Thrombotic State after a Hemorrhagic Diathesis, a Possible Complication of Therapy with Epsilon-Aminocaproic Acid

By RICHARD L. NAYE

THE HEMORRHAGIC diathesis sometimes associated with carcinoma of the prostate has usually been related to deficiencies of blood coagulation factors including fibrinogen. These deficiencies have most often been thought to be the consequence of proteolytic activity released into the blood stream by the carcinomatous tissue.\(^1\)\(^-\)\(^5\) Another possibility in such cases is that the malignant tissue activates the blood's own proteolytic system by release of plasminogen activator into the circulation.\(^6\)\(^-\)\(^7\) Neither of these mechanisms has been directly demonstrated in patients having hemorrhagic phenomena with prostatic carcinoma. The patient reported here had carcinoma of the prostate and developed a widespread thrombotic disorder after treatment of a severe hemorrhagic diathesis. It is possible that intravascular coagulation helped initiate the hemorrhagic disorder. Experimentally, widespread intravascular coagulation can lead to defibrination, secondary hyperplasminemia and severe hemorrhagic diathesis.\(^8\) Epsilon-aminocaproic acid may have enhanced such a thrombotic mechanism in this patient since widespread intravascular thrombosis appeared after its administration and continued to develop during the time renal failure apparently prevented excretion of the drug. Epsilon-aminocaproic acid is a potent inhibitor of the proteolytic enzyme plasmin and its activators.\(^9\)\(^-\)\(^13\)

CASE REPORT (087-075)

An 81 year old man was admitted to the Mary Fetcher Hospital on August 2, 1961 with acute abdominal pain. Seven years before he had a partial prostatectomy and bilateral orchiectomy for carcinoma of the prostate which had extended to the pelvic bones. During the interval he had received 24 mg. of chlorotriainisene\(^*\) daily without known further extension of the carcinoma. Several days before admission he developed bloody stools, hematuria and experienced unexpected nosebleeds. On the day of admission he awakened with persistent, severe right upper quadrant abdominal pain.

Physical examination revealed a lethargic, pale, elderly male with blood pressure of 60/45 mm. Hg., pulse 112/min. and temperature of 37.5 C. The most striking finding was tenderness in the right upper quadrant of the abdomen. Absence of bowel sounds suggested ileus. Gynecomastia was present bilaterally. Laboratory studies revealed hematocrit of 23 per cent, hemoglobin 8.0 Gm. per cent, leukocyte count 19,500/mm.\(^3\) with 79 per cent neutrophils, 15 per cent lymphocytes, 5 per cent monocytes and 1 per cent basophils. His urine had a specific gravity of 1.018 with a trace of protein. Blood urea nitrogen was

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35 mg./100 ml. Serum amylase was 39 Somogyi units/100 ml., bilirubin 0.2 mg./100 ml., alkaline phosphatase 68 King-Armstrong units/100 ml., sodium 134 mEq./L., potassium 4.5 mEq./L., chloride 98 mEq./L., carbon dioxide 18 mEq./L. X-ray examination of the abdomen disclosed numerous osteolytic lesions of the lumbar vertebrae and pelvic bones.

During the first hospital day, additional evidences of hemorrhagic diathesis appeared. When a tourniquet was applied, brisk bleeding appeared at previous vena puncture sites. Attempts to start intravenous fluids resulted in large hemorrhages. Fresh blood drained from a Levine tube in the stomach. Coma developed and urinary output decreased to 20 ml. in 12 hours. No improvement followed 500 ml. of compatible whole blood with the hematocrit increasing only 1 per cent to 24 per cent. Increasing shock and ileus were attributed to intra-abdominal hemorrhage. Special coagulation studies reported later in this paper suggested some increase of proteolytic activity in the blood. Since epsilon-aminocaproic acid* may inhibit such proteolytic systems within 30 minutes,14 the patient was given 15 Gm. of the drug intravenously over a 12-hour period. He also received 100 mg. of hydrocortisone intravenously. Hemorrhagic phenomena disappeared within a few hours and he regained consciousness after an additional 2000 ml. of whole blood had increased his hematocrit to 36 per cent. The next day his ileus disappeared and urinary output increased to 260 ml. Despite a daily urinary output above 700 ml. on succeeding days, the blood urea nitrogen increased to 115 mg./ml. on the sixth hospital day. This was attributed to a mild acute tubular necrosis developing during the earlier period of shock. Hydrocortisone, 125 mg., was given on the second and third days with a final dose of 75 mg. on the fourth day.

