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CLOSTRIDIAL SEPTICEMIA WITH INTRAVASCULAR HEMOLYSIS

A CASE REPORT

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In 1871 Bottini[1] demonstrated the bacterial nature of gas gangrene, but failed to isolate a causal organism. Clostridium perfringens, sometimes known as Clostridium welchii, was discovered independently during 1892 and 1893 by Welch, Frankel, Veillon and Zuber.[2] This organism is a saprophytic inhabitant of the intestinal tract, and may be a harmless saprophyte of the female genital tract occurring in the vagina in 4-6 per cent of pregnant women.

Clostridial organisms occur in great numbers and distribution throughout the world. Because of this, they are very common in traumatic wounds. Very few species of clostridia, however, are pathogenic, and still fewer are capable of producing gas gangrene in man. The latter are six in number, and are the Clostridium perfringens, novyi, septicum, bifermentans, histolyticum, and fallax. The pathogenicity of these organisms is due to their possession of soluble exotoxins which are capable of destroying various blood and tissue cells. With the exception of Clostridium botulinum and Clostridium tetani, clostridial infections are neither rare, nor are they very grave. It is only when they invade the blood stream or the muscles that they are considered to be very dangerous.

The organism of greatest importance in the production of gas gangrene is Clostridium perfringens. It causes 60-80 per cent of the cases of gas gangrene, with Clostridium novyi causing 30-60 per cent and Clostridium septicum, the causal agent in 5-20 per cent. It is the only gas gangrene associated organism which rarely forms spores. It is an anaerobe which ferments sugar and produces large quantities of gas with a characteristic odor. In the laboratory when cultured on blood agar, the colonies are seen to be surrounded by a zone of hemolysis. This target appearance is due to the distinct hemotoxins characteristic of Clostridium perfringens. In all, twelve toxins of Clostridium perfringens are recognized. The alpha toxin is hemolytic, dermonecrotizing and lethal. It is a relatively heat stable lecithinase which hydrolizes lecithin to phosphorylcholine and a diglyceride.[3] Certain strains of Clostridium perfringens have also been shown to produce a fibrinolysin.

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Clinical Considerations

Turning our attention now to the clinical condition of gas gangrene, we recognize it as an invasive anaerobic infection of muscle, which is characterized by profound toxemia, extensive local edema, massive death of tissue, and a variable degree of gas production. Anaerobic myositis and clostridial myositis are terms which have been offered to replace the name gas gangrene. These terms do not denote tissue necrosis, but rather suggest inflammation only. This is an untrue situation. The terms clostridial or anaerobic myonecrosis are good ones, but will probably not replace gas gangrene in our medical nomenclature. Clostridial wound infections are not bacteriological entities, but rather clinical concepts and accordingly, must be defined in clinical terms. Mac Lennan,[4] in 1962, classified clostridial infections as traumatic infections, nontraumatic infections and other clostridial infections. The traumatic infections he subdivides into wound infections and uterine infections. The wound infections he further subclassifies as: 1. Simple contaminations, 2. Anaerobic cellulitis and 3. Anarobic myonecrosis. Simple contaminations occur when the local conditions are not suitable for the proliferation of the clostridial organism. Such contamination causes very little or no pain to the patient, and there is usually no systemic reaction. This wound is frequently slow to heal. Anaerobic cellulitis is a gassy infection which is not associated with progressive involvement and destruction of muscle. Necrotic muscle is involved in anaerobic cellulitis, but it is the result of ischemia or trauma rather than bacterial action. Healthy muscle is not invaded in anaerobic cellulitis. Anaerobic myonecrosis, on the other hand, is an acute invasion of healthy living muscle. An essential factor in the production of anaerobic myonecrosis is trauma, particularly if it inflicts a deep and lacerating muscle wound. The incubation period is almost always less than three days, with the majority of cases developing within the first twenty-four hours.

