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Fatal Intravascular Consumption Coagulopathy in Typhoid Fever

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A patient with typhoid fever who died with a rapidly progressing hemorrhagic diathesis secondary to intravascular consumption coagulopathy (IVCC) associated with irreversible shock is discussed in detail.

It is postulated that the salmonella orgenism and especially the endotoxin it produces initiates accelerated intravascular clotting primarily by injurying the vascular âendothelium. It is suggested that IVCC may be a frequent occurrence in salmonellosis and should be looked for in all patients with this infection since early diagnosis and initiation of proper therapy may prevent death secondary to fulminating homorrhage and irreversible shock.

The occurrence of disseminated intravascular coagulation has now been recognized in association with a wide variety of acute infections (1), Often, endotoxin-containing organisms such as salmonella or gram-negative bacilli are involved (2-4).

We recently observed a case of overwhelming, rapidly fatal typhoid sepsis with disseminated intravascular coagulation in a relatively healthy, young woman. Review of the literature showed that acute coagulation abnormality is a consistent finding in patients dying with salmonella infections and disseminated intravascular coagulation.

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Case History:

A 19-year-old woman was admitted to The Department of Infectious Diseases, Pahlavi Medical School with fever, epistaxis, and mental confusion. There weeks earlier, while she was living in Tehran, anorexia developed with malaise and headache.

There days prior to admission she began to have loose brown stools, pain, epistaxis, and fever.

Physical examination revealed the patient to be ill, disoriented, and dehydrated. Her blood pressure was 110/80 mm Hg; pulse, 104 beats per minute; and rectal temperature, 104 F (40 C). There was dried crusted blood on the lips and nares. A discrete, pink, maculopapular rash which disappeared with pressure was present on the neck, chest, and upper part of the abdomen. The heart was normal. Fine crepitant rales were heard over left lower lung field and the abdomen was diffusely tender without rigidity or guarding. The liver and spleen were not palpable and the bowel sounds were normal. The stool gave a weakly positive benzidine reaction.

The urine contained a trace of protein. Hemoglobin value was 11.8 gm/100 ml and white blood cellcount was 3,400/cu mm with 35% neutrophils. 42% band forms, 19% lymphocytes, and 4% monocytes. The peripheral smear showed normocytic normochromic cells with decreased leukocytes and platelets. Levels of blood urea nitrogen, serum electrolytes, and amyase, results of liver function tests, and roentgenograms of the chest and abdomen were normal. Four blood cultures were positive for Salmonella typhosa (group D) and complement fixation titers of 1: 640 for 0 and H antigens were found. The bone marrow was hypercellular with many normal budding megakaryocytes and increased erythroid elements. It was not possible to demonstrate fibrin split products in the serum.

Blood coagulation studies were as follows: platelet count 45,000/mm3; prothrombin time, 35 sec. with a control of 13.5 sec; partial thromboplastin time, greater than 5 min with a control of 75 sec; and thrombin time, 40.4 sec. with a control of 17,4 sec. plasma fibrinogen level was estimated at 25 to 50 mg/100 ml.

The initial hospital course was stromy. Subconjunctival petchiae, echymoses, and bleeding from the bowel developed, which required blood transfusion.

The patient was treated was treaed initially with 1 g of chloramphenicol intravenously and was maintained on 1/2 g every 6 hours. Heparin sodium (10,000 units) was administered intravenously, followed by 4 g of fibrinogen. Methylprednisolone, 125 mg, and hydrocortisone, 500 mg, were also given. Despite these measures, the patient's condition deteriorated. Expiratory wheezing and coarse, were hard as well as a grade iii/vi systolic cardiac murmur along the left sternal border. She was resuscitated from cardiac arrests twice but died after a third cardiac arrest 8 days after admission.

At autopsy, performed 6 hr postmortem, there were extensive bilateral adrenal hemorrhages and scattered focal hemorrhages in the lungs, endocardium, gastrointestinal tract, and renal pelves. There was moderate, bilateral pulmonary congestion. The spleen weighed weighed 29 g and showed marked diminution of the normal follicular architecture with replacement by fibrous tissue. Follicles were hypoplastic without germinal centers.

Discussion:

Intravascular consumption of clotting factors has been observed in Gramnegative and Gram-positive septicemia; viral, and fungal disease; malaria; and recently in miliary tuberculosis (5-15). This process also has been described after cardiac surgery, abruptio placenta, amniotic fluid embolism, missed abortion, carcinomatosis, promyelocytic leukemia hemolysis, transfusion reaction, hemolyticuremic syndrome, purpura fulminans. fat embolism, and the kassabach-Merritt syndrome (5,16-23).

The appearance of renal cortical necrosis in the presence of disseminated intravacular coagulation simulates the pathological changes of the generalized Schwartzman reaction (24). Peripheral gangrene with bacteremia and disseminated intravacular coagulation has recently been reviewed (10). A patient who developed intravacular consumption of clotting factors, peripheral gangrene, anuria, and bilateral renal cortical necrosis after a dog bite has been described.

Since 1962 a number of reports have emphasized the sudden changes that can occur in the bloodclotting mechanism in patients with bacterial septicemia. The most common observation is probably thrombocytopenia, but a severe alteration in the hemostatic mechanism may result from disseminated intravascular coagulation. Although significant reduction in certain coagulation factors occurs, these patients may or not exhibit a hemorrhagic state, and the fibrin formed may be deposited in the peripheral blood vessels, thereby producing ischemic tissue damage. In addjtion, previous reports have suggested that anticoagulant therapy in septicemia may be beneficial when diffuse intravascular coagulation has been shown to exist.

