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Case report

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome: A case report

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ABSTRACT

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare form of paraneoplastic tenosynovitis, which is more prone to occur in elderly males. A 78-year-old male had a past history of gastric cancer 23 years ago and underwent subtotal gastrectomy then. He led a fair life after the surgery. However, fever, edema in four extremities, gait disturbance, and liver function impairment bothered him for 5 months, which caused significant physical functional decline. Despite of extensive laboratory and imaging examinations, no definite diagnosis and treatment were provided. He was referred to Kyoto University hospital and RS3PE was diagnosed. After the diagnosis of RS3PE syndrome was made, systemic steroid was given and fever, edema and liver function impairment improved dramatically within 7 days. The patient was well managed by oral prednisolone 30 mg per day after discharge. RS3PE should be considered when an elderly man with aforementioned presentations in order to prevent significant functional decline in daily living.

1. Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome was first reported by McCarty *et al.* in 1985.[1] It was characterized by acute onset symmetrical synovitis of upper and/or lower extremities with remarkable pitting edema of the soft tissue in dorsa of hands, giving the hands an appearance of "boxing gloves". It was also described as a unique form of synovitis, which was mostly found in elderly men. Previous studies showed an association of RS3PE with malignancies.[2] Herein, we present an elderly man with a past history of gastric cancer who was diagnosed RS3PE due to fever, progressive edema, gait disturbance, and liver function impairment.

2. Case report

A 78-year-old man was referred to our hospital on April 19, 2007 because of progressive edema of both hands and feet with gait disturbance and fever for 5 months. He had a past history of gastric cancer 23 years before this episode and he underwent subtotal gastrectomy when it was diagnosed. After the surgery, he led a relatively healthy life. He stopped cigarette smoking after the surgery of gastric cancer, but he had habitual alcohol consumption with beer 350 ml everyday. He received periodic follow-up after the surgery and no evidence of recurrence was noted during the follow-up period.

Five months before referral to our hospital, he started to experience progressive gait disturbance, which gradually deteriorated and he became unable to walk. Two months later, intermittent fever up to 38°C and exacerbated edema in distal extremities of four limbs were noted. He sought for medical assistance, but fever and edema never subsided. One month before referral, laboratory examinations done in a community hospital showed impaired liver function tests and elevated C-reactive protein, which was not noted

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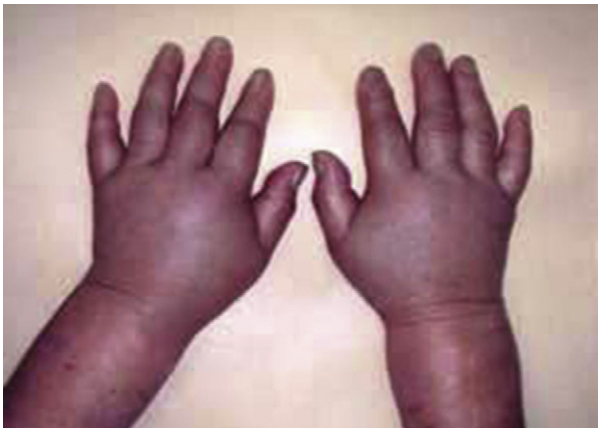

Fig. 1. Symmetrical erythematous swelling on both hands of a patient with remitting seronegative symmetrical synovitis with pitting edema syndrome.

in the past several months. Therefore, empiric antibiotics were given, but all his symptoms remained unresolved. Serial examinations were done for his unresolved fever, including gastric endoscopy, abdominal sonography, and computer tomography, but only gall bladder stone without signs of cholecystitis was noted. His muscle weakness and difficulties of walking were considered secondary to bed-bound status related disuse atrophy (physical deconditioning). However, due to unresolved fever, he was referred to Kyoto University hospital and was admitted on April 19, 2007.

At admission, his blood pressure was 118/72 mmHg and pulse rate was 102 beats/minute. Physical examinations revealed febrile status (body temperature 37.6°C), significant pitting edema in both hands (Fig. 1) as well as erythematous painful swelling of both wrists. Results of laboratory examinations were as follows: white blood cell count: 5700/mm^3, hemoglobin: 10.4 g/dL, platelet count: 338,000/mm^3, C-reactive protein: 11.7 mg/dL, erythrocyte sedimentation rate: 82 mm/hour, aspartate aminotransferase (AST): 56 IU/L, alanine aminotransferase (ALT): 37 IU/L, albumin: 2.6 g/dL, and total protein: 6.2 g/dL. The rheumatoid factor, anti-cyclic citrullinated peptite (CCP) antibody, anti-nuclear antibody, hepatitis B surface antigen, and anti-hepatitis C antibody were all negative. X-ray examinations of both wrists showed soft-tissue swelling, but intact joint space without erosion (Fig. 2). The diagnosis of RS3PE