Mac Lennan[4] also considers uterine clostridial infections in the category of traumatic infections. In spite of its frequent occurrence in the gravid vagina, Clostridium perfringens is an uncommon cause of post-abortal or puerperal sepsis. Also, a nongravid uterus is rarely involved with clostridial infections. Such infections are most frequently the result of attempts at criminal abortion. Less commonly, they follow spontaneous abortions, and still less often, develop during labor or during the puerperium. Unlike clostridial wound infections, they are often associated with icterus, hemoglobinemia, and hemoglobinuria. This then suggests their frequent and usual progression to true septicemia. Again, Clostridium perfringens is the most common of the clostridial organisms involved.

In Mac Lennan's[4] classification of nontraumatic clostridial infections, he mentions both idiopathic gas gangrene and infected vascular gas gangrene. Idiopathic gas gangrene, as such, may not exist. Many of these reported cases actually have clostridial spores which have been dormant for as long as 18-20 years. Frequently, too, there is some distant lesion in the gastrointestinal tract. Still, there are other cases in which no known trauma, dormant spores or gastrointestinal tract lesion can be demonstrated. Infected vascular gangrene may be manifest by the proliferation of

gas producing anaerobes in a gangrenous but anatomically intact muscle. The ischemic limb represents such a situation. The line of demarcation between healthy and dead muscle is usually distinct.

The incrimination of clostridial organisms etiologically in other conditions has come under much criticism in the past. Some authors,[5,6] have claimed Clostridium perfringens caused chronic rheumatism, osteomyelitis, pernicious anemia, and malignant diphtheria. More probable are certain cases of peritonitis, appendicitis, and in particular cholecystitis. Peculiar forms of gastroenteritis have on occasion been attributed to clostridial organisms. Food poisoning certainly may be due to a clostridial infection. The toxicity of bowel obstruction has also been attributed to the toxins of Clostridium perfringens.

Intravascular Hemolysis

Intravascular hemolysis occurs at times in Clostridium perfringens septicemia. Even though a severe, far-advanced case of clostridial myonecrosis may be evident, intravascular hemolysis may not necessarily be manifest. In fact, it does not occur unless there is also a concomitant clostridial septicemia. Such a phenomenon is usually not seen in wound infections, but is almost inevitable in uterine infections.[7] Alphoa or hemotoxin is liberated very slowly from areas of focal necrosis, and, therefore, only minimal degrees of intravascular hemolysis are detected. In the laboratory animal, intramuscular injection of toxic filtrates gives focal necrosis and death; whereas, intravenous injection of an identical filtrate will cause death and intravascular hemolysis as well. Massive intravascular hemolysis is clinically manifest by a rapidly developing anemia and free hemoglobin and metalbumin in the plasma. Microspherocytes have been reported as early evidence of Clostridium perfringens septicemia by some investigators. Increased fragility of the erythrocyte in clostridium septicemia has been demonstrated.

A patient may be noted to become icteric within hours of the onset of septicemia, if hemolysis occurs and will soon develop a characteristic bronze color. Generalized myalgias, neuritic and joint pains are frequent complaints. Although recognition of intravascular hemolysis is not a new entity, there is limited awareness of other associated phenomena. Specifically, there is an early and precipitous fall in the blood platelet count and there also may be an increased coagulation time, hypoprothrombinemia, and hypofibrinogenemia as well.

Case Presentation

A 43 year old, negro woman, (#089 89 18), was admitted to the Emergency Room on March 15, 1965. She had a history of vomiting for three days, and had been treated by her private physician for a flu syndrome. She was said to have vomited most of her intake during that period, and had been obstipated for the same period of three days. The patient also complained of intermittent abdominal pain, which occurred primarily following meals, and which was relieved by vomiting. Her last menstrual period was in January, 1965. Her past medical history revealed two operations in the early 1950's for tubal pregnancies.

At the time of this admission, examination revealed a temperature of 98.6° F, and a pulse of 84 per minute. The abdomen was found to be moderately distended with slight tenderness but no definite localization. Bowel sounds were audible and were considered to

be indicative of mechanical obstruction. A rectal examination was considered negative. The pelvic examination revealed a non-tender, slightly enlarged uterus.