On the second day after combined epsilon-aminocaproic acid and hydrocortisone therapy, cyanosis appeared in the fingers and toes. This was more than 24 hours after recovery from the period of shock. On succeeding days, gangrene appeared which involved all of the digits and the feet up to the subtalar joints. No cryoglobulins, cryofibrinogen or macroglobulins were found in the serum or plasma. No pulses were detected in the radial or dorsalis pedis arteries after the fifth day. On the seventh day, body temperature began to increase and reached 42 C. on the eleventh day when he expired.

At postmortem examination, metastases of the prostatic carcinoma were found in multiple paraaortic, perirenal and mesenteric lymph nodes, in the seminal vesicles, in perivesicle connective tissue, in multiple thoracic and lumbar vertebrae and at many sites in the pelvic bones. There were evidences of both hemorrhagic and thrombotic disorders. The peritoneal cavity contained 300 ml. of old fluid blood. The right diaphragm was elevated by a large subcapsular hepatic hematoma which contained about 500 ml. of partially organized blood. Occlusive thrombi or emboli with very early evidences of organization were found in the anterior descending branch of the left coronary artery, gastric and colonic veins, and in small vessels of the skin of the feet. Postmortem angiograms demonstrated occlusion of both the anterior and posterior tibial arteries in the left leg about 18 cm. above the ankle. Autopsy restrictions prevented further examination of the extremities. In addition to the gangrene of hands and feet, a myocardial infarct was found which involved the anterior portion of the interventricular septum and the apex of the left ventricle. It was thought to be two or three days old. Multiple, small, recent infarcts were also found in the stomach and colon. Two older thrombi or emboli were found in muscular arteries of the pulmonary arterial bed. They were almost completely organized and were the only thrombi thought to be older than 10 days. In the kidney, occasional epithelial cells of the distal convoluted tubules were vacuolated and had hyperplastic nuclei. Death was probably most directly related to the acute myocardial infarct and to gangrene of the extremities.

Materials and Methods

Plasmin and plasminogen were measured in serum by the method of Rojel.15 The assay is based on the ability of plasmin to hydrolyze protamine. Washed

*Supplied by Dr. W. M. Sweeney, Lederle Laboratories Division, American Cyanamid Co.
and suspended NPH insulin* is used as the source of protamine. In the plasminogen assay, the proenzyme was activated by streptokinase.†

Plasminogen activator in serum was determined by the method of Norman.‡ This assay is based on the ability of small quantities of human serum with streptokinase to activate much larger amounts of rabbit plasminogen. When standard amounts of rabbit euglobulin (which contains plasminogen) and streptokinase are added under standard conditions to specially prepared casein, the resultant level of caseinolytic activity will depend on the amount of activator activity in the added human test serum.

Plasmin inhibitor of the immediate type was measured by the method of Norman.† This test measures the inactivation of purified plasmin using a caseinolytic assay for determination of plasmin. Human plasma fraction III was used as the starting material! in preparation of purified plasmin by Clifton and Cannamela's modification§ of Kline's method.

Fibrinogen was measured by coagulation with thrombin, multiple washings of the resultant clot and Kjeldahl nitrogen determination. A modified Quick's method was used for the one-stage prothrombin time.¶ The Lee-White method was used for venous clotting time.

Epsilon-aminocaproic acid in serum was measured by the method of Buyske and Colucci.** The product that is formed by reaction of epsilon-aminocaproic acid with diazomethane is extracted at pH of 10.4 with chloroform. The extract is allowed to form a complex with methyl orange at pH 5.0. Upon acidification, a highly colored acid salt of methyl orange is formed and measured spectrophotometrically.

