Gangrenous Cellulitis Associated with Gram-Negative Bacilli in Pancytopenic Patients: Dilemma with Respect to Effective Therapy

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INTRODUCTION: Gangrenous (necrotizing) cellulitis is a progressive bacterial infection of skin and soft tissue; the infection can spread into subcutaneous tissue with involvement of superficial and deep fascia (necrotizing fasciitis). We describe two pancytopenic patients with polymicrobial gram-negative bacteremia and fulminating gangrenous cellulitis.

CASE REPORTS: Pseudomonas aeruginosa was isolated from a localized hemorrhagic area of the face in one patient. The chronology of infection in these two patients is documented in a series of dramatic color photographs. Despite appropriate antibiotic therapy, the infections progressed relentlessly and both patients died.

COMMENTS: We discuss the dilemma of establishing the correct diagnosis prior to the appearance of the characteristic cutaneous manifestations of hemorrhagic necrosis and gangrene. Once the diagnosis is established, surgical excision is universally recommended. Unfortunately, bleeding diatheses in pancytopenic patients with co-existing coagulation deficiencies pose logistic obstacles in urgent, real-life situations. The timing and conditions for surgery need to be elucidated in these patients. An approach to this infection is proposed. The utility of frozen-section biopsy of the involved tissue and computed tomographic scans of the involved area remains to be evaluated.

Gangrenous or necrotizing cellulitis is a well-described clinical entity [1]. This soft-tissue infection is characterized by rapid progression and spread with diffuse erythema followed by gangrenous necrosis of overlying skin and subcutaneous tissues. A number of other terms have been applied to this entity, including necrotizing dermatitis, infectious gangrene, and pyoderma gangrenosum [2–6]. “Necrotizing fasciitis” refers to progression into the subcutaneous fascial planes [6–8]. Most reports have implicated gram-positive or anaerobic bacteria [7–11]. Reports in the literature consistently emphasize the need for rapid diagnosis and aggressive surgical intervention for the aforementioned entities. However, we have learned that in the cases of cellulitis caused by multiple gram-negative bacteria in pancytopenic patients, standard recommendations may be quite problematic.

We present two dramatic cases of gangrenous cellulitis and review the fulminating hospital course in these patients. We discuss the difficulties in early diagnosis and the dilemma of physicians in assessing the need for immediate radical surgical debridement. Finally, we put forth recommendations for physicians to consider in the approach to these patients.

CASE REPORTS

Patient 1

This 49-year-old white woman with acute myelogenous leukemia had received multiple courses of chemotherapy from October 28 to November 26, 1986. She had also been successfully treated with ampicillin and gentamicin for Escherichia coli bacteremia (December 5 to December 18, 1986). When she was discharged, she was given oral ampicillin (2 g/day) and was taking it at the time of admission.

She was re-admitted on December 23, 1986, with fever, chills, and a painful, swollen right thumb of three days’ duration. The patient’s temperature was 38.9°C. The pulp of the right thumb was tense and echymotic (Figure 1). Necrotic skin was present on the paronychial and eponychial pads. The thenar eminence was also tense with erythema and petechiae. The skin on the exterior surface of the thumb was blue-gray. Red streaks extended from the thumb up the dorsum of her arm. Her admission white blood cell count was 200/mm³ (0 percent neutrophils, 44 percent lymphocytes, and 24 percent immature blast forms). Her platelet count was 9,000/mm³.

The eponychia and pulp of the thumb were incised and drained shortly after admission. Late that day, the patient became acutely hypotensive. Treatment with intravenous gentamicin, vancomycin, clindamycin, and ceftazidime was begun. Four blood cultures obtained on admission showed growth of Pseudomonas aeruginosa, Klebsiella pneumoniae, and E. coli.

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On the third hospital day, the swelling and erythema had extended beyond the wrist to the right forearm (Figure 2). Forearm amputation was offered to the patient as a therapeutic option, but she refused. The thumb appeared black and necrotic. By the fifth hospital day, the forearm and upper arm had become indurated and tender. The fingers appeared gangrenous. Her white blood cell count was 500/mm³.

Her temperature remained elevated at 38 to 39ºC and the infection continued (Figures 3 to 5). On the eighth day, her antibiotics were changed to piperacillin and tobramycin intravenously. By the 10th day, the swelling and erythema had extended beyond the shoulder to the chest wall. Purpura fulminans had developed on her lower extremities (Figure 6). On the 22nd day, the patient became confused and then unresponsive. She died that day.

