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cesses, typical scarcity of cytoplasmic organelles, relative prominence of free ribosomes, and the presence, albeit infrequent, of intercellular attachments. The presence of basal lamina surrounding individual cells, one of the more frequent reported findings in studies of pericytes and hemangiopericytomas,[2,9] was not identified in this case, which may be due to the lack of differentiation present. Others have noted difficulty in finding this feature in hemangiopericytomas.[7]

As noted above, this patient was treated with chemotherapy because of the initial, locally aggressive behavior of this neoplasm. Only a few cases of malignant hemangiopericytoma in childhood have been reported. The results of chemotherapy in these cases have been disappointing except for one case of hemangiopericytoma (not a congenital hemangiopericytoma) metastatic to bone in which the metastatic lesions responded to the chemotherapeutic regimen employed in this case.[10] Our patient had no untoward sequelae from her chemotherapy. It is not clear whether the favorable outcome in our patient is derived from the inherently benign nature of the tumor or because of the therapy administered.

In summary, a case of congenital hemangiopericytoma of the tongue and sublingual region is reported. Like those congenital hemangiopericytomas found in subcutaneous locations, this tumor has had a benign course, despite histologic features suggestive of a more aggressive behavior.

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Pathologic Hyperfibrinolysis Associated with Amyloidosis: Clinical Response to Epsilon Amino Caproic Acid

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Severe bleeding diathesis was the presenting problem in a patient with systemic amyloidosis characterized by generalized amyloid adenopathy. Epsilon amino caproic acid effectively reversed the fibrinolytic state with improvement of bleeding tendency and reduction of lymphadenopathy. The possible relationship and mechanisms of fibrinolysis are discussed. (Key words: Amyloidosis; Pathologic hyperfibrinolysis) Am J Clin Pathol 1984; 81: 382–387

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DURING THE PAST 20 YEARS, an unusual bleeding disorder has been described in patients with amyloidosis. Acquired deficiency of Factor X has been the most common form of coagulopathy.[2,6,8,13–15,20–22,26] Other clotting disorders, including combined factor deficiency of Factors IX and X,[17] intravascular coagulation,[3] fibrinolysis,[19,23,24] and thrombocytopenic purpura,[4] also have been reported. Although mechanisms for these coagulopathies are poorly understood, Factor X deficiency has been attributed to the direct binding of Factor X to amyloid fibrils that are exposed to circulating blood with resulting rapid clearance of Factor X from the circulation.[6,7] The pathophysiology of fibrinolysis and of disseminated intravascular coagulation in amyloidosis is essentially unknown.

Recently we have observed a case of systemic amyloidosis associated with a severe bleeding disorder sec-

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ondary to pathologic hyperfibrinolysis. The fibrinolytic state was corrected by the administration of epsilon amino caproic acid (EACA) with marked improvement of the bleeding tendency.

Report of a Case

A 55-year-old white man (KL) was admitted to the Good Samaritan Hospital and Health Center, Dayton, Ohio, with the chief complaint of generalized lymphadenopathy in the cervical, axillary, and inguinal regions, with multiple purpuric areas on the trunk and extremities for about eight weeks' duration. Six weeks prior to this admission, the patient experienced pain in his left hip and leg along with extensive multiple ecchymoses. The pain, lymphadenopathy, and rash improved during a short course of steroid therapy. One week prior to this admission, recurrent ecchymoses on the extremities developed and he became quite uncomfortable due to progressive axillary adenopathy.

Physical examination included pulse rate of 88 beats/minute, blood pressure 110/70 mmHg, respiration 20 breaths/minute, and weight 156 lbs. The patient was well developed and well nourished, alert and coherent, and not in acute distress. Neither conjunctival pallor nor scleral icterus was noted. Ears, nose, and throat were normal, without macroglossia, purpura, or signs of inflammation. The lungs were clear without rales. The heart revealed regular sinus rhythm without murmur or gallop. The abdomen was soft. The liver and spleen were not palpable. Lymphadenopathy was present in the cervical, axillary, and inguinal regions. The largest lymph nodes measured 3 × 3 cm in the left axilla and 1.5 × 1.5 cm in the inguinal area. Multiple ecchymotic lesions were noted on both upper and lower extremities and on the trunk. A large tender hematoma was present on the inner aspect of the left thigh.

