Diabetic Myonecrosis of Bilateral Thighs in Newly Diagnosed Type 2 Diabetes Mellitus

Muhammad Imran, M.D.[1], Zalina Ardasenov, M.D.[2], Kevin Brown, M.D.[3], Mehrdad Maz, M.D.[1], Julian Magadan III, M.D.[1]
University of Kansas Medical Center, Kansas City, KS
Department of Internal Medicine,
[1]Division of Allergy, Clinical Immunology and Rheumatology
[2]Division of General and Geriatric Medicine
[3]Department of Diagnostic Radiology

Introduction

Diabetes mellitus (DM) and its complications remain a global challenge to health care systems. Diabetic myonecrosis is a rare and under-diagnosed complication of DM that was first reported in 1965.[1] Diabetic myonecrosis affects patients with poorly controlled and longstanding type 1 diabetes mellitus (DM) and associated microvascular complications.[2] Recently, diabetic myonecrosis also has been reported in type 2 diabetes mellitus patients.[3] Elevation of muscle enzymes such as creatine phosphokinase (CPK) is present in half of all cases of diabetic myonecrosis. It can be misdiagnosed as cellulitis, inflammatory myopathy, deep vein thrombosis or fasciitis.[4] The diagnosis is based on the constellation of clinical, laboratory, imaging, and pathological findings. It is usually self-limited and responds well to conservative management if diagnosed early.[5] The short-term prognosis is usually good with slow recovery. Failure to recognize this condition can result in significant morbidity. Physicians should consider diabetic myonecrosis in the differential diagnosis of acute focal myalgia in a diabetic patient. We report two cases of diabetic myonecrosis in patients with type 2 diabetes mellitus.

Case Report

Our first case was a thirty-six-year old male with history of type 2 diabetes mellitus who had been diagnosed within the past six months and treated with oral hypoglycemic agents. He presented with bilateral thigh pain of two-month duration. The pain had worsened with progressive swelling of both thighs. The swelling was acute in onset and located diffusely over the thighs which severely impaired him from performing activities of daily living. The patient denied any history of trauma, intramuscular injections, infections, or drug abuse. He had similar history of pain and swelling in the right thigh five months prior, which resolved spontaneously. Medical records revealed that the patient was noncompliant and his diabetes was poorly controlled.

On examination, his vital signs were stable. He had a body mass index (BMI) of 29.3 kg/m^2. The physical examination revealed bilateral pitting pedal edema and diffuse swelling of the anterior, medial, and postero-lateral regions of the thigh along with induration and tenderness, but no inflammation, fluctuation, or crepitus. Peripheral pulses were palpable in the lower extremities. There was no focal weakness or sensory loss. Deep tendon reflexes were normal in all four limbs. The laboratory

studies included normal complete blood count with differential, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and thyroid stimulating hormone (TSH). His abnormal labs included a creatine phosphokinase (CPK) of 2531 IU/L (normal range 32-162), erythrocyte sedimentation rate (ESR) of 140 mm/h, C-reactive protein (CRP) of 25.6 mg/l, and hemoglobin A1c of 13.5%. Autoimmune serologies were normal or negative including anti-nuclear antigen (ANA), extractable nuclear antibodies, double stranded DNA, Jo-1, and serum complements. Radiographic studies of both the thighs and knees were unremarkable.

A Doppler ultrasonography of bilateral lower extremities did not reveal a deep venous thrombosis (DVT) or a collection of fluid in the muscle planes, but there was subcutaneous edema. Magnetic resonance imaging (MRI) of the bilateral thighs demonstrated high signal intensity on T2-weighted images showing diffuse myoedema and focal myonecrosis bilaterally and subcutaneous edema of the anteromedial compartment in the right thigh and the posterior medial compartment of the left thigh (Figures 1 and 2). A diagnosis of diabetic myonecrosis was made based on clinical presentation, negative immunological markers, ultrasound, and characteristic MRI findings. Management with bed rest, limb elevation, insulin therapy and analgesics was initiated. His pain and swelling improved significantly without the need for further evaluation, such as muscle biopsy. At the time of discharge, the patient was able to ambulate with assistance.

