

# A Novel Case of Diabetic Muscle Necrosis in a Patient with Cystic Fibrosis-Related Diabetes

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**Abstract**

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Cystic fibrosis (CF) is a recessive autosomal disease caused by mutations in the cystic fibrosis transmembrane conductance regulator gene. Cystic fibrosis-related diabetes (CFRD) is a common comorbidity of cystic fibrosis. Diabetic myonecrosis is a rare self-limited complication of poorly controlled diabetes mellitus that commonly presents with acute, intense pain and swelling of lower extremities and responds well to conservative management. We report the first case of diabetic myonecrosis in a patient with CFRD.

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**Keywords:** Cystic Fibrosis/complications; Cystic Fibrosis/physiopathology; Diabetic myonecrosis

**C**ystic fibrosis (CF) is a recessive autosomal disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR protein is an epithelial ion channel contributing to the regulation of absorption and secretion of salt and water in various tissues including lung, sweat glands, pancreas, and the gastrointestinal tract.<sup>1</sup> Cystic fibrosis-related diabetes (CFRD) is a common comorbidity of cystic fibrosis.<sup>2</sup> Diabetic myonecrosis is a rare, self-limited complication of poorly controlled diabetes mellitus (DM) that commonly presents with acute, intense pain and swelling of the lower extremities, with the thigh being the most commonly affected area, and responds well to conservative management.<sup>3</sup>

Notably, this case is unique in that it represents the first report of diabetic myonecrosis in an adult patient with CF. Adults with CF are a small but growing patient population due to increased survival. In 1991, over 32% of people in the United States Cystic Fibrosis Foundation Patient Registry were ages 18 years or older. This percentage increased to more than 48% in 2011. The registry contained 27,111 patients with CF in 2011, of whom 13,094 were adults.<sup>4</sup> The median age of survival of patients with CF is now into the late 30s. This presents providers of adult CF patients with new challenges in managing these patients. There is a need for additional information in diagnosing and treating these patients in the inpatient and outpatient settings where they may report with acute singularly unique presentations, as this case illustrates. Recognizing that CFRD can occur in adults with CF is important, because adults with CF have a tendency to develop CF-related arthropathy,<sup>5</sup> which is more likely to be suspected when these patients present with lower extremity pain. Diabetic myonecrosis is not currently included among differential diagnoses in patients with CF, because it has never been reported in CFRD patients before, and yet it is important that this diagnosis not be missed.

Muscle pain in a cystic fibrosis patient

## Case Presentation

A Caucasian male, aged 32-years, with CF, homozygous for delta F508 mutations, who underwent lung transplant in 2008, with uncontrolled CFRD presented with worsening pain in the left thigh and calf. The pain had been present for 3 weeks and was exacerbated by weight bearing. The patient attributed the origin of the pain to muscle strain secondary to increased physical activity. He reported no other complaints. He denied any recent trauma or any other constitutional symptoms including fever and chills

Medical history included a diagnosis of CF with double lung transplant 4 years earlier. He also suffered from CFRD, with diabetic nephropathy as evidenced by class III chronic kidney disease and urine microalbuminuria, diabetic retinopathy seen on dilated eye exam, and peripheral neuropathy as evidenced by symptoms and decreased foot sensation. He also presented with hyperparathyroidism secondary to chronic kidney disease, hypertension, had a history of an ileostomy for small bowel obstruction, and poorly controlled DM of 18 years' duration. Subsequent to his lung transplant, he was maintained on ongoing immunosuppressive therapy (with mycophenolate and tacrolimus) and steroid therapy (prednisone 5 mg by mouth daily), which exacerbated his CFRD. His other medications included amlodipine, metoprolol, insulin glargine, insulin lispro and lipase-protease-amylase. His family history was significant for diabetes and hypertension.

On physical examination, his vital signs were stable, and he was afebrile. Cardiac, respiratory, abdominal, and right lower extremity examination was unremarkable. By contrast, extension of

his left lower extremity was limited to only 20 degrees. No erythema, swelling, or deformity of the affected limb was present. The posterior thigh and calf were mildly tender to palpation.

Pulses were positive bilaterally in the extremities.