On admission the initial impression was lymphoma or chronic lymphocytic leukemia. Hemogram showed the red blood cell count of 4.66 $10^6/mm^3$, hemoglobin 13.9 g%, hematocrit 40.9%, and white blood cell count 14,900/mm^3, with 63% polymorphonuclear neutrophils, 4% bands, 32% lymphocytes, and 1% monocytes. The platelet count was 210,000/mm^3, and the reticulocyte count 1.7%. Urinalysis revealed specific gravity of 1.011, *p*H 7.0, WBC 8–10/high-power field, and RBC 10–20/high-power field. Chemistry profile including urea nitrogen and uric acid was normal. Initial coagulation studies were quite abnormal: prothrombin time was 17 seconds (control: 12 seconds), activated partial thromboplastin time 34 seconds (normal: 19–30 seconds), fibrinogen level 140 mg/dL (normal: 200–400 mg/dL). Antinuclear antibody and mono spot test for infectious mononucleosis were negative. The chest roentgenogram was abnormal, with interstitial markings suggestive of mild pulmonary fibrosis. The liver scan showed slight hepatomegaly and modest splenomegaly.

Bone marrow aspiration and biopsy were normal except for a slight increase in plasma cells to about 5% of the nucleated cell population. Following this procedure, the patient began to have continuous oozing of blood from the biopsy site at the left posterior superior iliac crest. The bleeding continued for several days in spite of pressure dressing and local measures. Control of bleeding also was extremely difficult at phlebotomy sites. Either pathologic hyperfibrinolytic state or disseminated intravascular coagulation was suspected on the basis of the abnormal coagulation profile. Lymph node biopsy was postponed due to the excessive bleeding tendency. Further coagulation studies, as well as markedly shortened euglobulin lysis time, suggested the diagnosis of pathologic hyperfibrinolysis. There was no clinical or laboratory improvement following a short course of high-dose steroid therapy. On the ninth hospital day, heparin was initiated at a modest dose of 700 U/hour by continuous intravenous infusion. EACA also was given at a loading dose of 5 g followed by 1 g orally every hour. The bleeding tendency gradually diminished with considerable improvement of the coagulation abnormalities. After three days, heparin therapy was discontinued; EACA maintenance therapy was given at a dose of 5 g every six hours. There was no recurrence of bleeding tendency. On the eleventh hospital day, a biopsy of the left axillary and left cervical node was performed. Pathology showed organizing hemorrhage within the lymph nodes. Amyloid deposits were present in the lymph node stroma. The patient was discharged on the twenty-fifth hospital day on EACA. Two weeks later, the lymphadenopathy was markedly diminished. While the patient was on the maintenance dose of EACA for about four months as an outpatient, the lymphadenopathy almost disappeared and bleeding diathesis did not recur. However, when EACA was discontinued, during the following three months recurrent and progressive cervical adenopathy and hepatic failure gradually developed. Biopsies of cervical nodes and gastric and rectal mucosa showed amyloid.

Immunologic and Histologic Studies

Protein Analysis

Serum protein electrophoresis was normal except for borderline hypogammaglobulinemia of 700 mg/dL. No monoclonal spike was noted. Quantitative immunodiffusion showed IgG of 600 mg/dL (normal: 564–1,765 mg/dL), IgM 140 mg/dL (normal: 53–375 mg/dL), and IgA 48 mg/dL (normal: 85–385 mg/dL). Total urinary protein was 14 mg/dL. Protein electrophoresis on concentrated urine showed a small amount of albumin and a tall monoclonal peak in the beta region. Urine immunoelectrophoresis revealed the protein to be a monoclonal lambda chain.

