Waterhouse-Friderichsen Syndrome Secondary to Capnocytophaga canimorsus Septicemia and Demonstration of Bacteremia by Peripheral Blood Smear

A Case Report and Review of the Literature

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Waterhouse-Friderichsen syndrome caused by Capnocytophaga canimorsus septicemia was fatal in a previously healthy 47-year-old woman. The patient died suddenly in less than 12 hours after presentation, in spite of supportive measures, including ventilation, antibiotic coverage, pressor therapy, and multiple transfusions of blood products. The diagnosis of infection due to an unusual organism was suspected earlier in the course of management after review of the peripheral blood smear. The importance of the findings in the blood smear and their correlation with infection due to this organism are discussed.

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REPORT OF A CASE

A previously healthy 47-year-old white woman awoke early one morning with a temperature of 39.5°C and shaking chills, after having experienced nausea and vomiting for the preceding 5 days. That afternoon, she developed diarrhea, left-sided abdominal pain, and low back pain, followed by dyspnea. Late in the afternoon, she presented to her private physician, at which time cyanosis, hypotension, and tachycardia were noted. The emergency medical services were called, and she was immediately transported to our hospital. In the emergency department, the patient was intubated, and intravenous fluids and dopamine for blood pressure support were administered. She was admitted to the intensive care unit with the presumptive diagnosis of septic shock.

Her medical history was contributory for right middle lobe bronchopneumonia in 1990, positive purified protein derivative (tuberculin) (remote), stress urinary incontinence, intermittent leg claudication, hay fever, and right toe arthritis. She was not taking any medications. There was no history of recent travel or dental procedures. The patient had a pet dog.

Physical examination on admission was remarkable for temperature of 39.1°C, pulse of 142/min, blood pressure of 82/54 mm Hg, and respiratory rate of 18/min (on ventilator). She was markedly cyanotic. Examination of the chest and abdomen was unremarkable. Rectal examination revealed blood-tinged heme-positive stool. Laboratory evaluation showed hemoglobin of 149 g/L, hematocrit of 0.43, and white blood cell count of 7.5 × 10^9/L with a differential of 62% polymorphonuclear leukocytes, 31% band forms, 3% lymphocytes, 1% atypical lymphocytes, 2% metamyelocytes, and 1% monocytes. Review of the peripheral blood smear showed toxic granulations in neutrophils and intracytoplasmic and extracellular bacterial rods. Bizarre nuclear changes were seen within granulocytes (Figure 1). Occasional nucleated erythrocytes and schistocytes were also noted. The platelet count was 17 × 10^9/L. Because of potential interference by persistent in vivo hemolysis, routine chemistry and coagulation studies (including prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, and fibrin degradation products) were not performed. Chest x-ray examination showed no obvious infiltrates or pleural effusions. Computed tomographic (CT) scan of the head was unremarkable, but CT scan of chest, abdomen, and pelvis showed small bilateral pleural effusions and bibasilar areas of atelectasis. No abscess or other source of sepsis was identified.

A preliminary diagnosis of septic shock of unknown etiology with disseminated intravascular coagulation was made. Stool culture and 2 sets of blood cultures were obtained, as well as stool specimens to test for ova and parasitic examination and Clostridium difficile toxin. Empiric antibiotic therapy with ceftriaxone, vancomycin, and imipenem was instituted. However, her condition deteriorated rapidly overnight. She developed refractory hypotension and started to bleed from her nose, rectum, and a triple lumen catheter puncture site in the left inguinal region. She also developed generalized ecchymoses that became confluent. Multiple units of fresh-frozen plasma, platelets, and packed red blood cells were transfused. In spite of these efforts she died less than 12 hours after admission. A complete autopsy was performed.

MATERIALS AND METHODS

Blood specimens for routine culture were inoculated into broth-based culture bottles and incubated in an automated blood
culture system (BACTEC 9120 Fluorescent Series, Becton Dickinson, Sparks, Md). Laboratory protocol at our institution dictates that the initial microbiologic evaluation for bacteremia include 2 sets of peripheral blood cultures collected from different sites at least 5 minutes apart. The first set consisted of 1 standard aerobic bottle and 1 lytic anaerobic bottle. The second set consisted of 2 standard aerobic bottles.

All autopsy tissues were fixed in 10% buffered neutral formalin, embedded in paraffin, and cut at 5 μm. All sections were stained with hematoxylin-eosin. Selected tissues were also

Figure 1. A and B, Neutrophils with intracytoplasmic rod shaped organisms. C and D, Bizarre nuclear changes within scattered granulocytes with ameboid and floral nuclear patterns. Also note reactive changes such as cytoplasmic vacuolization and toxic granules (Wright-Giemsa stain, original magnification ×1000).
stained with phosphotungstic acid–hematoxylin to highlight fibrin microthrombi or with tissue Gram stain to identify microorganisms. The antemortem peripheral blood smear slide stained with Wright-Giemsa method was reviewed.

RESULTS

Autopsy and Histologic Findings

Generalized purpura, petechial skin lesions, and central cyanosis were noted. No bite marks were identified. The mouth showed poor dentition. Bilateral pleural effusions and pneumomediastinum were observed. The peritoneal cavity contained approximately 1000 mL of serosanguineous fluid. The renal cortices were pale, and microscopic examination showed extensive cortical necrosis without suppurative inflammation and numerous fresh fibrin thrombi within glomerular capillaries and extraglomerular arterioles (Figure 2). Both adrenal glands showed diffuse intraparenchymal fresh hemorrhage with secondary cortical cell necrosis (Figure 3). The liver demonstrated focal acute centrilobular necrosis. Expansion and congestion of splenic red pulp with increased neutrophils and attenuated white pulp was present. The gastrointestinal tract showed partial autolysis of the mucosa with focal fresh microvascular fibrin thrombi within mucosal and submucosal vessels and patchy fresh hemorrhages in the lamina propria. There was no evidence of transmural bowel infarction, suppurative inflammation, or perforation. Gram stain of sections of spleen, bone marrow, and small and large intestine were negative for bacteria.

