Case report

Macrophagic myofascitis associated with rheumatoid arthritis

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Running title: macrophagic myofascitis in Japanese RA patients

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Abstract

Herein, we report the association of a rare muscle disease, macrophagic myofascitis, with Japanese rheumatoid arthritis (RA). Our case was not related to aluminum containing vaccinations and the respective etiologies are unknown. The possible link needs to be discussed.

Introduction

Macrophagic myofascitis (MMF) is known to be associated with vaccinations containing aluminum as an adjuvant.[1)] Herein, we describe a case of MMF unrelated to vaccination that presented as focal muscle tenderness in a Japanese patient with rheumatoid arthritis (RA). Magnetic resonance imaging showed evidence of unilateral myofascitis involving the anterior tibialis muscles. Muscle biopsy showed a pathological pattern typical of MMF. This observation suggests that the appearance of focal myalgia during the course of rheumatic diseases must arouse the suspicion of an association of macrophagic myofascitis, independent of the history of vaccination.

Case Report

A 53 year-old Japanese woman was admitted to our hospital due to stiffness and myalgia of the lower extremities on January 28, 2008. She had been diagnosed with rheumatoid arthritis and had been treated with methotrexate for 2 years. Three months prior to admission, she had complained of myalgia of the left lower extremities and gait disturbance as a consequence of the pain of these lesions. She had no history of immunization containing aluminum during the past 20 years.

On physical examination, her blood pressure was 120/72 mm Hg, pulse 82/min, and body temperature 36.6°C. Focal tenderness in the left lower limbs was noted with mild muscle weakness. Laboratory examination, including blood counts, biochemistry, thyroid function and angiotensin-converting enzyme (ACE) were normal. Mild elevations of CK (278 IU/ml) and aldolase (9.1 IU/ml) were noted. Serological tests for anti-neutrophil cytoplasmic autoantibodies (ANCA), cryoglobulin, Epstein-Barr virus, Parvovirus, hepatitis B and C virus were all negative. Cytomegalovirus antigen was not detected. Both the sedimentation rate (ESR) and the serum C-reactive protein (CRP) were slightly elevated (ESR 27mn/hr, CRP 1.11mg/dl). Anti-nuclear antibodies (ANA) were positive with low titers (× 40, speckled pattern) and anti-cyclic citrullinated

peptide antibodies were also detected (54.1 IU/ml; normal range <4.5IU/ml). Magnetic resonance imaging (MRI) of the left lower limbs showed hyper intense signals in the fascia of the left anterior tibialis muscle suggesting fascial inflammation (Figure 1). Muscle biopsy obtained from the anterior tibialis muscles revealed the massive infiltration of macrophages in the perifascial regions (Figure 2A). There was neither granuloma nor vasculitis. The macrophages were CD68-positive (Figure 2B) and some macrophages exhibited cytoplasm filled with periodic acid Schiff (PAS)-positive material (Figure 2C). The findings typical of cytophagic histiocytic panniculitis were not observed. Muscle necrosis in association with lymphocytic infiltration, typical finding for myositis was also not observed. The patient was diagnosed as having MMF.

The elevated levels of CK and aldolase were normalized by a moderate dose of corticosteroid (prednisolone 20mg/day), however, her symptoms were not improved. Therefore, we added tacrolimus in addition to the corticosteroid treatments. Treatment with tacrolimus (2.0mg/day) led to the disappearance of myalgia and stabilization of the muscle weakness.

Discussion

Macrophagic myofascitis is an unusual inflammatory myopathy, which has almost exclusively been reported in French adults with diffuse arthromyalgia.[1)] Diagnosis is based on muscle biopsy that usually shows specific histological abnormalities characterized by dense infiltration of $CD68^+$ macrophages with basophilic periodic acid-schiff (PAS)-positive content.[1)] We report a Japanese patient with MMF that was accompanied by RA, independent of vaccination. The clinical symptoms, affecting the lower limbs, and pathological findings were quite typical of MMF in the presence of remarkable myofascial involvement. Laboratory tests only showed slight elevations of muscle enzyme levels.