Histologic Studies

Biopsy of the left cervical lymph node showed small blood vessels and stroma infiltrated with amyloid (Fig. 1*A*). Hemorrhage was prominent. The material positive for Congo red appeared apple green under polarized light. Electron microscopy of the lymph node stroma showed fine-beaded fibrillar material characteristic of amyloid (Fig. 1*B*).

Coagulation Studies

Figure 2 shows the evolution of coagulation tests prior to and during treatment with EACA. Prior to treatment, the patient had a prolonged prothrombin time of 17 seconds, partial thromboplastin time of 34 seconds, and low fibrinogen level 140 mg/dL. Coagulation factor studies showed Factor II of 85%, Factor V 100%, Factor VII 100%, Factor VIII 18%, and Factor X 50%. The fibrin split product test was positive, as was the para-coagulation test with protamine sulfate. The euglobulin lysis time was shortened at 20 minutes (normal: over 60 minutes). The thrombin time was prolonged at 16 seconds (normal: less than 10 seconds). Whole blood clot lysis was increased. A normal platelet count and markedly shortened euglobulin lysis were compatible with pathologic hyperfibrinolysis. High dosage with prednisone did not improve either the bleeding tendency or the coagulation abnor-

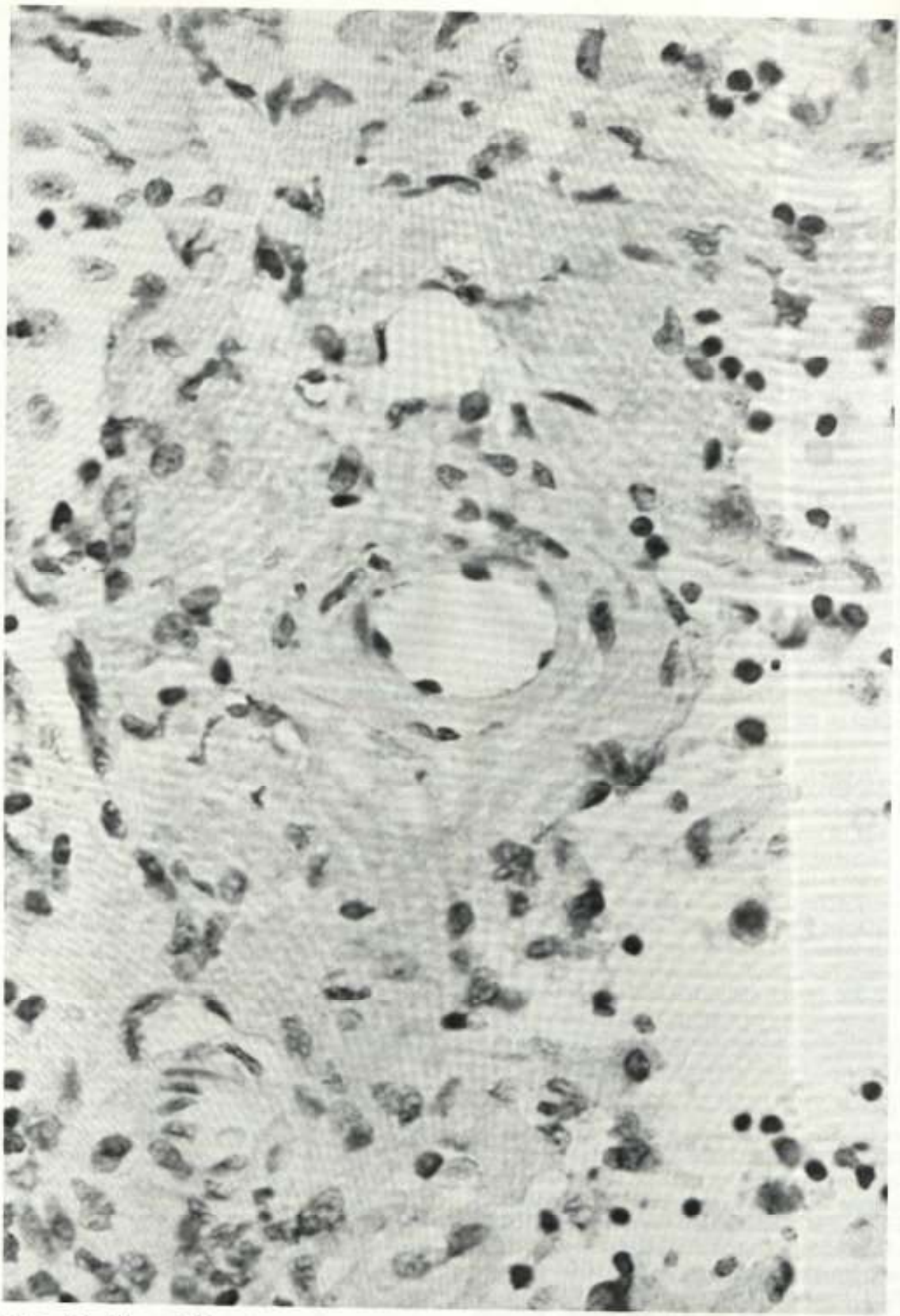

FIG. 1A. Pathology of the left cervical lymph node. A small muscular artery and adjacent stroma are infiltrated by amorphous material. The stain was positive and showed apple green birefringence. Congo red (×400).

malities. Prior to the initiation of heparin and EACA, prothrombin time was 20 seconds, activated thromboplastin time 48 seconds, thrombin time 17 seconds, fibrinogen level less than 40 mg/dL, Factor VIII 25%, and euglobulin lysis time 49 minutes. Coagulation tests began to improve dramatically within 48 hours after onset of the treatment of heparin and EACA. Progressive improvement of coagulation abnormalities while on EACA,

