

# Isolated Gastrocnemius Myositis Related to Crohn's Disease

Zainab Mogul, MD<sup>1</sup>

Seymour Katz, MD, FACP, MACG<sup>2</sup>

Teresa R. Bachman, MD<sup>3</sup>

Carlos Urmacher, MD, FASCP<sup>4</sup>

<sup>1</sup>Long Island Clinical Research Associates, Manhasset, New York; <sup>2</sup>Albert Einstein College of Medicine, North Shore University Hospital—Long Island Jewish Health System, and St. Francis Hospital, Manhasset, New York; <sup>3</sup>Arthritis Consultants, Reno, Nevada; <sup>4</sup>CBL Path, Ryebrook, New York

The prevalence of extraintestinal manifestations in inflammatory bowel disease patients ranges from 21% to 40%.<sup>1-3</sup> The most commonly involved organ systems are the musculoskeletal, mucocutaneous, ophthalmologic, and hepatobiliary. In several case series, it has been postulated that there may be a greater prevalence of extraintestinal manifestations in Crohn's disease patients.<sup>4</sup> Gastrocnemius myalgia syndrome is a rare extraintestinal manifestation that has been reported in 8 other published cases.<sup>5-13</sup> This case report may be the first presentation of this atypical extraintestinal manifestation of Crohn's disease to be reported in the United States. The patient's bilateral calf myalgia was distinctive and recurrent and required a novel therapeutic approach.

## Case Report

A 15-year-old white male with a 5-year history of ileocolonic Crohn's disease presented with acute onset of bilateral localized calf tenderness and Achilles pain for 1.5 weeks. The pain was described as burning, with a feeling of tightness localized to the gastrocnemius muscle, causing difficulty in ambulation. The patient's pediatric gastroenterologist prescribed methylprednisolone, which resolved the symptoms. His bilateral calf muscle pain returned after 1 month. Methylprednisolone was prescribed once again but produced only a transient response, with a return of symptoms over the subsequent 2 days. The patient reported that the calf muscle discomfort was not prompted by any trauma, and he did not experience any abdominal or systemic symptoms. The patient's previ-

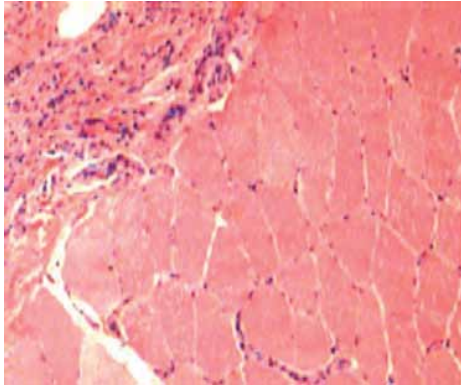
ous 3 hospital admissions, in 2001, 2003, and 2004, were related to his Crohn's disease. No other extraintestinal manifestations were reported.

Physical examination revealed significant tenderness of both calves and achilles tendons. No swelling, erythema, or indurated nodules were observed around the gastrocnemius muscle. The neurologic examination depicted a motor strength of 5 out of 5 throughout, with an intact sensory examination. His examination was otherwise unremarkable, with normal vital signs. The only medication he was taking at the time of presentation was controlled-release mesalamine (Pentasa, Shire) 100 mg 3 times daily. His family history was deemed to be non-contributory, and he denied any tobacco or alcohol use.

