

Recurrent Bilateral Focal Myositis

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Abstract

This report describes a rare case of recurrent bilateral focal myositis and its successful treatment via methotrexate. A 38-year-old man presented myalgia of the right gastrocnemius in May 2005. Magnetic resonance imaging showed very high signal intensity in the right gastrocnemius on short-tau inversion recovery images. A muscle biopsy revealed inflammatory CD4+ cell-dominant myogenic change. Focal myositis was diagnosed. The first steroid treatment was effective. Tapering of prednisolone, however, repeatedly induced myositis relapse, which progressed to multiple muscle lesions of both lower limbs. Initiation of methotrexate finally allowed successful tapering of prednisolone, with no relapse in the past 4 years.

Key words: focal myositis, recurrence, bilateral, nemaline, methotrexate

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Introduction

Focal myositis is an idiopathic inflammatory myopathy and a rare inflammatory pseudotumor of the skeletal muscle with unknown etiology (1). The disease typically disappears spontaneously, does not last more than 4 years, and has no recurrence (1, 2). This myositis can be treated successfully with steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) (1, 2). We herein describe the case of a man with recurrent episodes of bilateral focal myositis.

Case Report

A 38-year-old man presented with myalgia of the right gastrocnemius muscle in May 2005. A needle biopsy of the muscle was performed in another hospital and indicated no malignancy. The patient did not receive any treatment at this time. As his symptom did not improve, he visited our hospital in August 2005 with tenderness of the right gastrocnemius muscle. On physical examination, the vital signs were normal. No significant signs were detected on the skin, cardiovascular, respiratory, or abdominal examinations. Manual muscle testing indicated full scores except in the right gastrocnemius, which demonstrated grade 4 (of 5) because of

myalgia. Evaluations of his mental status, sensory, and cerebellar systems were normal. Tendon reflexes and sensitivity of the upper and lower limbs were also normal. Laboratory data indicated that the patient's serum creatine kinase (CK), aldolase, myoglobin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were within normal limits, and anti-Jo-1 autoantibody, anti-ARS autoantibody, and antinuclear antibody were negative (Table). Monoclonal gammopathy was not detected. Hepatitis B surface antigen (HBs Ag) was positive (cut-off >2,000), and HB virus DNA was negative (<3.7 LEG/mL). Human immunodeficiency virus (HIV) and hepatitis C virus antibody tests were negative (Table). Deep vein thrombosis was ruled out by echo of the limbs.

Electromyography was not performed because the patient was unable to cooperate due to myalgia. Magnetic resonance imaging (MRI) revealed very high signal intensity in the right gastrocnemius medial head muscle on a short-tau inversion recovery (STIR) image. Atrophic change of the muscle was also noted (Fig. 1a and b). A muscle biopsy of the right gastrocnemius revealed interstitial muscle infiltration by mononuclear inflammatory cells without findings of vasculitis, along with muscle fiber necrosis and regeneration (Fig. 2a and b).

Immunohistochemical staining of the muscle biopsy showed that the infiltrating cells predominantly consisted of

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Table. Laboratory Findings in August 2005.

WBC	6,900 / μ L	TP	7.9 g/dL	IgG	1,406 mg/ dL
Neut	65.1%	Alb	4.8 g/dL	IgA	261 mg/ dL
Ly	23.3%	T-Bil	0.7 mg/dL	IgM	130 mg/ dL
Mono	5.1%	AST	14 IU/L	C3	131 mg/ dL
Eosino	6.2%	ALT	16 IU/L	C4	24mg/ dL
Baso	0.3%	LDH	134 IU/L	CH50	44.4 U/ mL
RBC	4.82×10^6 / μ L	CK	74 IU/L	antinuclear antibody	<40
Hb	14.7 g/ dL	ALP	223 IU/L	anti-Jo-1 autoantibody	negative
Hct	41.9 %	BUN	11.4 mg/dL	anti-ARS autoantibody	negative
Plt	31.5×10^4 / μ L	Cre	0.78 mg/dL	Hepatitis B surface antigen	positive
ESR	6 mm/h	CRP	0.11mg/dL	anti-HCV antibody	negative
				HBV-DNA*	<3.7LEG/mL

*transcription-mediated amplification assay.

