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CASE REPORT

Atypical Remitting Seronegative Symmetrical Synovitis with Pitting Edema Syndrome in an Elderly Lung Cancer Patient

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ABSTRACT

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome develops in patients with various underlying diseases. The involvement of vascular endothelial growth factor in the development of this syndrome has been suggested and malignant disease could be one of the underlying diseases of RS3PE syndrome. This syndrome is interpreted as one of the paraneoplastic syndromes that often have a poor prognosis. There have been few reports of lung cancer patients who developed RS3PE syndrome, and the prognosis of these patients has been rarely discussed. The present case report describes a very elderly lung cancer patient with RS3PE syndrome. We believe he is the oldest patient with advanced lung cancer to have developed RS3PE syndrome. Edema of the dorsum of both hands disappeared by one month after the start of first-line chemotherapy. The relatively long disease control period of the first and later lines of chemotherapy led to a long-term survival of 45 months. The existence of a patient with such a slow clinical course should be considered valuable for future research. It is important to continue optimal treatment even in elderly patients with RS3PE syndrome, one of the paraneoplastic syndromes.

Keywords: paraneoplastic remitting seronegative symmetrical synovitis with pitting edema syndrome, rheumatoid arthritis, lung cancer.

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INTRODUCTION

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome was first reported in 1985 by McCarty *et al* (1). It is characterized by a symmetrical synovitis predominantly involving the wrists and flexor digitorum tendon sheaths associated with marked pitting edema of the dorsum of both hands (1). The diagnostic criteria by Olive *et al* (2) include the following findings: (i) bilateral pitting edema of both hands; (ii) sudden onset of polyarthritis; (iii) age > 50 years; and (iv) seronegative rheumatoid factor (RF). However, in recent years, there have been reports of RS3PE syndrome in which RF (3-5), anti-cyclic citrullinated peptide antibody (anti-CCP) (6), and matrix metalloproteinase-3 (7) were positive. Vascular endothelial growth factor (VEGF) is considered a key factor in the pathology of RS3PE syndrome (8-10). Abnormal levels of VEGF have been reported to cause this syndrome in patients with various underlying diseases such as inflammation and tumors (8-10). When a tumor is the underlying disease, cancers such as prostate cancer, gastrointestinal cancers, and hematological malignancies have been reported (11), but lung cancer was rare (7, 11-15). If tumors are the underlying diseases, RS3PE syndrome could be considered one of the paraneoplastic syndromes (16). Many of the paraneoplastic syndromes are untreatable, and the prognosis remains poor in such patients (16).

The present case report describes an elderly advanced lung cancer patient with RS3PE syndrome. He had an indolent clinical course for more than three years. Case reports discussing prognosis in patients with RS3PE syndrome are rare. It might be important to report the existence of patients who have a slow clinical course similar to that of our patient. ❑

CASE REPORT

An 86-year-old man was referred to our hospital due to edema of both hands for a month. His symptoms progressively worsened. He was not previously diagnosed with any cancer and did not receive any chemotherapy. He had no history of dementia and no higher cognitive dysfunctions. Physical examination revealed symmetrical peripheral pitting edema in both hands. His analytical findings were as follows: RF, 30 UI/mL (normal range, up to 15 UI/mL); erythrocyte sedimentation rate, 55 mm/h; C-reactive protein, 1.33 mg/dL; matrix metalloproteinase, 18 ng/mL (normal range, up to 121 ng/mL), and anti-CCP, 269 U/mL (normal range, up to 4.5 U/mL). Hand magnetic resonance imaging (MRI) showed soft tissue edema and thickening metacarpophalangeal joints without erosive lesions (Figure. 1A). Gallium scintigraphy showed multiple symmetric joint accumulations (Figure 1B). Meanwhile, chest radiograph at the time of admission incidentally revealed a nodule in the right lung. The patient underwent a chest computed tomography (CT) scan, which revealed a nodule in the right middle lobe with ipsilateral mediastinal lymph node enlargement accompanying the right pleural fluid (Figure 2). A transbronchial biopsy was performed and the histological examination confirmed the diagnosis of squamous cell carcinoma of the lung with no driver gene mutation. Clinical stage was T2aN2M1a, stage IVA. Based on these findings, he was diagnosed as suffering from paraneoplastic RS3PE syndrome. Considering the patient's general condition and age, vinorelbine monotherapy was started. Edema of the dorsum of both hands gradually improved. By one month after the start of vinorelbine monotherapy, the edema had disappeared, but the tumor size was not reduced. Four courses of vinorelbine monotherapy were performed, but the response status was stable disease (SD). After recurrence of the primary lesion, he received tegafur, gimestat and otastat potassium combined drug (S1, Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) for three months, docetaxel for 11 months and amrubicin for five months, and the response to each therapy was SD. Irradiation was performed due to regrowth of the primary lesion. Then, only supportive treatment was performed. A chest CT scan taken 41 months after the initiation of first-line chemotherapy showed enlargement of the primary tumor in the middle lobe of the lung (Figure 3). However, no new lesions appeared inside or outside the thorax. No prednisolone was administered, but RS3PE syndrome did not recur. At 45 months after starting first line chemotherapy for lung cancer, the patient was transferred to a palliative care facility due to progression of dementia. ❑