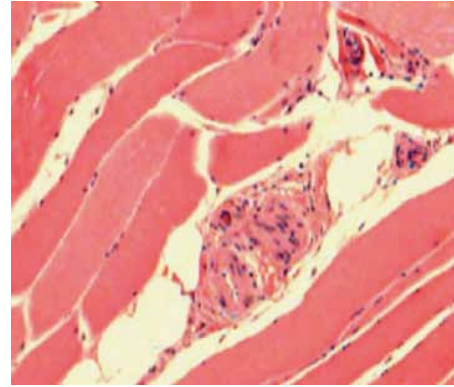
Laboratory values revealed a white blood cell count of  $11.5 \times 10^3/\mu\text{L}$  with elevated neutrophils (77%), a hemoglobin level of 12.4 g/dL with a mean corpuscular volume of 71 fL, a mildly elevated erythrocyte sedimentation rate of 26 mm/hr, and a serum globulin level of 3.2 g/dL. The patient's basic metabolic panel was within normal limits except for a glucose level of 104 mg/dL. His creatine kinase was 86 U/L (normal, 22–198 U/L) and amylase was 91 U/L (normal, 23–85 U/L), and his liver function tests and urinalysis were all within normal limits. The patient's antineutrophil cytoplasmic antibodies (c-ANCA) were negative (<1:20), as were his atypical perinuclear antineutrophilic cytoplasmic antibodies (<1:20) and his antimyeloperoxidase antibody (titer 1:2). An antinuclear antibody direct test measured 30 units (negative <100), and aldolase measured 5.9 U/L (normal, 1.2–7.6 U/L).

An ultrasound venous Doppler of the bilateral lower extremities revealed no deep venous thrombosis. Magnetic resonance imaging showed diffuse inflammation of the gastrocnemius and soleus muscle groups with contrast

Address correspondence to: Dr. Seymour Katz, 1000 Northern Blvd, Great Neck, NY 11021; Tel: 516-466-1051; Fax: 516-829-6421; E-mail: seymour.katz@hotmail.com; Web site: www.liclinical.com



**Figure 1.** Hematoxylin and eosin stain revealing a moderate, predominantly epimysial, mixed, chronic inflammatory infiltrate.



**Figure 2.** Hematoxylin and eosin stain revealing a mild perivascular lymphocytic infiltrate but no vasculitis.

enhancement that was consistent with a polymyositis. A biopsy of the left gastrocnemius muscle showed a moderate epimysial mixed chronic inflammatory infiltrate. Scant perivascular chronic inflammation was focally present around small capillaries within muscle fascicles (Figures 1 and 2). Vasculitis or degenerating/regenerating muscle fibers were not reported.

The patient was started on 40 mg daily of prednisone, which was tapered after reports of pain resolution 4 days later. The dose was further tapered to 10 mg daily (day 17) and resulted in pain located in the gastrocnemius muscle along with difficulty in ambulation. The patient continued to take 10 mg daily of prednisone. After reducing the dose to 2.5 mg, he experienced a flare of intestinal Crohn's disease that required hospitalization and treatment with methylprednisolone (Solu Medrol, Pharmacia and Upjohn). The patient was then started on 15–20 mg of methotrexate orally every week with 1 mg daily of folic acid. One year later, the patient reported no recurrence of bilateral calf myalgia on this regimen.

## Discussion

The cases of calf-limited myalgia reported in the literature all responded to prednisolone, except for 1 case reported by Dioszeghy and associates (Table 1).<sup>6-12</sup> Case reports of a 21-year-old female and a 26-year-old female described the use of a combination treatment regimen of prednisolone plus azathioprine or cyclophosphamide. Our patient initially responded to prednisolone, but the symptoms of calf myalgia returned. He required methotrexate 15–20 mg weekly for complete resolution of the pain.

The previously reported cases of gastrocnemius myalgia linked to Crohn's disease demonstrated occurrence in both genders, ranging from 19 to 50 years of age. The distribution of the muscle histology reported in previous cases showed 2 with granulomatous myositis, 2 with nonspecific myositis, and 3 with vasculitis.<sup>12</sup> To our knowledge, this is the first case reported in the United States. Most cases, as well as our own, displayed normal serum levels of creatine kinase and were negative for c-ANCA. However, a previous report of a 19-year-old female did note a presentation of high titers of c-ANCA at the time of the bilateral calf myalgia.<sup>12</sup>

In conclusion, gastrocnemius myositis is a rare extraintestinal manifestation that may be particularly troublesome or refractory. Our patient required dual therapy (ie, corticosteroids and methotrexate) for a sustained response.

