



ACUTE RHABDOMYOLYSIS AND MYONECROSIS COMPLICATING AEROMONAS BACTEREMIA IN NEUTROPENIC PATIENTS WITH HEMATOLOGIC MALIGNANCIES: REPORT OF TWO CASES

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ABSTRACT

Infections by *Aeromonas spp.* are a rare cause of systemic infection in normal and immunocompromised hosts. We report the cases of two patients with acute non-lymphoblastic leukemia who developed septic shock by *Aeromonas* species with unusual soft-tissue complications. One patient who was undergoing consolidation chemotherapy developed septic shock by *Aeromonas hydrophila* with rhabdomyolysis and subsequent soft-tissue destruction consistent with myonecrosis. She recovered with combination antibiotic therapy and supportive care. The second patient developed neutropenia due to ganciclovir treatment for post-

allogeneic transplant cytomegalovirus antigenemia. He developed a rapidly progressive septic shock due to *Aeromonas sobria* with rhabdomyolysis, multi-organ failure and bilateral lower limb myonecrosis, and died within 48 hours. The portal of entry was not identified in either case. These cases confirm the potentially aggressive nature of these bacteria in neutropenic cancer patients with an unusual tendency to produce muscular and soft-tissue destruction.

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Aeromonas spp. are infrequent etiologic agents of bacterial infection in neutropenic cancer patients; the usual presentation appears to be uncomplicated bacteremia.^{1,2} These waterborne gram-negative bacteria are known to cause soft-tissue infections in non-immunocompromised hosts, usually after local trauma, leech therapy or surgery.^{3,4} Similar complications have been described in neutropenic cancer patients, mainly after chemotherapy for acute leukemia.^{1,2}

We report the cases of two leukemia patients who developed fulminant sepsis from *Aeromonas spp.* as the presentation of an initial febrile episode during neutropenia; the patients presented clinical and laboratory evidence of rhabdomyolysis and eventually developed extensive cutaneous and muscular lesions consistent with myonecrosis.

Case Reports

Case #1. A 41-year-old female with acute non-lymphoblastic leukemia (ANLL) received remission-induction chemotherapy with idarubicin, etoposide and cytarabine in May 1995. Severe neutropenia (neutrophils < 0.2 × 10⁹/L) was reached on day 14 of therapy. On day 16, she developed a high fever (40.5°C) with chills, hypotension, obtundation, diffuse myalgias with marked generalized muscle tenderness and oliguria. Simultaneously, three ten-

der subcutaneous nodules appeared in the extremities (Figure 1). Three blood cultures were positive for *Aeromonas hydrophila*. The isolates were sensitive to second and third generation cephalosporins, carbapenems, piperacillin, aztreonam, aminoglycosides, fluoroquinolones and trimethoprim-sulfamethoxazole and were resistant to ampicillin, amoxicillin-clavulanic acid, ticarcillin and first generation cephalosporins. Biopsies of the skin nodules and stools failed to show any microorganisms. Blood biochemistry was marked by a rise in creatinine phosphokinase (CPK) to 1006 U/L (normal < 180), and the urine was positive for myoglobin, but renal failure did not result. Dopamine, however, was required to maintain the blood pressure and the urinary output. The patient was treated with ceftazidime (2 g tid), amikacin (500 mg bid) and ciprofloxacin (200 mg bid) for 15 days, and later received oral ciprofloxacin for a total of 21 days. Morphine was required during the first five days to control the intense myalgias. Her condition steadily improved, but she later required surgical drainage of a pseudoabscess in her right calf that proved to be necrotic muscle, consistent with a localized site of myonecrosis.

Case #2. A 50-year-old male with ANLL in a first complete remission received an allogeneic peripheral blood stem cell transplant in July 1996. On the



Figure 1. Tender subcutaneous nodule that appeared in the right arm of patient #1 shortly after she developed septic shock and rhabdomyolysis.

51st day after the procedure, grade two acute graft-versus-host disease of the gastrointestinal tract was diagnosed, and he was started on prednisone (120 mg/day) and later on anti-thymocyte globulin (15 mg/kg/day for 10 days). On the 68th day, cytomegalovirus was found in the peripheral blood both by an antigenemia assay and a shell-vial culture. Ganciclovir was begun (5 mg/kg/12 hrs. for 7 days followed by 5 mg/kg/day from Monday to Friday for three weeks). On the 80th day, post-transplant severe leukopenia was first noted (leukocyte count of $0.44 \times 10^9/L$), and granulocyte colony-stimulating factor (5 µg/kg/day sbc) was begun.