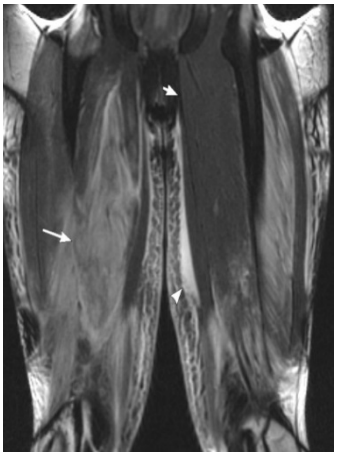

Figure 1. Coronal T2 fat saturation image shows diffuse increased muscle signal and edema bilaterally (long arrow), with areas of normal muscle signal (short arrow). There is also diffuse subcutaneous stranding and edema, as well as perifascicular fluid (arrowhead).

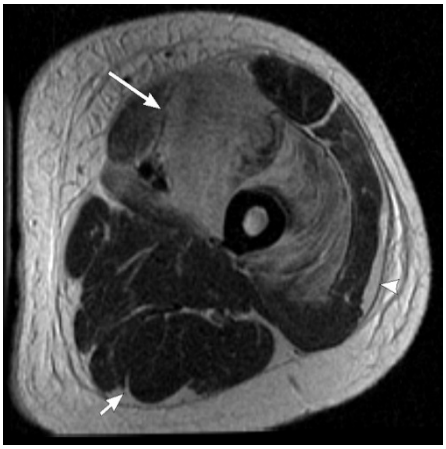

Figure 2. Axial T2 image in the same patient shows diffuse increased T2 signal consistent with muscle edema in the anterior compartment of the left thigh (long arrow) with normal muscle signal in the posterior compartment (short arrow). There is a small amount of perifascicular fluid (arrowhead).

The second case was a 48-year-old morbidly obese female with uncontrolled diabetes mellitus type 2 with complications of end-organ damage. The patient was admitted to the hospital with complaints of acute onset right thigh pain and swelling. She was afebrile on physical examination. There was a well-defined erythematous area of induration on the right posterior lateral thigh. Her right leg had a mottled

appearance with evidence of pitting edema. Pain was elicited on palpation of the right lower extremity. Muscle strength was intact. She had limited range of motion on flexion/extension of the knee and difficulty with weight-bearing activities on the right lower extremity due to pain. She had decrease sensation in her lower extremities distally secondary to known diabetic neuropathy. Peripheral pulses were intact.

Venous Doppler of the right lower extremity showed scarring associated with her previous DVT and a popliteal cyst. MRI imaging of the right thigh showed multiple areas of abnormal signal and contrast enhancement involving the muscles of the right thigh consistent with muscle infarcts (Figures 3 and 4). A punch biopsy of the area of erythema and induration revealed subcutaneous fat necrosis and trace dermal fibrin deposition. There was no evidence of infection on skin biopsy staining and culture. Abnormal laboratory studies included an elevated CPK of 7,491 IU/L, CRP 3.81 mg/dl, ESR 22 mm/h, and hemoglobin A1c of 7.7%. All other studies, such as thyroid function and autoimmune serologies to exclude an inflammatory myopathy, were negative.

The decision was made to wait for a muscle biopsy to reduce the potential for limb threatening complications due to need for a wide surgical debridement. The diagnosis of diabetic myonecrosis was established based on history, clinical examination, laboratory, and imaging studies.

The patient's symptoms and findings improved following pain control, bed rest, and better glycemic control. She presented to the outpatient internal medicine clinic eight weeks post-discharge with complete resolution of her thigh pain and swelling.

