INTERNAL MEDICINE

□ CASE REPORT □

Anti-citrullinated Protein Antibody-positive Rheumatoid Arthritis Associated with RS3PE Syndrome-like Symptoms and an Elevated Serum Vascular Endothelial Growth Factor Level in a Patient with Myasthenia Gravis

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Abstract

A 73-year-old man with a history of myasthenia gravis (MG) was diagnosed with rheumatoid arthritis (RA) based on a history of polyarthritis and positivity for anti-citrullinated protein antibodies (ACPA). He presented with a high level of serum vascular endothelial growth factor (VEGF) and RS3PE syndrome-like pitting edema in the extremities, which improved following treatment with low-dose prednisolone. This is an interesting case of ACPA-positive RA associated with RS3PE syndrome-like pitting edema and a high VEGF level.

Key words: myasthenia gravis, rheumatoid arthritis, RS3PE syndrome, vascular endothelial growth factor

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Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, first reported by McCarty et al. (1), is characterized by symmetrical polysynovitis of acute onset with pitting edema in the extremities. Although RS3PE syndrome may exist as a paraneoplastic condition and be accompanied by various autoimmune diseases, there are currently no reports of RS3PE syndrome or rheumatoid arthritis (RA) with RS3PE syndrome-like symptoms associated with myasthenia gravis (MG).

As a general rule, negativity for serum markers of RA, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), with the exclusion of other diseases manifesting with arthralgia or myalgia, such as RA and polymyalgia rheumatica, is necessary for a diagnosis of RS3PE syndrome. However, in a number of cases, it is difficult to distinguish between RS3PE syndrome and other rheumatic diseases based on physical findings and X-ray features. Serum vascular endothelial growth factor (VEGF) is a potential marker of RS3PE syndrome (2).

In this study, we describe a 73-year-old man with a history of MG accompanied by RA with RS3PE syndrome-like pitting edema of the hands and feet and an elevated serum VEGF level.

Case Report

A 73-year-old man who had never smoked cigarettes was admitted to our department with polyarthralgia and pitting edema in his extremities in late March 2011. He had a history of MG (Myasthenia Gravis Foundation of America classification class IIa) since 65 years of age and had been

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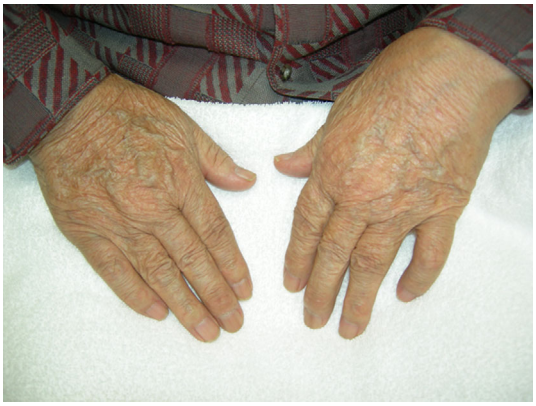

Figure 1. Physical examination of the patient performed on admission showing swelling of both hands and wrists.

