□ CASE REPORT □

# Myositis as a Manifestation of Chronic Graft-Versus-Host Disease

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## Abstract

**We report a 22-year-old man who had myositis in the course of chronic graft-versus-host disease after bone marrow transplantation for acute monocytic leukemia. The distribution of muscular involvement was different from idiopathic polymyositis. Muscular atrophy and weakness were noted in the distal muscles as well as in the proximal muscles of the upper extremities but there was little weakness in the proximal muscles of the lower extremities. However, histological and immunohistochemical study of the biceps brachii muscle showed findings similar to those of idiopathic polymyositis. It was suggested that myositis can be a manifestation of chronic GVHD caused by a cellular immune reaction by donor T cells.**
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*Key words:* bone marrow transplantation, polymyositis, inflammatory myopathy

## Introduction

Patients who have been treated with bone marrow transplantation (BMT) and survived beyond 100 days often have chronic graft-versus-host disease (GVHD). The manifestations include skin disease, keratoconjunctivitis, buccal mucositis, esophageal structures, small- and large intestinal involvement, pulmonary insufficiency, chronic liver disease, and general wasting (1). Myositis or myopathy is usually rare in chronic GVHD (2). In the present report, however, we describe a patient with polymyositis which emerged in the course of chronic GVHD after BMT and compare the clinical and pathological findings with those of idiopathic polymyositis and dermatomyositis.

For editorial comment, see p 444.

## Case Report

A 22-year-old man became aware of sore throat and general fatigue in February 1994, and was diagnosed as acute monocytic leukemia (AML) at our hospital. He underwent chemotherapy and complete remission was achieved. The disease relapsed in August 1995, which was alleviated again by chemotherapy followed by total body irradiation (12 Gy). In January 1996, he was treated with BMT from his younger brother, and had complete remission. Cyclosporin A and steroids had been given to prevent acute GVHD for several months. In November 1996, he had stomatitis, skin eruption and liver damage and was diagnosed as chronic GVHD. He had been treated with prednisolone for GVHD, and the symptoms improved. In April 1997, when daily dose of 12.5 mg peroral prednisolone was prescribed, he noted muscular atrophy, weakness and pain of the upper extremities and myalgia of the thighs. The symptoms had deteriorated progressively. On October 1, 1997, he was admitted to our hospital. The past history was unremarkable until the diagnosis of AML. The family history was negative.

On admission, he was 172 cm high and weighted 69 kg. Physical examinations elucidated no abnormality of heart, lung or abdomen. No lymphoadenopathy was noted. Whereas, the oral mucosa was reddish and painful, and the skin of the forearms and hands was sclerosed like scleroderma. The nails of the fingers and toes were deformed, and the nail of the left thumb was deformed like a spoon. Motion range of the elbow joints was slightly restricted. The Medical Research Council grade for the neck flexion and extension was 4, the deltoid and triceps muscles 4, and the biceps brachii 3. The right grasping power was 4 kg and the left 6 kg. Muscle atrophy was predominant in the forearm (Fig. 1). There was little weakness of proximal muscles of the lower extremities without atrophy. Deep tendon reflexes were absent in the upper extremities and normal in lower extremities, and pathological reflexes were negative.

Laboratory examinations revealed slight inflammatory changes including elevated serum C-reactive protein (Table 1).

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**Table 1. Laboratory Data on Admission**

| | | | |
|---|---|---|---|
| Hematology | | Lactate dehydrogenase | 405 IU/l |
| White blood cells | $7.1\times10^3$/μl | Creatine phosphokinase | 650 IU/l |
| Red blood cells | $4.55\times10^6$/μl | Aldolase | 13.4 IU/l |
| Hemoglobin | 14.9 g/dl | Myoglobin | 373 ng/ml |
| Hematocrit | 43.8% | C-reactive protein | 0.7 mg/dl |
| Platelet | $159\times10^3$/μl | | |
| ESR | 14 mm/h | Autoantibody | |
| | | Anti-nuclear antibody | 80 times (nucleolar) |
| Chemistry | | Anti-Jo-1 antibody | negative |
| AST | 48 IU/l | Anti-Scl-70 antibody | negative |
| ALT | 51 IU/l | | |

ESR: erythrocyte sedimentation rate, AST: asparate aminotransferase, ALT: alanine aminotransferase.

