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CASE REPORT

Magnetic Resonance Imaging for Chronic Graft-versus-host-disease–related Myositis and Fasciitis: a Rare Complication of Stem Cell Transplantation

CYY Kwong, JJK Ip, WWM Lam, MT Chau

Department of Radiology, Queen Mary Hospital, Pokfulam, Hong Kong

ABSTRACT

Chronic graft-versus-host disease is a cellular immune-mediated donor bone marrow versus patient rejection reaction, which is a major cause of morbidity and mortality following allogeneic bone marrow transplantation or stem cell transplantation. Chronic graft-versus-host-disease–related myositis and fasciitis, which have been described as rare complications in patients who develop chronic graft-versus-host disease after allogeneic bone marrow transplantation or stem cell transplantation, can severely impair a patient's quality of life. This report describes a patient with chronic graft-versus-host-disease–related myositis and fasciitis, and presented with progressive contracture. This report illustrates the imaging features and the role of radiology in the diagnostic process.

Key Words: *Bone marrow transplantation; Fasciitis; Graft vs host disease; Myositis; Stem cell transplantation*

中文摘要

慢性移植物抗宿主病相關性肌炎和筋膜炎的磁共振成像：一種罕見的幹細胞移植併發症

鄺彥頤、葉精勤、林慧文、周明德

慢性移植物抗宿主病是細胞免疫介導的骨髓移植宿主與病人之間的排斥反應，亦是同種異體骨髓移植或幹細胞移植致病和死亡的一個主要原因。慢性移植物抗宿主病相關性肌炎和筋膜炎被認為是病人進行異體骨髓移植或幹細胞移植後的罕見併發症，可嚴重損害患者的生活質素。本文報告一名患有慢性移植物抗宿主病相關性肌炎和筋膜炎的病例，臨床症狀為進行性關節攣縮。本文闡述了該病的影像學特徵及影像檢查在診斷過程中的作用。

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a cellular immune-mediated donor bone marrow versus patient rejection reaction, which may also lead to an autoimmune pathological process. cGVHD is a major cause of morbidity and mortality following allogeneic bone marrow transplantation (BMT) or stem cell transplantation (SCT). About 30 to 70% of BMT

Correspondence: *Dr Charlotte YY Kwong, Department of Radiology, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: (852) 2255 3284; Email: char.kwong@gmail.com*

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recipients who survive more than 100 days after BMT will develop cGVHD.[1] cGVHD-related myositis and fasciitis have been described as rare complications in patients who develop cGVHD after allogeneic BMT or SCT.[2] These conditions may be the sole manifestations of active GVHD, although patients typically have other organ involvement in addition to muscle.[3] cGVHD-related myositis and fasciitis present similarly as idiopathic myositis with proximal muscle weakness, myalgias or muscle pain, and increased creatinine phosphokinase (CPK) level.[4] Since the treatment response for myositis is fairly good, early diagnosis by magnetic resonance imaging (MRI) and prompt treatment are important to prevent persistent disability. We report on a patient with cGVHD-related myositis and fasciitis and presented with progressive contracture. The imaging features and the role of radiology in the diagnostic process are illustrated. To the authors' knowledge, this is the first local report of cGVHD-related myositis and fasciitis.

CASE REPORT

A 21-year-old man was referred to the Rheumatology Clinic, Queen Mary Hospital, Hong Kong, in August 2011 for investigation of decreased joint mobility and bilateral contracture of the elbows and knees. He had a history of precursor T-cell acute lymphocytic leukaemia and received matched unrelated donor haematopoietic stem cell transplantation (MUD-HSCT) from China in September 2010 at Queen Mary Hospital. He subsequently started cyclosporin A and mycophenolate mofetil.

The patient developed insidious onset of dry mouth, skin pigmentation, and skin tightening in March 2011, approximately 6 months after the MUD-HSCT. A clinical diagnosis of scleroderma-like cGVHD was made by the attending physician. Three months later, in June 2011, approximately 9 months after the MUD-HSCT, he also developed bilateral limited extension of the elbows and knees. Physical examination showed bilateral decreased range of motion of his elbows and knees with flexion contracture. There was also finger flexor muscle fibrosis with limited active flexion. The patient had to walk on tiptoe as his ankle dorsiflexion was limited to 10° to 20°.

