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## Inflammatory myopathy associated with chronic graft-versus-host disease

**Article abstract**—Damage of skeletal muscle in association with graft-versus-host disease (GvHD) has been referenced exceptionally. Eighteen months after bone marrow transplantation, a 22-year-old man developed polymyositis associated with manifestations of chronic GvHD, such as peripheral eosinophilia and localized morphea. Diagnosis of polymyositis was established by clinical, electromyographic, and histopathologic findings. His clinical condition improved with immunosuppressive therapy. At electronmicroscopy, some close and broad contacts between lymphocytes with activated appearance and degenerated muscle fibers were observed, suggesting a lymphocytotoxic mechanism. The findings support the idea that polymyositis can be considered a manifestation of chronic GvHD.

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**Between 25 and 40% of long-term allogeneic marrow-transplanted survivors** develop chronic graft-versus-host disease (GvHD).<sup>1</sup> The manifestation includes lichen planus and scleroderma-like changes, chronic liver disease, generalized Sjögren's syndrome, severe oral and esophageal mucositis, malabsorption, diffuse pulmonary fibrosis, and recurrent bacterial infection.<sup>1,7</sup> Myopathy is regarded as a "probable" manifestation<sup>4</sup> because there have been few cases, most from the same center.<sup>1,2,8</sup> We have studied a case of polymyositis in a recipient of an allogeneic bone marrow transplant (BMT).

**Case report.** In July 1982, this 22-year-old man had aplastic anemia according to conventional criteria.<sup>10</sup> He was treated with oxymetholone, 180 mg orally per day, and anti-lymphocytic globulin, 58,800 lymphocytotoxic units (Merieux) IV daily for 6 days. There was no response, and marrow was donated by his HLA-identical, MLC-negative sibling. He was conditioned with cyclophosphamide, 3,500 mg daily for 4 days, and 600 rads of thoracoabdominal irradiation. Conventional GvHD prophylaxis with methotrexate was carried out

for 102 days. On the 17th day, peripheral blood recovery was evident. On the 25th day, there was generalized rash, fever, jaundice, and diarrhea, with hepatomegaly and abnormal liver function test. Acute GvHD was diagnosed by skin, liver, and rectum histologic findings. Prednisone, 1,200 mg IV daily, was given, and the patient gradually improved. On the 31st day, he had intercostal herpes zoster, and on day 57, culture-negative endocarditis was detected; both resolved.

Eighteen months after BMT, induration of skin corresponding to the area of the herpes zoster infection was observed, and localized morphea was diagnosed on the basis of the skin biopsies of involved and noninvolved areas. Two weeks later, the patient developed progressive wasting and weakness of shoulder girdle muscles, with flexion contractures at the elbows. Serum CK, aldolase, and glutamic oxaloacetic transaminase were normal. Antinuclear antibodies, latex fixation test for rheumatoid factor, complement and serum immune complexes were normal or negative. Polyphasic, short and small units, and fibrillations were detected in EMG study of proximal muscles of the pelvic and shoulder girdles. Conduction studies of the sciatic, popliteal, and median nerves were normal.

An open biopsy of the skin, fascia, and left deltoid muscle was performed, and the specimens were processed for light and



Figure 1. Lymphocyte (arrow) with activated appearance contacting degenerating muscle fibers. Note that the contacts are close and broad, suggesting a cytotoxic mechanism (T.E.M.;  $\times 8,000$ ).



Figure 2. Capillary blood vessel with an increase in thickness of the endothelium cells, as well as a thickened and reduplicated basement membrane (T.E.M.;  $\times 10,000$ ).

electron microscopic studies. With light microscopy, the skin appeared normal, and the fascia showed thickening and mononuclear infiltration. Focal necrosis of muscle fibers with phagocytosis, evidence of regeneration, interstitial infiltrates by chronic inflammatory cells, and perimysial fibrosis were found by light examination of deltoid muscle. Histochemical findings were normal. On electron microscopy, there were necrotic and regenerating fibers as well as focal degeneration of myofilaments. In the endomysial space, increased collagen tissue and infiltration by mononuclear inflammatory cells, mainly lymphocytes and plasma cells, were seen. Some lymphocytes with elongated profiles that suggest cell activation were seen in contact with degenerating muscle fibers. The contacts were close and broad-based, suggesting a cytotoxic mechanism (figure 1). In addition, changes of the muscle blood vessels included increased thickness and number of the endothelium cells as well as thickened and reduplicated basement membranes (figure 2). One capillary endothelial cell showed a tubuloreticular inclusion. Therapy for chronic GvHD (prednisone, 120 mg orally per day, and azathioprine, 100 mg orally per day) was followed by improvement of weakness and contractures. The patient fully recovered in 5 months of treatment.

**Discussion.** Inflammatory myopathy has been seen with chronic GvHD.<sup>1,2,8,9</sup> Eighteen months after BMT, our patient had myopathic symptoms and histologic evidence of polymyositis.<sup>11</sup> We found no other possible etiology.<sup>12-15</sup> Herpes zoster infection was excluded because the patient had this infection 18 months before the onset of myopathy, and we did not identify viral particles in muscle. There was no rash of dermatomyositis, but there were localized morphea and histologic fasciitis, with no other signs of progressive systemic scleroderma.

The myopathy could be considered a GvHD manifestation with peripheral eosinophilia and localized morphea. The patient improved with treatment of chronic GvHD by prednisone and azathioprine, and histologic features in muscle were similar to the disease in other organs: there were necrosis of individual cells and a lymphoplasmocytic infiltrate with destruction of architectural features, as occurs in skin, oral mucosa, liver, and esophagus in chronic GvHD.<sup>1,2</sup> Electron microscopy showed lymphocytes in contact with degenerating muscle fibers (figure 1) with features similar to those of lymphocytes and keratinocytes<sup>1,16,17</sup> in skin GvHD. Lesions of GvHD are attributed to cytotoxic T lymphocytes, directly infused with the marrow inoculum or developed from thymus-processed stem cell. In our case, the vascular changes were slight, but lymphoid infiltration was marked and well associated with electron microscopic evidence of lymphocytotoxic muscle destruction. Therefore, myopathy is also part of the GvHD spectrum.

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