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Case Report

골수이식 이후의 다발근육염: 만성 이식편대숙주병의 드문 증상인가? 자가면역작용인가?

인제대학교 의과대학 부산백병원 신경과[1], 병리과[2], 인제대학교 임상연구소[3]

최원철[1] · 정용한[2] · 양영일[2,3] · 배종석[1]

Polymyositis After Bone Marrow Transplantation: As an Uncommon Manifestation of Chronic Graft-Versus-Host Disease? or Autoimmune Process?

Won-cheol Choi, M.D.[1], Yong Han Jung, M.D.[2], Yeong Il Yang, M.D.[2,3], Jong Seok Bae, M.D.[1]

Departments of Neurology[1] and Pathology[2], Inje University College of Medicine, Busan Paik Hospital, Institute for Clinical Research, Inje Univesity[3], Busan, Korea

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Chronic graft-versus-host disease (GVHD) is a well-known complication of allogeneic bone marrow transplantation (BMT) and has heterogeneous manifestations, with multi-organ involvement. Recently, polymyositis (PM) was reported to be a rare manifestation of chronic GVHD. Here, we report a 30-year-old woman who was diagnosed with PM after allogeneic BMT.

Key Words: Graft-versus-host disease, Polymyositis, Bone marrow transplantation

Graft-versus-host disease (GVHD) is a serious complication of allogeneic bone marrow transplantation (BMT). It involves an immunological reaction against antigens in the BMT recipient triggered by the immunocompetent donor graft.[1] Chronic GVHD is a heterogeneous syndrome with multi-organ involvement.[2,3] Thus, its major clinical manifestations are similar to those of autoimmune connective tissues diseases. Polymyositis (PM) is a very unusual manifestation of chronic GVHD; it can exist as the sole manifestation of chronic GVHD or along with other various features of chronic GVHD.[1,4,5]

Address for correspondence;
Jong Seok Bae, M.D.
Department of Neurology, Inje University College of Medicine, Busan Paik Hospital, 633-165 Gaegeum-dong, Busanjin-gu, Busan 614-110, Korea
Tel: +82-51-890-6148 Fax: +82-51-895-6367
E-mail: neurobae@yahoo.co.kr

Case Report

A 30-year-old woman came to our department because of progressively increasing muscle weakness without myalgia. One year earlier, she noticed posterior neck pain and difficulty in maintaining neck extension. Six months earlier, she developed symmetrical proximal muscle weakness of all limbs. Subsequently, her proximal limbs showed obvious changes of muscle atrophy.

She was diagnosed with aplastic anemia 9 years earlier and underwent allogeneic BMT 4 years ago. Two years ago, she developed dry eyes and dry skin with a skin rash. GVHD after BMT was diagnosed and a lower dosage of prednisolone was

prescribed at another hospital. After she developed the muscle weakness and atrophy, the prednisolone was stopped under a working diagnosis of muscle weakness caused by steroid myopathy. Despite discontinuing the steroid, her muscle weakness and atrophy progressed.

Her proximal muscle power was at most Medical Research Council (MRC) grade I in the upper limbs, grade II in the lower limbs, and her distal muscle power was grade V in all limbs. Her gait was a typical waddling gait. The muscle wasting was severe in all limbs. Deep tendon reflexes were absent bilaterally.

Needle electromyography detected mild spontaneous activity, consisting primarily of positive sharp waves, short amplitude, and short-duration myopathic motor unit action potentials, and early recruitment patterns. Histopathologically, a skeletal muscle biopsy showed typical features of polymyositis, such as scattered necrotic muscle fibers, regenerating muscle fibers, and interstitial and endomysial infiltration (arrow) of inflammatory cells (Figure 1A). The fascia contained an inflammatory cell infiltrate (arrow) around capillaries (asterisk), with mild deposition of collagen fibers (Figure 1B). The inflammatory infiltrates in the muscle and fascia were predominantly lymphocytes with some monocytes. Immunohistochemical staining of muscle revealed that the majority of the cells in the endomysial infiltrate expressed T cell markers, such as CD45RO (Figure 1C) and CD3 (Figure 1D), and the monocyte/macrophage marker CD68 (Figure 1E). Conversely, no $CD20^{+}$ B cell was observed in interstitium or endomysium (Figure 1F).

Initially, the serum creatine phosphokinase was 849 IU/L. A blood work-up for various connective tissue diseases was done. Only antinuclear antibody was positive, with a nucleolar pattern. The acetylcholine receptor antibody titer and thyroid function test was within the normal range.

We diagnosed her with PM, probably as a manifestation of chronic GVHD. She was started on a trial of high-dosage intravenous steroid and subsequently switched to maintenance high-dosage oral steroid therapy. Her muscle power improved slightly immediately after the initial intravenous steroid. During follow-up, however, her muscle weakness and wasting did not improve continuously or recover markedly. After therapy with oral steroid for about 6 months, her serum CPK had declined to 114 U/L.

