Features and Role of Magnetic Resonance (MR) Imaging of Chronic Graft-Versus-Host Disease (cGVHD)-Related Myositis and Fasciitis - A Rare Complication of Stem Cell Transplant (SCT) Recipients

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Learning Objectives

Chronic graft-versus-host disease (cGVHD) is a cellular immune-mediated donor bone marrow versus patient rejection reaction. It is a major cause of morbidity and mortality following allogeneic bone marrow transplantation (BMT) or stem cell transplantation (SCT). Chronic graft-versus-host disease-related myositis and fasciitis, which have been described as rare complications in patients who develop cGVHD after allogeneic BMT or SCT, can severely impair the patients' quality of life (QOL). In this article, we would like to expound a case of chronic graft-versus-host disease-related myositis and fasciitis, presented with progressive contracture; and illustrate the imaging features and the role of radiologist in the diagnostic process.
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 pathologic process. It is a major cause of morbidity and mortality following allogeneic bone marrow transplantation (BMT) or stem cell transplantation (SCT). About 30 - 70% of BMT recipients who survive more than 100 days after BMT will develop cGVHD.\(^1\) Chronic graft-versus-host disease-related myositis and fasciitis have been described as rare complications in patients who develop cGVHD after allogeneic BMT or SCT.\(^2\) It may be the sole manifestation of active GVHD although patients typically have other organ involvement in addition to muscle.\(^3\) Chronic graft-versus-host disease-related myositis and fasciitis present similarly as idiopathic myositis with proximal muscle weakness, myalgias or muscle pain, and an increased creatinine phosphokinase (CPK) level.\(^4\) Since the treatment response for myositis is fairly good, an early diagnosis by magnetic resonance imaging (MRI) and prompt treatment are important to prevent persistent disability. In this article, we would like to expound a case of chronic graft-versus-host disease-related myositis and fasciitis, presented with progressive contracture; and illustrate the imaging features and the role of radiologist in the diagnostic process.
Imaging Findings OR Procedure Details

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

The patient developed insidious onset of dry mouth, skin pigmentation and skin tightening in March 2011, when it is approximately 6 months after his MUD-HSCT. Clinical diagnosis of scleroderma-like chronic graft-versus-host disease (cGVHD) was made by attending physician. Three months later in June 2011, when it is approximately 9 months after his MUD-HSCT, he also developed limited extension of bilateral elbow and knee. Physical examination showed decrease in range of motion of bilateral elbows and knees with flexion contracture. There was also finger flexor muscle fibrosis with limited active flexion. The patient had to walk in tiptoeing since ankle dorsiflexion was limited to 10 - 20 degrees.

Autoimmune markers were negative in our patient. However, derangement of blood parameters were also noted along with his development of musculocutaneous symptoms. In December 2011, erythrocyte sedimentation rate (ESR) increased to 50 mm/hr (Normal range 0-10 mm/hr). C-reactive protein increased to 26.7 mg/dl in November 2011 but was later normalized in December 2011 (Normal range <0.76). Creatinine kinase level was deceased to 28 U/L in December 2011 (normal range 65-355U/L).

Plain radiographs taken in August 2011 showed only flexion contracture and revealed no bony abnormality, such as ankylosis. Muscles bulk was decreased. (Fig. 1,2,3,4)

Magnetic resonance imaging (MRI) of both elbows and knees was performed using a 3-Tesla General Electric Signa machine in December 2011. The imaging protocol included T1W, T2W FAT SAT and PD images of bilateral elbows and knees in three orthogonal planes. The patient's bilateral elbows and knees were in fixed flexion contracture. Subtle hyperintensities were present within the flexor muscles in the fat-suppressed T2 weighted images in bilateral elbows and knees with symmetrical involvement. Involved muscles included bilateral hamstrings, semi-tendinosus, semi-membranous and heads of gastrocnemius in the knees; and also bilateral brachialis and common flexor compartments in the elbows. Features were in keeping with myositis. (Fig 5,6,7,8) Thin film of fluid was also observed along fascial planes. Findings were suggestive of fasciitis. (Fig 9,10,11,12) Gadolinium contrast was not given due to impaired renal function.
In view of history of haematopoietic stem cell transplantation, diagnosis of chronic graft-versus-host disease (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 chronic GVHD requires: distinction from acute GVHD; presence of at least 1 diagnostic clinical sign of chronic GVHD or presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant tests; and exclusion of other possible diagnoses. 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 presentation of acute GVHD and they present >100 days after transplantation and autoimmune markers are negative for our patient, he fits into the new diagnostic guideline as having cGVHD.