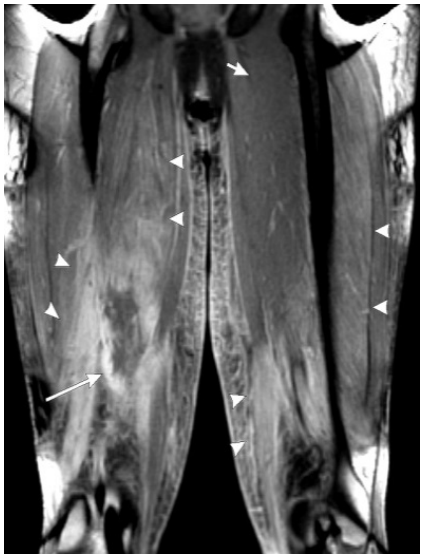

Figure 3. Coronal T1 fat saturation post contrast image shows diffuse scattered muscle enhancement (arrowheads), with areas of normal muscle (short arrow). There is a focal area of non enhancing muscle with peripheral rim like enhancement in the right thigh consistent with muscle infarction (long arrow).

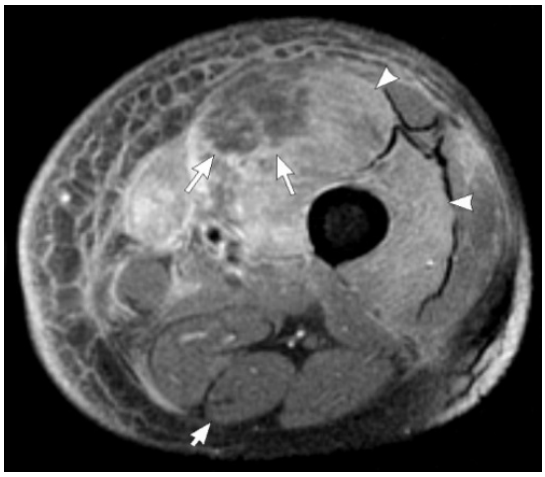

Figure 4. Axial T1 fat saturation post contrast image in the same patient shows diffuse increased signal consistent with enhancement in the anterior compartment of the thigh (arrowheads) compared to the normal muscle in the posterior compartment (short arrow). There is a focal area of non-enhancing muscle with peripheral enhancement in the anterior compartment consistent with infarction (long arrows).

Discussion

Diabetic myonecrosis is an uncommon complication of a long-standing and poorly controlled DM.[2] The majority of patients have diabetic end-organ damage such as retinopathy, neuropathy, and nephropathy.[3] Since it was first described in 1965, less than one hundred cases have been reported.[1] In most of these cases, diagnosis was delayed because of failure to recognize this condition.[4] Diabetes myonecrosis is more prevalent in women (61.5%) with mean age at presentation of 42.6 years, and mean duration of diabetes of 14.3 years.[5] Typically, it involves the thigh, but it can extend to the calf as well (19.2%).[5] Among the thigh muscles, it has a predilection for the quadriceps (62%, especially vastus medialis), hip adductors (13%), hamstrings (8%), and hip flexors (2%).[6] Rarely, can it involve the upper extremities and paraspinal muscles.[7-9]

The pathogenesis of this disease is unclear. Several hypotheses have been suggested. Muscle infarction could be caused by atherosclerosis and diabetic microangiopathy leading to ischemia of the muscle resulting in an intense inflammatory response, edema, hyperemia, and reperfusion. This generates oxygen-free radicals and increased pressure in the fascial compartment leading to muscle infarction.[10] Another hypothesis points to an alteration in the coagulation-fibrinolysis system as the cause of diabetic muscle infarction, as described by Palmer and Greco.[11] Gargiulo et al.[12] implicated a role for antiphospholipid antibodies in the progression of diabetes complications. Myonecrosis may occur in other disease states that predispose to peripheral vascular occlusion such as vasculitis, thromboembolism, trauma, compartment syndrome, and calciphylaxis.[13,14]

Patients with diabetic myonecrosis usually complain of abrupt onset of severe leg pain in the medial aspect of the anterior thigh. The pain is diffuse and may radiate to surrounding structures such as the low back, knees, and calves. The pain usually worsens over days to weeks. Examination early in the course reveals diffuse tenderness and swelling, which after several weeks may develop into a firm, discrete, and fusiform mass-like appearance. Pulses usually are palpable in the extremities and there are no signs of gangrene. Strength and sensation are unaffected, but movement may be limited due to pain.[14]