Initial laboratory evaluation showed several out of range values including sodium, 134 mmol/L (range 136-145 mEq/L), blood urea nitrogen, 29 mg/dL (range 5-20 mg/dL), creatinine, 1.7 mg/dL (range 0.6-1.2 mg/dL), random glucose, 305 mg/dL (range <200 mg/dl), hemoglobin, 12 g/dL (range 14-17 g/dL), segmented neutrophil 86%, C-reactive protein 8.6 mg/dL (range 0-1.0 mg/dL), erythrocyte sedimentation rate 66 mm/hr (range 0-17 mm/hr). Hemoglobin A1C (HbA1C) tested 3 months prior had been 10.3% (range 4%-6%). The creatinine kinase (CK) levels were normal at 67 (range 50-235 U/L). Other parameters were within normal range.

Doppler ultrasound of the left lower extremity ruled out deep venous thrombosis, and magnetic resonance imaging (MRI) revealed extensive edema with inflammatory changes involving several muscles in the thigh and calf on T1-weighted images. Significant intramuscular inflammation and edema were present, particularly in the left thigh, with some superficial edema and enhancement also seen along the fascia. Areas of inflammation were also seen along the deep fascia of the left posterolateral distal thigh. There was an area of non-enhancement of the left distal biceps femoris muscle which indicated muscle infarction (figure 1). Differentiation between presence of infection versus inflammation associated with muscle necrosis was distinguished by identifying elevated levels of inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), normal white cell count, and a normal CK (characteristically seen in diabetic myonecrosis despite the breakdown of muscle) . Prior history

of diabetes and chronic immunosuppression with steroids advanced diabetic myonecrosis as the most likely diagnosis, since the patient appeared nontoxic with a low index of suspicion for an infectious etiology.

Although biopsy is the gold standard for a definitive diagnosis of diabetic myonecrosis, no biopsy was performed on the patient because it was not in the clinical best interest of the patient for the following reasons. The patient described in this case report had undergone a bilateral lung transplant consequential to underlying cystic fibrosis. Because of his transplantation status, he was on chronic immunosuppressant medication. Furthermore, with an HbA1C of 10.3%, his risk for poor wound healing and infection were increased. The increased risks for complications including impaired wound-healing and hemorrhage,<sup>6</sup> prompted a cautionary approach to consideration of undertaking muscle biopsy. While lack of a confirmatory biopsy is a limitation of this report, the MRI findings were sufficiently robust to support the diagnosis.

Conservative management was initiated, with treatment including complete bed rest, analgesics, an antiplatelet agent, aspirin 81 mg/day, and adequate glycemic control. Physical therapy was specifically avoided. The patient reported significant improvement in symptoms within the 3-day period of hospitalization. He was off crutches within a week and completely pain-free by 4 weeks post-discharge.

## **Discussion**

In patients with CF, CFRD is a common comorbidity with prevalence as high as 50% in adult patients, increasing with age.<sup>2</sup> Combined characteristics of both type 1 and type 2 diabetes are

exhibited in CFRD, and it is primarily caused by underlying insulin insufficiency, although insulin resistance related to acute or chronic illness may play a role.<sup>2</sup>

First described by Angervall and Stener in 1965,<sup>7</sup> diabetic myonecrosis is an uncommon complication of poorly controlled DM. Since then, more than a hundred such cases have been reported. Trujillo-Santos,<sup>8</sup> in a systematic review of all reported cases of diabetic myonecrosis, found that it was more common in women (61.5% of all cases), in type 1 diabetes (59% of all cases), and in long-standing diabetes (mean duration of disease 14.3 years). Typical clinical presentation of diabetic myonecrosis consists of sudden onset of pain in the affected muscle associated with swelling, with thigh muscles most commonly affected followed by calf muscles.<sup>3</sup> In their survey of 115 cases of diabetic myonecrosis in 2003, Trujillo-Santos<sup>8</sup> reported that bilateral involvement was reported in only 14 cases (8.4% of the total surveyed). This would suggest that bilateral presentation is rarer, and that the presentation of unilateral symptoms in the index patient was consistent with the more common form of presentation of diabetic myonecrosis. Rarer case reports have cited involvement of paralumbar spine muscle<sup>9</sup> of the legs and the neck muscles.<sup>10</sup>

Our patient reported improvement in symptoms in a few days and complete resolution in a month. Trujillo-Santos<sup>8</sup> cited 2 to 17 weeks for resolution, with 4 weeks being average. Improvement with bed rest and steroids can be seen in days. Follow up visits at 1 week and 4 weeks indicated steady progress with complete resolution of symptoms (pain), and need for ambulatory assist aids within 4 weeks.