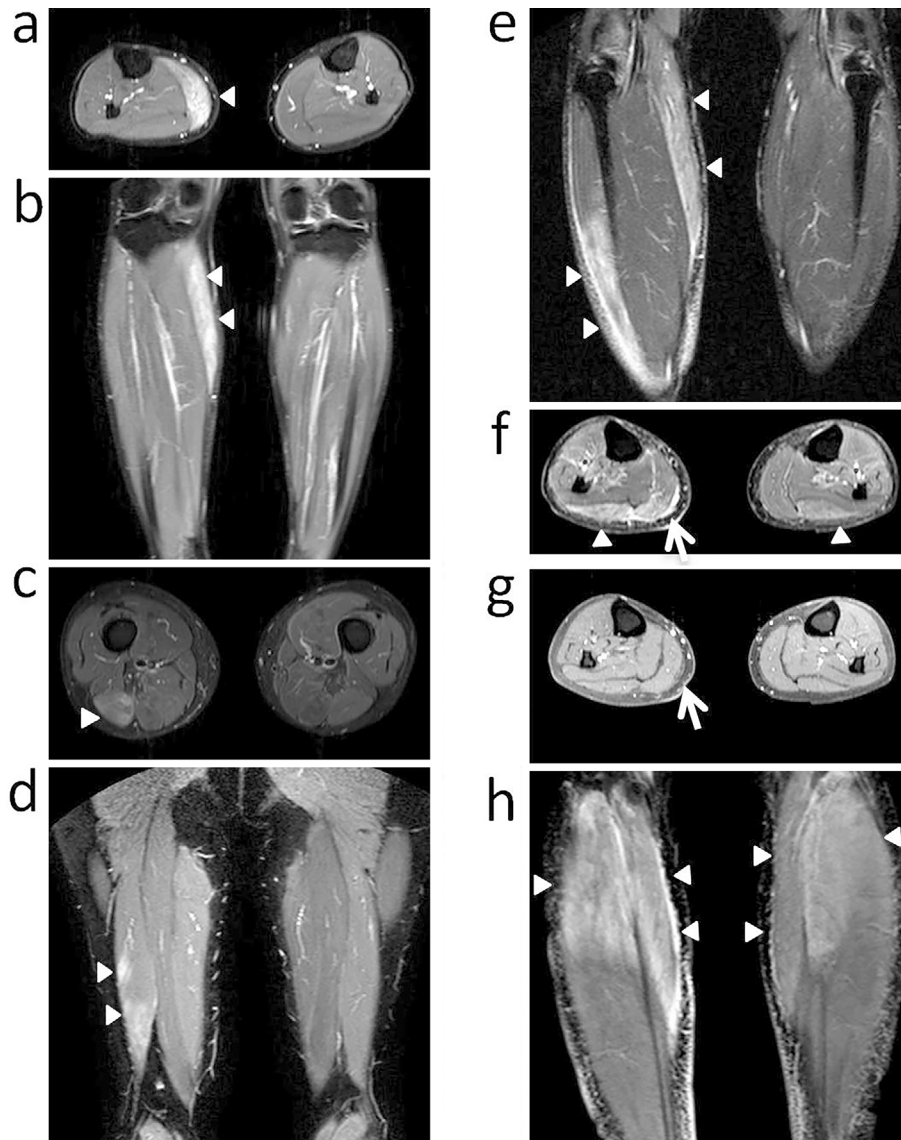


Figure 1. Magnetic resonance imaging (MRI) of the lower limbs. a, b: August 2005; c, d, e: June 2006; f, g, h: January 2008. a, b, e, f, h: Axial (a, f) and coronal (b, e, h). a-f: Unenhanced MRI image and g: gadolinium-enhanced MRI image. STIR images show high signal intensity in the affected muscles of the lower legs (white arrowhead). c, d: Axial and coronal STIR images show high signal intensity in the affected femoral muscles (white arrowhead). f, g: Axial gadolinium-enhanced MRI (g) shows no enhanced area in the thickened fascia of the right gastrocnemius, which showed high signal intensity on the unenhanced MRI image (f) (white arrow).