treated with steroid pulse therapy and oral prednisolone (PSL). His myasthenic symptoms had been relieved with PSL and occasional pyridostigmine for eight years. However, he developed arthralgia of the right wrist under the administration of 12.5 mg of PSL every other day in February 2011, which worsened to systemic arthritis one month later. A physical examination performed on admission showed pitting edema, with tenderness in the distal portions of all extremities and tenderness and swelling of the wrist and finger joints (Fig. 1). No evidence of specific neuromuscular symptoms, except for mild blepharoptosis of the right eye, was found. The patient's blood pressure was 119/72 mmHg, his heart rate was 72 beats per minute and his body temperature was 36.5℃. The results of laboratory tests performed on admission were as follows: white blood cell count, 10,900/μL; hemoglobin, 11.4 g/dL; platelet count, 316,000/μL; C-reactive protein (CRP), 4.65 mg/dL; erythrocyte sedimentation rate, 62 mm/h; blood urea nitrogen, 16 mg/dL; serum creatinine, 0.83 mg/dL; Na, 143 mEq/L; K, 3.3 mEq/L; Cl, 103 mEq/L; total protein, 6.3 g/dL; albumin, 2.9 g/dL; aspartate aminotransferase, 11 IU/L; alanine aminotransferase, 7 IU/L; alkaline phosphatase, 190 IU/L; and γ-glutamyl transpeptidase, 16 IU/L. Anti-acetylcholine receptor antibodies were positive (18.2 nmol/L), RF was negative (11.6 U/mL), ACPA were positive (226.8 U/mL), anti-SS-A antibodies were negative (0.3 U/mL), the matrix metaprotease-3 level was high (936.8 ng/mL) and the VEGF level was significantly elevated (2,007 pg/mL). No thymomas or other tumorous lesions were found on computed tomography or digestive tract fiberscopy. A hand X-ray revealed only narrowing of the space of the proximal interphalangeal joint of the fourth digit of the left hand. Hand ultrasound (US) revealed a power Doppler signal compatible with tenosynovitis and subcutaneous edema (Fig. 2). Hand magnetic resonance imaging (MRI) disclosed severe synovitis of the right wrist joint with mild synovitis of the left wrist joint and bilateral III-V metacarpal joints. Subcutaneous swelling over the dorsum of the right hand and extensor tenosynovitis of the right II-V fingers was also found (Fig. 3A). No bone erosion was detected on the above imaging procedures.

Based on the fact that the patient met the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA (3, 4), and it is necessary to rule out other connective tissue diseases, including RA, in order to make a diagnosis of RS3PE syndrome, we diagnosed him with RA. However, in addition, we speculated that an RS3PE syndrome-like pathomechanism existed in this case due to the patient's pitting edema, polyarthralgia and high serum VEGF level.

We initiated treatment with 20 mg/day of oral PSL. Soon after the start of PSL therapy, the edema in the extremities dramatically improved and the CRP level normalized, although the polyarthralgia persisted. We therefore began the weekly administration of methotrexate, with a first dose of 4 mg and subsequent doses of 6 mg. MRI revealed significant improvements in the tenosynovitis and subcutaneous edema (Fig. 3B), and the dose of PSL was gradually reduced without relapse.

Discussion

Approximately 4% of patients with MG also exhibit RA, based on a study by Tellez-Zenteno et al., who analyzed 132 patients with MG and found five patients with RA (5). However, there are no reports of RS3PE-like symptoms in MG patients. Therefore, the association between RS3PE syndrome and MG remains obscure. In the present case, the fact that the patient's neuromuscular symptoms of MG were relieved while RA and edema developed suggests that it is unlikely that the RA with RS3PE syndrome-like symptoms was caused by the MG.

The most interesting feature of this case is that the RA was complicated by RS3PE syndrome-like symptoms. Remitting swelling with pitting edema is observed in patients with various rheumatic diseases, including Sjögren's syndrome, polymyositis/dermatomyositis, systemic sclerosis and mixed connective tissue disease (6). There is a debate about whether RS3PE syndrome is a subset of RA or a separate syndrome. Pitting edema of different degrees may be present in patients with late-onset RA. Yao concluded that RS3PE is a distinct entity rather than a subset of RA because RS3PE syndrome always presents with pitting edema, negative RF, the absence of bony erosion, an excellent therapeutic response to small doses of glucocorticoids and a lack of the human leukocyte antigen (HLA)-DRB1 genotype that is present in the setting of both early- and late-onset RA (7). The physical characteristics of the current case were compatible with those of RS3PE syndrome. However, anti-CCP antibodies were positive. Anti-CCP antibodies may be positive in smokers, as well as patients with RA (8). However, the present patient had never smoked cigarettes. Therefore, the positivity for anti-CCP antibodies did not appear to be a false-positive result. The fact that the patient developed polyarteritis and pitting edema in the extremities under the administration of PSL (12.5 mg every other day) also supports a diagnosis of RA, rather than RS3PE syndrome,