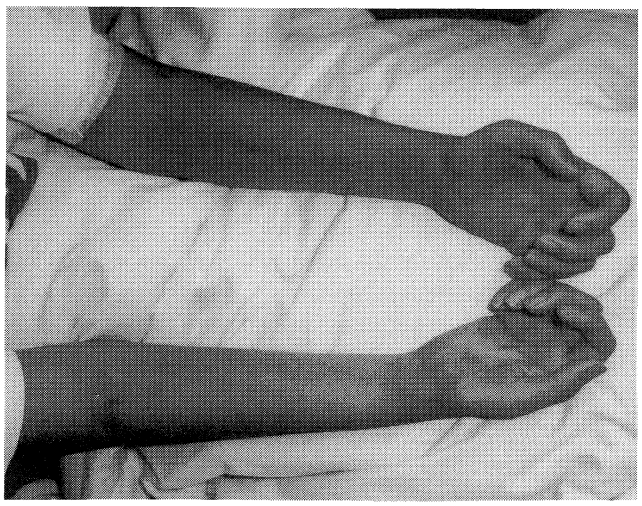

**Figure 1. Muscular atrophy and scleroderma-like skin changes of the forearms and hands.**

Serum muscle enzyme levels and serum anti-nuclear antiboby titer were increased, while anti-Jo-1 and Scl-70 antibodies were negative (Table 1). The percentages of CD3+ HLA DR+ cells (activated T cells) and CD8+ CD11– cells (cytotoxic T cells) were increased in peripheral blood (Table 2). Motor nerve conduction velocities were normal. Needle electromyographies showed a myopathic pattern in the upper limbs and a normal pattern in the lower limbs. Muscle biopsy was performed in the left biceps brachii.

Pathological findings showed that the variation in muscle fiber size was increased and necrosis and regeneration of muscle fibers were revealed. Moderate fibrosis was noted in the endomysium and perimysium, and replacement of muscle fibers by adipose tissue was detected in the perimysium. Inflammatory cells were moderately infiltrated into the endomysium and perimysium, and most consisted of mononuclear cells. Perifascicular atrophy and microinfarction were not found (Fig. 2). Immunohistochemical study revealed that most of the infiltrating cells were CD3+ cells (T cells). Numbers of CD4+ and CD8+ cells were equal in the perimysium (Fig. 3), whereas CD8+ cells were infiltrated more predominantly than CD4+ cells in the endomysium (Fig. 4). These pathological findings coincide with those of idiopathic polymyositis.

**Table 2. Lymphocyte Subset of peripheral blood**

| | |
|---|---|
| CD3+ cell (T cell) | 65% (58–81) |
| CD3+ HLA DR+ cell (activated T cell) | 36% (11–31) |
| CD4+ Leu8– cell (helper T cell) | undetectable |
| CD4+ Leu8+ cell (suppressor-inducer T cell) | undetectable |
| CD8+ CD11– cell (cytotoxic T cell) | 42% (14–32) |
| CD8+ CD11+ cell (suppressor T cell) | 7% (6–19) |

Methylprednisolone 125 mg was administered intravenously for 3 days, followed by peroral prednisolone 25 mg in two days. The serum CK level was rapidly normalized, myalgia of the upper and lower extremities decreased, and the muscle weakness improved slightly.

## Discussion

The occurrence of myositis in the course of chronic GVHD is rare. Sullivan et al reported four of 52 patients (7.6%) with chronic GVHD complicated with myositis (3). In 1996, Parker et al reported myositis present in 11 of 318 patients (3.5%) who developed chronic GVHD and nine patients had other associated organ involvement but in two patients myositis was the only manifestation of chronic GVHD (4). In the present case, stomatitis, liver damage and sclerotic skin changes in the forearms were also noted in the course of chronic GVHD. The restricted motion range of the elbow joints seemed to indicate joint constriction caused by muscle weakness, because rentogenogram of the elbow joints showed no deformity.

