Fulminant Necrotizing Fasciitis Caused by *Aeromonas sobria* in Neutropenic Patients

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**Abstract**

Infection with *Aeromonas* species has been reported to occur in neutropenic patients. Necrotizing fasciitis caused by *Aeromonas* species is uncommon but potentially life-threatening. We herein describe three cases of fulminant necrotizing fasciitis caused by *Aeromonas sobria* in neutropenic patients. These cases shared many clinical characteristics, including shock, coagulopathy, multiple organ failure and rapidly deteriorating and eventually fatal clinical courses. In all cases, *Aeromonas sobria* was resistant to most antibiotics, except quinolones. Our experience suggests that necrotizing fasciitis caused by *Aeromonas sobria* is a distinctive and fatal entity. As the use of quinolones is not usually considered in cases of febrile neutropenia, it is important to adjust the antibiotics in time when culture results become available. In some cases, early treatment with quinolones and surgical intervention should be considered, especially when this complication occurs in patients with profound neutropenia.

**Key words:** *Aeromonas sobria*, leukemia, necrotizing fasciitis, febrile neutropenia, quinolones

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**Introduction**

*Aeromonas* species are water-borne microorganisms of low virulence (1-4). Clinically significant *Aeromonas* infection may occur in immunocompromised hosts (3, 4). There is a wide spectrum of infection foci for *Aeromonas* species. Necrotizing fasciitis represents one of the deadliest forms of *Aeromonas* infection (5-7). We herein describe three cases of severe necrotizing fasciitis caused by *Aeromonas sobria* occurring within an interval of three months. The patients were cared by separate medical teams; therefore, cluster infection was unlikely. Susceptibility to antibiotics was defined according to the criteria published by the Clinical Laboratory and Standards Institute (CLSI). All patients had rapidly deteriorating clinical courses that resulted in mortality within several days. This serious complication is worth clinical attention because it can be devastating for patients with hematologic malignancies.

**Case Reports**

**Case 1**

A 60-year-old man received chemotherapy for precursor B-cell acute lymphoblastic leukemia. At diagnosis, routine screening of viral hepatitis B and C revealed negative results. A port-A catheter was implanted for further treatment. Complete remission was achieved and subsequent treatment was administered according to the German Multi-Center Therapy Study Group for Adult Acute Lymphoblastic Leukemia standard risk protocol published in July, 2009. Pretreatment renal and hepatic profiles were normal. The patient developed neutropenic fever up to 38.3°C after treatment with cytarabine and mitoxantrone. The white blood cell count was 100μL (0% neutrophils). The blood cultures were sterile. Empiric antibiotics (ceftazidime and teicoplanin) were administered to no effect. Amphotericin-B at a dose of 0.5 mg/kg per day was added on the third day. The patient reported mild, tolerable left ankle pain on the fifth day. The left ankle was slightly tender but not swollen. On...
the sixth day, leg swelling and sharp pain developed in the absence of any open wounds. Fever and agranulocytosis persisted. The patient reported dyspnea a few hours later. The leg swelling continued to extend to the proximal leg. A diagnosis of necrotizing fasciitis was made. Hemorrhagic bullae and foul smelling discharge were noticed. Although the antibiotics were changed to imipenem/cilastatin and vancomycin, the patient soon became anuric and nearly comatose on the same day. The laboratory data obtained on that day are shown in Table. The patient was intubated but still died on the seventh day of fever onset (the second day of overt necrotizing fasciitis). A culture of the purulent discharge yielded a Gram-negative bacillus. Esculin hydrolysis and arabinose fermentation tests were negative. Therefore, the microorganism was identified as *Aeromonas sobria*. The susceptibility test showed that the microorganism was resistant to ceftazidime, ertapenem and gentamicin, intermediately sensitive to ceftriaxone, amikacin and cefuroxime and sensitive to ciprofloxacin and levofloxacin according to the standards of the CLSI.

**Case 2**

A 39-year-old woman was diagnosed with T-lineage acute lymphoblastic leukemia. Before treatment, screening tests for hepatitis B and C were negative. A port-A catheter was implanted for further treatment. The patient exhibited hematological remission; however, residual leukemia cells were found in the right pleural effusion. She received subsequent chemotherapy of the induction II phase, which consisted of cyclophosphamide, cytarabine and mercaptopurine in September, 2009. Pretreatment renal and hepatic profiles were normal. Neutropenia was observed on day 13 after the start of treatment (absolute neutrophil count: 290 cells/μL). The patient complained of mild left calf pain with mild swelling and tenderness on day 21. Fever up to 39.7°C developed the following day. Antibiotic therapy with imipenem/cilastatin (imipenem: 250 mg every six hours) was administered. However, the leg swelling rapidly progressed to overt fasciitis, as shown on computed tomography (Figure). The laboratory data obtained on that day are shown in Table. Shock developed on the second day of fever. A surgeon was consulted and amputation was suggested. The operation was eventually not performed due to the patient’s intractable shock status. Levofloxacin was added on the third day of fever. The patient developed multiple organ failure and died on the third day of fever. Prior blood cultures yielded growth of Gram-negative bacilli that were later confirmed to be *Aeromonas sobria*. Esculin hydrolysis and arabinose fermentation tests were negative. The final sensitivity test showed that the bacteria were sensitive to levofloxacin only.

