PSEUDOMONAS SEPTICEMIA WITH INTRAVASCULAR CLOTTING LEADING TO THE GENERALIZED SHWARTZMAN REACTION*

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FIBRIN is deposited throughout the glomerular capillary bed of a young rabbit given two appropriately spaced injections of bacterial endotoxin. If the animal lives long enough, bilateral necrosis of the renal cortex follows. Slow intravascular coagulation and impaired clearance of damaged fibrinogen and fibrin are two of the probably multiple factors operating to produce this reaction, which is called the generalized Shwartzman reaction. For a reason as yet unknown a single injection of endotoxin invokes the complete reaction in a pregnant rabbit.

The difficulty in producing the reaction in animals other than the rabbit has raised the question of its relevancy for human disease. Nevertheless, striking similarities have been pointed out between the reaction and the arteriolar and capillary thrombotic lesions that may lead to necrosis of the renal cortex as a complication of premature separation of the placenta or of septicemia during pregnancy.[1,2] The generalized Shwartzman reaction has also been postulated as the cause for widespread fibrin thrombi found in infants dying of *Escherichia coli* gastroenteritis.[3]

The case reported below includes the clinical findings, the blood-coagulation studies and the autopsy findings in a man who died of a fulminant pseudomonas septicemia. The blood-coagulation studies strongly suggested extensive intravascular coagulation. The glomerular arterioles and capillaries were filled with material resembling fibrin. The findings in this patient clearly illustrate the devastating effect of the endotoxin-induced generalized Shwartzman reaction in man.

CASE REPORT

A 34-year-old man (L.A.C.G.H. 230-25-23) was admitted to the hospital in the early-morning hours of April 24, 1963. He had been taken ill about 30 hours earlier with abdominal pain, fever, aching and weakness of the extremities. Pain and numbness in the hands and feet, "like frostbite," increased progressively. At about 9 p.m. on April 23 he was in such severe pain that his wife left the house to telephone a doctor. She returned within a few minutes to discover that dark blotches had broken out over both his cheeks. He complained of great difficulty in breathing. He was rushed to the emergency room of another hospital, where he was found to have a blood pressure of 100/74 and a pulse of 144. A hemorrhagic rash was present on both cheeks. Rod-shaped bacteria were seen on a peripheral blood smear within granulocytes. Blood was taken for culture, and, after the administration of penicillin, morphine and dexamethasone (Decadron), he was transferred to this hospital.

He had felt completely well before the abrupt onset of this illness. The past medical history was not pertinent.

He appeared agitated, dyspneic and cyanotic. A striking hemorrhagic eruption was present on both cheeks and on the bridge of the nose. Petechiae and small purpuric spots were scattered over other areas of the face and back; a few were also seen on the trunk and extremities. The fingers and toes were blue and cold, and striking livedo reticularis was seen on the lower legs. The mouth and throat appeared extremely dry. The heart was normal except for sinus tachycardia. Moist rales were heard at the base of the right lung. The abdomen was soft, and no masses or organs were felt. Neurologic examination was negative although the patient complained of pain whenever the extremities were touched.

The temperature was 102°F., the pulse 156, and the respirations 32. The blood pressure was 100/70.

The hemoglobin was 14.0 gm. per 100 ml.; the red blood cells appeared normal in size and shape. The white-cell count was 20,000, with 36 per cent neutrophils, 46 per cent band forms, 7 per cent early metamyelocytes, 4 per cent myelocytes and 7 per cent lymphocytes. Gram-negative, rod-shaped bacteria were again noted in granulocytes. Marked toxic granulation was noted. In addition, many granulocytes contained multiple vacuoles of varying size (Fig. 1). A prolonged search of the peripheral blood smear disclosed only a rare platelet.