Initially, an en-bloc muscle biopsy was planned after the discussion among attending haematologists, rheumatologists, orthopaedics surgeons and radiologists. However, the patient developed progressive shortness of breath and further decreased exercise tolerance. Lung function test demonstrated restrictive lung function. Therefore, in view of high operative risk and the overall clinical picture was also compatible with cGVHD, the attending physician opted for conservative management over muscle biopsy. The patient was under multidisciplinary care. His motor and pulmonary function remained static after the adjustment of immune suppressant regimen. His musculoskeletal conditions were followed-up clinically and pending reassessment MRI.
Fig. 1: Flexion contractures were noted in bilateral elbows and knees clinically. Lateral radiographs of bilateral elbows show symmetrical decrease in muscle bulk and reveal no bony abnormality.

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**Fig. 2:** Flexion contractures were noted in bilateral elbows and knees clinically. Lateral radiographs of bilateral elbows show symmetrical decrease in muscle bulk and reveal no bony abnormality.

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Fig. 3: Flexion contractures were noted in bilateral elbows and knees clinically. Lateral radiographs of bilateral knees show symmetrical decrease in muscle bulk and reveal no bony abnormality.

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Fig. 4: Flexion contractures were noted in bilateral elbows and knees clinically. Lateral radiographs of bilateral knees show symmetrical decrease in muscle bulk and reveal no bony abnormality.

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**Fig. 5:** Fat-suppressed T2 weighted magnetic resonance imaging (MRI) of both knees and elbows shows T2 hyperintensities within the flexor muscles with symmetrical involvement. Abnormal T2 hyperintensities are observed in the flexor compartment in the knees, including bilateral hamstrings, semi-tendinous, semi-membranous and heads of gastrocnemius in the knees.

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Fig. 11: Fat-suppressed T2 weighted magnetic resonance imaging (MRI) also shows thin film of fluid along fascial planes (white arrows) in the elbows. Findings are suggestive of fasciitis.

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**Fig. 10:** Fat-suppressed T2 weighted magnetic resonance imaging (MRI) also shows thin film of fluid along fascial planes (white arrows) in the knees. Findings are suggestive of fasciitis.

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Fig. 9: Fat-suppressed T2 weighted magnetic resonance imaging (MRI) also shows thin film of fluid along fascial planes (white arrows) in the knees. Findings are suggestive of fasciitis.

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Fig. 8: Fat-suppressed T2 weighted magnetic resonance imaging (MRI) of both knees and elbows shows T2 hyperintensities within the flexor muscles with symmetrical involvement. Abnormal T2 hyperintensities are also observed in the flexor compartment of the elbows, including bilateral brachialis (white arrows). Features are in keeping with myositis.

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Fig. 7: Fat-suppressed T2 weighted magnetic resonance imaging (MRI) of both knees and elbows shows T2 hyperintensities within the flexor muscles with symmetrical involvement. Abnormal T2 hyperintensities are also observed in the flexor compartment of the elbows, including bilateral brachialis (white arrows). Features are in keeping with myositis.

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Fig. 6: Fat-suppressed T2 weighted magnetic resonance imaging (MRI) of both knees and elbows shows T2 hyperintensities within the flexor muscles with symmetrical involvement. Abnormal T2 hyperintensities are observed in the flexor compartment in the knees (white arrows), including bilateral hamstrings, semi-tendinous, semi-membranous and heads of gastrocnemius in the knees. Mild quadriceps thinning is also noted (broken-line arrows).

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**Fig. 12:** Fat-suppressed T2 weighted magnetic resonance imaging (MRI) also shows thin film of fluid along fascial planes (white arrows) in the elbows. Findings are suggestive of fasciitis.

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Conclusion

The number of patients, who undergo stem cell transplantation (SCT) from various stem cell sources, increases every year. By the end of 2008, a total of 1708 transplant procedures have been performed with 83% (1417) being first-time transplants and the rest (17%, 291) are repeated transplants mostly for relapsed patients.\textsuperscript{6} Chronic graft-versus-host disease (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. It occurs in 30 - 70% of recipients who survived beyond 100 days following transplantation, and it is dependent on the degree of human leukocyte antigen (HLA) mismatch with the donor and the source of the stem cells. It is also responsible for the death of 12% to 20% of graft recipients.\textsuperscript{1, 7-9}

The main target organs of chronic GVHD are skin, eyes, mouth, liver, esophagus, bowel, lung and serosa; and the manifestations of cGVHD have features resembling autoimmune and other immunological disorders such as scleroderma, Sjogren's syndrome, keratoconjunctivitis, buccomucositis, primary biliary cirrhosis, wasting syndrome, pulmonary insufficiency, bronchiolitis obliterans (BO), immune cytopenias and chronic immune deficiency.\textsuperscript{9,10} Patients with cGVHD have decreased performance status, impaired quality of life (QOL) and an 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.\textsuperscript{11-14} 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 occur over the areas of muscle involvement. The majority of patients present with elevated creatinine phosphokinase enzymes.