It is reported that the pathological findings of myositis in chronic GVHD parallel those seen in idiopathic polymyositis (4–6). The histological and immunohistochemical studies of

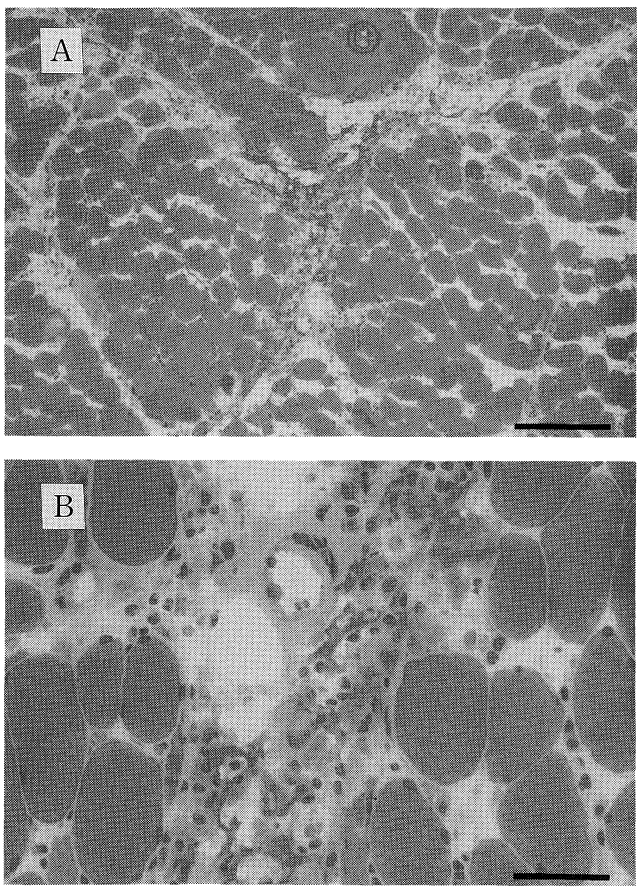


**Figure 2. Freshly frozen, cross-section of a muscle biopsy. (A) Increased variation in muscle fiber size, necrosis and regeneration of muscle fibers, fibrosis, and endomysial and perimysial inflammation are shown (HE, bar = 200 μm). (B) Most of the inflammatory cells consisted of mononuclear cells (HE, bar = 50 μm).**

the present case also showed findings identical to polymyositis rather than to dermatomyositis. That is, perifascicular atrophy or microinfarction were not shown and the infiltrating cells consisted of more CD8+ cells than CD4+ cells (7, 8). It is reported that polymyositis is a cellular immune-mediated syndrome and dermatomyositis is a humoral immune-mediated disease (7). The present patient showed an increased ratio of cytotoxic T cells in peripheral blood. Myositis of the present patient could be a manifestation of chronic GVHD caused by an abnormal cellular immune reaction by donor T cells. The skin lesions of the present patient also do not resemble those of dermatomyositis but scleroderma, although anti-Scl-70 antibody was not detected. Scleroderma-like skin changes are often reported in chronic GVHD (9, 10).

Distribution of the involved muscles in the present patient is not typical to that of idiopathic polymyositis. It is known that both polymyositis and myositis-associated GVHD usually involve the proximal muscles predominantly (4, 6, 11). But, our case showed weakness and atrophy predominantly in the distal muscles of the upper extremities. In the lower extremities, proximal muscles were involved predominantly but to a lesser extent compared to the upper ones.

Concerning the treatment, several authors have reported that patients with chronic GVHD-related myositis respond well to steroid with or without cyclosporine (4, 5, 11, 12). In our case, prednisolone normalized the serum CK levels but showed little benefit on the muscle weakness.

In conclusion, we presented polymyositis which emerged in the course of chronic GVHD. The myopathological findings were identical to those of idiopathic polymyositis, however the distribution of the involved muscles was different.