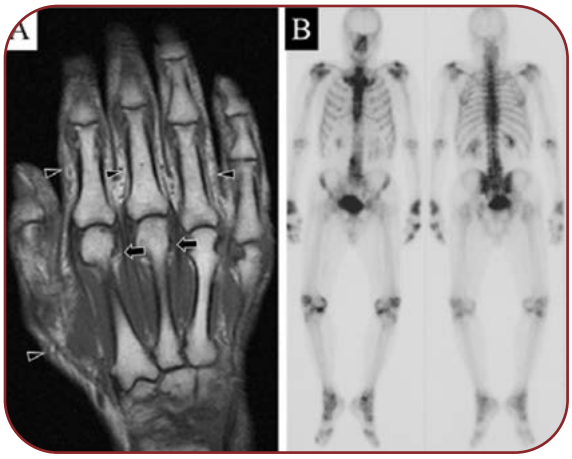

FIGURE 1. (A) Coronal T1-weighted magnetic resonance imaging at the time of presentation showing soft tissue edema (arrow heads) and thickening of metacarpophalangeal (MCP) joints (arrows) without erosive lesions; (B) Gallium scintigraphy showing almost symmetrical accumulation in wrist joints, MCP joints, knee joints, and ankle joints

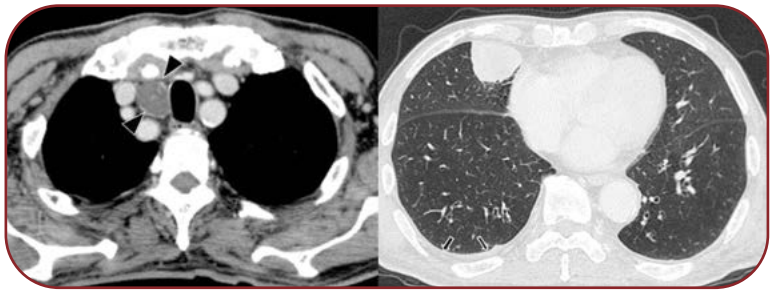

FIGURE 2. Chest computed tomography scan taken at the time of presentation showing a large mass in the middle lobe of the right lung – mediastinal lymph node swelling (arrow heads) and a small amount of ipsilateral pleural fluid (arrows) are also visible

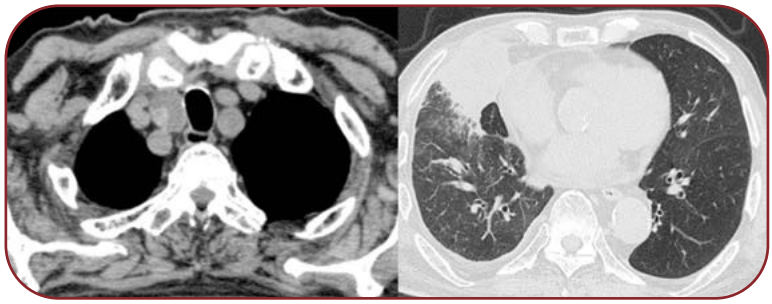

FIGURE 3. Chest computed tomography scan taken 41 months after initiation of first-line chemotherapy showing enlargement of the primary tumor in the middle lobe of the lung