## References

1. Evans PE, Pardi DS. Extraintestinal manifestations of inflammatory bowel disease: focus on the musculoskeletal, dermatologic, and ocular manifestations. *MedGenMed.* 2007;9:55.
2. Ricart E, Panaccione R, Loftus EV Jr, et al. Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case control study. *Inflamm Bowel Dis.* 2004;10:207-214.
3. Lakatos L, Pandur T, David G, et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. *World J Gastroenterol.* 2003;9:2300-2307.
4. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. *J Clin Gastroenterol.* 1996;23:29-34.
5. Bourikas LA, Papadakis KA. Musculoskeletal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis.* 2009;15:1915-1924.
6. Ménard DB, Haddad H, Blain JG, Beaudry R, Devroede G, Massé S. Granulomatous myositis and myopathy associated with Crohn's colitis. *N Engl J Med.* 1976;295:818-819.

**Table 1.** Reports in the Literature of Gastrocnemius Myositis in Patients With Crohn's Disease

Study	Country	Gender	Age (years)	Muscle biopsy findings	Laboratory findings	Treatment
Disdier P, et al. <sup>9</sup>	France	Female	21	Vasculitis	CK=normal	Prednisolone 1 mg/kg/day, 0.5 mg/kg/day + azathioprine
	France	Female	26	Vasculitis	CK=normal	Prednisolone + cyclophosphamide
Gilliam JH 3rd, et al. <sup>7</sup>	Israel	Male	19	Vasculitis	CK, LDH, AST=normal	Prednisolone 60 mg/day
Ménard DB, et al. <sup>6</sup>	Australia	Male	44	Granulomatous myositis	CK, rheumatoid factor, ANF=normal	Prednisolone 80 mg/day
Diószeghy P, et al. <sup>10</sup>	Hungary	Male	41	Granulomatous myositis	CK=normal	No response to steroid or nonsteroid anti-inflammatory medications
Drabble EM, Gani JS <sup>11</sup>	Australia	Male	50	Not performed	CK, ANF, C3, C4=normal	Prednisolone 30 mg/day
Hall MJ, et al. <sup>8</sup>	United Kingdom	Female	32	Myositis	CK, antismooth muscle antibodies, antimitochondrial antibodies, ANF, C3, C4, Jo-1=normal	Prednisolone 60 mg/day
Christopoulos C, et al. <sup>12</sup>	Greece	Female	19	Myositis	CK=normal	Prednisolone 0.5 mg/kg/day
This case study	United States	Male	15	Myositis	CK, aldolase, c-ANCA, p-ANCA, antimyeloperoxidase antibody, antinuclear antibody direct=normal	Methylprednisolone dose pack 4 mg and then methotrexate 15–20 mg per week

ANF=antinuclear factor; AST=aspartate aminotransferase; C3=complement 3; C4=complement 4; c-ANCA=antineutrophil cytoplasmic antibodies; CK=creatinine kinase; LDH=lactic dehydrogenase; p-ANCA=perinuclear antineutrophilic cytoplasmic antibodies.

7. Gilliam JH 3rd, Challa VR, Agudelo CA, Albertson DA, Huntley CC. Vasculitis involving muscle associated with Crohn's colitis. *Gastroenterology*. 1981;81:787-790.

8. Hall MJ, Thomas WE, Cooper BT. Gastrocnemius myositis in a patient with inflammatory bowel disease. *Digestion*. 1985;32:296-300.

9. Disdier P, Swiader L, Harlé JR, et al. Crohn's disease and gastrocnemius vasculitis: two new cases. *Am J Gastroenterol*. 1997;92:880-882.

10. Diószeghy P, Molnár M, Mechler F. Muscle involvement in Crohn's disease [in Hungarian]. *Orv Hetil*. 1994;135:1259-1261.

11. Drabble EM, Gani JS. Acute gastrocnemius myositis. Another extraintestinal manifestation of Crohn's disease. *Med J Aust*. 1992;157:318-320.

12. Christopoulos C, Savva S, Pylarinou S, Diakakis A, Papavassiliou E, Economopoulos P. Localised gastrocnemius myositis in Crohn's disease. *Clin Rheumatol*. 2003;22:143-145.

