

Tc-99m MDP bone scintigraphy of myositis as a manifestation of chronic graft-versus-host disease after non-myeloablative peripheral stem cell transplantation

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A 27-year-old man developed polymyositis as a manifestation of chronic graft-versus-host disease (GVHD) after non-myeloablative peripheral blood stem cell transplantation (PBSCT). Bone scintigraphy showed intense, striped, and heterogeneous accumulation of Tc-99m methylene diphosphonate (MDP) in the soft-tissue of his lower limbs, while faint activities were seen in the right upper limb. Tc-99m MDP scintigraphy was very useful for accurate and objective evaluation of the severity of the muscle injury and the extent of polymyositis caused by chronic GVHD.

Key words: bone scintigraphy, myositis, graft-versus-host disease

INTRODUCTION

Tc-99m phosphate compounds have the ability to detect nonosseous disorders. Muscular uptake on bone scintigraphy has been reported in various conditions including rhabdomyolysis, inflammatory muscle disease, traumatic myositis, polymyositis and dermatomyositis.^{1–4} Polymyositis is a rare complication of chronic graft-versus-host disease (GVHD) after allogeneic bone marrow transplantation, and is characterized by myalgias, muscle weakness, and increased creatinine phosphokinase levels (CPK). We describe here a striking demonstration of skeletal muscles by bone scintigraphy with Tc-99m methylene diphosphonate (MDP) in a 27-year-old man with polymyositis that was induced by chronic GVHD seven months after non-myeloablative peripheral blood stem cell transplantation (PBSCT). This is the first report, to our knowledge, of bone scintigraphy of myositis caused by chronic GVHD.

Received March 5, 2004, revision accepted August 2, 2004.

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CASE REPORT

A 27-year-old man with renal insufficiency requiring dialysis due to Henoch-Schonlein purpura nephritis that was diagnosed at the age of 6 years and with aplastic anemia diagnosed at the age of 19 underwent allogeneic PBSCT from his HLA-identical sister in June 2001. In the middle of December 2001, he was admitted with high fever, hypoxemia, and interstitial pneumonia. Pancytopenia, liver dysfunction, dry eye and dry mouth were apparent, and chronic GVHD was proven by salivary gland biopsy. Treatment with cyclosporine and prednisone was effective. At the end of January 2002, he found a mass and experienced pain in his right upper arm, and MR imaging showed a slightly contrast-enhanced lesion on the external side of right acromial part of the deltoid muscle (Fig. 1). The symptoms subsided within a few days, and he was discharged in early February 2002. He developed diffuse pain and muscle weakness over the bilateral proximal lower extremities two days after discharge, and was admitted to the hospital again. The laboratory findings on the second admission included the following values: CPK, 28,188 IU/l; erythrocyte sedimentation rate, 95 mm/hour; leukocytes, 7,700/ μ l; erythrocytes, 212×10^4 / μ l; hemoglobin, 8.4 g/dl; hematocrit, 24.9%; platelets, 3.1×10^4 / μ l; C-reactive protein, 0.72 mg/dl; lactate

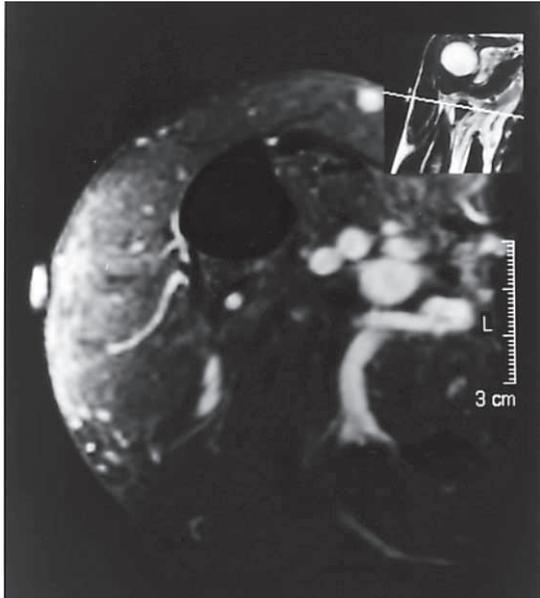


Fig. 1 Axial MR image (gradient echo; TR 41, TE 4.1 with fat suppression and Gd-DTPA) of right upper arm reveals Gd-DTPA enhancement in an acromial part of the deltoid muscle. Marking was on the skin surface where the patient found a mass and experienced pain.