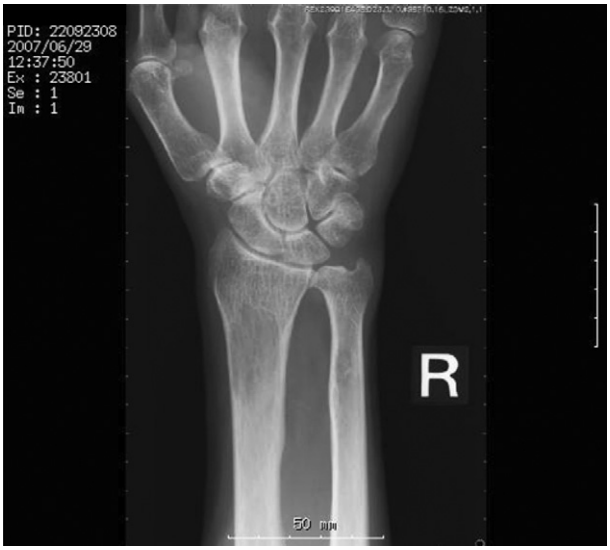

Fig. 2. X-ray of right wrist showed soft-tissue swelling with preserved joint space and absence of joint erosion.

was made because of fever, edema of both hands, synovitis of bilateral wrist, and negative rheumatoid factor. We started prednisolone 20 mg everyday since April 21, 2007 and his symptoms improved dramatically. Fever and edema disappeared 3 days after the treatment, so prednisolone was reduced to 18 mg everyday and he was discharged on May 8, 2007. In outpatient follow-up, the dosage of prednisolone was reduced to 15 mg everyday, but edema of both hands with weakness of lower extremities recurred. Therefore, the dosage was increased of prednisolone to 30 mg/day, and his symptoms were relieved very soon.

3. Discussion

RS3PE syndrome is a rare inflammatory arthritis, which was predominantly diagnosed in elderly males and an association with previous diagnosis of cancer had been reported.[2] Diagnosis of RS3PE was made by the following criteria: (1) pitting edema of bilateral hands, (2) sudden onset polyarthritis, (3) age $>$ 50 years, and (4) negativity of serum rheumatoid factor.[3] Moreover, laboratory examinations may also show elevated erythrocyte sedimentation rate and C-reactive protein. Differential diagnoses of RS3PE included polymyalgia rheumatica, elderly onset rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and mixed connective tissue disease.[1,4,5] In addition to typical symptoms and signs, this patient also had negative serum rheumatoid factors, anti-nuclear antibody and anti-cyclic citrullinated peptite antibody along with elevated C-reactive protein, and erythrocyte sedimentation rate, which were compatible with RS3PE.

The etiology of edema in RS3PE syndrome remained unknown. Previous ultrasonographic study showed tenosynovitis of extensor and flexor tendons at the wrists and metacarpal joints in patients with RS3PE.[6] Besides, magnetic resonance imaging revealed symmetrical subcutaneous edema and tenosynovitis in flexor tendon sheath.[7] After steroid therapy, edema and tenosynovitis might resolve completely.[7] Among these patients, 59% of them had HLA-B27 positivity in contrast to 24% in the general population,[8] but no causal relationship can be established yet. Moreover, biopsy proved that autoimmune hepatitis had been reported to be related to RS3PE syndrome.[9] In the reporting case, we found elevated aspartate aminotransferase and alanine aminotransferase, which imply mild hepatocellular damage in RS3PE syndrome. After steroid therapy, liver function tests improved gradually.

The connection between RS3PE syndrome and malignancy had been reported and RS3PE syndrome may be considered as paraneoplastic polyarthritis. Either solid tumor or hematologic malignancy may be associated with RS3PE syndrome. The time lapse between diagnosis of malignancy and onset of musculoskeletal disorder may be quite variable, but cancer was diagnosed somewhat earlier or concomitantly with RS3PE syndrome in most reported cases.[2] However, in this reporting case, RS3PE syndrome developed 23 years later than diagnosis of gastric cancer. This association may be coincidental, but survey for recurrence of underlying malignancy and regular follow-up are warranted. Developing RS3PE syndrome is considered as a poor prognostic factor for cancer patients.[10] A retrospective multicenter case series study of six patients showed that the mean survival of cancer patients simultaneously developed RS3PE syndrome was 11 months (range from 6–18 months).[11] For those patients with paraneoplastic RS3PE syndrome, anti-cancer therapy along with low dose steroid should be the treatment of choice.

The association between RS3PE and neoplasm was rarely addressed in the literature review of Taiwanese population. A previous case report of a 63-year-old Taiwanese man was diagnosed RS3PE with the presentation of swelling, stiffness, and tenderness in his hands, wrists, and knees and failed to response to

diuretics before being referred to a tertiary medical center.[12] After the treatment of prednisolone 10 mg/day, the symptoms disappeared within 2 weeks. In our case, the response to steroid therapy (20 mg prednisolone) occurred within 3 days. Higher dosage of steroid might fasten the initial response in the treatment of RS3PE syndrome.

Generally speaking, undiscovered malignancy should be suspected when constitutional symptoms including body weight loss and fever, insufficient response to steroid therapy or relapse after initial treatment were noted in a patient with RS3PE syndrome. A cancer survey should be done mainly according to the patient's symptoms, signs, and past medical history. In this reporting case, the occurrence of RS3PE syndrome and gastric cancer 23 years ago may be coincidental, but the possibility of existing occult cancer should be closely monitored.

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