

CLINICAL CARE CONUNDRUMS

A Sheep in Wolf's Clothing

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.



This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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A 51-year-old man presented with severe pain and swelling in the lower anterior right thigh. He stated that the symptoms limited his movement, and began 4 days prior to this presentation. He rated the pain severity a 10 on a 10-point scale. He denied fevers, chills, or history of trauma or weight loss.

Cellulitis of the lower extremity is the most likely possibility, but the presence of severe pain and swelling of an extremity in the absence of trauma should always make the clinician consider deep-seated infections such as myositis or necrotizing fasciitis. An early clue for necrotizing fasciitis is severe pain that is disproportionate to the physical examination findings. Erythema, bullous lesions, or crepitus can develop later in the course. The absence of fever and chills also raises the possibility of noninfectious causes such as unrecognized trauma, deep vein thrombosis, or tumor.



The patient had a 15-year history of type 2 diabetes complicated by end-stage renal disease secondary to diabetic nephropathy for which he had been on hemodialysis for 5 months, proliferative diabetic retinopathy that rendered him legally blind, hypertension, and anemia. He stated that his diabetes had been poorly controlled, especially after he started dialysis.

A history of poorly controlled diabetes mellitus certainly increases the risk of the infectious disorders mentioned above. The patient's long-standing history of diabetes mellitus with secondary nephropathy and retinopathy puts him at higher risk of atherosclerosis and vascular insufficiency, which consequently increase his risk for ischemic myonecrosis. Diabetic amyotrophy (diabetic lumbosacral plexopathy) is also a possibility, as it usually manifests with acute, unilateral, and focal tenderness followed by weakness involving a proximal leg. However, it typically occurs in patients who have been recently diagnosed with type 2 diabetes mellitus or whose disease has been under fairly good control and usually is associated with significant weight loss.



The patient was on oral medications for his diabetes until 1 year before his presentation, at which point he was switched to insulin therapy. His other medications were amlodipine, lisinopril, aspirin, sevelamer, calcitriol, and calcium and iron supplements. He denied using alcohol, tobacco, or illicit drugs. He lives in Chicago and denies a recent travel history. His family history was significant for type 2 diabetes in multiple family members.

The absence of drugs, tobacco, and alcohol lowers the risk of some infectious and ischemic conditions. Patients with alcoholic liver disease who live in the southern United States are predisposed to developing *Vibrio vulnificus* myositis and fasciitis after ingesting contaminated oysters during the summer months. However, the clinical presentation of *Vibrio* usually includes septic shock and bullous lesions on the lower extremity. Also, the patient denies any recent travel to the southern United States, which makes *Vibrio* myositis and fasciitis less likely. Tobacco abuse increases the risk of atherosclerosis, peripheral vascular insufficiency, and ischemic myonecrosis.



The patient had a temperature of 99.1°F, blood pressure of 139/85 mm Hg, pulse of 97 beats/minute, and respiratory rate of 18 breaths/minute. His body mass index was 31 kg/m². Physical examination revealed a firm, warm, severely tender area of swelling in the inferomedial aspect of the right thigh. The knee was also swollen, and effusion could not be ruled out. The range of motion of the knee was markedly limited by pain. The skin overlying the swelling was erythematous but not broken. No crepitus was noted. The strength of the right lower extremity muscles could not be accurately assessed because of the patient's excruciating pain, but the patient was able to move his foot and toes against gravity. Sensation was absent in most of the tested points in the feet but was normal in the legs. The deep tendon reflexes in both ankles were normal. The pedal pulses were mildly decreased in both feet. He also had extremely decreased visual acuity, which has been chronic. The rest of the physical examination was unremarkable.

The absence of fever does not rule out a serious infection in a diabetic patient but does raise the possibility of a noninfectious cause. Also, over-the-counter acetaminophen or nonsteroidal anti-inflammatory drugs could mask a fever. The patient's physical examination was significant for obesity, a risk factor for developing deep-seated infections, and a firm and severely tender area of swelling near the right knee that limited range of motion. Septic arthritis of the knee is one possibility; arthrocentesis should be performed

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FIG. 1. A T2-weighted, longitudinal, magnetic resonance imaging scan with gadolinium, of the right thigh, revealed extensive edema involving the vastus medialis and lateralis of the quadriceps femoris, sartorius, and biceps femoris muscles (circles), with an area of minimal postcontrast enhancement in the vastus medialis consistent with necrosis (black arrow).

as soon as possible. The absence of crepitus, because it is a late physical examination finding, does not rule out myositis or necrotizing fasciitis. The presence of unilateral lower extremity swelling also raises the suspicion for a deep vein thrombosis, which warrants compression ultrasonography. The localized tenderness and the lack of dermatological manifestations, such as Gottron's papules, makes an inflammatory myositis such as dermatomyositis much less likely.