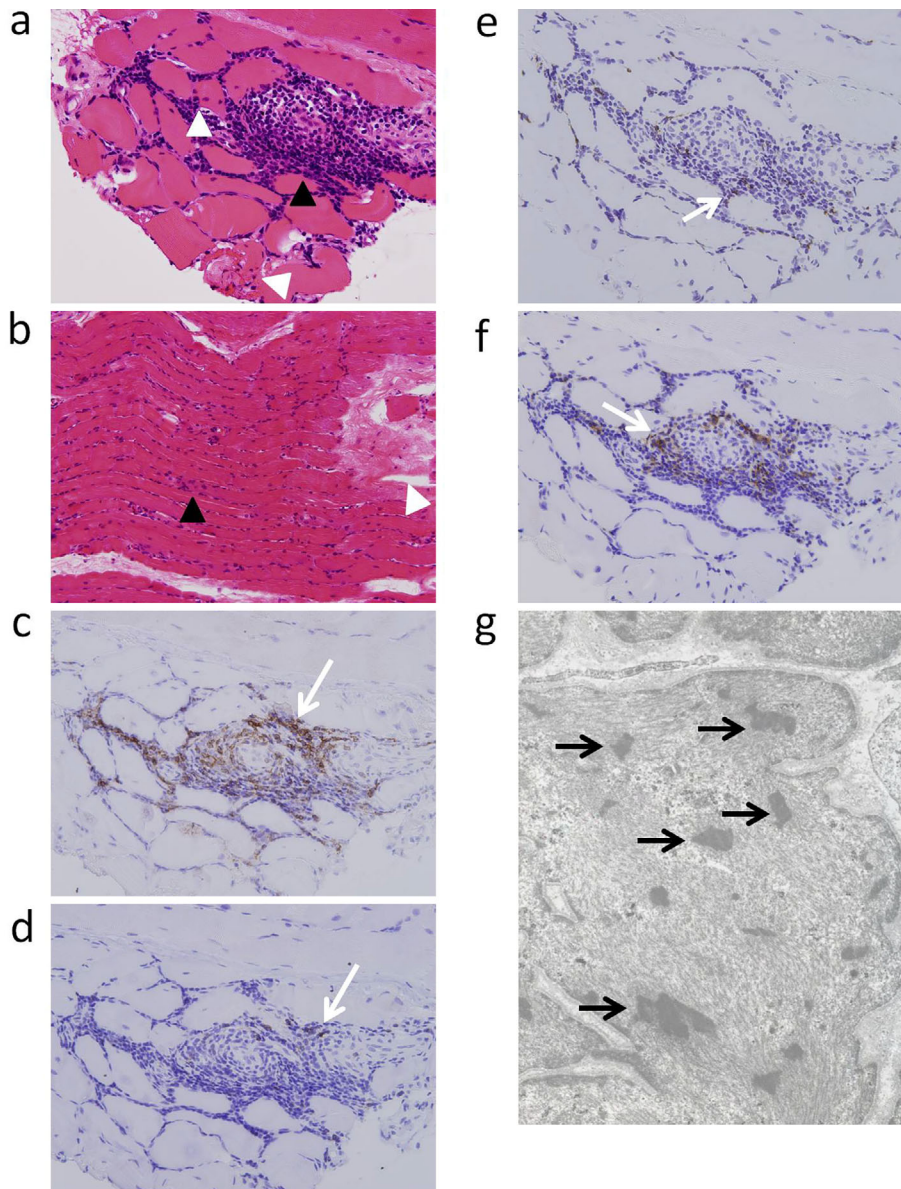


Figure 2. Muscle biopsy. a, b: Hematoxylin and Eosin staining, 400 \times ; c-f: immunohistochemical staining, 400 \times ; c: CD4; d: CD8; e: CD68; f: CD20; g: electron microscopy. A muscle biopsy of the right gastrocnemius reveals mononuclear inflammatory cells (a, b: black arrowhead) that infiltrated the interstitial spaces of the muscle without vasculitis findings, along with muscle fiber necrosis and regeneration (a, b: white arrowhead). Infiltrating cells predominantly consisted of CD4+T cells, CD68+macrophages, and CD20+B cells accompanied by a few CD8+T cells (c-f: white arrow). Electron microscopy of the muscle biopsy specimens reveals nemaline rods (g: black arrows).

CD4+ T cells, CD68+ macrophages, and CD20+ B cells accompanied by a few CD8+ T cells (Fig. 2b-f). Focal myositis was diagnosed.

As the patient was HBs Ag-positive, lamivudine treatment was initiated for the prevention of *de novo* hepatitis under immunosuppressive conditions. Prednisolone (PSL) (30 mg/day) was administered to treat the focal myositis in September 2005, and his symptoms and MRI findings were immediately improved. The clinical course is shown in Fig. 3. The PSL dosage was tapered to 15 mg daily in April 2006. The patient's muscle pain worsened gradually at around this time, and walking became difficult without a cane in June

2006. Although his CRP level was 0.4 mg/dL, the serum myogenic enzyme level was not re-elevated. MRI revealed multiple high-intensity areas in the lower limbs that included the femoral muscle (both sides of the vastus lateralis, the left vastus intermedius, the right biceps femoris, and the left gracilis) (Fig. 1c and d) and the right gastrocnemius (Fig. 1e) on STIR images. The myositis had expanded to both lower limbs and worsened. The PSL dosage was increased to 60 mg/day for relapse of myositis, and the patient's symptoms immediately improved.