Patient 2

This patient was a 26-year-old white woman with adult-onset Still's disease who was receiving prednisone, 80 mg a day, indomethacin, and weekly intramuscular injections of colloidal gold. She had just completed a two-week course of ampicillin and gentamicin for Listeria meningitis and was discharged home on December 1, 1986, with plans for an additional two weeks of intravenous ampicillin as an outpatient. One day prior to discharge, her leukocyte count was 13,000 mm³ with 65 percent neutrophils and 9 percent band forms. The hematocrit was 30.7 percent. Aurothioglucose injections of 50 mg were given on November 26 and December 3.

On December 4, she noted mouth pain. Four days later, she was seen in the outpatient clinic for this pain and was found to have a diffuse white exudate on her
tongue and buccal mucosa with some palpable submandibular nodes. A wet mount of the exudate revealed hyphae. Troches were prescribed for presumed oral candidiasis.

She presented to the emergency room the following morning on December 9, 1986, with edema of her upper lip and right cheek. Vital signs included a temperature of 37.8°C (oral), pulse of 84/minute, and blood pressure of 102/50 mm Hg. Her white blood cell count was 100/mm³ with 71 percent lymphocytes and no polymorphonuclear leukocytes. The hematocrit was 14.2 percent and the platelet count was 10,000/mm³.

Facial edema progressed rapidly over four hours, especially on the right side, and cheek tissues appeared pale and tense. Mucosal edema developed along her right cheek and floor of the mouth (Figure 7). Indirect laryngoscopy showed severe pharyngeal and hypopharyngeal edema; patency of the airway was secured with nasotracheal intubation. Treatment was begun with intravenous ceftazidime, gentamicin, and clindamycin. An antipseudomonal penicillin was not used because of the possibility that the patient’s bone marrow suppression might have been due to the ampicillin received previously. Shortly after admission the patient experienced an acute hypotensive episode that responded to volume expansion.

Within eight hours after admission, there was increased swelling, edema, and pallor of the face with a 2 × 3-cm area of dusky-appearing skin about the right nasolabial fold. Needle aspiration of the nasolabial fold showed multiple gram-negative rods but no white blood cells. Culture of this aspirate yielded heavy *P. aeruginosa*. Interestingly, aspirate of the advancing edge of erythema was nonrevealing by both Gram stain and culture. Cultures of blood drawn the day of admission grew *P. aeruginosa* and *E. coli* in six bottles.

Over the next 24 hours, clearly demarcated facial necrosis (Figure 8), metabolic acidosis, hypotension, and disseminated intravascular coagulopathy developed. Supportive therapy was given including white blood cells, packed red blood cells, platelets, fresh frozen plasma, cryoprecipitate transfusions, and vasoressor agents. Renal failure, intractable seizures, and respiratory insufficiency developed. The facial necro-
sis progressed rapidly and became gangrenous (Figure 9). Purpura fulminans developed on all extremities. She died five days after admission with multiple organ system failure.

COMMENTS

Gangrenous (or necrotizing) cellulitis has a typical clinical presentation and course [1]. On initial presentation, the skin may show some edema, but otherwise may appear normal and benign. The infection progresses to a swollen, tense, erythematous appearance without clear borders of demarcation. The area can be warm. Initially, the area is tender with increasing pain over time. The skin can become pale and cyanotic with appearance of bullae and ecchymoses. In the final stages, gangrene with blackened areas of necrosis is characteristic. Systemic signs including toxicity characterized by high fever and disorientation are typical.

Although the sites of infection were different, there were striking clinical features common to both of our patients. Both patients were relatively young (26 and 49 years, respectively). Both were re-admitted to the hospital shortly after discharge (eight days and five days, respectively) after antibiotic therapy for bacterial infection. Both had been discharged with amoxicillin therapy. Both patients were pancytopenic with polymicrobial gram-negative bacteremia.

Bleeding diatheses associated with thrombocytopenia and/or disseminated intravascular coagulation developed in both patients and these served as deterrents against aggressive surgery. Both patients showed striking signs of purpura fulminans [12] on their extremities later in their course. Neither patient received extensive surgical debridement (although Patient 1 had the pulp of the finger incised). Finally, both patients succumbed to the devastating effects of systemic infection.

Although the other gram-negative bacilli isolated from blood undoubtedly contributed to the fulminating course in both cases, the virulence of P. aeruginosa has been well documented for the neutropenic host. Exotoxins and proteases elaborated by P. aeruginosa can produce dermonecrosis and blood vessel invasion with thrombosis. Collagenases can open tissue planes, facilitating the spread of infection. This precipitates a cycle of further tissue ischemia, necrosis, and gangrene. In the absence of functional white blood cells, the characteristic findings of local inflammatory reaction may be diminished as they were in our two cases. Neither of our patients showed evidence of erythema or heat, the absence of which obscured the diagnosis at onset.