13. Braun-Moscovici Y, Schapira D, Balbir-Gurman A, Nahir AM. Inflammatory bowel disease and myositis. *Clin Rheumatol*. 1999;18:261-263.

# Review

Kofi Clarke, MD

Jason M. Swoger, MD, MPH

*Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania*

Musculoskeletal involvement is a common extraintestinal manifestation of inflammatory bowel disease (IBD), occurring in 6–46% of patients.<sup>1–4</sup> The most common presentations, including arthritis, myalgias, enthesitis, and both drug- and nondrug-related myopathies, have been well described in the literature. Mogul and coworkers<sup>5</sup> describe a case of isolated gastrocnemius myositis, a rare and poorly characterized musculoskeletal manifestation of IBD.

To date, only 9 cases of IBD-associated gastrocnemius myositis have been reported in the literature. Gender distribution has been essentially equal (5M:4F), and patient ages have ranged from 19 to 50 years of age. The presenting symptom of this rare myositis is isolated calf pain, and, based upon the few reported cases, it does not appear that the muscle symptoms mirror clinical bowel disease activity. However, it is possible that some patients have had smoldering mucosal disease and that the eventual resolution of their myalgia was due to the induction of remission of their luminal Crohn's activity with immunosuppressant medications. In the absence of larger case series describing the endoscopic evaluation of mucosal disease activity, inferences on the association with disease activity rely upon the information available in case reports.

The clinical presentation of musculoskeletal symptoms in IBD is protean, and an accurate diagnosis is often challenging. Symptoms can include localized joint pain, swelling, and warmth, as seen in pauci- or polyarticular arthropathies. Patients often present with characteristic back pain and stiffness, due to the axial skeleton involvement of spondyloarthropathies. Muscle stiffness, fibromyalgia-like symptoms, and localized muscle symptoms can all be manifestations of either a localized or generalized myopathy. Complicating the evaluation is the

fact that musculoskeletal symptoms can be a result of IBD therapy, including agents such as corticosteroids, 5-aminosalicylates, and azathioprine/6-mercaptopurine. When evaluating an IBD patient with myalgia, it is important to obtain a detailed medication history, specifically focusing on the temporal association between medication initiation and symptom onset. However, the limitations of this approach should be kept in mind, as localized gastrocnemius myositis has been reported to precede the clinical diagnosis of IBD.<sup>6</sup>

The differential diagnosis of IBD-associated myositis can be broadly divided into localized and nonlocalized entities. The main nonlocalized myositides include dermatomyositis, polymyositis, and medication-associated myositis.<sup>7–9</sup> Localized muscle involvement has been described in extraocular muscles, as well as proximal muscles, both related and unrelated to steroid treatment. In cases involving the extraocular muscles, clinical presentation mimics thyroid ophthalmopathy, and thyroid function testing should be pursued during evaluation.<sup>10,11</sup> Other considerations in the differential diagnosis of localized myalgia in IBD include trauma, cellulitis, and venous thromboembolic disease.

Despite the rarity of IBD-associated myositis, there have been pathophysiologic mechanisms postulated in the literature. There may be a shared underlying immune-mediated phenomenon responsible for both the bowel and muscle inflammation, as described in a case by Shimoyama and colleagues.<sup>12</sup> The authors described a case of a proximal myopathy associated with Crohn's disease, with a deltoid muscle biopsy showing myositic changes, including inflammatory infiltrates in the perimysium, endomysium, and perivascular locations. In addition, biopsies exhibited staining for CD68-positive macrophages and CD4- and CD8-positive T lymphocytes. The patient continued to have active and difficult-to-control bowel disease, resulting in colectomy. Pathologic examination of the colectomy specimen demonstrated CD68-positive macrophages, which, though nonspecific, may suggest a common immunologic pathogenesis. Heuss and associates<sup>13</sup> reported a case of steroid-responsive gastrocnemius myositis associated with Crohn's disease and postulated a T-cell-mediated inflammatory process. In this case, muscle biopsy demonstrated focal necrotic changes, together with peri- and endomysial inflammatory infiltrates predominantly consisting of CD67- and CD68-positive cells, accompanied by CD8- and CD4-positive cells. It is also worth noting that there was severe inflammatory infiltration of connective tissue septa with granulocytes, as well as CD8-positive cells, in areas of otherwise normal muscle.

