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Case Report

Complication of Chronic Eosinophilic Pneumonia in an Elderly Patient with Sjögren Syndrome

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An 81-year-old Japanese male with primary Sjögren syndrome (pSS) developed a low-grade fever and productive cough which were refractory to antibiotic therapy. Based on the high level of eosinophils observed in his bronchial alveolar lavage, he was diagnosed with chronic eosinophilic pneumonia (CEP) and successfully treated by oral prednisolone. Interstitial lung diseases associated with pSS (pSS-ILDs) usually present as nonspecific interstitial pneumonia or usual interstitial pneumonia; therefore, the present case is extremely unique in that the patient's condition was complicated with CEP. A diagnosis of advanced gallbladder cancer was made in the patient's clinical course, suggesting the advisability of a whole-body workup in cases of pSS, especially in elderly patients.

Key words: bronchial alveolar lavage, eosinophilic pneumonia, eosinophilia, interstitial lung diseases, Sjögren syndrome

Primary Sjögren syndrome (pSS) is an autoimmune disease characterized by the infiltration of lymphocytes in exocrine glands, followed by hypofunction of the glands [1–3]. Nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) and lymphocytic interstitial pneumonia (LIP) are well known as representative patterns of interstitial lung diseases associated with primary Sjögren syndrome (pSS-ILDs).

CEP is an idiopathic interstitial lung disease caused by an accumulation of eosinophils in the lungs. The cause and pathophysiology of CEP have not been clarified, and the complication of chronic eosinophilic pneumonia (CEP) in patients with pSS-ILD has scarcely been reported. Here we report the case of an elderly pSS patient who developed CEP and malignancy.

Case Report

An 81-year-old Japanese male was admitted to our hospital due to pneumonia that was refractory to various antibiotic therapies. He had been diagnosed with pSS 3 years earlier and had been followed without any treatment. He had suffered from a low-grade fever and productive cough for the prior 3 wks. The patient consulted a general physician and was prescribed several antibacterial agents including cefepime, minocycline, doripenem, levofloxacin and azithromycin under a diagnosis of bacterial pneumonia. His condition, however, did not improve and he developed

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Table 1 Laboratory data at admission to the hospital

WBC	11,580	/μl	RF	35.3	IU/μl
Nt	81.1	%	ANA	×80	
Ly	6.9	%	SS-A	>240	U/ml
Mo	4.4	%	SS-BB	27.5	U/ml
Eo	7.5	%	PR3-ANCA		(−)
Ba	0.1	%	MPO-ANCA		(−)
RBC	371	$\times 10^4/\mu l$	KL-6	304	U/ml
Hb	11.3	g/dl	SP-D	231	ng/ml
PLT	44.2	$\times 10^4/\mu l$	CEA	5.57	ng/ml
T.Bil	0.65	mg/dl	sIL-2R	1003	U/ml
AST	75	IU/l			
ALT	88	IU/l	β-D glucan	<6.0	pg/ml
ALP	369	IU/l	Aspergillus		(−)
γ-GTP	67	IU/l	Cryptococcus		(−)
LDH	220	IU/l	QFT-3G		(−)
BUN	12.3	mg/dl	U-Legionella		(−)
Cr	0.70	mg/dl	U-Pneumococcus		(−)
CRP	13.24	mg/dl			

progressing dyspnea.

His vital signs on arrival were as follows: body temperature, 38.3℃; blood pressure, 123/76 mmHg; pulse rate, 83/min; respiratory rate, >24/min; and oxygen saturation, 92% (during oxygen inhalation of 3L/min with nasal cannulas). A physical examination revealed hyperpnea with inspiratory coarse crackles in both lungs. Cardiac murmur was not observed. A chest X-ray showed bilateral shadows, and a chest computed tomography (CT) scan further demonstrated infiltrates in bilateral upper-dominant, peripheral lungs (Fig. 1A).

