SteroidTreatment of Remitting Seronegative Symmetrical Synovitis with Pitting Edema Syndrome Complicated by Pleural Effusion : A Case Report

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Case Report

Steroid Treatment of Remitting Seronegative Symmetrical Synovitis with Pitting Edema Syndrome Complicated by Pleural Effusion : A Case Report

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Abstract

We report the case of an adult male patient with seronegative remitting symmetrical synovitis with pitting edema (RS3PE) syndrome complicated by pleural effusion (PE). No malignancy was found, and antibiotics did not improve PE satisfactorily ; thus, the patient was initiated on prednisolone, a known effective treatment for RS3PE syndrome, which alleviated not only the symptoms in extremities but also the PE. Although PE associated with RS3PE syndrome is rare, clinicians should be cognizant of PE as a potential complication of RS3PE syndrome, which might be alleviated with steroid therapy.

Key Words : pleural effusion, remitting seronegative symmetrical synovitis with pitting edema syndrome, steroid

Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome is characterized by acute onset of symmetrical polysynovitis with pitting edema in extremities[1)]. Although the cause remains uncertain, RS3PE syndrome might manifest as a paraneoplastic condition[2)]. Further, serum vascular endothelial growth factor (VEGF) was reported to be a potential marker for RS3PE syndrome[3)]. Conversely, pleural effusion (PE) is a rare complication of RS3PE syndrome, with only six reported cases of PE associated with RS3PE syndrome to date[4~9)]. Herein, we present the case of a patient with RS3PE syndrome complicated by PE, which was alleviated with the introduction of steroid therapy.

Case report

A man in his sixties visited a neighboring hospital with swelling, arthralgia, and numbness in the right hand that later extended to the left hand and both feet. He had a history of partial gastrectomy for a gastric ulcer and stomach polyp, after which he developed exertional dyspnea and anorexia. He was suspected to have developed a connective tissue disorder including RS3PE syndrome and was admitted to our department for further evaluation.

At his initial visit to our hospital, he had a two-year history of diabetes mellitus and was taking oral hypoglycemic agents including sitagliptin phosphate hydrate and glimepiride. His hemoglobin A1c level was 7.0% according to the

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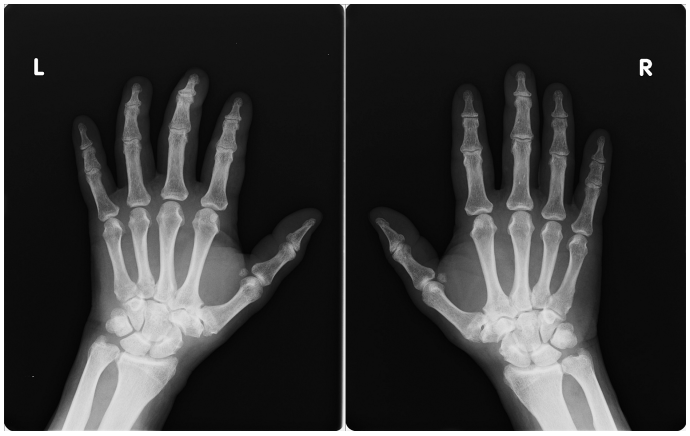

Fig. 1 Plain radiography of the hand shows soft tissue swelling but no bony erosions or joint space narrowing.

National Glycohemoglobin Standardization Program. On admission, physical examination revealed pitting edema with tenderness and swelling in distal portions of the extremities. Results of the laboratory tests on admission were as follows : white blood cell count, 8,400/μL (neutrophils, 80.4% ; lymphocytes, 13.6% ; monocytes, 4.4% ; eosinophils, 1.2% ; basophils, 0.4%) ; hemoglobin, 12.3 g/dL ; platelet count, 260,000/μL ; C-reactive protein (CRP), 3.97 mg/dL ; blood urea nitrogen, 21.8 mg/dL ; serum creatinine, 1.04 mg/dL ; Na, 137 mEq/L ; K, 4.2 mEq/L ; Cl, 107 mEq/L ; total protein 6.3 g/dL ; albumin, 3.3 g/dL ; aspartate aminotransferase, 32 IU/L ; alanine aminotransferase, 22 IU/L ; alkaline phosphatase, 259 IU/L ; and γ-glutamyl transpeptidase, 55 IU/L. Immunologic assessment revealed the following : anti-nuclear antibody, negative ; rheumatoid factor, negative ($<$15 U/mL) ; anti-citrullinated protein antibody, negative ($<$0.6 U/mL) ; and anti-SS-A antibody, negative ($<$1.0 U/mL). The patient was negative for both the proteinase 3 anti-neutrophil cytoplasmic antibody and the myeloperoxidase anti-neutrophil cytoplasmic antibody. His prostate-specific antigen level was within normal limits (1.47 ng/mL). Urinalysis revealed 50 mg/dL protein, negative occult blood, and no cellular casts in urine. Urinary protein excretion was 0.16 g/day. Plain radiography of the hand revealed soft tissue swelling, but neither bony erosion nor joint space narrowing was observed (Fig. 1). Chest radiography showed blunting of the right costophrenic angle (Fig. 2A), which was confirmed as PE on computed tomography (CT). In addition to PE, ground-glass infiltration of the right lung was also observed on CT (Fig. 2B). Sputum cultures for bacteria and fungi revealed normal respiratory flora. Staining for *Mycobacterium* was negative in three consecutive sputum specimens. Additionally, polymerase chain reaction of sputum specimens was negative for *M. tuberculosis, M. avium*, and *M. intracellulare*. A particle agglutination test for *Mycoplasma pneumoniae* antibody was negative. Tumorous lesions were not observed on systemic CT or digestive tract fibroscopy.