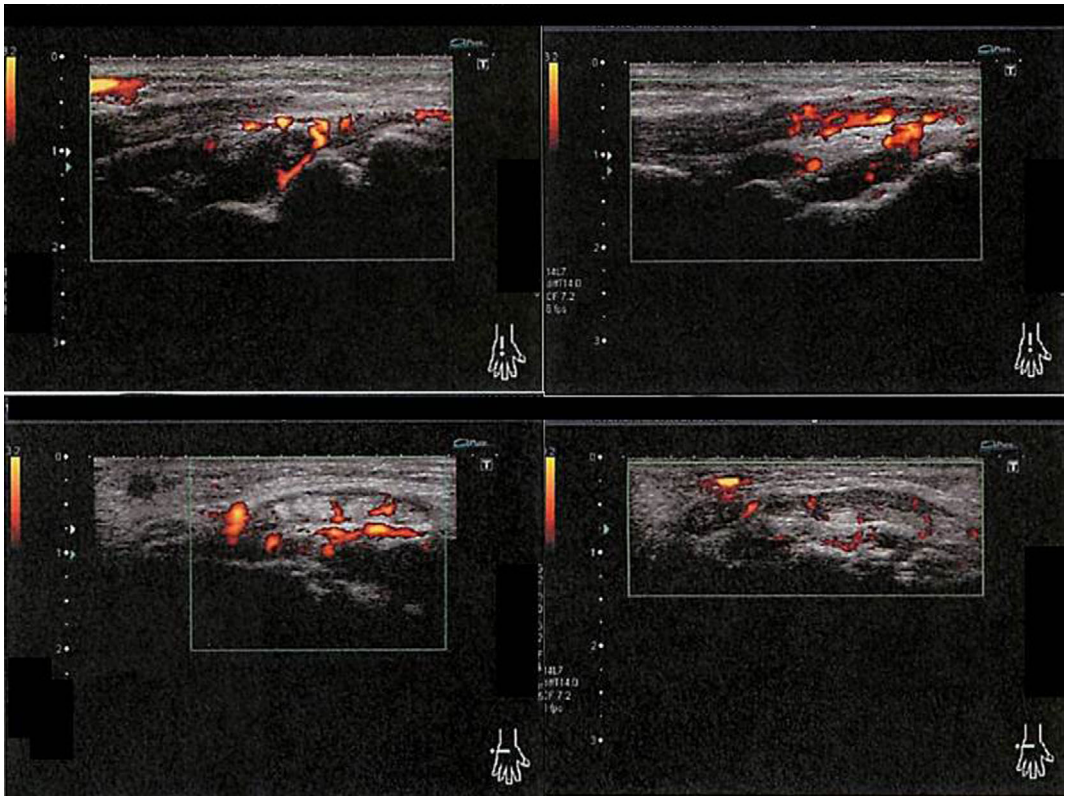

Figure 2. **Hand ultrasound examination performed on admission showing a power Doppler signal compatible with tenosynovitis and subcutaneous edema of the right wrist joint.**