**Case 3**

A 65-year-old man received induction chemotherapy (cytarabine: 100 mg/m² via continuous infusion for seven days) for acute myeloid leukemia in August, 2009. Screening of viral hepatitis B and C revealed negative results, and biochemistry profiles were normal. A port-A catheter was implanted for further treatment. Sixteen days following chemotherapy, the patient developed fever up to 40.5°C and severe shaking chills associated with pain in both lower legs. The serum myoglobin level was 51.4 ng/mL and the creatine kinase level was 27 units/liter, both of which were within the normal ranges. No lesions were found on the legs on admission. Blood cultures revealed growth of Gram-negative bacilli that were later confirmed to be *Aeromonas sobria*. Esculin hydrolysis and arabinose fermentation tests were negative. The sensitivity test showed that the microorganism was resistant to most antibiotics, except ciprofloxacin and levofloxacin, according to the criteria defined by the CLSI. Empiric antibiotics with ceftazidime at a dose of 1 g administered intravenously every eight hours were given. On the second day of fever, small erythematous spots were found on the left calf and thigh. The patient’s lower leg pain persisted. There were bouts of transient coma during febrile
episodes. Treatment with teicoplanin at a dose of 200 mg per day was added. On the third day of fever, the patient developed severe left leg swelling, hypotension, decreased urine output and respiratory distress. An arterial blood gas analysis revealed hypoxemia and metabolic acidosis. Other laboratory data revealed an impaired renal function, severe neutropenia, thrombocytopenia and marked coagulopathy (summarized in Table).

An endotracheal tube was inserted. Surgeons were consulted but the patient’s family eventually declined surgical intervention because it was considered high risk. Despite the administration of aggressive treatment, the patient’s condition continued to deteriorate and he eventually died on the sixth day of fever.

**Discussion**

*Aeromonas* species may cause serious infection in immunocompromised hosts such as patients with cancer, cirrhosis or diabetes mellitus (1-4). The mortality rate among cancer patients has been reported to be up to 70% (3). The clinical spectrum of *Aeromonas* species infection ranges from bacteremia (1-4) to peritonitis (2), liver abscess formation (8) and biliary tract (1, 3) and burn wound infection (1). Defining the species of *Aeromonas* is complex and may require genotype analyses. The pathogen isolated in this article is likely *Aeromonas veronii* biotype *sobria*. However, without performing molecular assays, the species could only be described as *Aeromonas sobria*.

*Aeromonas* infection may occur in patients with hematologic malignancies. Host factors probably play important roles in susceptibility to infection and treatment outcomes. According to Tsai et al., such infections occur in patients with various hematologic malignancies, including acute leukemia, myelodysplastic syndromes and non-Hodgkin’s lymphoma. Two thirds of affected patients have received anti-neoplastic treatment and half have severe neutropenia prior to infection. The overall prognosis is poor, with 35.6% of patients succumbing to infection within 14 days (4).

Necrotizing fasciitis is a destructive soft tissue infection characterized by extensive necrosis in subcutaneous tissues and fascia. A wide range of microorganisms are involved in the development of necrotizing fasciitis (9, 10). When the focus of infection is the extremities, skin flora are often involved (9, 10). In more recent studies, *Aeromonas* species have been implicated as one of the leading etiologies of necrotizing fasciitis. Most cases of necrotizing fasciitis caused by *Aeromonas* species involve fractures or open wounds, in which the source of infection is obvious (5, 6). In contrast, none of our patients had wounds on presentation. The source of infection was obscure. On the other hand, *Aeromonas* species infection may be related to indwelling catheters (11). In a study by Hsueh et al., one diabetic patient developed *Aeromonas sobria* necrotizing fasciitis following prior bacteremia and urinary tract infections. That case shared some features with our patients, as all cases involved port-A devices implanted before treatment. However, the case reported by Hsueh et al. involved neither cancer nor neutropenia. These features are important because when *Aeromonas* species cause necrotizing fasciitis in cancer patients, the outcomes are often poor even with effective antibiotic treatment.

The three patients in the present report shared strikingly similar clinical characteristics. All cases involved consciousness disturbance, multiple organ failure, coagulopathy and a short duration from fever onset to shock or death. The lower leg was the infection focus in all cases. Although environmental surveillance was not performed, cluster infection is relatively unlikely, as the patients were cared for by separate teams. The microorganism, *Aeromonas sobria*, identified in the three cases was unique. In all cases, *Aeromonas sobria* was resistant to most broad-spectrum antibiotics and sensitive to quinolones. The uncommon clinical and microbiological features of these cases suggested that such an infection is not coincidental and represents a specific entity that has not yet been fully appreciated. Similar features have been reported twice, according to our review (6, 7). As pain in the lower extremities presenting prior to the development of overt fasciitis was common to all cases, we advise that a diagnosis of necrotizing fasciitis should be highly suspected when neutropenic fever is accompanied by unexplained pain in the extremities.

Necrotizing fasciitis caused by *Aeromonas sobria* and the therapeutic role of quinolones deserve clinical attention, especially in neutropenic patients. As quinolones are not recommended as empiric antibiotics in the treatment guidelines for febrile neutropenia (12), the use of proper antibiotics in severe *Aeromonas* infection is often delayed until culture results are available. Such delay in the use of proper antibiotics may jeopardize patients. Our experience suggests that the use of quinolones should be considered in neutropenic patients when a diagnosis of necrotizing fasciitis is suspected. However, it is imperative to tailor the choice of antibiotics to the final culture report. In addition, timely surgical intervention is often the keystone to successful treatment of patients with necrotizing fasciitis. None of our patients underwent surgical debridement or amputation, and none survived. Although the clinical experience is limited, we believe that early surgical intervention should be considered in an attempt to improve the chance of treatment success.

The authors state that they have no Conflict of Interest (COI).

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