The patient was diagnosed with RS3PE syndrome based on the presence of edema in the extremities, the characteristics of which were compatible with those described by McCarty *et al.*[1]. Due to the findings suggestive of atypical pneumonia by CT despite the lack of signs of infection by sputum analysis and serum antibody tests, he was initiated on intravenous administration of ceftriaxone and azithromycin, which led to partial resolution of PE, as determined by plain radiography, and alleviation of dyspnea. We considered thoracentesis but postponed since PE decreased after the administration of antibiotics. However, edema, arthralgia, and elevated CRP

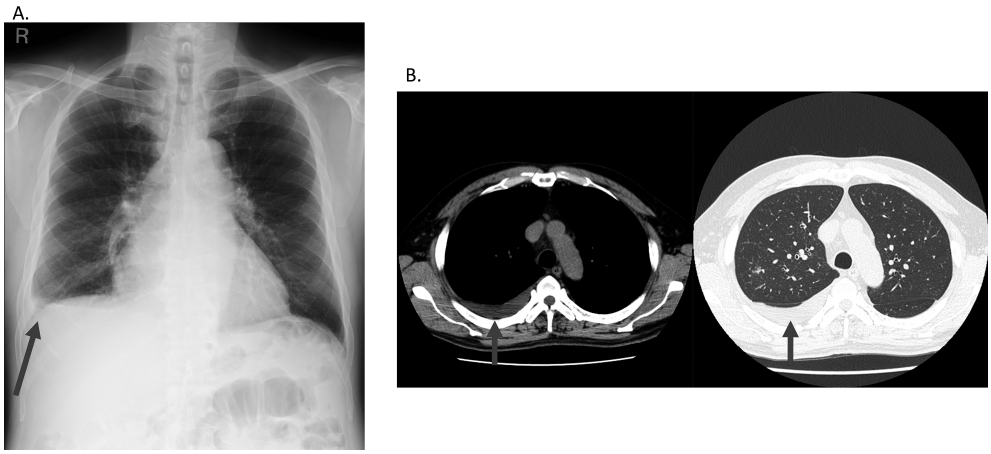

Fig. 2 **A** Plain radiography of the chest on admission to the hospital reveals blunting of the right costophrenic angle. **B** Computed tomography reveals right-sided pleural effusion and ground-glass infiltration of the right lung.

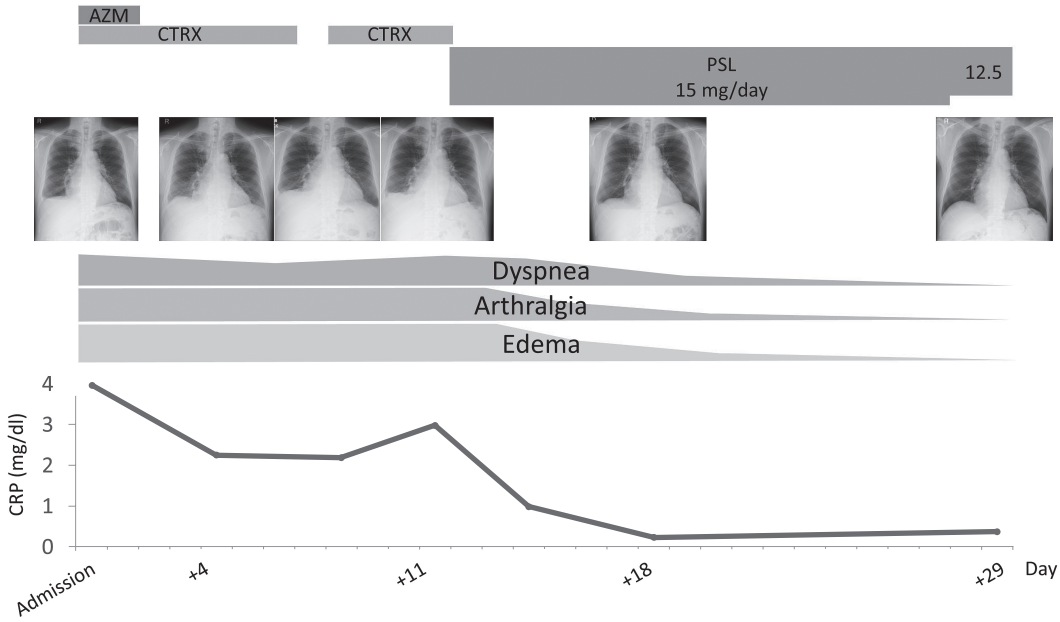

Fig. 3 Clinical course. Abbreviations : AZM, azithromycin ; CTRX, ceftriaxone ; PSL, prednisolone.