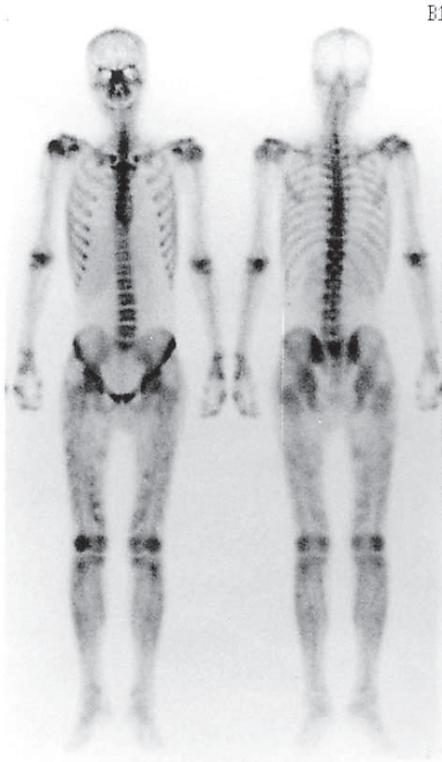


Fig. 2 Whole-body scintigram with Tc-99m MDP shows striking striped uptake in the hip, femoral and crural muscles bilaterally and faint uptake in the right upper arm focally. Neither femurs nor tibias are demonstrated.

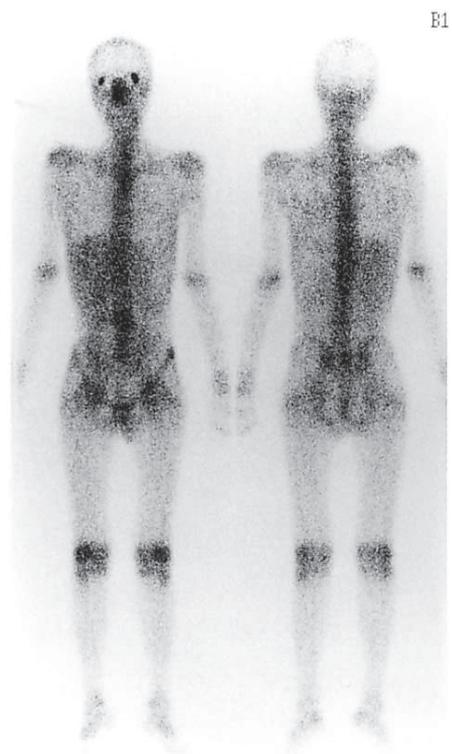


Fig. 3 Whole-body scintigram with Ga-67 shows no increased accumulation in either lower extremity.

dehydrogenase, 2,051 IU/l; total bilirubin, 0.5 mg/dl; aspartate aminotransferase, 455 IU/l; alanine aminotransferase, 76 IU/l.

He underwent whole-body bone scintigraphy 10 days after the onset of muscle weakness of the lower extremities. The scintigraphy was performed 3 hours after injection of 740 MBq Tc-99m MDP using a large field-of-view gamma camera (GCA-7200A/DI, Tokyo, Japan) with a low-energy, high-resolution collimator. A bone scintigram showed marked extrasosseous accumulation of Tc-99m MDP in the thighs and crura. The distribution of uptake in the muscles suggested myositis. Faint uptake of Tc-99m MDP was also seen in the soft tissue of the external lateral side of the right upper arm where a mass and pain had been present. Neither the femurs nor tibias were demonstrated in this bone scintigraphy. In addition, faint diffuse liver demonstration was noted (Fig. 2). After completion of bone scintigraphy, 111 MBq Ga-67 citrate was injected intravenously on the same day. Forty-eight hours after the administration of Ga-67 citrate, scintigraphy using a large field-of-view gamma camera with a middle-energy, high-resolution collimator and MRI examination were carried out on the same day. Whole-body scintigram with Ga-67 citrate revealed no abnormality anywhere including soft tissues in the legs (Fig. 3). MR imaging showed a diffuse high intensity on T2-weighted image and Gd-enhancement in femoral muscles bilaterally.