CPK levels may be elevated over three to four-fold and may become normal when the patients are tested after improvement of the acute event. Aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) levels may be elevated. The white blood cell count (WBC) typically is normal and erythrocyte sedimentation rate (ESR) may be quite elevated (50-150 mm/h).[15]

The most effective diagnostic modality in diabetic myonecrosis is MRI. The typical features of MRI in diabetic myonecrosis are high intensity signal on T2 weighted-images with marked muscle edema extending to the perifascicular and subcutaneous tissues.[1,13,16] Muscle biopsy is the gold standard diagnostic procedure. However, based on literature review and clinical experience, the muscle biopsy could be reserved for cases in which the clinical presentation is atypical or the diagnosis is uncertain, as well as when appropriate treatment fails to elicit improvement.[17] Additionally, muscle biopsy or surgical excision either could prolong the disease or acutely exacerbate the condition.[18] Usually MRI, clinical examination, patient history, and a reasonable exclusion of other etiologies suffice in securing the diagnosis. Other diagnostic tools that may be considered include Duplex venous ultrasound,

computed tomography scan (CT), bone scintigraphy, venogram, angiography, and electromyography (EMG).[15,19] Deep vein thrombosis ranks highest on the differential diagnosis of diabetic myonecrosis of the extremities, so Duplex venous ultrasound commonly is used to exclude deep vein thrombosis.

Other differential diagnoses of myonecrosis include cellulitis, compartment syndrome, superficial thrombophlebitis, necrotizing fasciitis, abscess, hematoma, pyomyositis, osteomyelitis, tumors (benign and malignant including sarcomas), dermatomyositis, proliferative or focal myositis, parasitic myositis, ruptured Baker's cyst, diabetic amyotrophy, muscle strain, exertional muscle rupture, bursitis, vasculitis, lymphedema, amyloidosis, sarcoidosis, myositis ossificans, drug related myositis (statin group) and bone fracture.[2,3,14,18,20,21,22] In the cases presented here, the differential diagnoses were excluded by the history, clinical examination, laboratory, and imaging investigations.

Treatment of diabetic myonecrosis includes adequate bed rest, short-term immobilization, analgesics (nonsteroidal anti-inflammatory medications, narcotics, or both), and most importantly optimal glycemic control. Some authors propose the use of antiplatelet therapy to treat the underlying microvasculopathy, although this has not been established as a standard of care.[22,23] Exercise or physical therapy exacerbates pain and extends infarction, thus is discouraged in the acute setting.[18,21] The long-term prognosis, especially when diagnosis and management are delayed, can be poor and recurrence rate could be as high as 50% with 8-9% involving the originally affected muscles and 39% involving other muscles. However, the short-term prognosis is good with supportive care and following tight glycemic control. Overall, patients with diabetic myonecrosis could have a poor prognosis, and most patients die within five years of diagnosis due to end-organ microvascular complications.[10,14,15]

Conclusion

Diabetic myonecrosis should be considered in diabetic patients who develop a painful and swollen muscle. It is a manifestation of poor glycemic control, and a marker of underlying progressive microvascular disease. Patients with diabetic myonecrosis should undergo evaluation for potential complications of diabetes, including retinopathy, nephropathy, neuropathy and atherosclerosis. Diabetic myonecrosis is another reminder that aggressive diabetic control is essential to prevent end-organ damage, morbidity and mortality.

These two cases are unique as they describe patients with type 2 diabetes mellitus who suffered from involvement of bilateral thighs.

References

1 Angervall L, Stener B. Tumoriform focal muscle degeneration in two diabetic patients. Diabetologia 1965; 1:39-42.

2 Trujillo-Santos AJ. Diabetic muscle infarction: An underdiagnosed complication of long standing diabetes. Diabetes Care 2003; 26(1):211-215. PMID: 12502683.

3 Naderi AS, Farsian FN, Palmer BF. Diabetic muscle necrosis. J Diabetes Complications 2008; 22(2):150-152. PMID: 18280448.