Plain radiographs taken in August 2011 showed only flexion contracture and revealed no bony abnormality such as ankylosis. Muscle bulk was decreased (Figure 1).

The patient had no autoimmune markers. However, derangement of blood parameters were noted along with the development of musculocutaneous symptoms. In November 2011, his C-reactive protein increased to 267 mg/dl (reference range, <0.80 mg/dl), but was normalised in December 2011 (to <0.35 mg/dl). In December 2011, his erythrocyte sedimentation rate increased to 50 mm/h (reference range, 0-20 mm/h) and creatine kinase decreased to 28 U/L (reference range, 50-200 U/L).

MRI of both elbows and knees was performed using a 3-Tesla Signa machine (GE Healthcare, Little Chalfont, UK) in December 2011. The imaging protocol included

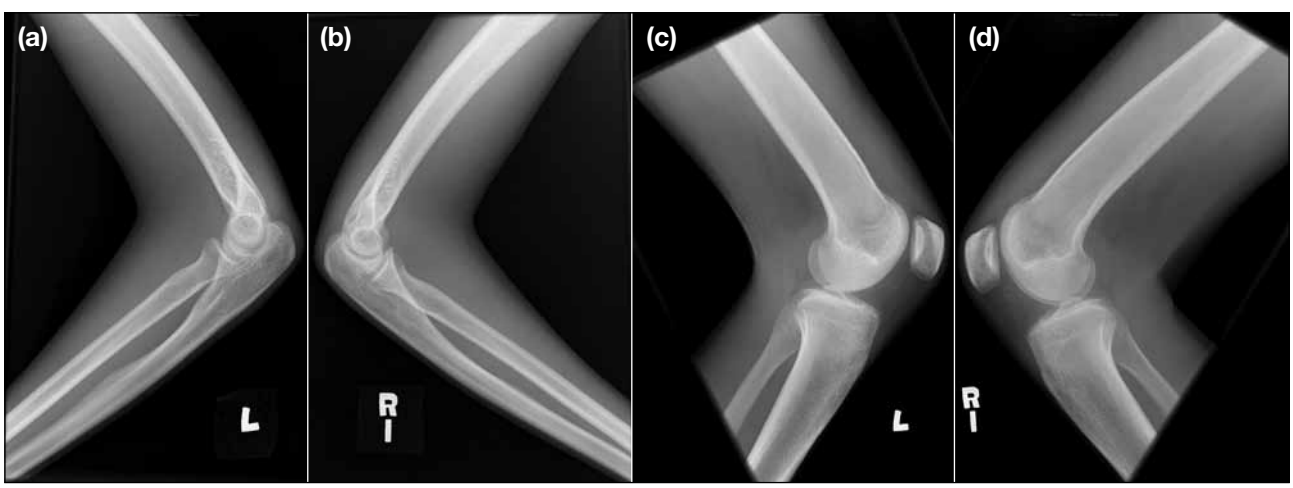

Figure 1. Bilateral flexion contractures are noted in both elbows and knees. Lateral radiographs of (a and b) bilateral elbows and (c and d) knees show symmetrical decreases in muscle bulk and reveal no bony abnormality.

bilateral T1-weighted, T2-weighted fat suppression, and proton density images of the elbows and knees in three orthogonal planes. The patient's elbows and knees were in fixed flexion contracture. Subtle hyperintensities were present within the flexor muscles in the fat-suppressed T2-weighted images of both elbows and knees with symmetrical involvement. The involved muscles included bilateral hamstrings, semi-tendinosus, semi-membranous and heads of gastrocnemius in the knees, and bilateral brachialis and common flexor compartments in the elbows. The features were in keeping with myositis (Figure 2). A thin rim of fluid was also observed along the fascial planes. These findings were suggestive of fasciitis (Figure 3). Gadolinium contrast was not given due to impaired renal function.