The urinary sediment contained many granular casts, no visible bacteria and 0 to 5 white blood cells per high-power field. Lumbar puncture revealed an initial cerebrospinal-fluid pressure equivalent to 200 cm. of water. The fluid looked slightly xanthochromic; cells were not seen on microscopical examination. The protein content was reported as greater than 125 mg., and the sugar as 75 mg. per 100 ml., and the chloride was 122 milliequiv. per liter.

An x-ray film of the chest showed a normal heart and lungs. The blood urea nitrogen was 34 mg., and the serum sugar 75 mg. per 100 ml. The serum sodium was 127

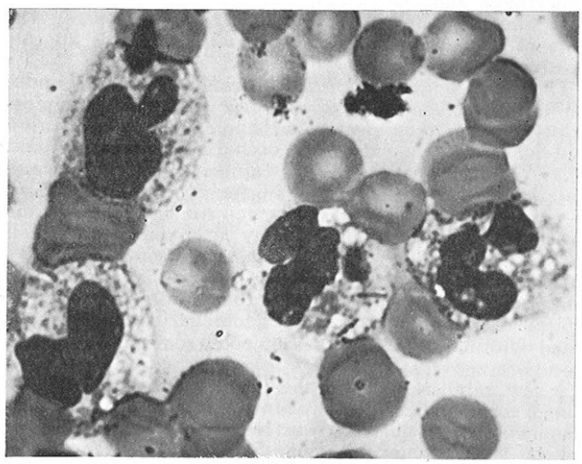

FIGURE 1. *Peripheral Blood Smear, Showing Rod-Shaped Bacteria and Vacuoles within Granulocytes, with Marked Toxic Granulation.*

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milliequiv., the serum potassium 4.2 milliequiv., and the serum bicarbonate 15 milliequiv. per liter. The arterial-blood pH was 7.25. The serum amylase was 87 Somogyi units.

The patient survived for 14 hours after entering the hospital. The temperature fluctuated between 102 and 106.6°F. by rectum. The systolic blood pressure was maintained between 90 and 100 mm. of mercury. A retention catheter inserted 4 hours after admission yielded 20 ml. of urine; no further urine was passed despite the administration of 7 250-ml. units of 6-month-aged plasma as well as a quantity of electrolyte solution estimated as between 2.5 and 3 liters.

He was given penicillin, chloramphenicol, streptomycin and colistimethate. He also received 1 mg. of digoxin parenterally. In the afternoon of April 24 he experienced an episode of cardiac arrest from which he was resuscitated. After this he was given 100,000 International Units of heparin intravenously. A few minutes later he experienced a 2d episode of cardiac arrest from which he could not be revived.

Blood for clotting studies was drawn about 5 hours before death, when he was receiving his 7th 250-ml. unit of 6-month-aged plasma. Approximately 5 ml. of blood was placed in a small glass tube. The blood failed to clot within 30 minutes, but a small clot was found when the tube was re-examined at 90 minutes. This clot did not lyse on standing overnight at 37°C.

Blood for plasma was taken into a balanced citrate anticoagulant with the use of the "silicone technic" as described in detail elsewhere.[4] The plasma was dark pink, indicating intravascular hemolysis. The multiple coagulation abnormalities found are summarized in Table 1, which also refers to the test methods used.

At post-mortem examination, performed 18 hours after death, hemorrhagic foci were widespread throughout the body, both externally and internally. The "butterfly" area of the face was strikingly discolored by a slightly raised, confluent, deeply hemorrhagic lesion. The eyelids were moderately edematous. Serosanguineous fluid was present in the pleural and pericardial cavities; the peritoneal cavity contained 1 liter of partially clotted blood, the source of which was not identified.

The lungs (the right weighing 1040, and the left 870 gm.) showed multiple pleural hemorrhages. Bloody fluid oozed from cut surfaces and was also present in the tracheobronchial tree. The heart (weight, 270 gm.) revealed epicardial and endocardial hemorrhages and some flabbiness of the musculature but was otherwise not remarkable. The liver, which weighed 1830 gm., appeared pale yellow but was otherwise normal. The spleen (weighing 280 gm.) was extremely congested, with obliteration of follicular markings. The lymph nodes were small.