4 Buckingham R, llyas M, Goyer S, et al. Skeletal muscle infarction in diabetics. [Abstract.] Arthritis Rheum 1995; 38(suppl):S325.

5 Campbell IL, Kay TW, Oxbrow L, Harrison LC. Essential role for interferon-gamma and interleukin-6 in autoimmune insulin-dependent diabetes in NOD/Wehi

mice. J Clin Invest 1991; 87(2):739-742. PMID: 1899431.
[6] Osamura N, Takahashi K, Endo M, Kurumaya H, Shima I. Lumbar paraspinalmyonecrosis after abdominal vascular surgery: A case report. Spine (Phila Pa 1976) 2000; 25(14):1852-1854. PMID: 10888957.
[7] Kim SW, Kim SS. Myonecrosis of paralumbar spine muscle. Spine (Phila Pa 1976) 2011; 36(17):1162-1165. PMID: 21343859.
[8] Mukhopadhyay P, Barai R, Philips CA, Ghosh J, Saha S. An unusual case of myonecrosis. Case Rep Endocrinol 2011; 2011:624020. PMID: 22937288.
[9] Kapur S, Brunet JA, McKendry RJ. Diabetic muscle infarction: Case report and review. J Rheumatol 2004; 31(1):190-194. PMID: 14705241.
[10] Palmer GW, Greco TP. Diabetic thigh muscle infarction in association with antiphospholipid antibodies. Semin Arthritis Rheum 2001; 30(4):272-280. PMID: 11182027.
[11] Gargiulo P, Schiaffini R, Bosco D, et al. Diabetic microangiopathy: Lupus anticoagulant dependent thrombosis tendency in type 1 (insulin-dependent) diabetes mellitus. Diabet Med 1997; 14(2):132-137. PMID: 9047090.
[12] Mirra JM. Calcific myonecrosis . Clin Orthop Relat Res 1996; (327):308-310. PMID: 8641079.
[13] Umpierrez G, Stiles RG, Kleinbart J, Krendel DA, Watts NB. Diabetic muscle infarction. Am J Med 1996; 101(3):245-250. PMID: 8873484.
[14] Wintz RL, Pimstone KR, Nelson SD. Detection of diabetic myonecrosis. Complication is often missed sign of underlying disease. Postgrad Med 2006; 119(3):66-69. PMID: 17128647.
[15] Kattapuram TM, Suri R, Rosol MS, Rosenberg AE, Kattapuram SV. Idiopathic and diabetic skeletal muscle necrosis: Evaluation by magnetic resonance imaging. Skeletal Radiol 2005; 34(4):203-209. PMID: 15700181.
[16] Chester CS, Banker BQ. Focal infarction of muscle in diabetics. Diabetes Care 1986; 9(6):623-630. PMID: 3803154.
[17] Keller DR, Erpelding M, Grist T. Diabetic muscle infarction by avoiding excisional biopsy. Arch Intern Med 1997; 157(14):1611-1612. PMID: 9236564.
[18] Nagdev A, Murphy M, Sisson C. Bedside ultrasound for the detection of diabetic myonecrosis. Am J Emerg Med 2008; 26(8):969.e3-4. PMID: 18926375.
[19] Chason DP, Fleckenstein JL, Burns DK, Rojas G. Diabetic muscle infarction: Radiologic evaluation. Skeletal Radiol 1996; 25(2):127-132. PMID: 8848740.
[20] Van Slyke MA, Ostrov BE. MRI evaluation of diabetic muscle infarction. Magn Reson Imaging 1995; 13(2):325-329. PMID: 7739375.
[21] Singer S, Rosenberg AE. Case records of the Massachusetts general hospital. Weekly clinicopathological exercises. Case 29-1997. A 54-year-old diabetic woman with pain and swelling of the leg. N Engl J Med 1997; 337(12):839-845. PMID: 9297115.
[22] Kapur S, McKendry RJ. Treatment and outcomes of diabetic muscle infarction. J Clin Rheumatol 2005; 11(1):8-12. PMID: 16357690.

Keywords: diabetes mellitus, diabetic complications, necrosis, muscles