While the pathogenesis of diabetic myonecrosis remains unclear, atheroembolism of the small vessels has been proposed.<sup>11</sup> However, since the genetic defect in cystic fibrosis leads to malabsorption of fats, cystic fibrosis patients generally exhibit low total and low density lipoprotein (LDL) cholesterol. Given the low cholesterol levels in our patient, atheroembolism of the small vessels as a pathogenic mechanism seems unlikely. Furthermore, despite low total cholesterol and LDL levels, the patient had developed microvascular disease (diabetic nephropathy and peripheral neuropathy), suggesting that microvascular disease may not be as dependent upon atherosclerosis in this group of patients. An alternative mechanism proposed for diabetic myonecrosis includes underlying abnormalities in the clotting cascade or fibrinolytic pathway, although this has not been well elucidated. The fact that cystic fibrosis patients can develop diabetic myonecrosis while presenting with a history of low cholesterol levels suggests that further research is warranted in elucidating mechanism(s) underlying this complication of diabetes. Furthermore, the patient exhibited high levels of inflammatory markers (CRP was 8.6 and ESR 66). This pro-inflammatory state, along with his unusually poor diabetic control (HbA1C of 10.3%) may have played a role in the pathogenesis of diabetic myonecrosis in this patient.

In our patient, poor control of his diabetes was likely exacerbated by continuation of steroidal treatment necessitated by the lung transplantation in 2008. In this context, diabetic myonecrosis has been reported in patients with orthotopic heart transplant<sup>12</sup> and islet cell transplant<sup>10</sup> and was attributed to emergent diabetes which developed consequential to immunosuppressive treatment.<sup>13</sup> It is not certain how common diabetic myonecrosis is in transplanted patients. In our review of the literature using the MeSH term ‘diabetic myonecrosis’ we found only 2 reports<sup>10,12</sup>

of diabetic myonecrosis in occurring in transplant patients. Potentially, patients with cystic fibrosis are at increased risk for diabetic myonecrosis due to underlying cystic fibrosis-related diabetes mellitus coupled with post-transplant steroid-induced hyperglycemia.

Exhibiting features of both type 1 and type 2 diabetes, CFRD is associated with decreased insulin production and increased insulin resistance. Although the primary contributing defect is decreased production of insulin due to destruction of beta cells, emerging insulin resistance is initially the main stimulus of CFRD, secondary to acute infections. Affected patients exhibit decreased peripheral glucose uptake and poor insulin suppression of hepatic glucose production which concomitantly increases insulin resistance.<sup>14</sup> Patients with CFRD have poorly controlled diabetes in general because of malabsorption and consequential high caloric needs associated with an underlying deficiency in pancreatic enzymes, leading to abnormalities in bile salts, mucosal transport problems, and variance in motility.

The imaging modality of choice for soft tissue evaluation is MRI, which shows findings of increased signal on T2 imaging in patients presenting with edema and no discrete masses. Although tissue biopsy can be used to confirm the diagnosis, it is not required for diagnosis, since MRI and a thorough clinical evaluation are generally sufficient.<sup>7</sup> In the case of our patient who was being treated with immunosuppressive medication, biopsy was not pursued since the diagnosis was well supported by MRI findings, and the risk of performing a biopsy outweighed its benefits. CK levels in our patient were normal (67U/L [normal range: 50-235 U/L]). In their survey of 115 diabetic myonecrosis cases in 2003, Trujillo-Santos<sup>7</sup>, similarly reported that normal CK levels in 52.7% of the cases. Differential diagnoses of diabetic myonecrosis should

include abscess, cellulitis, mass, hemorrhage, polymyositis, dermatomyositis, and deep vein thrombosis.

Diabetic myonecrosis is normally self-limited, and good glycemic control with supportive care is the mainstay of treatment. Analgesia and immobilization can aid in decreasing pain. Exercise or physical therapy should be expressly avoided, as it may worsen pain and myonecrosis. The index patient responded well to these therapeutic approaches.

## **Conclusion**

To our knowledge, this is the first published case of a CFRD patient presenting with diabetic myonecrosis. The only other report found was a very recent abstract of a case presented by Kopp et al<sup>15</sup> at the American Thoracic Society International Conference in May 2012. A high index of suspicion for diabetic myonecrosis is warranted when a patient with CFRD presents with lower extremity pain.

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**Figure Legend**

**Figure 1:** Fluid sensitive magnetic resonance coronal image of bilateral lower extremities taken posteriorly at the thighs. Image shows extensive left biceps femoris edema. There was an area of nonenhancement of the left distal biceps femoris muscle, suspicious for muscle infarction.