DISCUSSION

Paraneoplastic syndromes have been postulated to occur secondary to substances secreted by tumors or as a result of cross-reactivity of tumor-targeted antibodies with other tissues. Patients with this syndrome often have a poor prognosis (16). In paraneoplastic syndrome, the presence of cancer may cause changes in cancer immunity as well as the production of cytokines by the cancer cells themselves, and it is speculated that such pathological conditions are involved in the prognosis of patients (16). Even if the mechanism is elucidated, paraneoplastic syndrome might be prognostic in the absence of established standard therapy (16). When the underlying disease is a malignant tumor (16), RS3PE syndrome is considered one of the paraneoplastic syndromes. The incidence of malignancy as a complication of RS3PE syndrome varies among reports. Yao *et al* (11) reported a high incidence of malignancy (31%-54%), while Manger and Schett (16) reported that 25% of patients with RS3PE syndrome had an underlying neoplasia. In a systematic review and meta-analysis of 331 patients, Karmacharya *et al* (9) reported that 54 patients (16.3%) had paraneoplastic RS3PA syndrome. In the pathogenesis of RS3PE syndrome, it is becoming clear that the involvement of vascular endothelial growth factor is important (8-10, 17). When the syndrome was first described, the RF-negative finding was given weight (2). However, RS3PE syndrome has been reported in patients positive for RF (3-5) and for anti-CCP (6). In this present case report, the patient was positive for both RF and anti-CCP. As these findings accumulate, the result of RA-negativity may not necessarily be an essential finding.

Although the development of RS3PE syndrome has been reported in many malignant diseases (9, 11, 16), its occurrence in lung cancer patients was rare (7, 13-15). In 2007, Matsuoka *et al* (12) reviewed 12 patients with RS3PE syndrome whose underlying disease was lung cancer. Since then, including our patient, we found only four similar patients reported in the English literature (7, 13-15). The median age of these 16 patients was 71 years (range, 55-86 years). Our patient was the oldest among them. The histological type was described in 13 patients, and five of them had adenocarcinoma. There were three patients with lung squamous cell carcinoma, including our patient. Of the 16 patients reported, RS3PE syndrome preceded lung cancer by 1-13 months in three patients, while it occurred at the same time as lung cancer in the remaining

13 patients. RS3PE syndrome is highly responsive to corticosteroids; indeed, there were eight patients who reported the administration of corticosteroids for RS3PE syndrome, and six of them had a complete response of this syndrome. There were reports that anticancer drugs were effective without corticosteroid for RS3PE syndrome (7, 13), and the syndrome itself is unlikely to have a poor prognosis (17). Therefore, control of the underlying tumor defines prognosis. Therapy for lung cancer was documented in seven patients: five of them had surgical resection, one subject received epidermal growth factor receptor-tyrosine kinase inhibitor (7), and the remaining one was given an immune checkpoint inhibitor (ICI) (13). The epidermal growth factor receptor-positive patient received gefitinib for more than four years (7), but the one who took the ICI, pembrolizumab, for 14 months finally died from lung cancer (13). Survival was reported in eight of the 16 patients, with a median of 16 months (range 8-48 months).

In our patient, the possibility of slow progression of lung squamous cell carcinoma could not be ruled out. But we evaluated that the relatively long disease control period of each chemotherapy led to long-term survival rather than that lung squamous cell carcinoma had special characteristics. In lung cancer participants in the study conducted by Sakamoto *et al* (7), RS3PE syndrome was controlled by gefitinib alone without prednisolone. In our patient, RS3PE syndrome was also controlled with anticancer therapy for lung cancer.

In recent years, cancer patients have been treated with ICIs, and various immune-related side effects have been reported. Interestingly, there have been reports of patients receiving ICIs who developed this syndrome as an immune-related RS3PE syndrome (18-21). These patients seemed to respond well to prednisolone (18-21). Details of the pathogenesis of this syndrome should be further elucidated in order to identify the potential association with immune-related side effects. ❑

CONCLUSION

Symmetrical polyarthritis with an acute onset of punctate edema and a good response to corticosteroids, even if RF-positive or anti-CCP-positive, would be diagnosed as RS3PE syndrome. As observed in our case, some lung cancer patients might have a slow disease progression, despite this paraneoplastic syndrome. ❑

Ethics statement: The present study was approved by the institutional ethics committee of our institute (NO 1639). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Conflicts of interest: none declared.

Financial support: none declared.

Authors' contributions: SO and HS designed the study; SO, GO, YS and HS collected the data; SO and HS analyzed the data and prepared the manuscript. All authors approved the final version of the article.

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