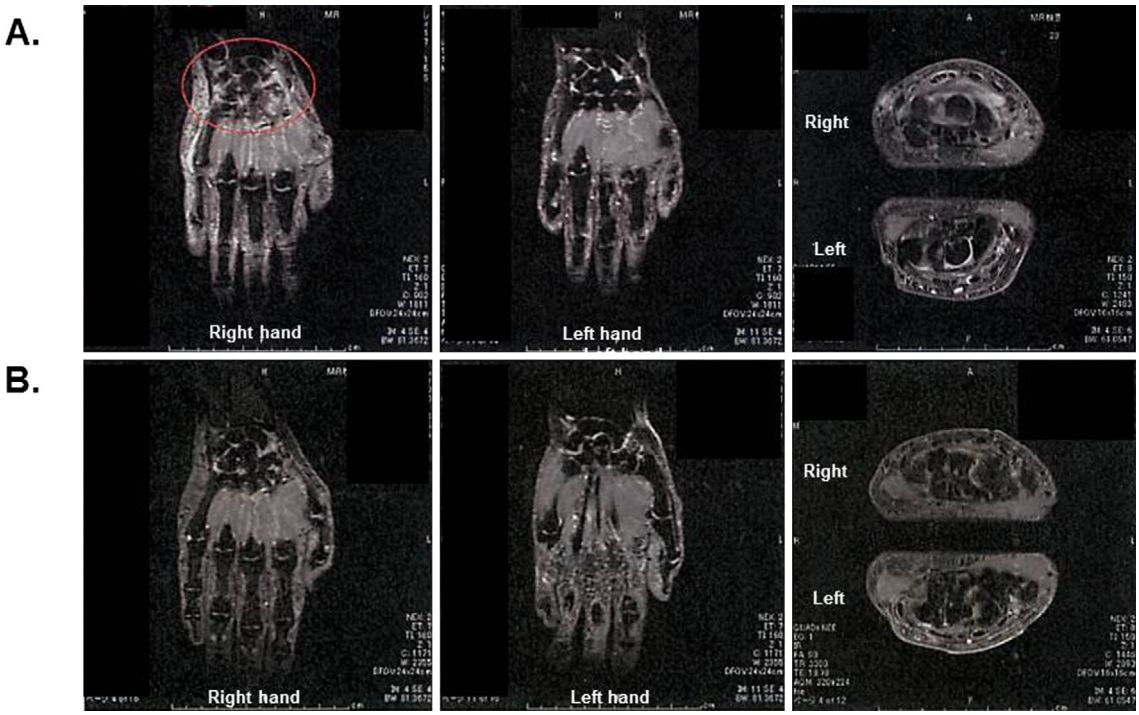

Figure 3. **Hand magnetic resonance imaging. A. On admission: Severe synovitis of the right wrist joint, mild synovitis of the left wrist joint and bilateral III-V metacarpal joints and subcutaneous swelling over the dorsum of the right hand and extensor tenosynovitis of the right II-V fingers. B. After treatment: Significant improvements in the tenosynovitis and subcutaneous edema.**

which is usually responsive to low-dose steroids. For these reasons, we diagnosed the patient with 'RA with RS3PE syndrome-like symptoms.'

We previously reported that RS3PE syndrome is charac-

terized by an elevated serum VEGF level with multiple and symmetrical tenosynovitis and hypervascularity in the presence of subcutaneous edema of the extremities on MRI and US (2, 9). The serum VEGF levels in patients with RS3PE syndrome are significantly higher than those observed in patients with various connective tissue diseases, including RA, systemic lupus erythematosus, mixed connective tissue disease, polymyositis/dermatomyositis and vasculitis syndrome, suggesting that measuring the level of VEGF is useful in the diagnosis and assessment of the disease activity of RS3PE syndrome (2). In addition, we previously reported that subcutaneous edema and tenosynovitis in the extremities in patients with RS3PE syndrome respond to steroid treatment, thus indicating that hand US and MRI are useful tools for detecting subcutaneous edema and synovitis and monitoring the disease activity in patients with RS3PE syndrome (9). In the present case, the high VEGF level and hand MRI and US findings were compatible with the characteristics of RS3PE syndrome. The fact that good steroid reactivity was observed supports the possibility of RS3PE syndrome, although the definitive diagnosis was RA. While several previous reports have described cases of RA associated with pitting edema in the extremities (10, 11), precise assessments based on various factors (VEGF, MRI and US) were not conducted; therefore, the details were not clarified. Further studies are required to identify the characteristics of RA patients presenting with pitting edema in the extremities and positivity for ACPA.

This is the first report describing a case of MG complicated with RA and RS3PE syndrome-like pitting edema in a patient presenting with a high VEGF level. RA may complicate RS3PE syndrome-like symptoms. Further prospective follow-up is warranted to elucidate the associations between MG, RA and RS3PE syndrome, particularly the relationship between the latter two conditions.

The authors state that they have no Conflict of Interest (COI).

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