The right kidney weighed 130, and the left 140 gm.; both were deeply congested, with a few surface petechiae. The adrenal glands were of normal size, but the cut surfaces exhibited multiple cortical hemorrhagic foci. The small and large intestines showed varying degrees of mucosal hemorrhage and edema and contained bloody fluid within their lumens. The sphenoid sinus contained several milliliters of thin, tarry fluid. The remaining organs appeared grossly normal.

The striking microscopical abnormalities were found in the kidneys. Almost all glomerular tufts within multiple kidney sections showed an amorphous, eosinophilic, periodic acid-Schiff-reacting material occluding capillary lumens (Fig. 2). Focal thickening of capillary walls with similar material was also prominent. Fibrinoid necrosis of the wall of numerous arterioles was present. An amorphous thrombotic coagulum was seen in many arteriolar lumens; some of these thrombotic masses contained basophilic debris of possible nuclear origin. A few of the larger arterioles showed only hemorrhage within their walls and contained typical thrombi. No distinct endothelial proliferation was noted within any of the vessels. Well defined tubular necrosis was not seen.

A few capillaries within the lung and the pancreas contained eosinophilic thrombi. Marked congestion, with focal hemorrhage and necrosis, was seen in the adrenal glands, but no vasculitis was present. Fresh hemorrhage of varying degree was scattered throughout most of the tissues examined.

The original blood culture, of a specimen drawn before therapy, grew a gram-negative bacillus identified as belonging to the pseudomonas species. No organisms were grown from 3 cultures of blood drawn after admission to this hospital or from cultures of blood and bile taken at autopsy. *Staphylococcus albus* was grown from the peritoneal fluid. Specimens taken from each lung, from the spleen and from the sphenoid sinus showed budding cells on smear and *Candida albicans* on culture. Cultures of the bowel yielded *Esch. coli* 026:BX, paracolon bacillus and *C. albicans*.

TABLE 1. *Clotting Studies in a Patient with the Generalized Shwartzman Reaction Induced by a Pseudomonas Septicemia.*

SCREENING COAGULATION STUDIES	
Quick "prothrombin time"[5]:	
Control	14.6 sec.
Patient	30.0 sec.
Partial thromboplastin time with kaolin[6]:	
Control	48 sec.
Patient	102 sec.
Thrombin time[5]:	
Control	21 sec.
Patient	89 sec.
SPECIFIC ASSAYS	
Plasma thromboplastic factors:	
Hageman factor (factor XII)[7]	72%
Plasma thromboplastin antecedent (factor XI)[4]	33%
Plasma thromboplastin component (factor IX)[8]	50%
Antihemophilic globulin (factor VIII)[7]	25%
Prothrombin complex:	
P & P test[5]	16%
Specific prothrombin assay[7]	22%
Proconvertin (factor VII)[9]	26%
Stuart factor (factor X)[10]	34%
Proaccelerin-accelerin (factor V):	
Assay with brain thromboplastin[11]	17%
Assay with Russell-viper venom[12]	19%
Fibrinogen (normal range, 250-350 mg./100 ml.)[13]:	
Plasma when fresh	80 mg./100 ml.
Plasma after standing for 24 hr.	100 mg./100 ml.