In view of the patient's history of haematopoietic SCT, a diagnosis of cGVHD-related myositis and fasciitis was suggested. According to the working group report of the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease, the diagnosis of cGVHD requires: distinction from acute GVHD; presence of at least one diagnostic clinical sign of cGVHD or presence of at least one distinctive manifestation confirmed by pertinent biopsy or other relevant tests; and exclusion of other possible diagnoses.[5] Sclerotic features of the skin and joint contracture of the musculoskeletal system are both diagnostic clinical signs. Myositis suggested by MRI would be a distinctive manifestation. Since these features are not classical presentations of acute GVHD, they presented more than 100 days after transplantation, and autoimmune markers were negative for this patient, the signs were commensurate with the new diagnostic guideline for cGVHD.

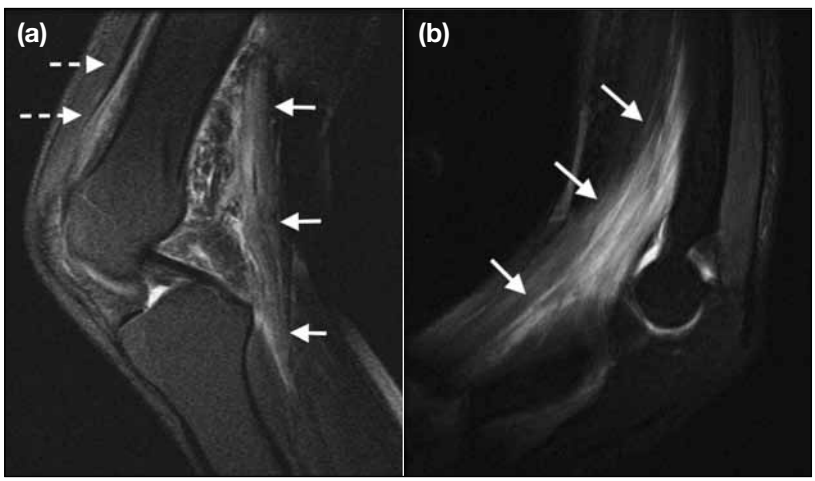

Figure 2. Fat-suppressed T2-weighted magnetic resonance imaging of both knees and elbows shows T2 hyperintensities within the flexor muscles with symmetrical involvement. (a) Abnormal T2 hyperintensities in the flexor compartment in the knees (white arrows), including bilateral hamstrings, semi-tendinosus, semi-membranous, and heads of gastrocnemius in the knees. Mild quadriceps thinning is also noted (broken arrows). (b) Involved muscles in the elbows are also in the flexor compartment, including the bilateral brachialis (white arrows).

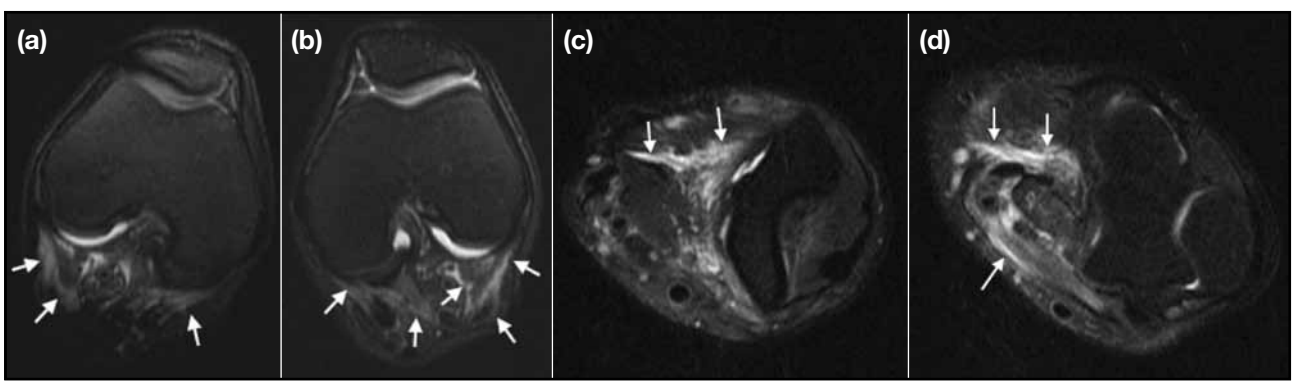

Figure 3. Fat-suppressed T2-weighted magnetic resonance imaging of the (a) right and (b) left knees and (c and d) left elbow in axial plane showing a thin rim of fluid along the fascia planes (white arrows) with fascia thickening in the knees and elbows. Symmetrical findings are noted in the right elbow (not shown).

