CASE REPORT

Remitting seronegative symmetrical synovitis with pitting edema syndrome complicated with primary lung cancer

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Abstract Remitting seronegative symmetrical synovitis with pitting edema syndrome has been reported to be associated with malignant tumors. However, few cases occurring with lung cancer have been reported. We here report a case of remitting seronegative symmetrical synovitis with pitting edema syndrome complicated with lung cancer. A 77-year-old man presented with poly arthritis (both shoulders, knees, and hands), swelling of the hands, and an elevated C-reactive protein level. As the patient's rheumatoid factor was negative, he was diagnosed with remitting seronegative symmetrical synovitis with pitting edema syndrome. At the same time, computed tomography revealed a nodule suspicious of lung carcinoma in the right lower lobe. Right lower lobe lobectomy was performed, and the nodule was diagnosed as adenocarcinoma. Pathologically, pleural invasion and visceral pleural dissemination were detected, and the tumor was diagnosed as a primary lung carcinoma, p-T2aN0M1a, stage IV. During the preoperative interval, the remitting seronegative symmetrical synovitis with pitting edema syndrome had been successfully treated with prednisolone 20 mg/day, which was later reduced to 6 mg/day. Eighteen months after surgery, the patient's carcinoembryonic antigen levels increased, and the same symptoms recurred, this time more severely. We performed cranial magnetic resonance imaging

and whole body positron emission tomography, but we did not detect any cancer recurrence. To treat the recurred remitting seronegative symmetrical synovitis with pitting edema syndrome, the patient has required not only prednisolone, but also azathioprine; however, the symptoms have not been controlled effectively. In our case, matrix metalloproteinase-3 levels were elevated, as shown in the tumor cells by immunohistochemistry. If higher matrix metalloproteinase-3 levels cause the symptoms, in our case, then remitting seronegative symmetrical synovitis syndrome might be considered a paraneoplastic syndrome. However, we could not conclusively determine if the subsequent reduction in matrix metalloproteinase-3 levels was the result of the surgery or the prednisolone treatment. Furthermore, based on the patient's progress following surgery, it is still not clear if the remitting seronegative symmetrical synovitis with pitting edema syndrome complicated with primary lung cancer in this case may be a paraneoplastic syndrome.

Keywords Remitting seronegative symmetrical synovitis with pitting edema syndrome · Lung cancer · Paraneoplastic syndrome · EML4-ALK · Matrix metalloproteinase-3

Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome has been reported to be associated with malignant tumors [1, 2] and has been thought to be associated with an aspect of paraneoplastic syndrome. Many malignancies have been reported, but there are few reported cases of RS3PE co-occurring with lung cancer. We describe here a case of RS3PE syndrome complicated with lung cancer and provide a review of similar cases

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reported in PubMed and the Japan Medical Abstract Society.

In 1985, McCarty first described a disease that he characterized as Remitting, Seronegative, Symmetrical and Synovitis with Pitting Edema [3]. Some diseases have features similar to those in RS3PE syndrome, such as polymyalgia rheumatica and rheumatoid-factor-negative rheumatoid arthritis and it is very difficult to distinguish them. In our case, although myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA) results were positive, the patient had no symptoms suspicious of ANCA-associated vasculitis but had symptoms suited to McCarty's concept, so we diagnosed the patient with RS3PE syndrome.

We performed a search of Japanese and non-Japanese literature using the Japan Medical Abstracts Society and PubMed. We found 10 case reports of 11 patients diagnosed with RS3PE syndrome associated with lung cancer (Table 1). The mean age of the patients was 80.3 years, and there were 9 men and 1 woman; the sex of 1 patient was not specified. There was no characteristic histology among these cases, and most were at an advanced stage. In 9 cases, were reported to have undergone corticosteroid therapy, 3 cases did not improve and 2 cases relapsed. In 6 cases reported to have undergone therapy for the malignancy, 3 cases completely improved due to the therapy for the malignancy alone.