A hemorrhagic diathesis associated with a number of seemingly diverse diseases characterized by thrombocytopenia and a decreased concentration of multiple clotting factors including severe hypofibrinogenemia has been ascribed to the intravascular clotting of blood (6). In 1961 Lasch et al. (8) introduced the term intravascular consumption coagulopathy (IVCC) to define the process. Studies from many centers shown that IVCC is frequently associated with secondary activation of the fibionlytic system (9). The diagnosis of IVCC rests more or less on demonstrating that the circulating plasma bas been depleted of certain labile clotting factors such as fibrinogen, prothromin, factors and VIII and platelets. In other words, the plasma tends to resemble serum. In addition, because of secondary fibrinolysis, fibrinogen split-products usually are demonstrable in the serum (7).

The mechanisms initiating accelerated intravascular clotting in salmonellosis are un-known, although its endotoxin is one prime suspect. En-

dotoxin, at least in the experimental animal, can initiate clotting through several mechanisms. In vitro, endotoxin is capable of activating Hageman factor and either directly or through Hageman factor causes release of platelet factor III from thrombocytes (11). Activaced Hageman factor and platelet factor III would then activate prothrombin via the intrinsic clotting system and initiate clotting (9). A second effect of endotoxin in the experimental animal is the production of endothelial cell necrosis (12). The mechanism is uncertain. It may result from a direct effect on the endothelial cell or it may be related to intravascular leukocyte lysis (13) with subsequent intravascular fibrin-leukocyte-platelet clots which could result in thrombosis and endothelial cell death. Presumably, the severe vascular disruption produced liberates procoagulant materials which are thromboplastic in nature (16). In addition, exposure of underlying collagen may also activate Hageman factor (17).

The following sequence of events occurring in our patients with fulminating typhoid fever is thus proposed: Initially, blood stream invasion with bacteria occurs. Favorable growth conditions in the blood lead to rapid bacterial multiplication, causing vasculitis, thrombosis and hemorrhage by direct bacterial invasion possibly supplemented by release of endotoxin. With bacterial proliferation a point is reached where there is sufficient bacterial autolysis to produce a significant level of circulating endotoxin. It would appear that as a result of this circulating endotoxin, widespread endothelial degeneration occurs in many organ systems, causing changes in the endothelial surface and exposure of the underlying structures. Whether endothelial cell necrosis is a direct result of the action of endotoxin or occurs secondary to intravascular clot formation and subsequent vascular thrombosis is not known. Accelerated intravascular clotting presumably follows because of direct effects of endotoxin on the clotting mechanism (18). activation of the intrinsic clotting system secondary to surface contact and seeding of the blood with procoagulant material from continued blood vessel damage. With continued utilization of clotting factors, the blood be comes hypocoagulable, with disproportionate hemorrhage at points of altered vascular integrity.

Diagnosis and Therapy. The association of IVCC with sepsis is not the exclusive right of the typhoid, meningococcus (19-25). Serratia marcescens (26), Pneumococcus (27,28), Pseudomonas (29) Esherichia coli (30-32) and Paracolon (33) organisms have all been associated with severe conagulation abnormalities and fibrin deposition.

Retrospective analysis of our patients and other patients with proved IVCC associated with the typhoid or other organism suggests clues that may be of help in arriving at a diagnosis of a coagulopathy. These include the appearance of oozing about venapuncture sites, the sudden appearance of purpura or a rapid worsening of purpura, and shock or unexplained hypotension occurring any time during the course of a septic process. Unfortunately, this constellation of fondings reflects marked abnormalities in coagulation tests which occur in the course of accelerated blood clotting and may be difficult to correct as will be mentioned in the section dealing with therapy. Therefore, if a disease with the potential for initiationg IVCC is clinically suspected, it is vitally important to confirm rapidly whether a coagulopathy exists before severe alteration in coagulation test cocur and before pronounced hemorrhagic signs develop.

We suggest that on admission all patients with septicemia should have the following studies: an estimation of the number of platelets, a partial thromboplastin time, a measure of the level of fibrinogen and a simple test to note the presence or absence of fibrinogen split products.

The diagnosis of IVCC is suggested when there is thrombocytopenia, a prolonged partial thromboplastin time, hypofibrinogenemia and usually the presence of fibrinogen split products. In extreme emergencies a blood smear for platelets, a partial thromboplastin time and the Fi test on serum will rapidly confirm the diagnosis of intravacular coagulation with secondary activation of the fibrinolytic system. If the initial tests are normal we repeat the partial thromboplasin time and platelet count in two hours and thereafter if there is a change in the clinical picture using the criteria listed in the preceding paragraph. Patients with shock should be monitored even more closely for evidence of coagulopathy.

Therapy of IVCC at the present time is largely empirical in nature and is dictated by the changes in coagulation test as related to the clinical picture. Although accelerated clotting is occurring as manifested by a serial prolongation of the partial thromboplastin time and a decreasing concentration of platelets, anticoagulation is the treatment of choice.

Heparin is the preferred drug because of its immediate antithromboplastic and antihrombin action (35). After accelerated clotting has consumed clotting factors, heparin may increase the hemorrhagic tendency. When this stage is reached, it is suggested that replacement with fresh whole blood of plateletrich plasma be added to the therapeutic regimen.

In extreme emergencies fibrinogen can be substituted for fresh whole blood or plasma until donors can be located. The use of adrenal cortical steriods is controversial (36) and is presently being evaluated in some patients. Unfortunately, even if one is able to control hemostasis, irreversible shock may contribute to the patient's death. With this in mind, we wish again to emphasiz the need for early diagnosis of IVCC in septicemia and the use of heparin while accelerated blood clotting is occurring and before complete defibrination takes place. Hopefully, this will aid in preventing life-threatening hemorrhage and irreversible shock.

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