Initially, en-bloc muscle biopsy was planned after discussion among the attending haematologists, rheumatologists, orthopaedic surgeons, and radiologists. However, the patient developed progressive shortness of breath and his exercise tolerance further decreased. Lung function test demonstrated restrictive lung function. Therefore, in view of the high operative risk and the overall clinical picture being compatible with cGVHD, the attending physician selected conservative management over muscle biopsy. The patient was cared for by a multidisciplinary team. His motor and pulmonary function remained static after adjustment of the immunosuppressive regimen. His musculocutaneous condition was followed up clinically and is pending reassessment by MRI.

DISCUSSION

The number of patients who undergo SCT from various stem cell sources increases every year. By the end of 2008, a total of 1708 transplant procedures had been performed, with 83% (n = 1417) being first-time transplants and the rest (17%, n = 291) being repeated transplants, mostly for patients who have relapsed.[6] cGVHD is still a major cause of morbidity and mortality after SCT, and is caused by an immunological reaction against antigens in the SCT recipient by the immune competent donor graft. cGVHD occurs in 30 to 70% of recipients who survive beyond 100 days following transplantation, and is dependent on the degree of human leukocyte antigen mismatch with the donor and the source of the stem cells. cGVHD is responsible for the death of 12 to 20% of graft recipients.[1,7-9]

The main target organs of cGVHD are the skin, eyes, mouth, liver, oesophagus, bowel, lung, and serosa, and the manifestations of cGVHD have features resembling autoimmune and other immunological disorders such as scleroderma, Sjögren's syndrome, keratoconjunctivitis, buccal mucositis, primary biliary cirrhosis, wasting syndrome, pulmonary insufficiency, bronchiolitis obliterans (BO), immune cytopenias, and chronic immune deficiency.[9,10] Patients with cGVHD have decreased performance status, impaired quality of life (QOL), and increased risk of mortality.

Muscle-related complications, fasciitis and myositis, are rare cGVHD manifestations, and their clinical features resemble autoimmune eosinophilic fasciitis and idiopathic polymyositis.[11-13] Muscle cramps are a common complaint, although the pathophysiology is not understood. Myositis, with tender muscles and elevated muscle enzymes, may start as a proximal myopathy, but it is rare. The common clinical symptoms of myositis are moderate-to-severe proximal muscle weakness, myalgia, fever, contractures, and skin indurations occurring over the areas of muscle involvement. Most patients present with elevated CPK enzymes.

The new cGVHD diagnostic guidelines proposed fasciitis as diagnostic, and myositis as a distinctive manifestation of cGVHD.[5] Patients with fasciitis develop skin swelling, and thereafter the skin becomes taut, bound down to the underlying tissue, and irregularly thickened, and demonstrates multiple small depressed areas, giving rise to the 'peau d'orange' appearance. Contractures and joint stiffness are also observed. Muscle biopsy in cGVHD myositis usually demonstrates non-specific changes such as degeneration, necrosis, and regeneration of muscle fibres and infiltrates of inflammatory cells. En-bloc biopsy, with sampling of both muscle and fascia, can give a more definite diagnosis. The pathological findings of fasciitis include lymphocytic infiltration in oedematous fascia and a subsequent increase of collagen fibres. The infiltration is diffuse and often extends from the fascia into the interstitium of the muscles.