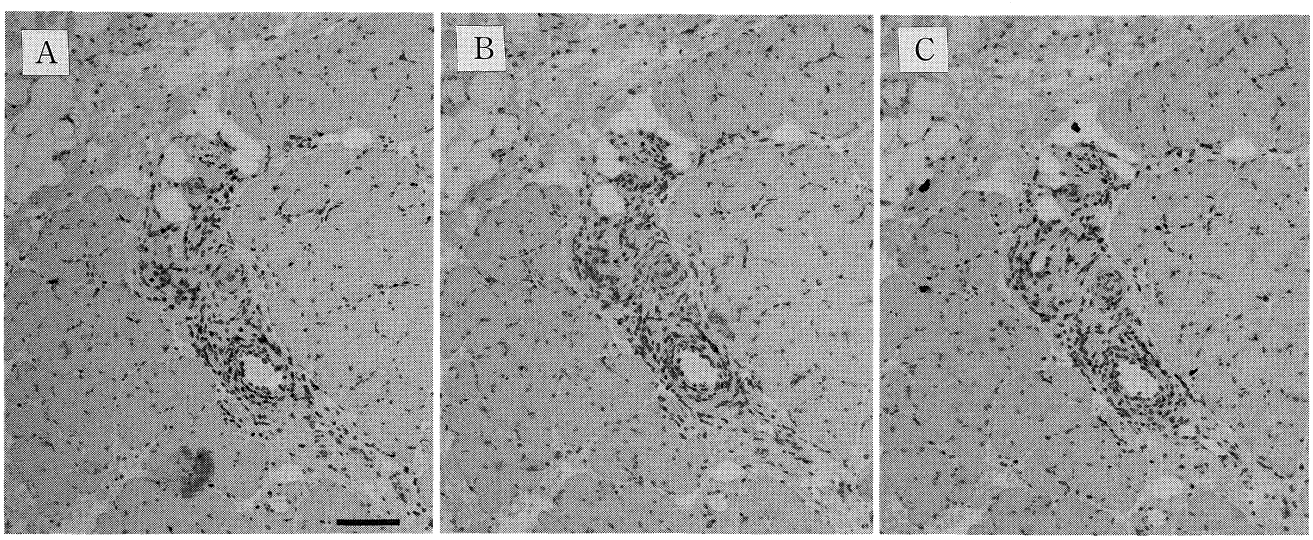


**Figure 3. Serial sections of muscle stained immunohistochemically for CD3 (A), CD4 (B), and CD8+ cells (C). Most of the infiltrating cells were CD3+ cells (T cells) and the numbers of CD4+ and CD8+ cells were equal in the perimysium (bar = 100 μm).**

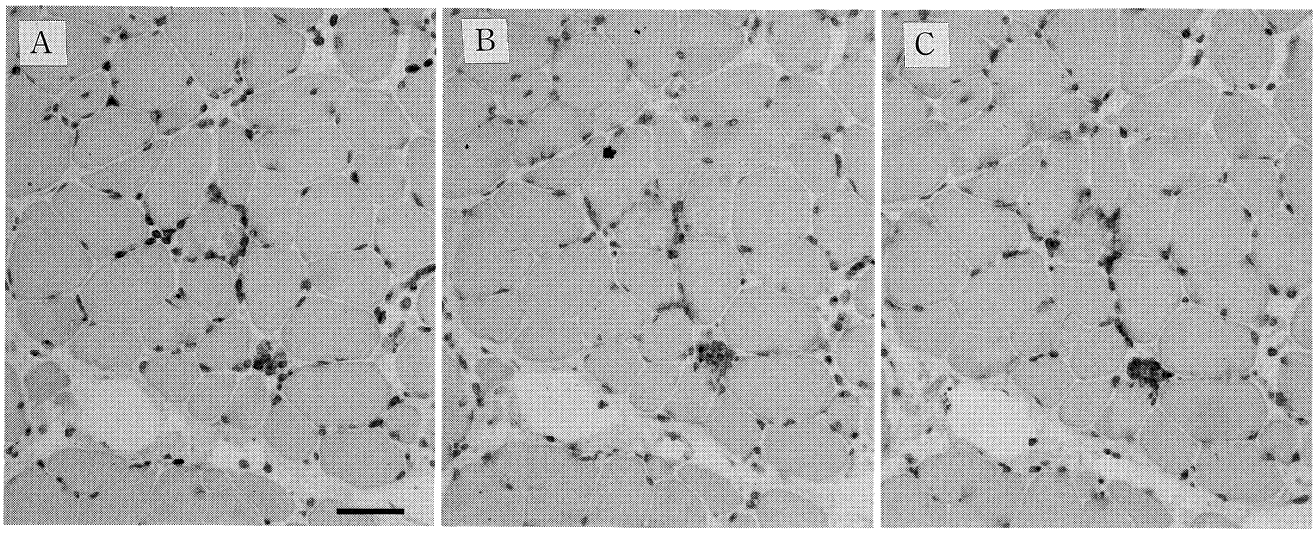


**Figure 4. Serial sections of muscle stained immunohistochemically for CD3 (A), CD4 (B), and CD8+ cells (C). CD8+ cells infiltrated more predominantly than CD4+ cells in the endomysium (bar = 50 μm).**

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