Case report

A 77-year-old man presented with poly arthritis in both shoulders, knees, and hands, swelling of the hands and legs, and elevated C-reactive protein (CRP) levels. As his rheumatoid factor was negative and matrix metalloproteinase-3 (MMP-3) was increased (720.1 ng/mL), he was diagnosed with RS3PE syndrome. Because RS3PE syndrome is often associated with malignancy, he underwent computed tomography, which revealed a nodule suspicious of lung carcinoma in the right lower lobe. Therefore, he visited our hospital and began corticosteroid therapy for RS3PE syndrome. The symptoms were successfully treated by prednisolone 20 mg/day, and the prednisolone was reduced to 6 mg/day. A transbronchial lung biopsy was performed, but the nodule was unable to be diagnosed, so we decided to perform a surgical biopsy.

When we first met the patient, his symptoms had completely improved. Laboratory tests revealed no significant elevation of inflammatory markers (white blood cell count, 6080/ μ L; CRP concentration, 0.34 mg/dL), but carcinoembryonic antigen (CEA) levels were elevated (14.0 ng/mL). Other markers associated with autoimmune disease were negative (rheumatoid factor and anti-cyclic

Table 1 Reported cases of RS3PE syndrome with lung cancer

No	Author	Age/sex	Stage	Pathology	Time onset of RS3PE	Corticosteroid dose	Corticosteroid response	Therapy for lung cancer	Cancer therapy response to RS3PE
1	Cantini [1]	78/M	Not reported	Undifferentiated carcinoma	Concurrent	Prednisone 50 mg/day	Absent	Not reported	Not evaluate
2	Suga [4]	83/M	IV	Squamous cell carcinoma	10 months before	Not reported	Complete	None	Not evaluate
3	Terada [5]	60/M	IA	Large cell carcinoma	Concurrent	Prednisolone 10 mg/day	Complete	Surgery (lobectomy)	Not evaluate
4	Russell [2]	70/Not reported	Not reported	Squamous cell carcinoma	12 months before	Not reported	Not reported	Not reported	Not reported
5	Medrano [6]	72/M	Not reported	Large cell carcinoma of a squamous nature	Concurrent	Prednisone 15 mg/day	Incomplete	Surgery (lobectomy)	Complete
6	Mattace-Raso [7]	78/F	IIIA	Unknown	Concurrent	Not reported	Not reported	Not reported	Not reported
7	Allain [8]	62/M	Not reported	Adenocarcinoma	Concurrent	Not reported	Not evaluate	Chemotherapy	Not evaluate
8	Hamanaka [9]	79/M	IB	Combined large cell neuroendocrine carcinoma with squamous cell carcinoma and adenocarcinoma component	Concurrent	None	Not evaluate	Surgery (lobectomy)	Complete
9	Origuchi [10]	80/M	Not reported	Unknown	Concurrent	Prednisolone 5 mg/day	Complete	Not reported	Not reported
10		83/M	Not reported	Unknown	13.2 months before	Prednisolone 20 mg/day	Complete relapse+	Not reported	Not reported
11	Ferrao [11]	60/M	IIIB	Adenosquamous carcinoma	Concurrent	Deflazacort 30 mg/day	Incomplete	Surgery	Complete
12	Our case	78/M	IV	Adenocarcinoma	Concurrent	Prednisolone 20 mg/day	Complete	Surgery (lobectomy)	Relapse+

citrullinated peptide were negative), except for MPO-ANCA (82.8 U/mL). Computed tomography revealed a 2.5×2.3 cm nodule in the right lower lobe without hilum and mediastinal lymphadenopathy (Fig. 1). Positron emission tomography with 2-deoxy-2-{fluorine-18} fluoro-D-glucose integrated with computed tomography demonstrated a lesion with a standardized uptake value of 2.59 in the early phase and of 2.39 in the delayed phase at the right lower lobe and showed no metastasis (Fig. 2).