The reports in the literature are unanimous in emphasizing the initial role of early surgical intervention [6,7,13,14]. However, we point out that in our patients, although surgical intervention was constantly considered and discussed, there was justified hesitancy because of the presence of severe bleeding diatheses. In the first patient, although the original site of infection was the distal thumb, there was reluctance to proceed with amputation of this important digit given what appeared initially to be a localized infection. In the second patient, because the location of the cellulitis was on the patient's face, aggressive excision and debridement were tempered by expected blood loss given the noted vascularity of the face. Furthermore, resec-

... tion would have included the entire oral commissure including lips, nasal filtrum, and cheek; thus, major cosmetic deformity requiring extensive reconstructive efforts would be expected if she survived. Finally, in both patients, uncertainty existed as to the extent of the soft-tissue involvement in the initial phase of the infection.

We point out that the criteria for diagnosis of gangrenous cellulitis are somewhat subjective and imprecise. Furthermore, the major hallmark of the disease, viz, the fulminating course leading to gangrene, is not foreseeable at the time of initial presentation when the benefits of surgery would be maximal. By the time the diagnosis is evident, the patient's condition may have deteriorated to a level where surgical intervention may be fruitless. Thus, the diagnostic dilemma lies in recognizing the potential of the infection to progress to gangrenous cellulitis prior to the development of gangrene.

A previously reported case [15] is similar to that of our Patient 2. In this case, cellulitis of the face with black eschar on both eyelids developed in a 29-year-old woman with systemic lupus erythematosus. Culture of debrided material from her eyelids and neck grew P. aeruginosa, Klebsiella, Bacteroides, and Candida. She experienced neutropenia, but not to the nadir of our Patient 2, nor was she thrombocytopenic at the time of surgical debridement. She was also less "toxic" and not bacteremic. This patient ultimately survived and skin grafting of the face was later performed.

On the basis of our experience, we offer the following approach: Any area of progressive cellulitis must be viewed with vigilance in the pancytopenic host. It is important to realize that erythema, heat, and other local signs of infection may be absent with neutropenia. Needle aspiration of the central area of cellulitis, any necrotic area, and the advancing edge should be performed immediately. If gram-negative rods are seen on Gram stain, parenteral antibiotic therapy that includes coverage for Pseudomonas must be initiated immediately. Blood cultures should be obtained prior to empiric antibiotic therapy.

Progression of the cellulitis or appearance of necrosis during antibiotic therapy should be viewed as an urgent indication for surgical debridement. Waiting for clear tissue demarcation as practiced in cases of uninfected vascular compromise may allow generalized sepsis to supervene and preclude surgical intervention. Consideration for more radical dissection needs to be individualized depending on the clinical circumstances. As our two cases dramatically demonstrate (Figures 1 to 9), progression may be measured in hours, not days, so rapid decisions and expedient surgical planning are critical. Hemodynamic monitoring and aggressive supportive therapy for septic shock may be necessary even before local tissue necrosis is evident. Once systemic sepsis has advanced to preclude surgical intervention, survival is unlikely. In these cases, treatment options must be tailored to the specific situation and developed in discussion with colleagues and family.

Stamenovic and Lew [16] have proposed that examination of frozen-section biopsy specimens of the involved soft tissue can suggest the diagnosis of necrotizing fasciitis. Histologic criteria included an intact...
dermis with necrosis, vascular thromboses, and polymorphonuclear infiltrate seen in the superficial fascia and deep dermis. However, none of their reported infections were caused by gram-negative bacilli nor occurred in neutropenic patients. Computed tomographic scans of the involved areas may possibly be useful in separating a deep compartmental infection from a superficial cellulitis, although, to our knowledge, no studies for this application have been published.

It is clear that this syndrome needs to be more precisely defined with regards to characteristic clinical manifestations, diagnostic modalities, timing and indication for surgery, and ultimate outcome. Case reports from other physicians would be most useful in this regard. Details of previous antibiotic treatment, hematologic status, precise chronology of the spread of infection, and timing of intervention should be included in any case report. Since we may be underestimating the frank realities of postoperative hemorrhage in these patients whose conditions are desperately complex and unstable in pressing for more aggressive surgical intervention, other reports of surgically-treated cases of gangrenous cellulitis in pancytopenic bacteremic patients should be published.

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REFERENCES