Cutaneous Anthrax Associated With Microangiopathic Hemolytic Anemia and Coagulopathy in a 7-Month-Old Infant

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A 7-month-old infant with cutaneous anthrax developed severe systemic illness despite early treatment with antibiotics. The infant displayed severe microangiopathic hemolytic anemia with renal involvement, coagulopathy, and hyponatremia. These findings are unusual with cutaneous anthrax, but have been described in illness resulting from spider toxin and may delay correct diagnosis. The systemic manifestations of the disease persisted for nearly a month despite corticosteroid therapy, but resolved.

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ary pediatricians treated him with amoxicillin/clavulanate potassium for presumed cellulitis, but he required admission to the hospital after the third dose, due to increased swelling and drainage of the lesion, and his difficulty in tolerating oral medication.

The infant did not have a significant medical history but he had recently played outdoors in a New York park and had also visited his mother at her workplace, the offices of a national television news organization, for an hour the day before his symptoms began. Anthrax spores were subsequently found at his mother’s workplace.

On admission, the infant was alert, afibrile, and in no apparent distress. Laboratory studies revealed significant leukocytosis and hyponatremia (Table). Blood was not sent for culture, but intravenous ampicillin/sulbactam was initiated. Surgical incision and drainage performed under local anesthesia revealed no underlying abscess, but dark red fluid was expressed from the lesion. Bacterial cultures were not performed.

On hospital day 2, the left arm showed massive, nonpitting, non-tender edema with a dark red macule approximately 2 to 3 cm in diameter. There was copious, yellow serous drainage from the wound and paler erythema extending across the anterior thorax to the sternum. No axillary adenopathy was palpable. The hyponatremia was managed with fluid restriction and clindamycin was added to the antibiotic regimen. An infectious disease consultation was obtained. A gram stain of the wound drainage showed neither white blood cells nor organisms. Differential diagnoses considered were infection of bone, soft tissue, or both; arachnid bite; and obstructive mass lesion. Ultrasound of the left upper extremity revealed diffuse inflammation without abscess, and minimal axillary lymphadenopathy. Doppler studies excluded deep vein thrombosis or other vascular compromise to the limb. Later that day, the patient became febrile (39.2°C) and developed significant thrombocytopenia.

During the next 2 days, the arm edema decreased slightly, a 3-mm area of central necrosis was noted at the wound site, and petechiae appeared on the left anterosuperior thorax and

### Table. Laboratory Findings, Maximal Daily Temperature, and Therapy of a 7-Month-Old Infant With Cutaneous Anthrax, Microangiopathic Hemolytic Anemia, and Coagulopathy

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<td>28</td>
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<td>10</td>
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<td>22</td>
<td>23</td>
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<td>37.3</td>
<td>29.9</td>
<td>23.3</td>
<td>18.7*</td>
<td>14.3</td>
<td>23.6</td>
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<td>&gt;5, &lt;20</td>
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<td>No</td>
<td>No</td>
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<td>Yes</td>
<td>Yes</td>
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*Value from smear of schistocytes and fragmented red blood cells.
†To convert to mmol/L, multiply by 0.357.
‡To convert to µmol/L, multiply by 88.4.
axilla. The patient’s hematocrit decreased to 23.3%, and low-grade fever, hyponatremia, thrombocytopenia, and leukocytosis persisted, now with a significant number of band forms. Due to loss of intravenous access, the antibiotic regimen was changed to oral cephalaxin and clindamycin.

By hospital day 5, the fever resolved and the arm edema had decreased considerably. The lesion appeared as a circumscribed erythematous plaque (4.5 × 5 cm) with a central eschar of less than 1 cm (Figure 1A). A magnetic resonance image of the upper extremity (previously published) revealed extensive soft tissue inflammation extending from the left lateral chest wall to the hand, but there was no bone involvement, soft tissue gas or fluid collection, or mass lesion. The hematocrit decreased to 18.7%. The glucose-6-phosphate dehydrogenase enzyme level was normal, but the peripheral blood smear revealed schistocytes and fragmented red blood cells. A serum lactate dehydrogenase level of greater than 5000 U/L, along with evidence of mild increases in serum urea nitrogen and creatinine levels, supported a diagnosis of microangiopathic hemolytic anemia.