DISCUSSION

This patient's course paralleled the sequence of events classically invoking the generalized Shwartzman reaction in the rabbit — namely, repeated entrance of endotoxin into the systemic circulation, leading to intravascular coagulation and deposition of fibrin aggregates within afferent glomerular arterioles and glomerular capillary loops and, to a much lesser extent, within capillaries in other or-

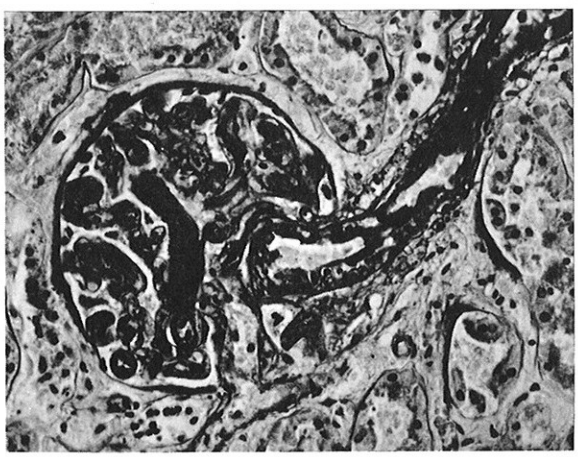

FIGURE 2. *Glomerulus, Showing Amorphous Deposits in Capillary Walls and Lumens (PAS Stain X215).*

An afferent arteriole shows similar deposits and early fibrinoid necrosis.

gans. Although overwhelming evidence supports the view that intravascular coagulation triggers the endotoxin-induced generalized Shwartzman reaction in the rabbit[14-20] the evidence in human beings is much less complete. Fibrin-like material within glomerular vessels, with or without associated necrosis of the renal cortex, has been described in a number of patients dying of infection.[1-3,21-23] In addition, clotting studies indicative of intravascular coagulation have been reported in 2 women with shock and anuria complicating septic abortion.[24,25] Since these patients recovered, pathological evidence of the generalized Shwartzman reaction is lacking. The present case, unfortunately, provides both kinds of evidence: laboratory evidence of intravascular coagulation; and the pathological confirmation of fibrin thrombi throughout the glomerular vasculature.

Although the portal of entry is unknown, endotoxin clearly entered the systemic circulation. Not only was a pseudomonas species grown from the blood but also rod-shaped bacteria were found within circulating granulocytes (Fig. 1). The white blood cells contained multiple vacuoles resembling those described after exposure of whole blood to endotoxin[26] in vitro. Intravascular hemolysis, evident from the plasma drawn for coagulation studies, has also been reported after the administration of endotoxin to animals.[27]

Endotoxin probably first entered the circulation shortly before the onset of symptoms. The first clear-cut evidence of the generalized Shwartzman reaction — the hemorrhagic eruption on the face — appeared about thirty hours later. (The rash resembled that shown in the color picture in the article by Lasch and his associates.[25]) The discovery of organisms within circulating granulocytes makes it reasonable to assume that endotoxin gained access to the systemic circulation repeatedly, if not continuously, during these thirty hours. Indeed, one must postulate this to relate the patient's course to the experimental generalized Shwartzman reaction, which requires two injections of endotoxin twelve to twenty-four hours apart unless the animal is pregnant or has been pretreated either with cortisone or with a reticuloendothelial-blocking agent.

Intravascular coagulation can account for all the blood-coagulation abnormalities found in this patient. The marked thrombocytopenia could have resulted from destruction of platelets during clotting or sequestration of platelets damaged by endotoxin[26,28,29] or both processes. The low levels of fibrinogen, prothrombin, proaccelerin and antihemophilic globulin are readily explained by intravascular clotting since these factors are consumed when human blood clots in a glass tube. The low values for factors that persist in serum in vitro — plasma thromboplastin antecedent of 33 per cent, plasma thromboplastin component of 50 per cent, Stuart factor of 34 per cent and proconvertin of 26 per cent — are more difficult to understand at first glance. Nevertheless, a fall in serum factors has been documented in rabbits given two injections of endotoxin.[30] Moreover, low proconvertin levels were found in the 2 women mentioned earlier who are thought to be examples of the generalized Shwartzman reaction complicating septic abortion.[24,25]