Laboratory studies demonstrated a hemoglobin A1C of 13.0% (reference range, 4.3–6.1%), fasting blood glucose level of 224 mg/dL (reference range, 70–99 mg/dL), white blood cell count of 8300 cells/mm³ (reference range, 4500–11,000 cells/mm³) without band forms, erythrocyte sedimentation rate of 81 mm/hr (reference range, <14 mm/hr), and creatinine kinase level of 582 IU/L (reference range, 30–200 IU/L). Routine chemistries were normal otherwise. An x-ray of the right knee revealed soft tissue edema. The right knee was aspirated, and fluid analysis revealed a white blood cell count of 106 cells/mm³ (reference range, <200 cell/mm³). Compression ultrasonography of the right lower extremity did not reveal thrombosis.

Poor glycemic control, as evidenced by a high hemoglobin A1C level, is associated with a higher probability of infectious complications. An elevated sedimentation rate is compatible with an infection, and an increased creatinine kinase intensifies suspicion of myositis or myonecrosis. A normal white blood cell count decreases, but does not eliminate, the likelihood of a serious bacterial infection. The fluid analysis rules out septic arthritis, and the compression ultrasonography findings make deep vein thrombosis very unlikely. However, the differential diagnosis still includes myositis,

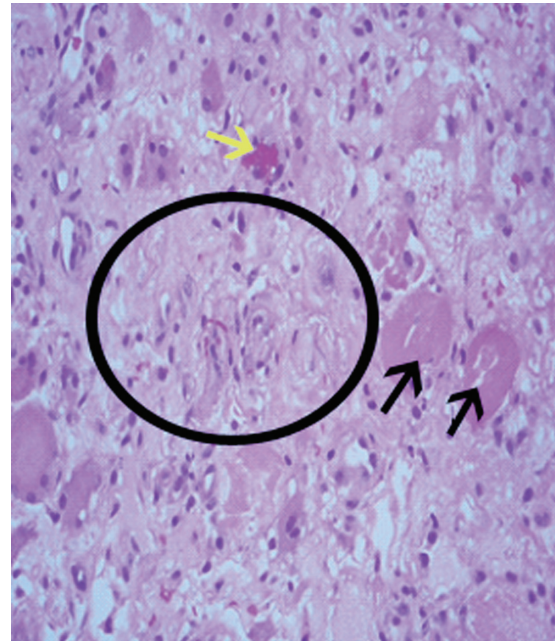


FIG. 2. Histopathological analysis of muscle biopsy specimen revealed ischemic skeletal muscle fibers with areas of necrosis (circle) and degenerated fibers (black arrows). A fibrin thrombus in a small vessel is also present (yellow arrow).

clostridial myonecrosis, cellulitis, and necrotizing fasciitis. The patient should undergo magnetic resonance imaging (MRI) of the lower extremity, and a surgical consultation should be obtained to consider the possibility of surgical exploration.


Blood and the aspirated fluids were sent for culturing, and the patient was started on empiric antibiotics. MRI of his right thigh revealed extensive edema involving the vastus medialis and lateralis of the quadriceps as well as subcutaneous edema without fascial enhancement or gas (Figure 1).

The absence of gas and fascial enhancement makes clostridial myonecrosis or necrotizing fasciitis less likely. The absence of a fluid collection in the muscle makes pyomyositis due to *Staphylococci* unlikely. Broad-spectrum antibiotic coverage (usually vancomycin and either piperacillin/tazobactam or a carbapenem) targeting methicillin-resistant *Staphylococcus aureus*, anaerobes, *Streptococci*, and *Enterobacteriaceae* should be empirically started as soon as cultures are obtained. Clindamycin should be part of the empiric antibiotic regimen to block toxin production in the event that *Streptococcus pyogenes* is responsible.

Surgical biopsy of the right vastus medialis muscle was performed, and tissue was sent for Gram staining, culture, and routine histopathological analysis. Gram staining was negative, and histopathological analysis revealed ischemic skeletal muscle fibers with areas of necrosis (Figure 2). Cultures from blood, fluid from the right knee, and muscular tissue samples did not grow any bacteria.

The muscle biopsy results are consistent with myonecrosis. Clostridial myonecrosis is possible but usually is associated with gas in tissues or occurs in the setting of intra-abdominal pathology or severe trauma, and tissue culture was negative. Ischemic myonecrosis due to severe vascular

insufficiency would be unlikely given the presence of pedal pulses and the absence of toes or forefoot cyanosis. A vasculitis syndrome is also unlikely because of the focal nature of the findings and the absence of weight loss, muscle weakness, and chronic joint pain in the patient's history. Calciophylaxis (calcific uremic arteriopathy) might be considered in a patient with end-stage renal disease who presents with a thigh pain; however, this condition is usually characterized by areas of ischemic necrosis that develop in the dermis and/or subcutaneous fat and infrequently involve muscles. The absence of the painful subcutaneous nodules typical of calciophylaxis makes it an unlikely diagnosis.

