A 55-Year-Old Man With Fever, Renal Failure, and Hip Pain*

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A 55-year-old man with diabetes mellitus was in his usual state of health until the day before admission, when he experienced severe abdominal pain that was relieved by a bowel movement several hours later. The following day, he developed excruciating right hip pain while driving. He presented to an emergency department with a temperature of 40°C (104°F) and no focal signs. He was given a dose of IV ceftriaxone. The patient was transferred to our institution for further care.

The patient denied trauma to the extremity, fevers, chills, or numbness or tingling in his extremities. His medical history was significant for chronic renal insufficiency (baseline creatinine, 2.5 mg/dL) due to his type II diabetes, previous osteomyelitis, hypertension, and peripheral vascular disease with a past revascularization of the right leg.

Physical Examination

After transfer, the patient’s temperature was 37.4°C (99.3°F), respirations were 20 breaths/min, and BP was 94/37 mm Hg. He appeared to be in severe pain. He was tachycardic with an S4 gallop, and had a soft abdomen with normal bowel sounds. His right hip and posterolateral thigh were erythematous with subcutaneous crepitus over the hip and iliac crest. The coccyx was tender to palpation. An old, well-healed surgical scar was noted on the right medial thigh extending to the medial malleolus. The rest of the examination was noncontributory.

Laboratory Findings

Initial laboratory investigations revealed a WBC count of 14,900 cells/µL, hemoglobin of 8.7 g/dL, BUN of 75 mg/dL, creatinine of 5.3 mg/dL, creatine phosphokinase of 20,000 IU/L, and myoglobin of 30,620 g/L. A urinalysis revealed a large amount of hemoglobin, protein > 300 mg/dL, and no RBCs;

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Figure 1. Radiograph of the right thigh (top) and CT of the pelvis (bottom).
results of the leukocyte esterase and nitrite tests were negative. A radiograph of the right thigh and a CT of the pelvis were performed (Fig 1).

Hospital Course

A culture of fluid aspirated from the right thigh wound was taken. Treatment with piperacillin/tazobactam, clindamycin, and ceftriaxone was initiated, pending culture results. The patient was stabilized hemodynamically with dopamine and phenylephrine hydrochloride. Continuous venous-to-venous hemofiltration was performed.

What is your diagnosis and what immediate intervention is indicated for this patient?

After patient stabilization, what additional diagnostic test is warranted?
Diagnosis: Myonecrosis and acute renal failure due to infection with Clostridium septicum requiring surgical debridement

Answer: Colonoscopy

Discussion

The differential diagnosis of gas within subcutaneous tissues (gas gangrene) includes necrotizing fasciitis and myonecrosis caused by Streptococcus pyogenes, Staphylococcus aureus, clostridial species, and, rarely, Gram-negative enteric organisms (eg, Klebsiella and Escherichia coli). The presence of large amounts of free myoglobin (as measured in this patient as hemoglobin by urine dipstick) in the absence of RBCs in the urine strongly supports the diagnosis of myonecrosis.

Gas gangrene is a rapidly progressive and often fatal illness. In the literature, 50% of cases of gas gangrene occur after trauma, 30% after surgery, and 20% occur without any trauma. The atraumatic form of gas gangrene results almost exclusively with clostridial infections, with two thirds attributed to Clostridium perfringens and one third to C septicum. The source of bacterium in atraumatic myonecrosis is usually the GI tract. Following invasion of luminal bacteria into the bowel wall, infection may occur locally in the abdomen, or distally through hematogenous spread causing metastatic infections.

When C septicum is identified as the etiologic agent of atraumatic myonecrosis, an underlying malignancy is present in 80% of patients. Various malignancies can alter the integrity of bowel mucosa and produce a portal of entry for colonic bacteria to enter the bloodstream. Hematologic malignancies can alter the integrity of bowel mucosa and may also predispose to metastatic infection. Patients with diabetes are more likely to present with C septicum infection as an initial manifestation of an underlying malignancy.

