, 13 days after reinduction chemotherapy, the patient had recurrent hematuria and gum bleeding, but this was now thought to be due to thrombocytopenia since the fibrinolytic parameters were normal. Control of bleeding occurred after the patient received 10 units of random donor platelets. Epsilon-aminocaproic acid was stopped on May 11th, and the patient was discharged two days later, having completed chemotherapy and now in a clinically stable state.

However, at home the patient began vomiting with hematemesis. He arrived in the Emergency Room in shock on May 14th. He was in severe respiratory distress, having aspirated vomitus. His coagulation parameters now indicated the presence of DIC. Despite intensive supportive measures, the patient died five hours later. The pertinent relationships between chemotherapy, fibrinolytic therapy, and laboratory values during the clinical course of this patient are depicted in Fig 3.

Discussion

Fibrinolysis as a primary factor causing significant bleeding in leukemia is controversial. It is usually thought to be a secondary response to DIC, but, with the use of techniques for the measurement of plasminogen and plasmin, its occurrence as a primary phenomenon in leukemia has been observed (18,19). Fibrinolytic activity derived from the proteases, elastase and cathepsin G, and from plasminogen activators have been recovered from disrupted normal and leukemic granulocytes and monocytes (27-29). A case of acute myelomonocytic leukemia (FAB:M4) with symptomatic fibrinolysis has been reported, in which a protease with fibrinolytic activity and a plasminogen activator were demonstrated in the serum (18). Chan et al (19) described two patients with promyelocytic leukemia, in whom low plasminogen and alpha-2-plasmin inhibitor levels were associated with severe bleeding and in whom transexamic acid, a potent analog of epsilon-aminocaproic acid available in Europe (30), was therapeutically effective. Schwartz et al (16) claim a predictive value in finding less than 30% levels of serum al-

pha-2-plasmin inhibitor in patients with promyelocytic leukemia. Such patients showed evidence of increased fibrinolysis and responded to aminocaproic acid treatment, but they also received heparin because of evidence of DIC.

Our case represents the apparent rarity of pure monocytic leukemia associated with severe fibrinolysis, manifested clinically by severe bleeding. Decreased fibrinogen and plasminogen with elevated fibrin split products, a persistently negative protamine sulfate paracoagulation test, and a normal platelet count prior to chemotherapy strongly suggest the presence of marked (probably primary) fibrinolysis. The favorable, although gradual, response to aminocaproic acid gives further support to this impression. There is also indirect evidence to implicate the leukemic cell as the source of fibrinolytic activity, since progressive hemostatic improvement paralleled the reduction in leukemic cell population induced by chemotherapy. Transient worsening of the bleeding diathesis at the onset of chemotherapy was likely due to the greater release of fibrinolytic activators by the initial disruption of leukemic cells. After resolution of the hemostatic defect, as shown by the patient's clinical stability and the normalization of his coagulation parameters, the subsequent terminal bleeding episode was related to sepsis and shock which produced the not unexpected DIC. This was confirmed by a strongly positive protamine sulfate paracoagulation test and by other abnormalities indicating excessive consumption, ie, decreased Factors V and VIII. At autopsy the presence of small fresh fibrin thrombi in several pulmonary and a few renal capillaries gave further evidence of late-occurring DIC.

Regarding treatment of the fibrinolytic episode, we found epsilon-aminocaproic acid to be effective, but prolonged and high dose (24 g/day intravenously) was necessary. Replacement of fibrinogen through transfusions of cryoprecipitate was additionally helpful.

Because it is certainly an uncommon clinical problem in the course of acute leukemia, the presence of fibrinolysis could go unrecognized, overshadowed by the ubiquitous thrombocytopenia, or mistaken for DIC. We wish to draw attention to this possibility, since therapeutic options are critical; and we stress the value of the protamine sulfate paracoagulation test and the measurement of the serum plasminogen in the evaluation of the bleeding leukemic patient.

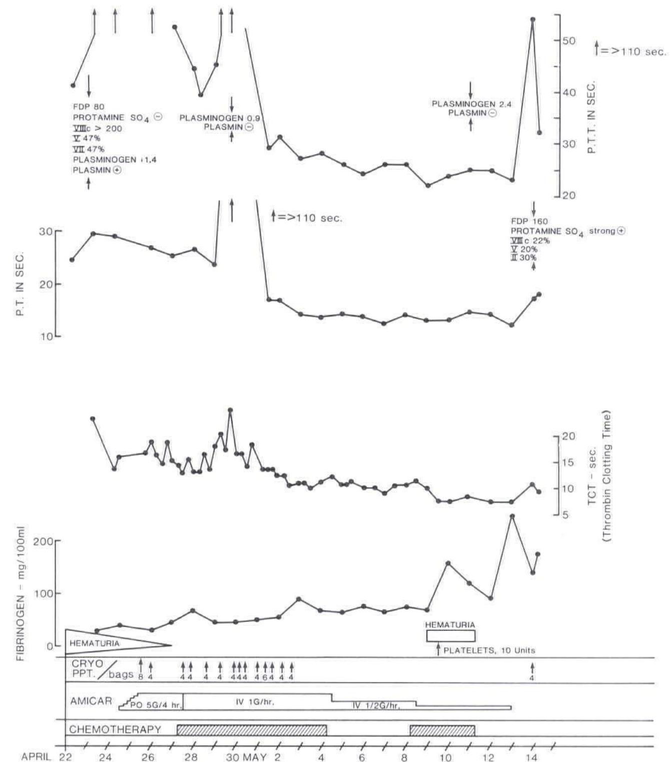

Fig 3—Relationship between chemotherapy, fibrinolytic therapy, and laboratory values during the clinical course.

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