Fig. 4 Coronal MR images (spin echo; TR 2000, TE 70 with fat suppression) of the thigh reveal diffuse high intensity in femoral muscles bilaterally.

ally (Fig. 4). After the dose of cyclosporine was increased to 150 mg/day, the myalgias and CPK level gradually decreased and muscle strength recovered in one month.

Although muscle biopsy was not carried out in this case, the patient was diagnosed with chronic GVHD by salivary gland biopsy one month before the crisis of myositis.

DISCUSSION

Chronic GVHD is a cellular immune-mediated donor bone marrow versus patient rejection reaction, and consists of 2 major phases, acute and chronic. Acute GVHD occurs 1–2 months after bone marrow transplantation (BMT), and shows clinical manifestations consisting of erythematous skin, diarrhea and liver impairment. Twenty-five to 40% of patients who survive longer than 100 days after transplantation present chronic GVHD. The manifestations of chronic GVHD include skin disease, sicca syndromes (dry eye and dry mouth), bronchiolitis obliterans in the lungs, gastrointestinal tract involvement, cholestasis in the liver, and variable cytopenia. The incidence of myositis as a manifestation of chronic GVHD is low, being reported is only 3.5–7.6% of cases.^{5–8}

It is known that myositis-associated GVHD in general, predominantly involves the proximal muscles of the extremities.^{7,8} In the current case, bone scintigram showed

high accumulation of Tc-99m MDP in both the proximal and distal lower extremities bilaterally in addition to slight uptake in the right upper proximal extremity. In the thighs, the stripe extraosseous accumulation of Tc-99m MDP seemed to be along the muscle structures. Basically, as this patient has been suffering from chronic renal insufficiency and has been undergoing dialysis, both kidneys and urinary bladder were not demonstrated and the bone condition seemed to be renal osteodystrophy. In this bone scintigram, the bilateral femurs and tibias were not visualized while the pelvic bones, spine, ribs, skull and upper extremity bones were well demonstrated. One possible explanation for the lack of visualization of the lower extremity bones might be a shortage of Tc-99m MDP. Thus, Tc-99m MDP was shifted to the extraosseous soft tissues, and the amount of Tc-99m MDP was not sufficient to accumulate in the whole bone. Another possibility might be inflammatory obliteration of nutrient vessels to the bones. Since progression of muscle inflammation caused obliteration of nutrient vessels, Tc-99m MDP could not reach the bones. His bone scintigram with Tc-99m MDP in 2003 well demonstrated whole bones including those in the lower extremities (Fig. 5). In addition, this patient suffered from aplastic anemia. The intensity of bone marrow shown in MRI was modified by the disease. His bone marrow scintigram with In-111 Cl₃ in 1999 had revealed femurs and tibias as peripheral bone



Fig. 5 Whole-body scintigram with Tc-99m MDP performed 20 months after the crisis of myositis showing whole bones including those of the lower extremities. Decreased uptake of Tc-99m MDP was also seen in the major joints after non-myeloablative PBSCT. Faint diffuse liver uptake of Tc-99m MDP is still demonstrated.

marrow expansion.

