

Diabetic myonecrosis in a cystic fibrosis patient

Benjamin T. Kopp, MD^{1*}, Stephen Kirkby MD¹, Don Hayes, Jr., MD¹, Kevin M. Flanigan, MD²

¹Section of Pediatric Pulmonology, Nationwide Children's Hospital, Columbus, OH.

Department of Pediatrics, The Ohio State University, Columbus, OH

²Division of Neurology, Nationwide Children's Hospital, Columbus, OH

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*Address correspondence to: Benjamin Kopp, Nationwide Children's Hospital, Section of Pulmonary Medicine, Columbus, OH 43205; tel. 614-722-4766; fax 614-722-4755; e-mail: Benjamin.Kopp@NationwideChildrens.org

Running Title: Diabetic myonecrosis in CF

Abstract:

Cystic fibrosis-related diabetes is an increasingly common co-morbidity in cystic fibrosis (CF) patients with scarce data on end-stage complications in the CF population. We report the case of a 32 year old with poorly controlled diabetes presenting with sub-acute leg pain and focal quadriceps tenderness. The patient was found to have diabetic myonecrosis through careful neuromuscular testing and imaging after an extensive workup. This first reported case of diabetic myonecrosis in CF highlights the need for pulmonary physicians to recognize this diabetic complication in CF patients, which is associated with a poor long term prognosis and existing microvascular complications.

Keywords: Cystic fibrosis, diabetes mellitus, leg pain, microvascular, myonecrosis, non-compliance

Introduction:

Pharmacologic, nutritional, and screening advancements in cystic fibrosis (CF) have led to dramatic improvements in life expectancy. However, due to advancing patient age, the incidence of co-morbidities is increasing. In particular, the most common co-morbidity, CF-related diabetes mellitus (CFRD), is present in about 20% of adolescents and nearly 50% of adults with CF¹. Concerns over plateauing patient life expectancy rates have led to interest in the impact of CFRD on CF morbidity and mortality. We present a case with a rare, but important complication of poorly controlled diabetes in a CF patient that is potentially under-recognized by respiratory clinicians.

Case Report:

A 32-year-old female with CF with a baseline FEV1 of 37% predicted, poorly controlled CFRD with a hemoglobin A1C of 11.1, chronic renal insufficiency with resolved microalbuminuria, and osteoporosis presented with a one month history of fatigue, weight loss, dyspnea, and right thigh pain. The patient had baseline concerns of medication compliance as noted by her extremely elevated hemoglobin A1C. At presentation, she noted onset of the pain over one week, and originally attributed it to muscle strain. Over the ensuing month the pain became severe, and she noted increasingly exquisite tenderness to palpation of her thigh. She denied any weakness or functional loss, and she was able to continue working.

She was admitted to the hospital for evaluation. She was afebrile and her examination showed no skin or nail bed abnormalities. Her cranial nerve examination was normal,

without cranial neuropathies. She was thinly-muscled throughout. She had marked tenderness to palpation of the right anterior and superior thigh muscles, with a thigh circumference that was 5 mm larger on the right. Isolated muscle testing showed 5/5 strength in all groups except at shoulder abduction (4+ bilaterally), hip flexion (4+ on the right, and 5 on the left), knee extension (4+ on the right, 5 on the left), and great toes abduction (4/5 bilaterally). Pinprick sensation was reduced in a stocking fashion, normalizing at the mid-calf, and was notably normal across the thighs bilaterally. Vibration was diminished in a stocking-glove fashion and ankle jerks were absent bilaterally.

Plain films of the right leg revealed no acute fractures. A bone scan revealed no occult infection or injury, but increased radiotracer uptake at the patella. An initial knee MRI demonstrated a small right knee joint effusion, but an MRI of the thighs demonstrated abnormal enhancing T2 signal within the anterior thigh musculature (Figures 1,2). At the time of admission, her serum CK was normal at 69 u/L (nl=37-289 u/l), rheumatoid factor was <7 IU/ml, lactate dehydrogenase 538 U/L and white blood cell count 10.7K/cu mm. Her erythrocyte sedimentation rate was elevated at 53 mm/h.