After tapering the PSL dosage to 17.5 mg/day, a second myositis relapse occurred in October 2007. The myositis

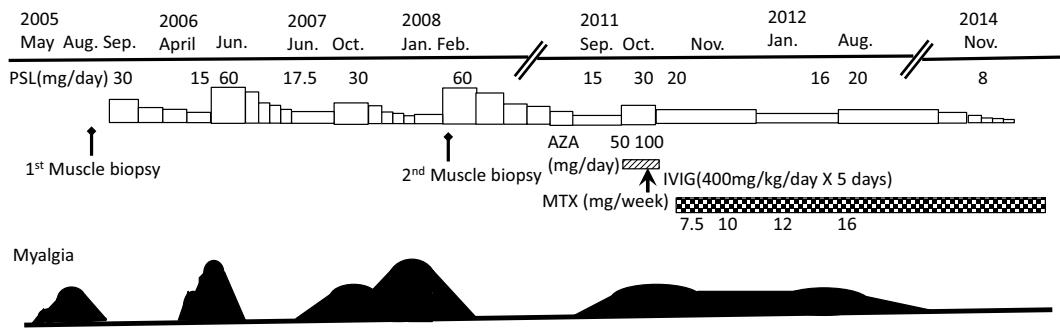


Figure 3. Clinical course of the patient. PSL: prednisolone, MTX: methotrexate, AZA: azathioprine, IVIG: high-dose intravenous immunoglobulin

again worsened. MRI findings revealed high signal intensity of the bilateral gastrocnemius (Fig. 1f and h), left popliteus muscle, and right semimembranosus on STIR images (data not shown), and mild edema was evident in the subcutaneous tissue in both lower limbs in January 2008. As thickening of the fascia of the right gastrocnemius on the STIR image (Fig. 1f, white arrow) demonstrated no gadolinium contrast enhancement (Fig. 1g, white arrow), it was considered to result from edema. Because the patient was unusually resistant to the treatment for focal myositis, we performed a muscle biopsy of the left gastrocnemius to re-confirm the diagnosis, which showed a similar result to the first biopsy (data not shown). Electron microscopy of the muscle biopsy specimens in February 2008 revealed nemaline rods (Fig. 2g, black arrows). The dosage of PSL was again increased to 60 mg/day for the third relapse of myositis.

Thereafter, we administered azathioprine (max 100 mg/day) for a steroid-sparing effect, but it failed to bring the patient persistent relief from his myalgia and gait disturbance. Therefore, we were forced to continue to administer 15 mg/day or more of the steroid in order to maintain remission. In September 2011, the relapse of myositis involved myalgia of both lower limbs and arthralgia of both foot joints. The patient's PSL dosage was increased from 15 mg/day to 30 mg/day, however, the effect was incomplete. As he had a compression fracture of the vertebrae due to steroid-induced osteoporosis, high-dosage PSL treatment was avoided. Intravenous immunoglobulin (IVIG) failed to induce remission. Methotrexate (MTX) (7.5 mg/week) was initiated with PSL 20 mg/day in October 2011, as hepatitis B virus (HBV) infection had been controlled by lamivudine. The dosage of MTX was gradually increased to 16 mg/week by August 2012. We decreased the PSL dosage to 8 mg/day in November 2014. The patient has had no myositis relapse since 2011. MRI findings in December 2014 revealed no inflammatory change (Fig. 1f). The patient can maintain standing on his heels, but not on his tiptoes. We consider this issue to indicate muscle weakness as a sequela of myositis.

Discussion

This patient had myositis that developed in the right gas-

trocnemius muscle. The differential diagnoses of inflammatory myopathy were postulated to be polymyositis, dermatomyositis, inclusion body myositis, eosinophilic myositis, and sarcoidosis. He had no past medical history and no other organ disorders including those affecting the skin and lung. The lesion originated from the distal muscle, with no eosinophilia or increase of CK or CRP in the peripheral blood. The pathology of the muscle biopsy revealed myositis and did not indicate granulomas, eosinophilic infiltration, or vacuoles. Therefore, focal myositis was diagnosed.