Microbiologic Studies

Antemortem stool cultures were negative for enteric pathogens. Stool examination for ova and parasites and C difficile toxin was also negative. After incubation for 3 days, the 3 aerobic blood culture bottles became positive, while the anaerobic bottle remained negative for the entire 5-day protocol. Gram stain of the positive bottles showed gram-negative, thin, fusiform rods. These organisms grew...
rabbit bloodagar at 35°C to see optimal growth on 5%. The organism showed optimal growth on blood and chocolate agar in the presence of 10% carbon dioxide but not on MacConkey agar. An identification of the bacterium as Capnocytophaga canimorsus was made. The specimen was sent to the Connecticut State Health Department Laboratory and then to CDC for characterization and identification of the species. The organism showed optimal growth on 5% rabbit blood agar at 35°C and was positive for catalase, oxidase, and arginine dihydrolase. Negative reactions were obtained for sucrose, raffinose, xylose, mannitol, nitrate reduction, and indole production. These results and the cellular fatty acid profile by chromatography identified the bacterium as C. canimorsus.

COMMENT

This report describes an intriguing case of C. canimorsus sepsis with disseminated intravascular coagulation, generalized purpura, bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome), and multiorgan failure. Premortem blood cultures grew an unusual facultative anaerobic gram-negative bacillus, namely, C. canimorsus. This organism was first isolated in 1976 from blood and cerebrospinal fluid of a patient following a dog bite. The “dog bite organisms” were initially placed in CDC group DF-2 (dysgonic fermenter). Later in 1989, Brenner and colleagues proposed the name C. canimorsus (Latin for “dog bite”) for this group of organisms. Capnocytophaga canimorsus is part of normal gingival flora of cats (17%) and dogs (24%). The DF-1 organisms, primarily found in the human oral cavity, include Capnocytophaga gingivalis, Capnocytophaga sputigena, and Capnocytophaga ochracea. These are easily distinguished from DF-2 organisms by the absence of catalase and oxidase production.

To date, approximately 140 cases of C. canimorsus infection have been reported worldwide, with an age range of 4 months to 77 years and greater frequency in men (74%). Host risk factors include immunosuppression and conditions such as asplenia, alcoholism, chronic lung disease, hematologic malignancies, cirrhosis, and oral ulceration. Of note, no case of C. canimorsus infection in a patient with the acquired immuno deficiency syndrome has been described to date. The spectrum of clinical features ranges from mild to fulminant. Fever, chills, myalgia, vomiting, diarrhea, abdominal pain, malaise, dyspnea, mental confusion, and headache are seen in decreasing order of frequency. Only 2 cases of fatal Waterhouse-Friderichsen syndrome caused by C. canimorsus infection have been described. The first reported case was in a 57-year-old splenectomized woman with no history of animal bite. The second case was in a 57-year-old man with no known risk factors and with a history of dog bite. The patient in the present case had no identifiable predisposing condition. Although she did have a pet dog, no history of dog bite was elicited, and no animal bite marks were noted on postmortem examination. In a report of DF-2 organism sepsis in a patient who had undergone splenectomy, Martone et al recovered the organism from the oral and nasal secretions of the pet dog, although the dog had not bitten the patient. We were unable to perform such a study on our patient’s pet dog. Nevertheless, it is conceivable that close animal contact or a trivial lesion may have been the inciting event. History of dog bite has been elicited in only 43% to 57% of cases, and exposure to dogs without bites or scratches has been reported in 12% to 27% cases. In patients with intact spleens, a defective serum lytic activity associated with quantitative or qualitative complement abnormalities has been described as a possible explanation for such a fatal outcome. We have no evidence to confirm or refute that such a condition existed in this case.

This case illustrates that infection with C. canimorsus may be seen after even casual exposure to a pet canine, with ominous results. In such circumstances the diagnosis may be unfortunately delayed due to the absence of a definitive history of animal bite. However, observation of abundant intracytoplasmic 1- to 3-μm fusiform rods within neutrophils on peripheral blood smear has allowed presumptive diagnosis of C. canimorsus infection in the proper clinical setting. In addition, bizarre neutrophil morphology (as seen in this case) may reflect a cytotoxic effect of the organism. Shurin and coworkers had earlier demonstrated that abnormal neutrophil morphology and function were a direct result of Capnocytophaga infection. Their data, derived from studies on patients infected with a species of Capnocytophaga responsible for human dental infection, indicate that the bacterium or one of its products causes neutrophils to act more like macrophages with active phagocytosis and oxygen metabolism. Our report suggests that such morphologic changes in neutrophils may be seen with C. canimorsus infection. Recently, it has been shown that C. canimorsus produces a cytotoxin that may contribute to the disease.
In summary, given the slow growth of this organism in culture, the peripheral blood smear may provide an earlier diagnosis and successful treatment of overwhelming septicemia caused by this microbe, even in the absence of a definitive history of animal bite. This will allow timely institution of proper antibiotic therapy that may be life saving.

References