Given her clinical course including a history of uncontrolled diabetes with microvascular complications, the characteristic myonecrosis as demonstrated by examination and MRI imaging, and the absence of laboratory evidence for another infectious or rheumatologic cause, a diagnosis of diabetic myonecrosis was made. Along with treatment with intravenous antibiotics and chest physiotherapy for a pulmonary exacerbation, she was

placed on bed rest with temporary avoidance of physical activity. She required narcotics for pain control (oxycodone BID), and was encouraged to maintain strict glycemic control. Her acute symptoms resolved over approximately 2 weeks, but she has had chronic leg pain requiring long term pain clinic follow-up. Her distal lower extremity sensory abnormalities persist due to diabetic neuropathy and are treated with gabapentin and she has no known ophthalmologic abnormalities. Additionally, her glycemic control has only modestly improved to a hemoglobin A1C of 10.1 despite physician interventions.

Discussion:

First reported in 1965², diabetic myonecrosis has since been reported in approximately 100 cases worldwide, but to our knowledge this is the first case associated with CFRD. A rare complication of uncontrolled diabetes, myonecrosis is essential to recognize as an ominous sign of worsening diabetes because many patients die within 5 years of onset due to existing or worsening microvascular complications³. Diabetic myonecrosis is caused by muscle infarction leading to acute muscle pain in the absence of trauma, usually located in the quadriceps. Pain is typically unilateral, but is bilateral in up to 8% of cases⁴. The pathogenesis is still unknown with some groups advocating diabetic microangiopathy, while others speculate an association with hypercoagulable factors⁵. Serum markers, including creatine kinase, are normal in approximately 50% of cases⁴. Radiologic imaging characteristic of the diagnosis include MRI imaging with increased T2-weighted signal in the affected muscle secondary to edema and to inflammatory changes from infarction⁶. Bedside ultrasound can be a useful imaging technique to rule

out other causes of leg pain and detail muscle architecture⁷. Needle electromyography (EMG) is often done clinically if the diagnosis is uncertain, but results can be variable and non-specific, limiting the diagnostic use in this setting unless the diagnosis is in doubt. Muscle biopsy may help to exclude other syndromes such as focal nodular myositis, which may present with similar radiographic and clinical features⁸, but in the appropriate clinical setting it is not necessary for diagnosis and is not routinely recommended due to associated complications such as delayed wound healing⁹. Other diagnostic considerations to exclude in making the diagnosis include infections such as pyomyositis and necrotizing fasciitis, tumor, thrombosis, dermatomyositis, and diabetic lumbosacral radiculoplexus neuropathy, as several of these can be acutely life-threatening and could require a tissue biopsy.

Treatment of diabetic myonecrosis is aimed at improving glycemic levels along with control of generally exquisite pain through non-steroidal anti-inflammatories and opioid analgesics. Strict bed rest helps improve the self-limiting nature of diabetic myonecrosis, and physical therapy has been reported to prolong symptoms in about 14% of cases. Recurrences occur in nearly half of the cases, with a new muscle affected in 82% of these recurrences⁹. The use of anti-coagulants has been suggested, but not proven to be of benefit¹⁰. Although short term prognosis for patients affected with diabetic myonecrosis is good, 5-year survival rates are poor due to existing microvascular complications of uncontrolled diabetes³. Additionally, females with CFRD have decreased overall survival rates compared to males even in the absence of diabetic myonecrosis, putting our particular subject at even greater risk¹¹.

Macrovascular complications of CFRD are currently rare in CF, presumably due to low cholesterol levels from cystic fibrosis transmembrane conductance regulator ion channel defects or fat malabsorption. However, microvascular defects are common in patients with diabetic symptoms greater than 10 years in duration¹², and upwards of 27% of CF patients on insulin have been reported to have other microvascular complications such as diabetic retinopathy¹³. It is therefore essential that respiratory caregivers recognize the clinical syndrome of diabetic myonecrosis, and understand that it may signal impending microvascular catastrophe and be alert for this diagnosis in patients with existing microvascular complications. Screening for CFRD is recommended to start at age 10 with an annual oral glucose tolerance test to help identify patients early and prevent development of microvascular complications.¹⁴ Quarterly hemoglobin A1C measurements with a goal less than 7% are recommended to prevent microvascular complications in CF¹⁴. Annual neurologic, ophthalmologic, and proteinuria screenings are also recommended starting 5 years after the diagnosis of CFRD. Although our patient had a history of resolved microalbuminuria, there is a high incidence (21%) in patients with CFRD compared to type 1 diabetics, which may reflect other disease and medication factors in CF¹⁵.

In summary, diabetic myonecrosis is a rare, but ominous complication of uncontrolled diabetes that respiratory physicians need to be aware of in patients with poorly controlled CFRD who present with leg pain.