Classically, C septicum infection begins with abdominal pain followed by exacerbating pain in an extremity. Hemorrhagic, rapidly progressive bullae may emerge followed by subcutaneous crepitus. Eventually, a compartment syndrome may develop. Myonecrosis with myoglobinuria and acute renal failure are common. Overall, survival is approximately 30%. A presentation of C septicum myonecrosis distant from the abdomen due to metastatic infection is associated with an 80% mortality.

Early treatment with appropriate antibiotics is crucial in myonecrosis to improve survival. Antibiotic regimens should be initiated that can inhibit bacterial toxin production. In 1952, Eagle provided an explanation for the observed treatment failures of appropriate antibiotics in toxin-mediated streptococcal infections. He compared the efficacy of penicillin in early phases of infection when the bacteria are in logarithmic stages of growth to the efficacy of penicillin in late infection, when bacterial growth has reached a plateau. He found that penicillin was only effective when bacteria were actively dividing. This limitation of antibiotics in toxin-mediated infection has been referred to as the Eagle or innoculum effect. This effect does not apply to antibiotics that inhibit protein synthesis and thus toxin production. These antibiotics are effective during any stage of bacterial growth.

Since Eagle’s first report, several studies have corroborated these findings and have found improved morbidity and mortality with metronidazole, erythromycin, gentamicin, and clindamycin; these antibiotics inhibit protein synthesis and thus toxin production. Of these antibiotics, clindamycin is the most effective. Two studies have evaluated synergy of clindamycin and penicillin. One study revealed an additive effect with both antibiotics, while the other showed that clindamycin alone was just as effective as the combination of penicillin and clindamycin.

Surgical intervention as an adjunct to antimicrobial therapy is necessary in the disease management. Debridement prevents necrotic muscle from serving as a nidus for further infection. Noncontractile muscle is removed. Often, multiple debridements are necessary.

The use of hyperbaric oxygen (HBO) in treatment of gas gangrene has been controversial. Several animal studies have shown a protective effect of HBO when treatment begins immediately following inoculation with C perfringens. In a dog model of C perfringens infection, the efficacy of surgical debridement, HBO, and antibiotics were evaluated. The study reported that survival with penicillin alone was 50%; with antibiotics and HBO, 55%; with antibiotics and surgery, 70%; and with all three modalities, 95%. A second more recent study of C perfringens infection evaluated HBO with penicillin or antibiotics that inhibit protein synthesis. This study showed that HBO alone was ineffective. HBO improved survival when used with penicillin. However, HBO did not have an additive effect with clindamycin. The greatest survival was achieved with clindamycin alone. HBO therapy may be even less useful in C septicum infection; C septicum is 300
times more aerotolerant than *C. perfringens*. From these data, it does not appear that HBO adds benefit to patients already managed with appropriate antibiotic and surgical interventions.

Following initiation of antibiotics, surgical debridement, and additional stabilization, patients with atraumatic *C. septicum* myonecrosis should be investigated for an underlying malignancy, most often with colonoscopy to evaluate for colon cancer.

In the present patient, the thigh radiograph and pelvic CT scan demonstrated subcutaneous gas and gas within the gluteus maximus muscle. The presence of positive results on the dipstick test for hemoglobin without RBCs in the urine supported the diagnosis of myonecrosis. The patient underwent immediate surgical debridement after initiation of antibiotic therapy. The right thigh needle aspirate sample grew *C. septicum*. The initial antibiotics were changed to piperacillin/tazobactam and clindamycin. The wound was left to heal by secondary intention. A week later, colonoscopy was performed. A 5-cm cecal mass was identified and thought to be the portal of entry for *C. septicum* to the bloodstream. The patient was referred for hemicolectomy.

**Clinical Pearls**

1. Immediate surgical debridement is fundamentally important in the management of myonecrosis.
2. Clindamycin, with its antitoxin and bactericidal effects, is an important adjunct to surgical intervention. HBO is not likely to improve survival in otherwise adequately managed patients.
3. Patients who present with *C. septicum* infection should be evaluated for an underlying malignancy. Colonoscopy should be the first line of investigation.

**Selected Readings**

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