RESULTS

Blood coagulation studies were started the day after admission during the severe hemorrhagic diathesis (fig. 1). Venous blood failed to clot in a glass test tube. No clot formed during determination of the one-stage prothrombin time or during an attempted fibrinogen determination. Plasmin levels in the serum were 1.7 times normal and plasminogen activator titers were 2.2 times normal. In contrast, plasminogen values were reduced to 10 per cent of normal and the plasmin inhibitor level to 57 per cent of normal. The platelet count was 62,000/mm.³, about one-third of our normal laboratory value.

After five Gm. of epsilon-aminocaproic acid had been given, apparent plasminogen activator levels decreased to 110 per cent of normal, but there was little change in the elevated plasmin activity. At the end of 12 hours, when the drug infusion was completed, activator levels had further decreased to a value of 65 per cent of normal. At this time, a decrease in plasmin activity to just below the mean normal level was recorded. It is quite probable that both

*Eli Lilly and Co.
†Varidase from Lederle Laboratories Division, American Cyanamid Co.
‡Human fraction III supplied by E. R. Squibb and Sons, through the courtesy of James H. Pert, American Red Cross.
§Performed through the courtesy of Dr. W. M. Sweeney, Lederle Laboratories.
the decreased levels of plasmin and its activator reflected the activity of epsilon-aminocaproic acid in the patient's serum since the drug was purposely not separated from the serum before analysis. It was hoped that any in vitro interference with proteolytic activity by the drug would reflect a corresponding activity in vivo. By the time of completion of the infusion of the drug, the plasma fibrinogen had increased sharply to 130 mg./100 ml. and the prothrombin time activity to 20 per cent of normal. Subsequently, plasminogen activator decreased to about one-half of the normal value where it continued until death. Serum plasmin activity remained slightly below normal levels until death, whereas fibrinogen levels and prothrombin time activity increased to near normal values. A continued elevation of serum epsilon-aminocaproic acid may best be attributed to a failure of the kidneys to excrete the drug. This remaining drug in the serum probably interfered with the plasminogen assays which gave apparent low serum values until death. This can be deduced from the fact that plasminogen was measured after its activation to plasmin and that serum levels of epsilon-aminocaproic acid were adequate to inhibit the activity of plasmin.21
Discussion

Many reports have appeared of an overt hemorrhagic state which develops in a small proportion of patients with disseminated carcinoma of the prostate.\textsuperscript{1,2,22,24} Since carcinomatous prostatic tissue in vitro has been found to have high levels of proteolytic activity, it has been postulated that the carcinomatous tissue in vivo may occasionally release proteolytic activity into the circulation, thus initiating fibrinolysis and multiple hemostatic defects.\textsuperscript{1-5} There is no conclusive evidence that this mechanism played any significant role in the current case. The increased levels of plasmin and of plasminogen activator during the hemorrhagic phase seem too small to account for the bleeding diathesis. The available evidence suggests, rather, that intravascular coagulation initiated the hemorrhagic disorder. Intravascular coagulation in other instances has led to a hemorrhagic diathesis with many similarities to the current case.\textsuperscript{25} Like other tissues of the body, prostatic tissue presumably has thromboplastic activity.\textsuperscript{5,7} Experimental injection of thromboplastin into the blood stream results in widespread intravascular thrombi, defibrination, secondary hyperplasminemia and severe hemorrhagic diathesis.\textsuperscript{8} Rapid disappearance of the deposited fibrin in such instances may be the consequence of secondary fibrinolysis. It seems reasonable to postulate that in the case reported here, epsilon-aminocaproic acid or hydrocortisone may have “unmasked” such intravascular coagulation by inhibiting the secondary fibrinolysis.