Laboratory studies done at the time of admission revealed a white count of 7,400 with 77 per cent polymorphonuclear leukocytes. Her serum chloride level was 87 mEq/liter, and Co_2 was 36.4 mEq/liter. The prothrombin time was 18 seconds with a control of 15. X-ray examination of the abdomen revealed distended loops of small bowel.

The patient was treated with intestinal intubation for decompression during which period her fluid and electrolyte status were restored. Although her clinical condition seemed to improve somewhat, the follow-up films of the abdomen revealed essentially no alteration in the status of the mechanical small bowel obstruction. After 2½ days of conservative management, therefore, operative intervention was deemed necessary.

The patient was taken to the Operating Room on March 17, 1965, at which time an adhesive band was found extending from a portion of small bowel down to the left lateral wall of the pelvis. Caught beneath this band was a knuckle of ileum. With removal of this band, a small impression was left on the now liberated small bowel. It was not felt that this area of small bowel was jeopardized, but the serosa was imbricated across it for added protection. Another area of ileum was found to be adherent to the anterior abdominal wall at the site of the previous surgery. This was dissected free, and once again, the small bowel determined to be viable. The patient tolerated the operation without consequence, but approximately 30 hours later, was found to be quite apprehensive and complained of her legs feeling tired. She expressed an opinion that she "was going to have a stroke". A question of scleral icterus was raised at this time, and a blood specimen was sent for a quantitative bilirubin. The laboratory reported the blood specimens would not clot and appeared to be heparinized. Approximately 36 hours postoperatively, the patient was suddenly found to be hypotensive. Her systolic blood pressure was 60 mm. Hg. This responded to the intravenous use of norepinephrine. Rales were audible at the right base and it was suspected that the patient might have had a pulmonary infarction, although there had been no previous objective evidence of thrombophlebitis. An emergency angiogram was decided upon as a possible means of detecting a pulmonary embolus. An area of ecchymosis over the upper portion of the abdomen, and subcutaneous emphysema over the right lateral chest cage were also evident at this time. Urine flowing from the Foley catheter was found to be grossly bloody for the first time. While the patient was being readied for transfer to the X-Ray Department, her blood pressure once again dropped and could not be elevated. In spite of resuscitative efforts she expired approximately two hours after first lapsing into a comatose state.

Blood studies obtained immediately prior to her death revealed a free plasma hemoglobin of 4,700 milligrams percent; the normal is usually considered to be less than 6 milligrams percent. The serum fibrinogen level was 331 milligrams percent, a level which is considered normal. The prothrombin time was 36 seconds with a control of 15 seconds. The partial thromboplastin time was 160 seconds with a control of 59 seconds. A peripheral smear demonstrated a toxic left shift of the leukocytes. No erythrocytes could be identified on the smear. A few spherocytes were seen. Blood cultures were obtained immediately before her death and directly post mortem,

the latter being from an intracardial source. These showed an abundant growth of gram positive rods which were later identified as Clostridium perfringens. An autopsy was obtained and revealed the presence of intravascular hemolysis and gas production. Although the necropsy was performed less than four hours post mortem, the body had the appearance of having lain unattended for one or two days. The abdominal viscera had a darker color than one would normally anticipate. Bacilli were identified in the liver, spleen, lungs and in the interstitial spaces of the heart. The cardiac fibers were separated so as to suggest gas production in this organ. The peritoneal, pleural and pericardial spaces each contained unclotted bloody fluid. A pulmonary embolus was not found. Several small mucosal ulcers were present in the small intestine. These were not considered to be acute ulcerations, however, as their bases were well organized with granulation tissue and their surfaces covered over by fibrin.

Summary

A case of massive intravascular hemolysis caused by a Clostridium perfringens septicemia is reported. Although this condition has been described in the literature, it is distinctly an unusual occurrence in the absence of a uterine infection. The small mucosal ulcerations in the intestine undoubtedly represented the site of entrance for the organisms in this particular case. The fulminant clinical picture and rapidity of events leading to the patient's demise are particularly striking. The degree of anxiety and apprehension which the patient exhibited prior to lapsing into coma, and the profound terror of impending catastrophe which she expressed are characteristic of clostridial infections and specifically clostridial septicemia.

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