In addition, an abdominal plain CT scan showed some low-density areas (LDAs) in the liver (Fig. 1B). Arterial blood gases (oxygen inhalation of 5L/min with nasal cannulas) showed pH of 7.45, PaO_2 of 162.6 Torr and $PaCO_2$ of 29.1 Torr. The patient's pulmonary function could not be measured due to the severity of his respiratory condition. A laboratory examination (Table 1) revealed increased inflammation reaction (C-reactive protein, CRP: 13.24 mg/dL),

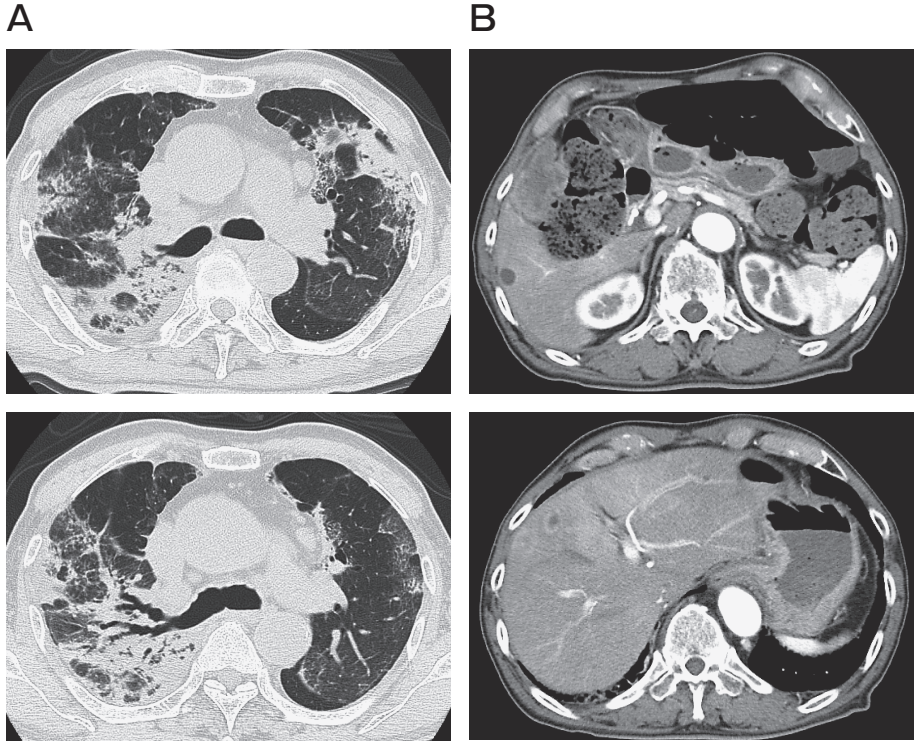

Fig. 1 Chest and abdominal CT images: Bilateral, upper lobe-predominant, and peripheral consolidative and ground-glass opacities were shown by chest high-resolution CT (A). Abdominal contrast-enhanced CT also revealed border irregularity and wall thickening of the gallbladder and ringed enhancement of LDAs in the liver (B).

leukocytosis (white blood cell count: 11,580/μL) with a left shift, and moderate abnormality of liver functions. The serum level of the sialylated carbohydrate antigen KL-6 (KL-6) was within the normal range, and the serum levels of surfactant protein-D (SP-D: 231 ng/mL) and carcinoembryonic antigen (CEA: 5.57 ng/mL) were moderately elevated. Serum beta-D glucan, galactomannan antigen, cryptococcal antigen and cytomegalovirus antigen were all negative.

Moderate peripheral blood eosinophilia was observed (868 counts/μL) and the serum IgE level was 44 IU/mL (reference range <170 IU/mL) on admission. Anti-nuclear antibodies and rheumatoid factor were positive. SS-A and SS-B, indicating Sjögren's syndrome, were also confirmed to be elevated (>240 U/mL and 27.5 U/mL, respectively). Subsequently, a labial minor salivary gland biopsy was performed, and it revealed an atrophic gland with disappearance of acinar cells and a focal collection of lymphocytes. Bronchial alveolar lavage (BAL) revealed an increased total cell number (8.5×10^5/mL) with a markedly high ratio of eosinophils (58%) (Fig. 2). Two days later, the peripheral blood eosinophil level was increased to 1,654 counts/μL.

Under a diagnosis of CEP, oral prednisolone administration (50 mg/day) was initiated, and the patient's fever pattern, respiratory symptoms and the chest infiltrates on radiography then improved rapidly. The dosage of prednisolone was gradually tapered to 7.5 mg/day for 3 months without recurrence (Fig. 3).