The patient was given 1500 ml. of six-month-aged plasma in the eight hours before the blood for clotting studies was taken. This plasma contains only traces of clotting-factor activities. Thus, dilution could explain part of the fall in serum factors; however, it could not account for levels one fourth to one third of normal. The serum factors have been shown to be activated during clotting in vitro — for example, plasma thromboplastin antecedent and plasma thromboplastin component during intrinsic clotting,[7,31] proconvertin during both intrinsic and extrinsic clotting[32] and Stuart factor during clotting mediated by Russell-viper venom or trypsin.[33,34] Activation during intravascular clotting, with subsequent rapid clearance of activated moieties as the blood circulates through the liver,[35,36] seems to us a reasonable explanation for the low levels of plasma thromboplastin antecedent and plasma thromboplastin component, proconvertin and Stuart factor in this patient.

It should be emphasized that increased fibrinolytic activity was not detected in the patient's blood. The poor clot that formed in a whole-blood sample failed to lyse in twenty-four hours at 37°C. No evidence of fibrinogenolysis could be demonstrated, for the fibrinogen level did not fall when the plasma was allowed to stand for twenty-four hours. McKay[37] has recently called attention to the possible role of inadequate fibrinolysis in the pathogenesis of the experimental generalized Shwartzman reaction.

Bilateral necrosis of the renal cortex has been considered the cardinal pathological feature of the generalized Shwartzman reaction.[38] However, a laboratory animal often dies before ischemic infarcts appear, at a time when the kidneys show only plugging of glomerular capillaries with fibrin. Moreover, necrosis of the renal cortex may occur without preceding glomerular thrombosis, as from vasospasm produced by staphylococcal toxin.[39] For these reasons, McKay[37] has redefined the characteristic morphologic criterion of the generalized Shwartzman reaction as glomerular capillary thrombosis. The extensive plugging of glomerular arterioles and capillaries by fibrin-like material in our patient (Fig. 2) fits this morphologic criterion. The failure to secrete urine in the fourteen hours before death, despite an adequate blood pressure and large amounts of plasma and electrolyte solution, attests to the functional significance of this glomerular lesion.

In retrospect, we question the wisdom of the administration of large amounts of six-month-aged plasma to the patient. Lee has presented evidence[40,41] that fibrin deposits within the glomerular vasculature in the generalized Shwartzman reaction because the reticuloendothelial system cannot

clear fibrin aggregates from the circulation. Therefore, in any clinical situation in which the possibility of intravascular clotting must be considered it seems a potential danger to present the reticuloendothelial system with the added task of clearing large amounts of denatured plasma protein in the form of transfused aged plasma.

Heparin can prevent the experimental generalized Shwartzman reaction.[14] The 2 women mentioned above who are thought to have survived the generalized Shwartzman reaction received large amounts of heparin.[24,25] Our patient received 100,000 International Units a few minutes before he died — clearly too late to have influenced the outcome. Hemorrhage secondary to the multiple hemostatic defects arising after intravascular clotting makes one fear to use heparin. Nevertheless, we are convinced that the best therapy for such patients consists of a combination of fresh whole blood and, if necessary, a fibrinogen preparation to correct the coagulative defects preceded by large amounts of heparin to stop the intravascular clotting.

The clotting studies in the 3 patients described by Pfau, Lasch and Günther,[24] by Ratnoff and Nebehay[42] and by us above establish that septicemia can trigger extensive intravascular clotting in the human being. The extensive process uncovered in these patients must represent the rare, extreme situation. It seems reasonable to suspect that less extensive intravascular clotting occurs much more frequently. Indeed, such lesser degrees of intravascular coagulation are thought to be responsible for significant clinical manifestations of the septicemic state.[23]

Summary and Conclusions

The clinical and pathological findings and blood-coagulation studies in a patient with pseudomonas septicemia are described. The blood-clotting studies indicated extensive intravascular coagulation. Histologic examination of the kidneys disclosed the widespread deposition of material staining like fibrin within the glomerular vessels. These findings clearly demonstrate that bacterial endotoxin may induce a generalized Shwartzman reaction in man.

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