At this point, the working diagnosis was cutaneous and systemic loxoscelism, as the clinical course and the evolution of the skin lesion (Figure 1A) seemed more consistent with envenomation than an infectious process. Dermatologic consultation concurred with this diagnosis. Oral prednisolone was begun and antibiotics were discontinued. While the patient’s arm edema improved and he remained febrile, his hematologic status worsened during the next few days. The hematocrit decreased to 14.3% with accompanying tachycardia, necessitating 2 transfusions of 15 mL/kg of packed red blood cells. Coagulopathy was evident, with ongoing thrombocytopenia and elevated D-dimer levels and fibrin degradation products. A persistent hypofibrinogenemia required transfusion of 4 U of cryoprecipitate. Renal insufficiency, with elevated serum urea nitrogen, hematuria, proteinuria, transient oliguria, and hypertension (systolic blood pressure of 130 mm Hg and diastolic blood pressure of 85 mm Hg), were present. By hospital day 12, these laboratory abnormalities were resolving and the patient was clinically stable. However, a 2-cm black eschar was present in the center of the cutaneous lesion (Figure 1B).

That day, the first case of cutaneous anthrax in New York was reported and the New York Department of Health was notified that this infant was potentially infected with anthrax. Two skin biopsies of the lesion were performed the next day, and these, as well as blood obtained on hospital day 2, were sent to the Centers for Disease Control and Prevention for polymerase chain reaction diagnosis and immunohistology, respectively. Two days later, these tests were reported as positive for B anthracis, with significant anthrax DNA present in the serum sample and immunohistochemical detection of fragmented anthrax bacilli in the biopsy tissue. Western blot testing of serum samples from day 13 of illness revealed both an IgM response to the 83-kd protective factor and an IgG response (Figure 2).

On day 20 of the patient’s illness, the IgM response decreased but the IgG response intensified and extended to the edema and lethal factors band of 89 to 93 kd. The patient was discharged home on day 17 of illness, receiving oral ciprofloxacin, the treatment recommended by the Centers for Disease Con-
trol and Prevention. His platelet count and fibrinogen level were normal, but evidence of a mild hemolysis persisted. After 2 weeks of ciprofloxacin, when the other anthrax isolates were shown to be susceptible to penicillin, amoxicillin was used as the antibiotic. Hematuria, anemia, and elevated D-dimer levels slowly resolved over the next 2 weeks, 30 days after admission.

Figure 1. The Lesion of Cutaneous Anthrax

Hospital Day 5

Hospital Day 12

2 Months After Discharge

Serum urea nitrogen and creatinine levels were normal at 12 days after admission and the skin lesion healed with little evidence of scarring by day 60 (Figure 1C).

COMMENT

Cutaneous anthrax is primarily a local infection and may resolve spontaneously. Untreated cutaneous anthrax may cause systemic disease with up to 20% mortality, although with antibiotic treatment the mortality rate is less than 1%.10 Antimicrobial treatment has been reported to sterilize the skin lesion within 24 hours, thus prompt institution of antibiotics appears to limit hematogenous spread of the organism, but does not change the local, toxin-mediated effects. Signs of systemic infection may range from fever and leukocytosis to septic shock, meningitis, and death.

Cutaneous anthrax in children is reported less frequently than in adults; a review of MEDLINE revealed 30 case reports between 1967 and 2001, mostly in rural settings in developing nations. The disease has been reported in neonates, children, and adolescents. While infants and young children may acquire anthrax from infected bedding or other fomites, reports suggest that skin-to-skin contact may be an important route of transmission in this age group. One case involved an infant whose mother had an anthrax lesion on her cheek,11 the other involved 2 young children who slept in the same bed.12 In another case series of 11 patients with periocular anthrax, 6 children were younger than 6 years. The authors speculate that young children may be more likely to rub their eyes with spore-contaminated fingers or to have spore-carrying insects swarm on their eyelids.13 The origin of cutaneous anthrax in the infant described in this article is probably related to the finding of anthrax spores at the mother’s workplace. One possible scenario is that spores present on the hands of someone in the workplace who lifted or held the child may have contacted an exposed or possibly abraded area of the child’s skin.
The clinical presentation of cutaneous anthrax in children as reported in the literature is similar to that in adults, with an initial painless papulovesicular lesion surrounded by massive interstitial edema, which develops an eschar within 2 to 5 days. Children also can develop systemic symptoms, such as fever and leukocytosis, particularly if treatment is delayed and bacteremia develops. A review of cases from the first half of the 20th century reveals that more than half of anthrax meningitis cases in children were preceded by cutaneous disease.13 While the patient described in this article had a fairly typical clinical course with respect to the cutaneous lesion, several features of this case have not, to our knowledge, been described previously in the context of cutaneous anthrax.

First, this child’s illness was complicated by severe hematologic abnormalities requiring multiple transfusions of blood products. Between admission and hospital day 6, he developed a severe microangiopathic hemolytic anemia with significant thrombocytopenia, renal involvement, and coagulopathy. To date, there has been only 1 case report of coagulopathy resulting from cutaneous anthrax. In this case, a 20-year-old Iranian woman with cutaneous anthrax developed septic shock associated with thrombocytopenia, hypofibrinogenemia, elevated fibrin degradation products, and elevated prothrombin time,9 with associated hematuria, hypoproteinemia, and hyperkalemia. In another report, involving a 57-year-old British man, the patient had a normal hematologic profile but developed elevated creatine kinase levels and renal failure.15 Neither of these patients exhibited the combination of acute hemolysis, coagulopathy, and renal insufficiency found in the patient described here.