The new cGVHD diagnostic guidelines proposed fasciitis as diagnostic, and myositis as a distinctive sign and symptom of cGVHD manifestation.\textsuperscript{5} Patients with fasciitis develop skin swelling, and thereafter the skin becomes taut, bound down to the underlying tissue, and irregularly thickened; and thereafter demonstrating multiple small depressed areas, giving rise to '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 fibers and infiltrates of inflammatory cells. En-bloc biopsy, with sampling of both muscle and fascia, can give more definite diagnosis. The pathological findings of fasciitis include lymphocytic
infiltration in edematous fascia and a subsequent increase of collagen fibers. The infiltration is diffuse and it often extends from the fascia into the interstitium of the muscles.

Magnetic resonance imaging (MRI) is useful in SCT recipient presented with weakness, decreased range of movement, contracture or other symptoms and signs suggestive of chronic graft-versus-host disease-related myositis and fasciitis; and it can effectively confirm the affected muscles or muscle groups. MRI can be helpful for diagnosis and management in 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 therapeutic response. Abnormal T2 prolongation in muscle fibers is a constant MRI finding of myositis. In a retrospective study of 16 patients by Horger et al., MRI showed musculocutaneous abnormalities reflecting different degrees of inflammation and collagen tissue involvement of the skin, subcutaneous fat tissue, muscle fasciae, subfascial muscular septae, or findings compatible with myositis. 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. Increased signal of involved tissues on STIR-images and fat-saturated post-gadolinium T1-weighted images represented the most frequent MR-signal abnormalities. Fatty infiltration and wasting are also seen in the affected muscle bulk in chronic cases. Increased fluid signal along fascial planes and fascial enhancement, on the other hand, are features of fasciitis. Although different in degree and extent, the thickness and hyperintensity of the involved fascia and the infiltration of subcutaneous septa and muscles are well suited for visualization with MRI. In general, there was good concordance between clinical and MRI findings.

It is not mandatory for making a diagnosis of fasciitis or myositis; however, these two diagnoses carry different prognoses. The cases of almost all patients with fasciitis or myositis were complicated with other manifestations of chronic GVHD, but there were different tendencies regarding the involved organs among the patients with fasciitis and myositis. In patients with fasciitis, lung disease (BO) and sicca syndrome were more frequent than oral and skin involvement. Pulmonary complications will affect the patient's prognosis, because they can cause severe respiratory failure. Hence, the fact that patients with fasciitis tend to have pulmonary complications 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 the 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. The preferential involvement of fasciae and superficial structures before involvement of muscles in eosinophilic fasciitis aids differentiation from cGVHD-related myositis and fasciitis. On the other hand, MRI findings in idiopathic polymyositis are similar to those in cGVHD-related myositis and fasciitis; diagnosis may rely on histopathological diagnosis and clinical history. MRI can yield accurate information about the extent of muscle involvement and guide muscle biopsy.

Both fasciitis and myositis caused by chronic GVHD can result in disabilities that reduce the patient's QOL. Since the treatment response for myositis is good, an early diagnosis by MRI; biopsy, which includes fascia and muscle; and prompt treatment are important to prevent impairment of the patient's 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. 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 the complications. An early MRI should be arranged in SCT or BMT patients, who present with muscle cramps, myalgia, and weakness etc. musculoskeletal symptoms, to diagnose the condition early and guide biopsy.

The muscle-related complications of fasciitis and myositis, caused by chronic graft-versus-host disease (cGVHD) after stem cell transplant (SCT) are rare, but at times will severely impair a patient's quality of life (QOL). MRI is useful for establishing the diagnosis, guiding the choice of biopsy site, and assessing treatment response. As the treatment response for myositis is fairly effective, an early diagnosis by magnetic resonance imaging (MRI) and biopsy, which includes fascia and muscle; and prompt treatment are important and crucial to prevent the impairment of the patient's QOL with persistent disability.
References