This patient demonstrated diffuse hepatic uptake of Tc-99m MDP on bone scintigraphy. Diffuse hepatic uptake of a bone imaging agent has been reported, with prior liver scintigraphy, diffuse hepatic necrosis, elevated serum aluminum level, injection of contrast medium after bone agent injection, repeated iron dextran injections, and amyloidosis.⁹ In the current case, the patient had not received liver scintigraphy, iron therapy, contrast medium administration. Several authors reported that patients with hepatic injury demonstrate diffuse hepatic uptake of bone agents on bone scintigraphy. Shih and Coupal reported that bone agent uptake in the liver might indicate a related degree of hepatic damage reflected by elevated liver enzymes values.¹⁰⁻¹² Our patient showed mild to moderate elevation of serum transaminase and lactate dehydrogenase, which might reflect hepatic damage due to GVHD, leading to liver uptake of Tc-99m MDP.

Soft tissue uptake of bone-imaging agents is seen in a wide variety of conditions, including neoplastic, hormonal, inflammatory, ischemic, traumatic, excretory, and artifactual entities. It is also known that bone scintigraphy

is used to evaluate various conditions of muscular diseases including rhabdomyolysis, inflammatory muscle disease, traumatic myositis, and involvement by human immunodeficiency virus.^{13,14} Among possible mechanisms for increased extraosseous uptake of Tc-99m MDP that include extracellular fluid expansion, enhanced regional vascularity and permeability, and elevated tissue calcium concentration or presence of other metallic ions,¹³ calcium concentration might play the most important role for scintigraphic visualization of damaged muscles. Meroney et al., and Shen and Jennings reported data suggesting that at least a part of the abnormal calcium accumulation occurred in mitochondria of the injured cells in traumatized skeletal muscle and cardiac muscle injured by transient ischemia. Also, intramitochondrial calcifications were demonstrated in electron micrographs of cardiac muscles in two patients who died following vascular surgery.¹ Bone-imaging agents have a high affinity for these intracellular accumulations of calcium, accounting for the abnormal images observed in polymyositis.^{15,16}

Tc-99m MDP bone scintigraphy provides a valuable tool for not only early diagnosis, but also to localize and quantify muscular involvement in the disease. Furthermore it is useful in monitoring the therapeutic response.^{15,17,18} In our case, when bone scintigraphy with Tc-99m MDP was performed 10 days after the onset of muscle weakness and 8 days after increasing the cyclosporine dose, the value of CPK was decreased to 2,823 IU/l. Bone scintigraphy showed marked striped extraosseous accumulation in the legs and relatively faint uptake in the right upper arm, where he noticed pain and swelling approximately 10 days before the initial symptom of femoral muscle weakness started. We might have obtained the most positive findings, if bone scintigraphy had been performed when the CPK level was at its peak. However, faint uptake in the right upper arm was demonstrated even 3 weeks after the episode, even though the symptom of the right upper arm was mild and subsided within a few days. Bone scintigraphy with Tc-99m MDP seemed to be a very useful tool to detect occult muscle lesions.

As clinical application of non-myeloablative PBSCT is developed to treat non-malignant diseases as well as refractory hematological malignancies, the incidence of GVHD will increase. MR imaging is a useful tool to detect muscle injury, however, the area of examination is limited. Several authors demonstrated Ga-67 uptake in inflammatory muscle disease,^{19,20} and Buchpiguel et al. reported that both Tc-99m pyrophosphate and Ga-67 could be useful in the detection of the active phase of muscle disease.²¹ We expected Ga-67 accumulation in this case. However, Ga-67 scintigraphy was not informative even though the value of C-reactive protein was increased to 5.87 mg/dl at time of the examination. As contrast material of Gd-DTPA in MRI examination was

injected 48 hours after the administration of Ga-67, Gd-DTPA was not thought to have affected the distribution of Ga-67 in this case. Prednisone that had been administered to this patient from the middle of December might be a reason why Ga-67 did not accumulate in the muscles.

Bone scintigraphy should be carried out as the first choice in patients who are suspected of having myositis caused by chronic GVHD, in order to obtain accurate and objective evaluation of the distribution and severity of muscle injury even after the start of treatment.

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