MRI is useful for SCT recipients who present with weakness, decreased range of movement, contracture, or other symptoms and signs suggestive of cGVHD-related myositis and fasciitis, and it can effectively confirm the affected muscles or muscle groups. MRI can be helpful for diagnosis and management by determining the depth of soft tissue involvement, particularly within fasciae and muscles, which is related to the severity of the disease. MRI can determine the best site for biopsy and also monitor the therapeutic response.[14] Abnormal T2 prolongation of muscle fibres is a consistent MRI finding of myositis. In a retrospective study of 16 patients by Horger et al,[14] MRI showed musculocutaneous abnormalities reflecting different degrees of inflammation and collagen involvement of the skin, subcutaneous fat tissue, muscle fasciae, subfascial muscular septae, and findings compatible with myositis.[14-16] The most frequently involved muscle fasciae comprised those of the vastus lateralis muscle, biceps femoris muscle, gastrocnemius medialis muscle, serratus anterior muscle, and latissimus dorsi muscle.[14,16] Increased signal of involved tissues on short TI inversion recovery images and fat-saturated post-gadolinium T1-weighted images represent the most frequent MRI signal abnormalities.[16] Fatty infiltration

and wasting are also seen in the affected muscle bulk in chronic disease. Increased fluid signal along fascia planes and fascia enhancement, however, are features of fasciitis. Although different in degree and extent, the thickness and hyperintensity of the involved fascia and infiltration of the subcutaneous septa and muscles are well suited for visualisation with MRI.[16] In general, there is good concordance between clinical and MRI findings.

It is not mandatory to make a diagnosis of fasciitis or myositis; however, these two diagnoses carry different prognoses. Almost all patients with fasciitis or myositis have complications of other manifestations of cGVHD, but there are different manifestations among the involved organs of patients with fasciitis and myositis. In patients with fasciitis, lung disease (such as BO) and Sjögren's syndrome are more frequent than oral and skin involvement. Since pulmonary complications can result in severe respiratory failure, the fact that patients with fasciitis tend to have pulmonary complications more frequently than patients with myositis may be related to their poor prognosis. It is rare for myositis patients to develop respiratory failure, and therefore, they usually have better prognosis than fasciitis patients.

Due to similarities in their clinical manifestations, autoimmune eosinophilic fasciitis and idiopathic polymyositis are both differential diagnoses of cGVHD-related myositis and fasciitis. In eosinophilic fasciitis, MRI reveals characteristic findings, including thickening, signal abnormalities, and contrast enhancement of the superficial and, to a lesser extent, deep muscle fasciae.[17] The preferential involvement of fasciae and superficial structures before involvement of muscles in eosinophilic fasciitis aids differentiation from cGVHD-related myositis and fasciitis. Such preferential involvement is not observed in cGVHD-related myositis and fasciitis. However, MRI findings in idiopathic polymyositis are similar to those in cGVHD-related myositis and fasciitis and the diagnosis may rely on histopathology and clinical history. MRI can yield accurate information about the extent of muscle involvement and guide muscle biopsy.

Both fasciitis and myositis caused by cGVHD can result in disabilities that reduce a patient's QOL. Since the treatment response for myositis is good, early diagnosis by MRI and biopsy (including fascia and muscle), and prompt treatment are important to prevent impairment of QOL with persistent disability. Furthermore, once muscle atrophy occurs, it has been suggested that the muscle may not recover despite increased immune suppression and control of the inflammatory process.[14,16] For this reason, a high clinical index of suspicion is needed for accurate diagnosis so that early diagnosis and prompt treatment for fasciitis and myositis can be offered to prevent or curb further progression of complications. Early MRI should be arranged for SCT or BMT patients who present with muscle cramps, myalgia, and weakness, and other musculoskeletal symptoms to diagnose the condition early and guide biopsy.

CONCLUSION

The muscle-related complications of fasciitis and myositis, caused by cGVHD after SCT are rare, but at times will severely impair a patient's QOL. MRI is useful for establishing the diagnosis, guiding the choice of biopsy site, and assessing treatment response. As the treatment for myositis is fairly effective, early diagnosis by MRI and biopsy, which includes fascia and muscle, and prompt treatment are crucial to prevent the impairment of QOL with persistent disability.

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