Laboratory evaluation in cases of gastrocnemius myositis is not particularly revealing, and the published cases

Address correspondence to:

Dr. Jason M. Swoger, Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, 200 Lothrop Street, C-Wing, Mezzanine, Pittsburgh, PA 15213; Tel: 412-648-2344; Fax: 412-648-9378; E-mail: swogerjm@upmc.edu

have almost always reported normal results. Commonly ordered tests have included a complete blood count, muscle enzymes (creatinine kinase, aldolase), sedimentation rate, antineutrophil cytoplasmic antibody, liver function tests, and antinuclear antibody. These tests are most helpful for excluding alternate etiologies of muscle pain, and not for confirming the presence of myositis. In previously reported cases of myositis associated with features suggestive of polymyositis and dermatomyositis, aldolase and creatine kinase levels were increased.<sup>8</sup> Imaging is more useful for providing information regarding the underlying disease process. An initial venous Doppler ultrasound is indicated, depending upon the clinical presentation, to exclude thromboembolic disease, a common complication in IBD patients. Earlier case reports of gastrocnemius myositis have used magnetic resonance imaging, which demonstrates diffuse inflammation of the involved muscle groups with contrast enhancement. The gold standard for diagnosis is muscle biopsy, though histologic findings have varied among the reported cases.

Histologic findings in the reported cases of gastrocnemius myositis span the spectrum of granulomatous myositis, nonspecific myositis, and vasculitis.<sup>6,14</sup> The vasculitis described on histologic examination can be either necrotizing, resembling changes seen in polyarteritis nodosa, or nonnecrotizing. Typically, these cases have not had concomitant evidence of systemic myositis or vasculitis.<sup>14-16</sup> The various histologic findings on muscle biopsies in this condition make interpretation of the disease entity difficult. Are we dealing with the same disease, or is this a heterogeneous condition with multiple subsets? In the reported cases, response to steroids has not been related to the varied histologic subsets, though it is too early to draw any inferences from the limited data on this entity.

The majority of previously reported cases of gastrocnemius myopathy associated with Crohn's disease have responded to steroids,<sup>5</sup> though at doses much higher than those used to treat luminal IBD (up to 60–80 mg daily). However, 3 of the 9 cases have required the addition of an immunomodulator in order to completely control muscle symptoms. Two cases reported by Disdier and coworkers<sup>14</sup> required the addition of cyclophosphamide and azathioprine to systemic corticosteroids. Additionally, the case reported by Diószeghy and colleagues<sup>17</sup> did not respond to either steroids or nonsteroidal anti-inflammatory drugs. With a longer follow-up, it is possible that some of the other case reports would have required immunomodulators for maintenance of remission, as with the case described by Mogul and associates. As mentioned above, histologic findings do not appear to be related to treatment response or to the need for the addition of an immunomodulator. Although the cases reported by Disdier and coworkers showed vasculitis

on biopsy and required additional immunomodulator treatment, another case by Gilliam and associates<sup>18</sup> had similar findings on pathology, but the patient responded to prednisolone monotherapy. The addition of more aggressive treatment, in our view, should be limited to patients who have confirmatory muscle biopsies and who are either steroid-refractory or, as in this case, exhibit symptom recurrence following the cessation of steroids. Additionally, treatment escalation should be considered if there is evidence of active intestinal inflammation, as the link between myositis and active intestinal inflammation remains unclear.

The current reported data on gastrocnemius myositis, an uncommon extraintestinal manifestation of IBD, is limited to case reports. As such, there are no good evidence-based guidelines on the standard evaluation and treatment of this rare condition. It is reasonable to proceed on a case-by-case basis, beginning with a noninvasive work-up, realizing that laboratory testing is often unrevealing, and excluding the differential diagnoses of localized and systemic myositis detailed above. Imaging, particularly magnetic resonance imaging, may be helpful for demonstrating inflammation surrounding the involved muscles. The gold diagnostic standard, muscle biopsy, should be performed to confirm the diagnosis, though histologic findings in IBD-associated myositis can be varied. Treatment escalation to immunomodulator medications or biologic treatments should be limited to patients who have confirmatory pathology, unless there is concern for active bowel inflammation that warrants more aggressive therapy. Based upon the available reports, approximately one third of patients require additional immunosuppressive therapy beyond corticosteroids.