That same day, he complained of severe bilateral pain and tenderness in both calfs, but was otherwise asymptomatic. Twelve hours later, he developed a high fever, hypotension, oliguria, obtundation and intense generalized myalgias and muscle tenderness, particularly in the lower limbs. Severe metabolic abnormalities consistent with septic shock were present. The level of CPK peaked at 24,000 U/L and intense myoglobinuria was present. Creatinine rose to 247 mmol/L (normal < 82), and vasoactive drugs were required to maintain the blood pressure and urinary output. Both legs rapidly developed a necrotic appearance below the knees with liquefaction of the subcutaneous tissue and large hemorrhagic bullae. Antibiotic therapy with ceftazidime and amikacin was started, and three blood cultures were positive for *Aeromonas sobria*. The strains were sensitive to second and third generation cephalosporins, carbapenems, piperacillin, aztreonam, aminoglycosides, fluoroquinolones and trimethoprim-sulfamethoxazole and were resistant to ampicillin, amoxicillin-clavulanic acid, ticarcillin and first generation cephalosporins.

Over the following 48 hours multi-organ failure developed which was refractory to supportive therapy in the intensive care unit, and the patient died three days after the onset of symptoms. A *post-*

mortem examination revealed diffuse rhabdomyolysis in all skeletal muscles studied and extensive necrosis of muscle, subcutaneous and cutaneous tissues in both legs.

Discussion

Aeromonas spp. are gram-negative bacilli that are uncommon pathogens in human infection.^{4,5} Their role in provoking diarrheal disease after consumption of contaminated fluids has been well described.⁴ Non-bacteremic skin and soft tissue infections in immunocompetent hosts have also been described; previous surgery or local trauma in an aqueous environment are the usual predisposing factors.^{3,4} Other types of infections are rare, but virtually every organ system may be involved.^{4,6}

Several small case series or single reports of infections in neutropenic cancer patients have been described.^{1,2,7} The usual presentation in this setting is uncomplicated bacteremia with no evident source.^{1,2} There have been, however, several descriptions of skin or soft tissue manifestations in cancer patients with bacteremic infections. Localized cellulitis,¹ ecthyma gangrenosum^{1,2,7} and clostridium-like gangrenous cellulitis¹ have been the main manifestations, while localized myonecrosis has been reported only in patients without cancer.^{6,8,9} These soft-tissue infections have been reported to occur in approximately 20% of neutropenic cancer patients with sepsis,^{1,2,7} although there is a tendency to report only unique or interesting cases. The overall mortality in this setting is about 36%,^{1,2,7} similar to the 30% mortality rate of sepsis in non-immunocompromized subjects.⁶

At our institution, we have seen only four *Aeromonas spp.* bacteremias in patients with hematologic malignancies over the past five years (three *Aeromonas hydrophila* and one *Aeromonas sobria*). Two were uncomplicated bacteremias, and the other two are reported herein. As in immunocompetent subjects, local inoculation may be the portal of entry, but in most cancer patients there is no evidence of previous trauma. Additionally, Sherlock *et al.*¹⁰ found evidence that neutropenic cancer patients may have higher rates of gastrointestinal colonization by *Aeromonas spp.*, suggesting that this may be the source for most bacteremias, as with other gram-negative bacteremia in this setting. In neither of our cases, however, was there evidence of local trauma nor was *Aeromonas spp.* isolated from stool samples. Thus, *Aeromonas spp.* seem to have a tendency to produce skin and soft tissue damage. The development of acute rhabdomyolysis, however, has not been previously described. It is tempting to speculate on the specific virulence factors that may contribute to this soft-tissue destruction. Several virulence factors that lead to subcutaneous and skeletal muscle damage have been identified,⁶ and mus-

cle destruction has been described in an animal model.³ These factors, however, were not studied in our isolates. Since these bacteria are usually susceptible to many types of antibiotics,⁶ empiric combination regimens with a broad-spectrum β -lactam plus an aminoglycoside, a fluoroquinolone or trimethoprim-sulfamethoxazole are usually appropriate. Our cases, however, prove that a rapidly progressing sepsis with rhabdomyolysis and multi-organ damage may be the form of presentation, and its early identification with intensive supportive measures may be critical for a better outcome.

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