Figure Legends:

Figure 1: T2-weighted axial magnetic resonance imaging of the anterior thigh showing diffusely abnormal signal intensity within the thigh musculature. The white arrow points to highest signal within the vastus lateralis. Diffuse sub-cutaneous tissue edema is also noted.

Figure 2: Coronal magnetic resonance imaging of the thigh shows diffuse abnormal signal intensity, greatest in the right vastus lateralis as shown by white arrow.

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Abbreviations:

CF Cystic Fibrosis

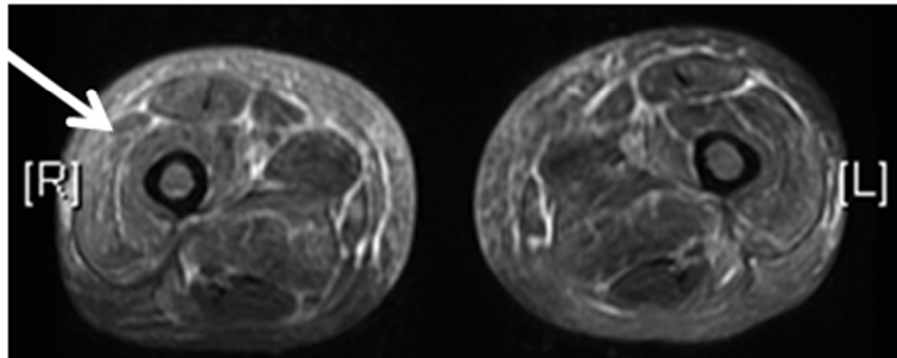
CFRD Cystic fibrosis-related diabetes mellitus

EMG electromyography

References:

1. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care* 2009;32(9):1626-1631.
2. Angervall L SB. Tumoriform focal muscular degeneration in two diabetic patients. *Diabetologia* 1965;1:39-42.
3. Rocca PV, Alloway JA, Nashel DJ. Diabetic muscular infarction. *Semin Arthritis Rheum* 1993;22(4):280-287.
4. Trujillo-Santos AJ. Diabetic muscle infarction: an underdiagnosed complication of long-standing diabetes. *Diabetes Care* 2003;26(1):211-215.
5. Palmer GW, Greco TP. Diabetic thigh muscle infarction in association with antiphospholipid antibodies. *Semin Arthritis Rheum* 2001;30(4):272-280.
6. Jelinek JS, Murphey MD, Aboulafia AJ, Dussault RG, Kaplan PA, Snearly WN. Muscle infarction in patients with diabetes mellitus: MR imaging findings. *Radiology* 1999;211(1):241-247.
7. Nagdev A, Murphy M, Sisson C. Bedside ultrasound for the detection of diabetic myonecrosis. *Am J Emerg Med* 2008;26(8):969 e963-964.
8. Jelinek J, Kransdorf MJ. MR imaging of soft-tissue masses. Mass-like lesions that simulate neoplasms. *Magn Reson Imaging Clin N Am* 1995;3(4):727-741.
9. Chester CS, Banker BQ. Focal infarction of muscle in diabetics. *Diabetes Care* 1986;9(6):623-630.

10. Bjornskov EK, Carry MR, Katz FH, Lefkowitz J, Ringel SP. Diabetic muscle infarction: a new perspective on pathogenesis and management. *Neuromuscul Disord* 1995;5(1):39-45.
11. Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. *Diabetes Care* 2005;28(9):2141-2144.
12. Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla C, et al. Microvascular complications in cystic fibrosis-related diabetes. *Diabetes Care* 2007;30(5):1056-1061.
13. Andersen HU, Lanng S, Pressler T, Laugesen CS, Mathiesen ER. Cystic fibrosis-related diabetes: the presence of microvascular diabetes complications. *Diabetes Care* 2006;29(12):2660-2663.
14. Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care* 2010;33(12):2697-2708.
15. van den Berg JM, Morton AM, Kok SW, Pijl H, Conway SP, Heijerman HG. Microvascular complications in patients with cystic fibrosis-related diabetes (CFRD). *J Cyst Fibros* 2008;7(6):515-519.



T2-weighted axial magnetic resonance imaging of the anterior thigh showing diffusely abnormal signal intensity within the thigh musculature. White arrow pointing to highest signal within the vastus lateralis. Diffuse sub-cutaneous tissue edema also noted.
119x47mm (96 x 96 DPI)



Coronal magnetic resonance imaging of the thigh showing diffuse abnormal signal intensity, greatest in right vastus lateralis as shown by white arrow.
67x79mm (96 x 96 DPI)