The role of vaccines containing aluminum hydroxide in the pathogenesis of MMF has been suggested.[2)] However, there is a discrepancy between the wide usage of aluminum hydroxide-containing vaccines and the very limited numbers of reported cases of MMF. Furthermore, systemic symptoms are observed despite the fact that histological abnormalities are present only at the site of vaccination. This case report suggests that additional factors, other than vaccination, may influence the occurrence of MMF. Many patients with MMF exhibit preexisting autoimmune diseases, including thyroiditis, systemic lupus erythematosus, Sjögren's syndrome and RA.[3)] The

association of MMF with autoimmune diseases suggests that autoimmune mechanisms might play a critical role in its pathogenesis. Chronic immune stimulation, which results from persistence of aluminum hydroxide, has been proposed as a possible cause of MMF. [4] While a chance association between MMF and RA cannot be ruled out, RA-related altered immunity, such as inflammatory cytokine regulation, may contribute to the occurrence of MMF. The direct connection between MMF and RA remains unclear. However, one interpretation of the occurrence of both MMF and RA in our patient suggests that immune activation contributed to the macrophage perifascicular infiltration and subsequent fascicular inflammation.

Some efficacies have been reported for a variety of treatments against MMF, including antibiotics, glucocorticoids and immunosuppressants. [1, 5, 6] Tacrolimus is an immunosuppressant that is widely used in transplantation and rheumatoid arthritis. [7] The primary immunosuppressive effect of tacrolimus is suppression of activated T cells via calcineurin inhibition, however, actions against monocytes have also been demonstrated. [8] Interestingly, Ida *et al.* reported the impressive effect of tacrolimus in TNF receptor-associated periodic syndrome (TRAPs), which is characterized by monocytic fasciitis due to the uncontrolled macrophage activation. [9] Further clinical studies are required to evaluate the efficacy of newer immunosuppressive agents,

including tacrolimus, for the treatment of resistant cases of MMF.

In summary, the findings of the present case suggest that MMF is rarely observed in the Japanese population, independent of vaccination. It is likely that MMF remains under-diagnosed and clinicians should consider MMF in focal myalgia with elevated CK during the course of rheumatic diseases, independent of the history of vaccination.

References

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Figure Legends

Figure 1 STIR axial magnetic resonance imaging demonstrating a high intensity signal in the fascia of the left anterior tibialis muscle.

Figure 2: Findings of lt anterior tibialis muscle biopsy

A: Massive perifascicular infiltration of large macrophages (Hematoxylin-eosin; original magnification × 100)

B: $CD68^+$ immunoreactivity showing a large predominance of macrophages. (immunoperoxidase procedure; original magnification × 400)

C: Focal perifascicular accumulation of macrophages filled with PAS-positive materials. (periodic acid Schiff; original magnification × 400).