Other data also suggest that proteolysis may not have been the major mechanism responsible for the hemorrhagic diathesis in this patient. Tagnon et al.\textsuperscript{1,2} have shown that as many as 12 per cent of persons with carcinoma of the prostate may have some increase in proteolytic activity in their blood, whereas only a small proportion develop hemorrhagic phenomena. It has not yet been fully established that hyperplasminemia alone can hydrolyze fibrinogen at a rate sufficiently rapid to result in severe fibrinogenopenia.\textsuperscript{7,26} Apparent total activation of plasminogen has been produced experimentally and maintained in man without resulting in severe hypofibrinogenemia or severe hemorrhagic phenomena.\textsuperscript{27} The mild thrombocytopenia noted in the current patient has been previously recorded in hemorrhagic syndromes with carcinoma of the prostate.\textsuperscript{1,12,23} It may be related to platelet sequestration associated with intravascular coagulation or possibly to invasion of bone marrow by the neoplasm.\textsuperscript{28}

Therapy in the present case deserves additional mention. Hydrocortisone and related compounds have given prompt remission of the hemorrhagic syndrome associated with prostatic carcinoma in several instances and may well have had an effect in the present case.\textsuperscript{29-30} How these drugs act in such cases is unknown. Although there are no previous reports of thrombosis following their use in patients with hemorrhage and prostatic carcinoma, this possibility cannot be excluded in our case since thrombosis has followed use of the corticosteroids in other disorders.

In the current case, there is additional evidence that the thrombotic disorder was related to administration of epsilon-aminocaproic acid. Although
McNicol considered the relationship coincidental, he recently reported that vascular thromboses developed in two patients after use of epsilon-aminocaproic acid following prostatic surgery. In our patient, decrease of plasminogen activator levels by more than 50 per cent within four hours coincides with the known specific action of epsilon-aminocaproic acid. Serum levels of the drug were elevated until death and were within range where effective inhibition of plasmin activator and plasmin might be expected. Postmortem findings suggest that all but two of the thrombi formed during the period when blood levels of the drug were known to be elevated. The continued elevation of serum drug levels presumably reflected failure of renal excretion, since normally 65 per cent to 95 per cent of a given dose is excreted via the urine within 12 hours. A delay in excretion of the drug with uremia has previously been noted. The 15 Gm. dose in our patient presumably was not excessive since some individuals have received as much as 36 Gm. a day without untoward sequellae. Renal failure was not anticipated when the drug was given to our patient.

Epsilon-aminocaproic acid appears to be a valuable therapeutic agent for the control of hemorrhagic disorders primarily related to increased proteolytic activity of blood or urine. It has been used with success in such disorders by a number of investigators without the complication of intravascular thrombosis. In the current case, one must consider the possibility that the drug potentiated or “unmasked” a thrombotic disorder when a hemorrhagic diathesis had been primarily initiated by intravascular coagulation. Appropriate use of the drug in a variety of hemorrhagic disorders may have to await a better understanding of the pathogenesis of each.

**Summary**

A hemorrhagic state with afibrinogenemia developed in an 81 year old man with disseminated carcinoma of the prostate. Following administration of epsilon-aminocaproic acid and hydrocortisone, widespread intravascular thromboses developed. It is postulated that epsilon-aminocaproic acid inhibited fibrinolysis and thereby helped to “unmask” a process of intravascular coagulation that had initiated the hemorrhagic diathesis. Although the evidence is less convincing, the administered hydrocortisone may also have contributed to the thrombotic disorder.

**Summario in Interlingua**

Un stato hemorrhagic con afibrinogenemia se disveloppava in un homine de 81 annos de etate qui havaeva disseminate carcinoma del prostata. Post le administration de acido epsilon-aminocaproic e hydrocortisona, extense thromboses intravascular se disveloppava. Es postulate que le acido epsilon-aminocaproic inhibiva fibrinolyse e assi adjutava a “dismascar” un processo de coagulation intravascular que havaeva initiate le diathese hemorrhagic. Ben que le evidentia es minus convincente, il es possibile que le hydrocortisona que eseva administrate etiam contribueva al disordine thrombotic.
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