Focal myositis is a type V idiopathic inflammatory myopathy, classified by Bohan and Peter as miscellaneous myopathies (3). Focal myositis is a rare, broad spectrum disease (1, 2, 4-10). The levels of acute phase reactants and myogenic enzymes, such as CK, and the site of the involved muscle also vary in myositis (1, 2, 4-10). In this case, the patient's myalgia began in the right gastrocnemius and spread to both lower limbs. He had almost no elevation of serum CRP or CK.

The CRP and CK levels vary in focal myositis. Smith et al. reported that serum CK was normal in five of eight patients (2). Moreover, Sekiguchi et al. reported that normal serum CRP and CK levels might be associated with mild muscle inflammation in patients with focal myositis (11). Although the mechanism of muscle pain is not fully understood, inflammatory muscle pain was related to molecules including interleukin (IL)-6, tumor necrosis factor- α , IL-1 β , and kinin in experiments using animal models (12, 13). Dina et al. reported a novel experimental model of chronic muscle pain induced by mild acute muscle inflammation (14). In fact, the histopathological findings indicated muscle inflammation in the present patient. PSL is presumed to have led to the alleviation of symptoms by suppressing muscle inflammation.

The etiology of myositis is unknown. Some reports have reported an association between chronic HBV infection and myositis (15-17). Lamivudine or entecavir, antiviral therapies for HBV infection, improved symptoms in patients with myositis (18, 19). Toti et al. reported that the investigation of possible viral etiology via polymerase chain reaction was negative in focal myositis (20). BCG vaccine was also reported to trigger the onset of myositis (21). The present pa-

tient was an HBV carrier, however, antiviral therapy did not affect his myositis. The relationship between HBV and myositis is unknown. Although electron microscopy of specimens from the second muscle biopsy revealed nemaline rods, we judged the finding to be a non-specific change because his clinical syndrome was not characteristic of nemaline myopathy (24), and there have been several reports concerning the non-specific finding of nemaline rods in inflammatory myopathies (polymyositis and dermatomyositis) (22-25).

The majority of focal myositis cases involve a limited lesion, and bilateral lesions are rare. In our case, the patient demonstrated myositis progression from the right gastrocnemius to both sides approximately 1 year after onset and recurrent myalgia, and the myositis had temporary femoral muscle involvement. Heffner Jr et al. reported six patients with polymyositis beginning as a focal process that rapidly progressed 3-6 months from the onset, and some cases of bilateral focal myositis have been reported (26). Additionally, some reports have discussed the difference between focal myositis and polymyositis (27, 28). Conversely, there are also some reports of polymyositis cases with distal muscle involvement or without elevation of serum CK (29-34). The muscle biopsy in our case showed mononuclear inflammatory infiltrates that predominantly consisted of CD4+ T cells. This finding is similar to that of dermatomyositis (35, 36). Previous studies also reported CD4+-dominant cell infiltration in the muscle in focal myositis (37, 38) and dermatomyositis (35, 36), but not in polymyositis (39). In our patient, muscle weakness derived from myalgia was present but not progressive, and his immunohistochemical findings indicated focal myositis rather than polymyositis. It appears that focal myositis and polymyositis have different pathophysiological mechanisms; however, whether focal myositis is a subtype of polymyositis remains to be determined.

Focal myositis usually shows a good response to treatment with PSL and NSAIDs (2). It has a good prognosis and might be a self-limiting disease (1-3). Recurrent cases are rare (6, 40-50). Furthermore, the response to NSAIDs is often good even in cases of repeated relapse (41-43), and some cases of spontaneous remission have occurred (8, 49). Steroid-resistant cases are also rare (47, 51). Although the present patient demonstrated a good response to steroid treatment, PSL dose reduction induced the recurrence of myalgia. Because he experienced repeated myositis relapses when the PSL dose was reduced to 15-17.5 mg, it became necessary to use immunosuppressive agents for a steroid-sparing effect. Azathioprine and IVIG did not affect the patient's myositis. Because his HBV infection was successfully controlled with lamivudine, we used MTX and were able to reduce the PSL dose. Reports of immunosuppressive therapy for focal myositis are limited (6, 47, 51, 52), and only one previous case report, in a child, described MTX treatment for this condition (47). Further studies are needed in order to clarify the sparing effect of treatment via MTX in steroid-

resistant cases of focal myositis.

The authors state that they have no Conflict of Interest (COI).

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