Figure 1

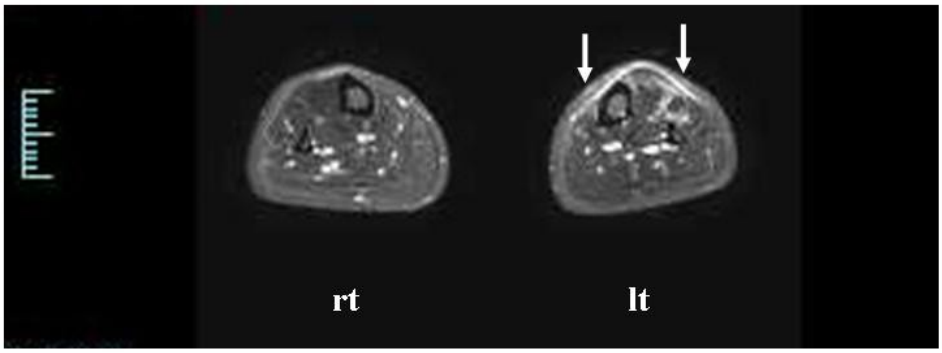

Figure 2A

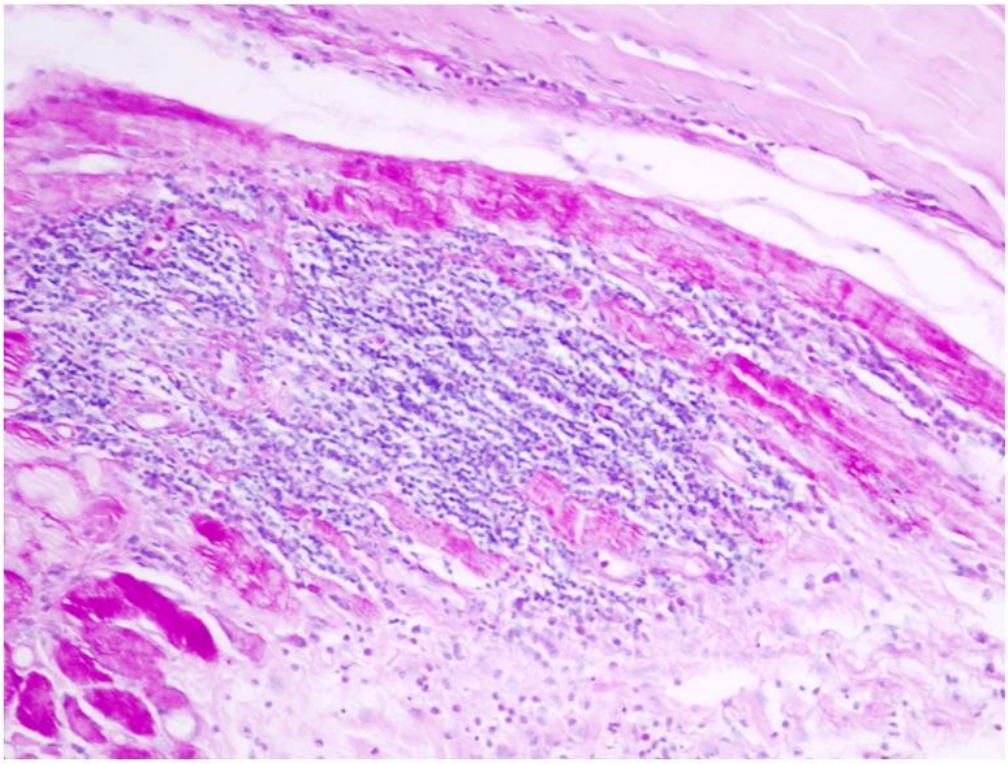

Figure 2B

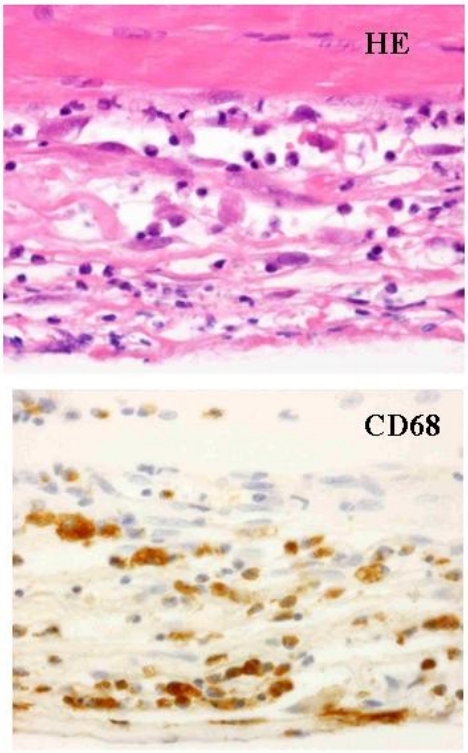

Figure 2C