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. The generalized Shwartzman reaction has also been postulated as the cause for widespread fibrin thrombi found in infants dying of Escherichia coli gastro-enteritis.  

The case reported below includes the clinical findings, the blood-coagulation studies and the autopsy findings in a man who died of a fulminating 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. Red-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, red-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 Red-Shaped Bacteria and Vacuoles within Granulocytes, with Marked Toxic Granulation.
TABLE 1. Clotting Studies in a Patient with the Generalized Shwartzman Reaction Induced by a Pseudomonas Septicemia.

<table>
<thead>
<tr>
<th>Test</th>
<th>Control</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quick prothrombin time</td>
<td>14.6 sec</td>
<td>30.0 sec</td>
</tr>
<tr>
<td>Partial thromboplastin time with kaolin</td>
<td>46.0 sec</td>
<td>102 sec</td>
</tr>
<tr>
<td>Thrombin time†</td>
<td>21.0 sec</td>
<td>65.0 sec</td>
</tr>
</tbody>
</table>

**Specific Assays**

- **Plasma thromboplastic factors**:
  - Hageman factor (factor XII): 72.0%  
  - Plasma thromboplastin antecedent (factor XI): 33.0%  
  - Plasma thromboplastin component (factor IX): 50.0%  
  - Antithromophilic globulin (factor VIII): 25.0%

- **Prothrombin complex**:  
  - P & P test: 10.0%  
  - Specific prothrombin assay: 22.0%  
  - Fibrinogen (normal range, 250-350 mg/100 ml): 10.0%  
  - Plasma when fresh: 80.0 mg/100 ml  
  - Fibrinogen after standing for 24 hr: 10.0 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 arteries and glomerular capillary loops and, to a much lesser extent, within capillaries in other organs to the pseudomonas species. No organisms were grown from 3 cultures of blood drawn after admission to this hospital or cultures of blood and bile taken at autopsy.

**Figure 2. Glomerulus, Showing Amorphous Deposits in Capillary Walls and Albus (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 Schwartman reaction in the rabbit, 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. In addition, clotting studies indicative of intravascular coagulation have been reported in 2 women with shock and anuria complicating septic abortion. Since these patients recovered, pathological evidence of the generalized Schwartman 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 in vitro. Intravascular hemolysis, evident from the plasma drawn for coagulation studies, has also been reported after the administration of endotoxin to animals.

Endotoxin probably first entered the circulation shortly before the onset of symptoms. The first clearcut evidence of the generalized Schwartman 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.) 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 Schwartman 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 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. Moreover, low proconvertin levels were found in the 2 women mentioned earlier who are thought to be examples of the generalized Schwartman reaction complicating septic abortion.

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, proconvertin during both intrinsic and extrinsic clotting and Stuart factor during clotting mediated by Russell-viper venom or trypsin. Activation during intravascular clotting, with subsequent rapid clearance of activated moieties as the blood circulates through the liver, 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 has recently called attention to the possible role of inadequate fibrinolysis in the pathogenesis of the experimental generalized Schwartman reaction.

Bilateral necrosis of the renal cortex has been considered the cardinal pathological feature of the generalized Schwartman reaction. 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. For these reasons, McKay has redefined the characteristic morphologic criterion of the generalized Schwartman 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 that fibrin deposits within the glomerular vasculature in the generalized Schwartman 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.4 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 coagulable 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,34 by Ratnoff and Nebehay43 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.33

**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. Histo logic 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.

**REFERENCES**