Initially, an intraoperative needle biopsy was performed, and a frozen section diagnosis revealed nodule adenocarcinoma. Thus, we continued the operation and performed a right lower lobectomy. Pathologically, pleural invasion and visceral pleural dissemination were detected, and the tumor was diagnosed as a primary lung carcinoma (acinar predominant adenocarcinoma) (Fig. 3), p-T2aN0M1a, in stage IV. Additionally, an EML4-ALK gene fusion was detected by fluorescence in situ hybridization and immunohistochemistry.

One month after surgery, the patient experienced stiffness in his shoulders and loss of leg strength. Laboratory

tests revealed an elevated white blood cell count (10050/ μ L) and, CRP concentration (7.4 mg/dL). We thought the symptoms indicated a relapse of the RS3PE syndrome, and the patient required prednisolone 20 mg/day, so we could not administer adjuvant chemotherapy. Computed tomography did not indicate recurrence of the lung cancer. The white blood cell count and CRP concentration were normalized immediately, but the symptoms persisted. Therefore, we performed magnetic resonance imaging, and diagnosed the patient with cervical and lumbar spinal canal stenosis. After the diagnosis, the prednisolone dose was reduced to 10 mg/day for 1 year.

Eighteen months after the surgery, the patient's CEA levels and MMP-3 levels had increased again (7.0 and 753.6 ng/mL, respectively). At the same time, the shoulder stiffness and leg weakness became more severe. We performed cranial MRI and whole body PET immediately, but lung cancer recurrence was not detected. To treat the recurred RS3PE syndrome, the patient has required not only prednisolone but also azathioprine; however, the symptoms are poorly controlled.

Fig. 1 Computed tomography of the chest demonstrates a 2.5×2.3 cm nodule in the *right* lower lobe

Fig. 2 Positron emission tomography with 2-deoxy-2-{fluorine-18} fluoro-D-glucose integrated with computed tomography demonstrates a lesion showing standardized uptake values of 2.59 in the early phase and 2.39 in the delayed phase in the *right* lower lobe

Fig. 3 Microscopic findings [hematoxylin and eosin (HE) staining]. The tumor displays a ductal structure that produces mucus

Discussion

It has been reported that the response of patients with RS3PE syndrome complicated with a malignancy to corticosteroid therapy is not sufficient, and symptoms in such cases have often been reported to improve in response to the therapy for the malignancy. Because of these features, many cases of RS3PE syndrome complicated with lung cancer may have features of paraneoplastic syndrome, as with other malignancies.

Interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and MMP-3 reportedly play important roles in the pathogenesis of RS3PE syndrome [12]. Additionally, RS3PE with malignancy has been described to have higher IL-6, VEGF, and MMP-3 levels than has RS3PE without malignancy [9, 10, 13]. On the other hand, lung cancer patients also show elevated IL-6, VEGF, and MMP-3 levels [9, 14, 15]. Thus, lung cancer patients with elevated cytokines levels may show the symptoms of RS3PE. Based on this, most cases of RS3PE syndrome complicated with lung cancer may present with paraneoplastic syndromes of the lung cancer.

In our case, the MMP-3 level was elevated, but IL-6 and VEGF were not measured. We performed immunostaining

and identified only MMP-3 in the cytoplasm of the cancer cells. VEGF was slightly stained, and IL-6 was not identified (Fig. 4). After surgery, the patient's MMP-3 level decreased immediately (287.3 ng/mL). Currently, 18 months after treatment, the patient has experienced a relapse of the RS3PE syndrome. An elevated CEA level is the only indication that the cancer may have recurred; if this elevated CEA level represents a recurrence of the cancer, the elevated MMP-3 level and the worsening symptoms may be due to an increased number of cancer cells.

Cytokines that are elevated in lung cancer patients may cause RS3PE syndrome. If cytokine levels are elevated, physicians should determine whether the elevation was due to the cancer cells, and, as in our case, cases of RS3PE syndrome complicated with lung cancer in which the cytokines were determined to be produced by the cancer cells may be cases indicative of a paraneoplastic syndrome of the lung cancer.