levels persisted. Furthermore, PE worsened as soon as antibiotic therapy was concluded. Therefore, he was restarted on ceftriaxone, which did not improve PE. Since the clinical course and the laboratory findings were not compatible with a possible link between PE and pulmonary infection or malignancy, albeit the lack of thoracentesis to rule out this possibility, PE was predicted to be related to RS3PE syndrome. Thus, the patient was started on 15 mg/day oral prednisolone (PSL), which led to a significant improvement in edema and arthralgia in the extremities and a significant reduction in the CRP. Chest radiography obtained after the start of the prednisolone therapy revealed the regression of PE. The prednisolone dosage was reduced at our outpatient clinic with no relapse of arthralgia, and PE was ultimately resolved based on radiographs (Fig. 3). Since PE did not emerge again during the admission, thoracentesis had not been done.

Discussion

RS3PE syndrome is associated with a negative rheumatoid factor status, with no evidence of bony erosions, and has a generally excellent therapeutic response to low-dose steroid therapy[10]. The patient presented herein was diagnosed with RS3PE syndrome based on the presence of typical physical manifestations of RS3PE[1], lack of autoantibodies and bony erosions, and a clinical course that was compatible with RS3PE syndrome as described by Yao *et al.*[10].

PE is not a typical complication of RS3PE syndrome. There are currently only six reported cases of PE in patients with RS3PE syndrome. The previously reported six cases were all relatively old (68–88 years old) and revealed high serum CRP levels. PE was ascertained to be exudative in four of the six cases. Importantly, PE was successfully treated with steroids in five of the six patients, whereas one of the patients who had angioimmunoblastic T-cell lymphoma died[4~9]. These findings suggested PE found in RS3PE syndrome was generated by inflammatory mechanism. Although thoracentesis was not performed in the present case, a diagnosis of PE due to RS3PE syndrome was reached, as the findings suggested that other possible PE causes such as infection and malignancy were unlikely ; in addition, the therapeutic effect of prednisolone on PE was correlated with the disappearance of edema and arthralgia. VEGF, which induces angiogenesis and vascular permeability[11], might contribute to the pathogenesis of RS3PE syndrome. Serum VEGF levels were reported to be significantly elevated in patients with RS3PE syndrome compared with those suffering from other connective tissue diseases, including rheumatoid arthritis[3]. Thus, VEGF is a potential therapeutic target. The possibility remains that VEGF might play a role in the development of PE in the setting of RS3PE syndrome. VEGF levels should be determined not only in sera but also in PE specimens in future studies on patients with RS3PE syndrome.

In this case, pleural effusion was limited to the right side and infection was suspected before the start of PSL. The case of RS3PE syndrome reported by Kikuchi revealed chest X-ray revealed a right-sided dominant pleural effusion, in which antibiotics were not effective but was improved by 20 mg/day of PSL. They speculated infection might be a trigger of RS3PE syndrome[7]. More studies with adequate sample size are required to clarify the relationship between RS3PE syndrome and infection.

In summary, we herein described a case of RS3PE syndrome complicated by PE, which was successfully treated with prednisolone. Although a differential diagnosis that includes malignancy-related PE is indispensable, if physicians encounter patients with RS3PE syndrome who develop PE—and other causes of PE, such as infection and malignancy, are ruled out—administration of low-dose steroid might be beneficial for both definitive diagnosis and treatment.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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（和文抄録）

ステロイド投与により四肢症状と胸水の改善を認めた RS3PE 症候群の 1 例

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症例は 60 歳代，男性．四肢末端の浮腫及び関節痛を生じ当科紹介受診．労作時呼吸困難と胸部画像所見での右側胸水も認めていた．急性の発症様式，滑膜炎症状，リウマトイド因子陰性，X 線上骨びらんを認めないことから RS3PE 症候群と診断．画像所見上異型肺炎の合併も否定できず，抗菌薬の投与を先行して行ったものの，胸水はわずかに減少したのち再度の増加を認めた．悪性腫瘍など，胸水の原因となりうる他の疾患を認めなかったため，RS3PE 症候群に関連した胸水と判断しプレドニゾロン（PSL）15 mg/日の投与を開始した．開始後速やかな四肢末端症状と胸水の改善を認め，PSL 減量後も再燃は認めなかった．胸水は RS3PE 症候群における稀な合併症であるが，感染症や悪性腫瘍等他の原因が否定的である場合には，四肢症状のみならず胸水に対してもステロイド治療が有効である可能性を考慮し治療を試みることも選択肢として考えられる．

キーワード：胸水，RS3PE 症候群，ステロイド