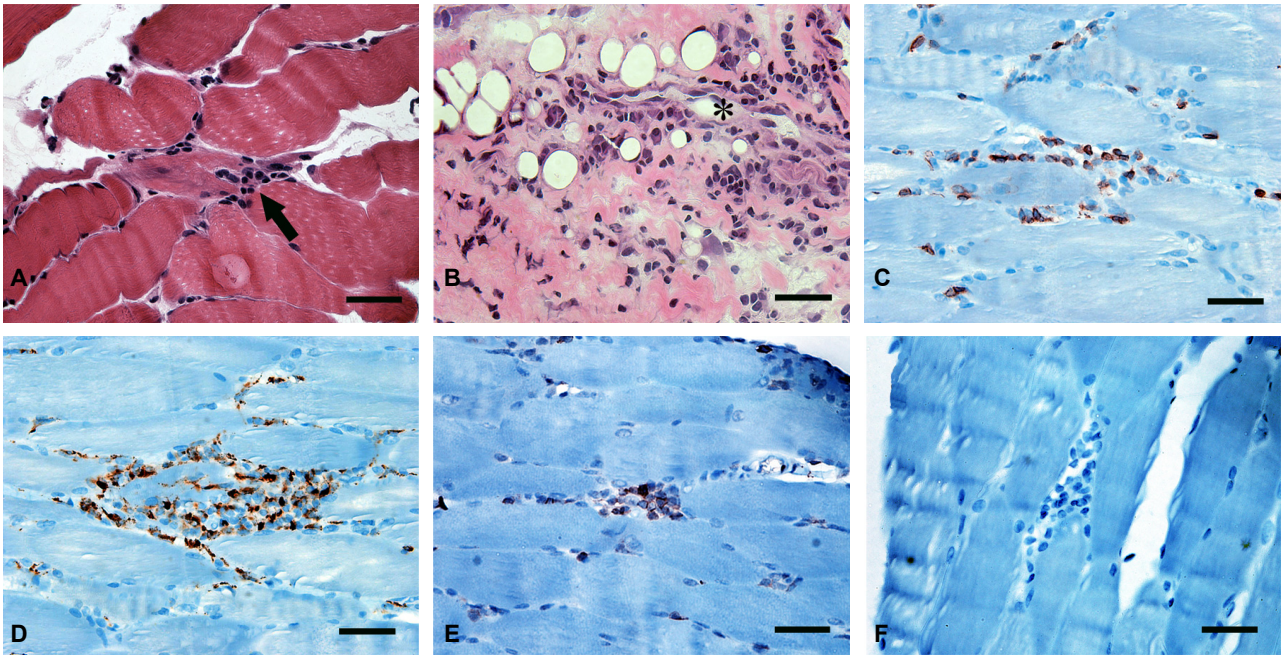

Figure 1. Microscopic images of muscle and fascia. Cryosections of (A) skeletal muscle and (B) fascia show a mononuclear cell infiltration in the interstitium and endomysium (arrow) of muscle and around a capillary (asterisk) in the fascia (hematoxylin and eosin staining). Immunohistochemical staining of skeletal muscle demonstrated that the infiltrating cells were (C) CD45RO and (D) CD3-positive T cells and (E) CD68+ monocytes, while no CD20-positive B cell was observed. Scale bar=100 μm.

Discussion

Polymyositis has been reported in chronic GVHD. PM in patients with chronic GVHD has a similar clinical presentation, with proximal muscle weakness, pain, and an elevated CPK in most cases. The histopathology is also similar, with a characteristic mononuclear perimysial inflammatory infiltration and, in more advanced cases, muscle fiber necrosis.[6] There are no obvious predictors of PM, such as age or pre-BMT disease diagnosis.[7] Thus, we suggest that PM is a rare manifestation of chronic GVHD, very similar to idiopathic PM. It is difficult to predict the occurrence of PM. Nevertheless, PM in GVHD may be more frequent than suspected because its manifestations may be missed easily, especially in the face of other concomitant complications of chronic GVHD.[6,7]

Until recently, it has been controversial whether PM is a manifestation of chronic GVHD or occurs coincidentally.[4,5,8] Most reports have been single cases. Additionally, like our case, many cases involved PM after BMT for aplastic anemia.[9] One large case series suggested that the frequency of PM in chronic GVHD was too high to be merely coincidental because 11 of 1,201 allogeneic BMT patients developed PM at single hospital. If confined to patients who developed chronic GVHD, 3.4% of the GVHD patients developed PM.[7]

One study also described the precise clinical features of PM.[7] The onset of PM is typically between 7 and 24 months after BMT. All patients were in hematologic remission with donor grafts when their symptoms developed. Weakness of the proximal muscles with myalgia were characteristic findings. The symptoms were only severe enough to warrant hospitalization in 2 of 11 patients. All patients had elevated CPK levels ranging from 700 to 4,500 U/L (normal 0-160) and responded promptly to the reinstitution or increase in the dose of prednisone with or without cyclosporine. Thus, we feel that these cases were milder PM than in our case.

The pathogenesis of PM in chronic GVHD remains to be determined. In chronic GVHD, the donor cells infiltrate the skin and mucous membranes. Presumably, the lymphocyte infiltration found in chronic GVHD-associated myositis is also composed of donor cells, because the circulating host cells have been eliminated in the pretransplantation conditioning regimen.[5] Some HLA types are strongly associated with idiopathic polymyositis. HLA DRw52 is present in 75% of the patients with idiopathic PM and >90% of the patients with idiopathic PM have anti-Jo-1 antibody.[10] HLA B8, DR3 (DRb*0301), and DQA1*0501 have also been reported more frequently in patients with idiopathic PM.[1] However, our patient refused HLA typing and antibody tests.

In summary our patient showed typical clinical, electrophysiological, and pathological manifestations of PM. However, her CPK level was relatively low and the response to treatment was poor. We believe that this originated from the severe loss of muscle tissue, due to the delayed initiation of immunotherapy. The etiology of PM can be either as a complication of GVHD or idiopathic. We believe that her PM was a rare manifestation of chronic GVHD. Awareness of this complication may allow earlier diagnosis and intervention, thereby preventing the morbidity associated with extensive myositis. Additionally, clinicians can start therapy earlier, because there may be a tendency to develop chronic GVHD when PM is the sole initial manifestation.

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