However, it was not possible to obtain any data on the patient's MMP-3 levels prior to the surgery, so it is unclear whether the reduction in MMP-3 levels was brought about by the prednisolone treatment or the surgery. Furthermore, based on the patient's progress after the surgery, it is still

Fig. 4 **a** (Low power field), **b** (high power field): MMP-3 immunostaining with an anti-MMP-3 antibody. The cytoplasm of the tumor cells show immunostaining for MMP-3. In particular, the acinar components of the tumor are stained stronger than the repidic components are. **c** (Low power field), **d** (high power field): VEGF

immunostaining with a VEGF antibody. The cytoplasm of the tumor cells show slight immunostaining for VEGF. **e** (Low power field), **f** (high power field): IL-6 immunostaining with an anti-IL-6 antibody. Tumor cells do not show immunostaining for IL-6

unclear if the RS3PE syndrome was a paraneoplastic syndrome.

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Compliance with ethical standards

Disclosure of potential conflicts of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article contains study with human participants. Informed consent was obtained from the patient as a document explaining the use of his participants obtained by the surgery to the future studies.

Informed consent Informed consent was obtained from all individual participants for whom identifying information is included in this article.

References

- Cantini F, Salvarani C, Olivieri I (1999) Paraneoplastic remitting seronegative symmetrical synovitis with pitting edema. *Clin Exp Rheumatol* 17:741–744
- Russell EB (2005) Remitting seronegative symmetrical synovitis with pitting edema syndrome: followup for neoplasia. *J Rheumatol* 32:1760–1761
- McCarthy DJ, O'Duffy JD, Pearson L et al (1985) Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. *JAMA* 254:2763–2767
- Suga M, Yamazaki K, Hamada K et al (2004) A case of squamous cell lung cancer in association with remitting seronegative symmetrical synovitis with pitting edema(RS3PE) syndrome. *Jpn J Lung Cancer* 44:61–66
- Terada T, Ishimura H, Iwagaki T et al (2004) Anesthetic management for a patient with remitting seronegative symmetrical synovitis with pitting edema(RS3PE) syndrome. *Jpn J Anesth* 53:1039–1041 [Article in Japanese]
- San Ildefonso MM, Mauri Llerda JA (2007) Remitting seronegative symmetrical synovitis with pitting edema(RS3PE): a paraneoplastic syndrome? A new case. *Clin Exp Rheumatol* 25:342
- Mattace-Raso FU, van der Cammen TJ (2007) Remitting seronegative symmetrical synovitis with pitting oedema associated with lung malignancy. *Age Ageing* 36:470–471
- Allain J, Mékinian A, Stirnemann J et al (2010) Remitting seronegative symmetrical synovitis with pitting edema and lung carcinoma. *Rev Prat* 60:750 [Article in French]
- Hamanaka R, Murakami S, Yokose T et al (2011) Lung cancer associated with remitting seronegative symmetrical synovitis with pitting edema-like features. *Jpn J Lung Cancer* 51:253–258 [Article in Japanese]
- Origuchi T, Arima K, Kawashiri S et al (2012) High serum matrix metalloproteinase 3 is characteristic of patients with paraneoplastic remitting seronegative symmetrical synovitis with pitting edema syndrome. *Mod Rheumatol* 22:584–588
- Ferrao C, Faria RM, Farrajota P et al (2013) Lucky to meet RS3PE. *BMJ Case Rep*. doi:10.1136/bcr-2013-010363

12. Li H, Altman RD, Yao Q (2015) RS3PE: clinical and research development. *Curr Rheumatol Rep* 17:49
13. Sibia J, Friess S, Schaeferbeke T et al (1999) Remitting seronegative symmetrical synovitis with pitting edema(RS3PE): a form of paraneoplastic polyarthritis? *J Rheumatol* 26:115–120
14. Katsumata N, Eguchi K, Fukuda M et al (1996) Serum levels of cytokines in patients with untreated primary lung cancer. *Clin Cancer Res* 2:553–559
15. Radisky DC, Przybylo JA (2008) Matrix metalloproteinase-induced fibrosis and malignancy in breast and lung. *Proc Am Thorac Soc* 5:316–322