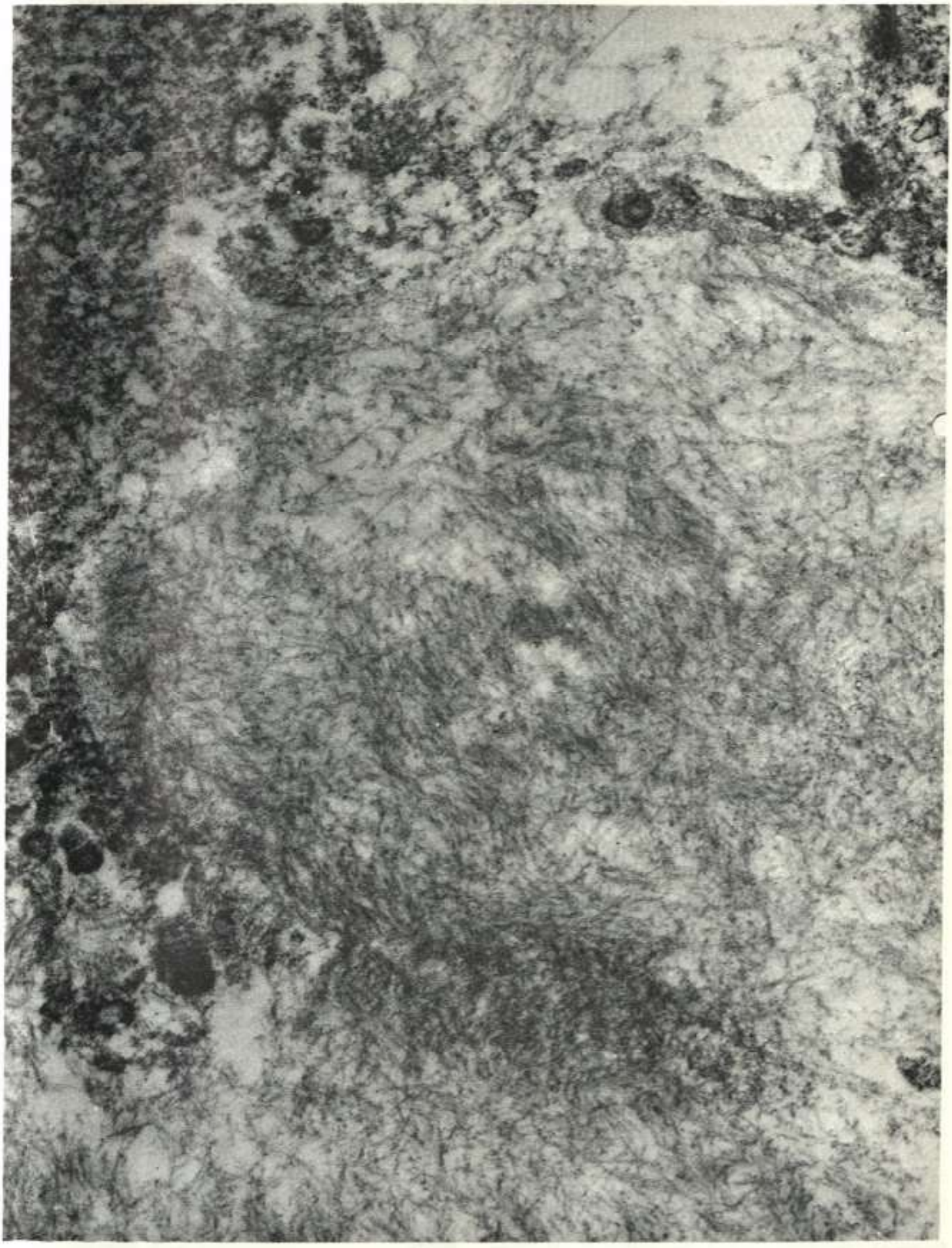

FIG. 1*B*. Electron micrograph of the stroma from the left cervical lymph node. Beaded finely fibrillar material is characteristic of amyloid (×12,500).