 A diagnosis of diabetic myonecrosis was made. Antibiotics were discontinued, and the patient was treated symptomatically. His symptoms improved during the next few days. The patient was discharged from the hospital, and conservative management with bed rest and analgesics for 4 weeks was prescribed. Four months later, however, the patient returned with similar symptoms in the contralateral thigh. The patient was diagnosed with recurrent diabetic myonecrosis by MRI and muscle biopsy findings. Conservative management was advised, and the patient became pain-free in a few weeks.

DISCUSSION

Diabetic myonecrosis (also known as diabetic muscle infarction) is a rare disorder initially described in 1965¹ that typically presents spontaneously as an acute, localized, severely painful swelling that limits the mobility of the affected extremity, usually without systemic signs of infection. It affects the thighs in 83% of patients and the calves in 17% of patients.^{2,3} Bilateral involvement, which is usually asynchronous, occurs in one-third of patients.⁴ The upper limbs are rarely involved. Diabetic myonecrosis affects patients who have a relatively longstanding history of diabetes. It is commonly associated with the microvascular complications of diabetes, including nephropathy (80% of patients), retinopathy (60% of patients), and/or neuropathy (64% of patients).^{3,5} The pathogenesis of diabetic myonecrosis is unclear, but the disease is likely due to a diffuse microangiopathy and atherosclerosis.^{2,5} Some authors have suggested that abnormalities in the clotting or fibrinolytic pathways play a role in the etiology of the disorder.⁶

Clinical and MRI findings can be used to make the diagnosis with reasonable certainty.^{3,5} Although both ultrasonography and MRI have been used to assess patients with diabetic myonecrosis, MRI with intravenous contrast enhancement appears to be the most useful diagnostic technique. It demonstrates extensive edema within the muscle(s), muscle enlargement, subcutaneous and interfascial edema, a patchwork pattern of involvement, and a high signal intensity on T2-weighted images.^{4,7} Gadolinium enhancement may reveal an enhanced margin of the infarcted muscle with a central nonenhancing area of necrotic tissue.^{4,5} Muscle biopsy is not typically indicated because it may prolong recovery time and lead to infections.^{8–11} When performed, however, muscle biopsy reveals ischemic muscle fibers in different stages of degeneration and regeneration, with areas of necrosis and edema. Occlusion of arterioles and capillaries by fibrin could also be seen.¹ Although the patient underwent a muscle biopsy because infection could not be excluded definitively on

clinical grounds, we believe that repeating the biopsy 4 months later was inappropriate.

Diabetic myonecrosis should be considered in a diabetic patient who presents with severe localized muscle pain and swelling of an extremity, especially if the clinical features favoring infection are absent. The differential diagnosis should include infection (eg, clostridial myonecrosis, myositis, cellulitis, abscess, necrotizing fasciitis, osteomyelitis), trauma (eg, hematoma, muscle rupture, myositis ossificans), peripheral neuropathy (particularly lumbosacral plexopathy), vascular disorders (deep vein thrombosis, and compartment syndrome), tumors, inflammatory muscle diseases, and drug-related myositis.

No evidence-based recommendations regarding the management of diabetic myonecrosis are available, although the findings of one retrospective analysis support conservative management with bed rest, leg elevation, and analgesics.¹² Physiotherapy may cause the condition to worsen,^{13,14} but routine daily activity, although often painful, is not harmful.¹⁴ Some authors suggest a cautious use of antiplatelet or anti-inflammatory medications.¹² We would also recommend achieving good glycemic control during the illness. Owing to the rarity of the disease, however, no studies have definitively shown that this hastens recovery or prevents recurrent diabetic myonecrosis. Surgery may prolong the recovery period; one study found that the recovery period of patients with diabetic myonecrosis who underwent surgery was longer than that of those who were treated conservatively (13 weeks vs 5.5 weeks).¹² Patients with diabetic myonecrosis have a good short-term prognosis. Longer-term, however, they have a poor prognosis; their recurrence rate is as high as 40%, and their 2-year mortality rate is 10%, even after one episode of the disease. Death in these patients is mainly due to macrovascular events.¹²

TEACHING POINTS

1. Diabetic myonecrosis is a rare complication of longstanding and poorly controlled diabetes. It usually presents with acute localized muscular pain in the lower extremities.
2. Although a definitive diagnosis of diabetic myonecrosis is histopathologic, a clinical diagnosis can be made with reasonable certainty for patients with compatible MRI findings and no clinical or laboratory features suggesting infection.
3. Conservative management with bed rest, analgesics, and antiplatelets is recommended. Surgery should be avoided, as it may prolong recovery.

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