Second, the patient developed persistent hyponatremia, which required careful fluid management during his hospital course. Electrolyte abnormalities, particularly hyperkalemia, occasionally have been described in patients with cutaneous anthrax, usually in connection with severe sepsis and shock. Mild hyponatremia has been noted in 5 of the 10 individuals with bioterrorism-related inhalational anthrax.14 Hyponatremia in this infant coincided with the massive edema of his left upper extremity and was probably related to the degree of fluid shift in his 7-month-old body, something that might not be seen in a larger child or an adult. The hyponatremia began to resolve with the administration of corticosteroids, which have been reported to be beneficial in the treatment of the edema associated with anthrax.17

Third, the patient had severe systemic symptoms despite timely institution of antibiotic and corticosteroid therapy. Most case reports suggest that cutaneous anthrax in children is, for the most part, a mild infection, with few serious consequences provided that treatment with antibiotics is provided.18,19 Mortality and significant morbidity are consistently described as the result of delay in treatment and are proportional to the clinical status of the patient at presentation. Occasionally, bacteremia or meningitis occurs in children with cutaneous disease.2 In this patient, systemic signs occurred 36 to 48 hours after antibiotics were started. Bacterial DNA was detected in a peripheral blood sample suggesting that significant bacteremia or circulating toxin was already present, despite the patient remaining afebrile and having largely normal laboratory values. The role of surgical debridement in the dissemination of bacteria or toxin is unclear.

Fourth, many of the signs and symptoms, including edema, fever, leukocytosis, thrombocytopenia, hemolysis, renal failure, and disseminated intravascular coagulation, while rarely associated with cutaneous anthrax, are associated with envenomations, particularly that of Loxosceles reclusa.20,21 Although this spider has rarely been found in New York, cutaneous anthrax had never before been diagnosed in an infant prior to October 2001.

Possibly the most useful clinical features for distinguishing anthrax from other diagnoses, such as cellulitis or insect bite, are the relatively large extent of the associated edema and the painlessness of the lesion. The culture of the organism from a site of inflammation prior to the initiation of antibiotics is a diagnostic response. Serological responses to anthrax toxins, particularly the protective antigen, have previously been used to define infection in humans and animals. One study in humans found that only 24% of infected individuals had detectable antiprotective antigen antibodies within the first week of infection. This increased to 83% when a serum sample was obtained after the first week.22 Only 1 report has compared serological responses in children and adults.23 In this case, antibodies were seen in 8 of 17 adults and in 2 of 8 children, with much lower titer levels in children, suggesting that they may be less responsive than adults. The infant in this article had evidence of an evolving primary immune response, particularly to the protective antigen, by day 13 of illness on Western blot. We hypothesized that the prolonged evidence of hemolysis may have been due to the absence of antibody production to the toxins. The kinetics of the response did correlate with the increase in platelets but not with the ongoing hemolysis.

As this case illustrates, cutaneous anthrax in an infant or child may quickly progress to a severe systemic disease; thus, if the diagnosis is suspected, the patient should be admitted to the hos-
pital, electrolyte and hematological status should be monitored carefully, and intravenous antibiotics should be instituted. A presumptive diagnosis can be made by blood culture or Gram stain prior to initiating antibiotics, or more definitively by serum polymerase chain reaction and skin biopsy. Although the strain of anthrax recovered from the recent US cases is susceptible to penicillin, doxycycline, and fluoroquinolones, the use of the latter 2 drugs in young children is potentially problematic. After this infant was diagnosed, it was recommended that he be treated with ciprofloxacin for the remainder of the 60 days from the onset of infection, as per the initial recommendations of the Centers for Disease Control and Prevention. Fluoroquinolones are theoretically toxic to developing cartilage but the American Academy of Pediatrics recommends their use, as the benefits outweigh the risks. Doxycycline is another option despite its propensity to stain the enamel of developing teeth. The Centers for Disease Control and Prevention now recommends that a second antibiotic be added to the initial therapy of systemic disease. The addition of clindamycin to this infant’s therapy may have provided additional benefit. Although ciprofloxacin was initiated once the diagnosis was established, therapy was changed to amoxicillin after a week because of concerns about potential toxicity and since the organism was sensitive to this agent.

In this new era of bioterrorism, anthrax should be considered in the differential diagnosis of acute progressive inflammatory disorders of the skin as well as the other syndromes with which it is associated.

Acknowledgment: We are grateful to the patient’s mother for granting permission to publish this information about her son for the medical community.

REFERENCES