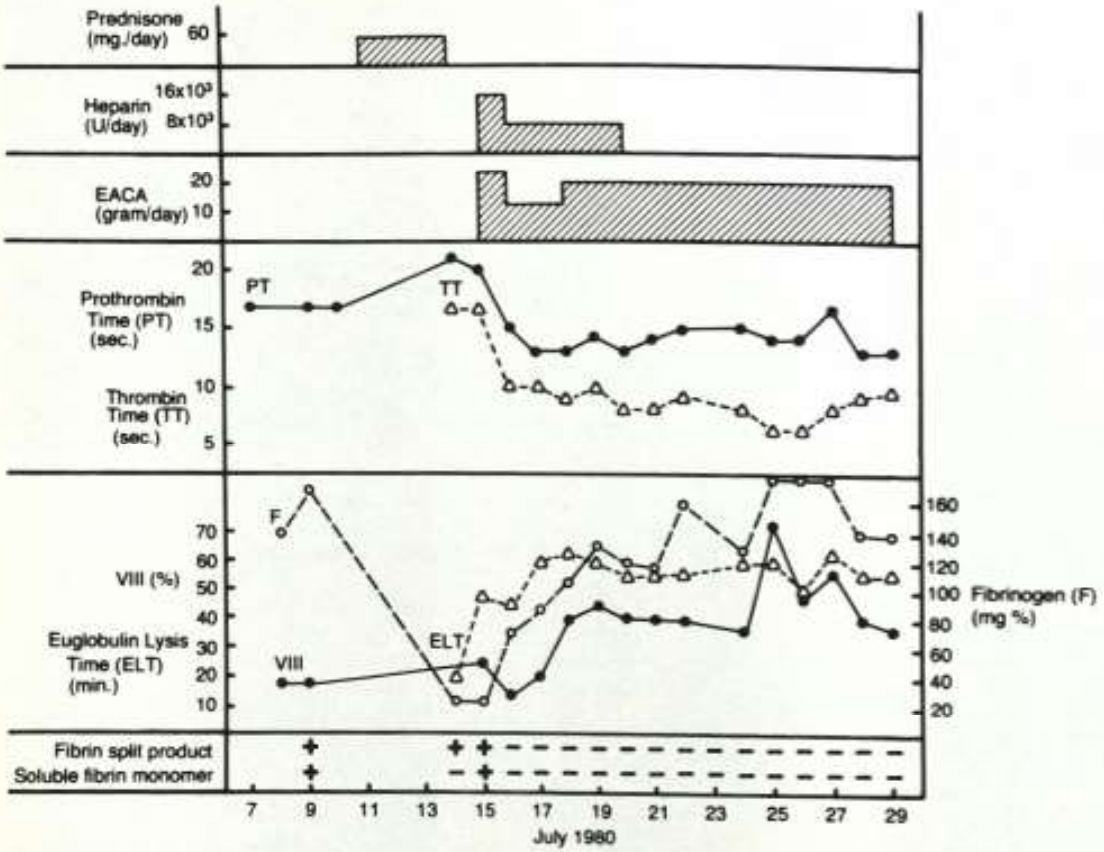

FIG. 2. Changes of coagulation tests prior to and during the treatment with EACA. Please note increased fibrinolytic activity prior to the treatment and gradual improvement during the course of EACA administration.

and after discontinuing heparin, was thought to be characteristic of hyperfibrinolytic state. Factor VIII level gradually improved (as seen in Figure 2). Some of the coagulation tests, however, did not return completely to normal. During hospitalization, a screening test for circulating anticoagulant was negative. Antithrombin III activity was 78% (normal: 77–110%). A repeat Factor X level was 67%, and the platelet count was 240,000/mm^3. The patient was discharged on EACA, 5 g every six hours orally, to be followed as an outpatient.

Discussion

Pathologic hyperfibrinolysis is a rare acquired coagulation disorder resulting from excessive plasma proteolytic enzyme activity. Three mechanisms have been postulated in the literature for the production of the condition. First, it may be caused by an excessive release of plasminogen activator from activator-rich neoplastic tissue, as seen in metastatic carcinoma of the prostate, or in response to profound stimuli such as severe anoxia, shock, or following extensive surgical procedures, particularly on the lung and following prolonged cardiac bypass.[12,18,25] Second, an impaired inhibitory mechanism may be responsible. The breakdown of the plasminogen activator may be delayed due to lack of clearance in the liver, as seen in cirrhosis, especially following portocaval shunt.[5,11] Third, a proteolytic enzyme or proteolytic enzyme-like substance other than plasmin may appear in the circulation and result in fibrinolytic state. This may be seen in leukemia.[16]

Our patient is very unique, since he had both pathologic hyperfibrinolysis and extensive amyloid lymphadenopathy. The literature reports a few cases of amyloidosis associated with hyperfibrinolytic state.[19,23,24] However, no mechanism has been established to explain this association. EACA has as its principal activity the inhibition of plasminogen activator substances. It also has antiplasmin activity to a lesser extent.[1] In view of the successful inhibition of fibrinolysis with EACA, and in the absence of liver disease, this patient's hyperfibrinolytic state probably is caused by the first above-described mechanism, *i.e.*, by excessive presence of plasminogen activator. Continuous release of a plasminogen activator, perhaps related to the amyloidosis, could have caused the hyperfibrinolytic state and the bleeding diathesis. Amyloid fibrils consist of immunoglobulin light chains and light chain fragments. It is known that proteolytic enzymes may digest light chains and other proteins to make fibrils with the appearance of amyloid.[10] However, it is unlikely that in this patient the amyloidosis was the result of the pathologic hyperfibrinolysis. It is interesting to note that the correction of the hyperfibrinolytic state with EACA resulted in amelioration of the bleeding tendency and in marked reduction of the lymphadenopathy. The decrease in lymphadenopathy while the patient was on EACA therapy probably was because of decreased hemorrhage into the nodes.