The rarity of gastrocnemius and other forms of IBD-associated myositis make them difficult to study on a large scale. Additional case reports in the literature may provide a better understanding of the diagnosis and treatment of this disease and will hopefully raise the awareness of clinicians to consider this rare extraintestinal manifestation of IBD. Through continued awareness and reporting of this diagnosis, hopefully, we will be able to formulate more specific and useful guidelines regarding clinical and pathologic evaluation, which will lead to greater insight into more effective therapies and therapeutic strategies.

## References

1. Evans PE, Pardi DS. Extraintestinal manifestations of inflammatory bowel disease: focus on the musculoskeletal, dermatologic, and ocular manifestations. *MedGenMed.* 2007;9:55.
2. Salvarani C, Vlachonikolis IG, van der Heijde DM, et al. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. *Scand J Gastroenterol.* 2001;36:1307-1313.

3. Ricart E, Panaccione R, Loftus EV Jr, et al. Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis*. 2004;10:207-214.
4. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. *J Clin Gastroenterol*. 1996;23:29-34.
5. Mogul Z, Katz S, Bachman TR, Urmacher C. Isolated gastrocnemius myositis related to Crohn's disease. *Gastroenterol Hepatol*. 2010;6:453-455.
6. Christopoulos C, Savva S, Pylarinou S, Diakakis A, Papavassiliou E, Economopoulos P. Localised gastrocnemius myositis in Crohn's disease. *Clin Rheumatol*. 2003;22:143-145.
7. Leibowitz G, Eliakim R, Amir G, Rachmilewitz D. Dermatomyositis associated with Crohn's disease. *J Clin Gastroenterol*. 1994;18:48-52.
8. Kulkarni A, Ravi TJ, Brodmerkel GJ Jr, Agrawal RM. Inflammatory myositis in association with inflammatory bowel disease. *Dig Dis Sci*. 1997;42:1142-1145.
9. Chugh S, Dilawari JB, Sawhney IM, Dang N, Radotra BD, Chawla YK. Polymyositis associated with ulcerative colitis. *Gut*. 1993;34:567-569.
10. Taylor SR, McCluskey P, Lightman S. The ocular manifestations of inflammatory bowel disease. *Curr Opin Ophthalmol*. 2006;17:538-544.
11. Durno CA, Ehrlich R, Taylor R, Buncic JR, Hughes P, Griffiths AM. Keeping an eye on Crohn's disease: orbital myositis as the presenting symptom. *Can J Gastroenterol*. 1997;11:497-500.
12. Shimoyama T, Tamura Y, Sakamoto T, Inoue K. Immune-mediated myositis in Crohn's disease. *Muscle Nerve*. 2009;39:101-105.
13. Heuss D, Hauser I, Riess R. Atypical inflammatory myopathy associated with Crohn's disease. *Clin Neuropathol*. 1996;15:150-154.
14. Disdier P, Swiader L, Harle JR, et al. Crohn's disease and gastrocnemius vasculitis: two new cases. *Am J Gastroenterol*. 1997;92:880-882.
15. Bourikas LA, Papadakis KA. Musculoskeletal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis*. 2009;15:1915-1924.
16. Hall MJ, Thomas WE, Cooper BT. Gastrocnemius myositis in a patient with inflammatory bowel disease. *Digestion*. 1985;32:296-300.
17. Diószeghy P, Molnár M, Mechler F. Muscle involvement in Crohn's disease [in Hungarian]. *Orv Hetil*. 1994;135:1259-1261.
18. Gilliam JH 3rd, Challa VR, Agudelo CA, Albertson DA, Huntley CC. Vasculitis involving muscle associated with Crohn's colitis. *Gastroenterology*. 1981;81:787-790.