Twenty-one days after the initiation of the corticosteroid therapy, pneumothorax occurred in the patient's right lung. Contrast-enhanced CT revealed border irregularity and wall thickening of the gallbladder with ringed enhancement of LDAs in the liver (Fig. 1B). Cytology and histology examinations

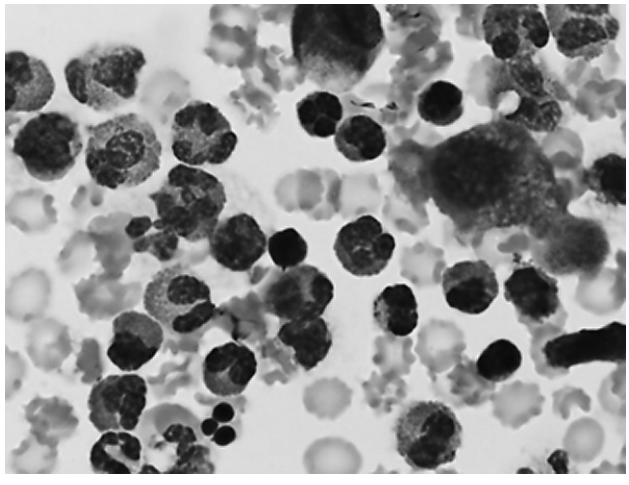

Fig. 2 BAL fluid revealed an increased total cell number with a markedly high ratio of eosinophils (58%).

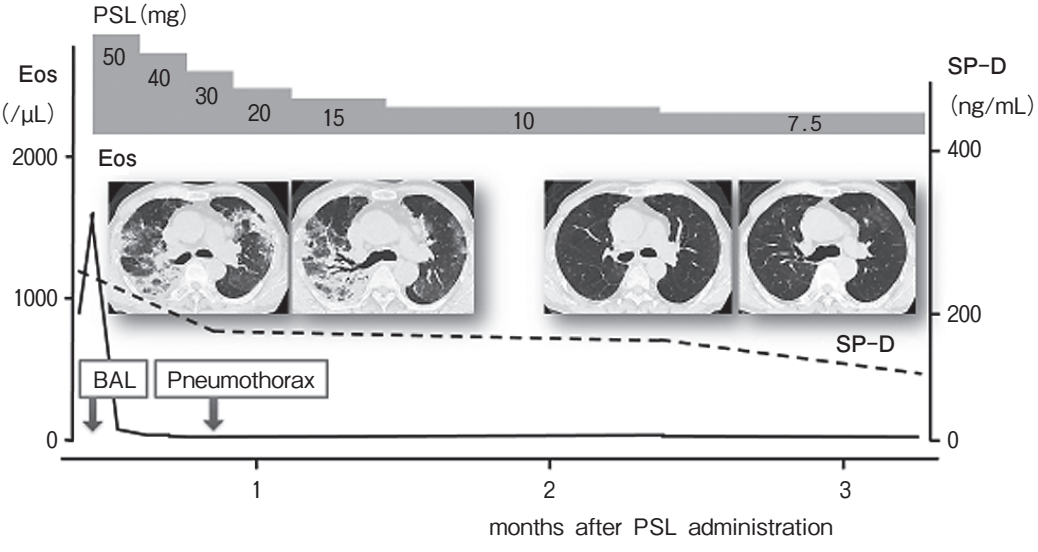

Fig. 3 Clinical course of the patient's CEP treatment: The fever pattern, cough, dyspnea and chest imaging showed rapid improvement by treatment with prednisolone (50 mg/day). The dosage was gradually reduced to 7.5 mg/day for 3 months. In the process of therapy, the patient developed pneumothorax and was diagnosed with gallbladder cancer. Eos, eosinophil count; SP-D, surfactant protein-D.

revealed gallbladder cancer and multiple liver metastases.

Discussion

Primary Sjögren syndrome (pSS) is a chronic inflammatory autoimmune disease characterized by decreased salivary and lacrimal gland function that is associated with lymphocytic infiltration of the exocrine glands. Among the variety of extraglandular complications observed in pSS patients, lung involvement is common with a prevalence of 9% to 75% [4–6]. The classification of pSS-ILD is currently based on the 2002 American Thoracic Society/European Respiratory Society consensus classification of idiopathic interstitial pneumonias (2002 ATS/ERS classification of IIPs) [7]. Based on the results of a few studies focusing on pathologically proven pSS-ILD [8, 9], the disease is generally associated with NSIP and UIP [10]. CEP secondary to pSS-ILD, as seen in the present case, is an extremely rare condition.

CEP was first described by Carrington *et al.* in 1969 [11]. The disease is common among middle-aged women with an atopic history. Asthma precedes CEP in one-half of the cases, but the involvement of such a condition is not required for the development of CEP [12, 13]. Expected laboratory findings include elevated inflammatory markers such as CRP and peripheral eosinophilia (seen in 80% to 90% of cases) [12].

A chest X-ray of a CEP patient generally shows bilateral peripheral shadows, the so-called "photographic negative," showing a migratory pattern in the clinical course [11]. A high-resolution CT image exhibits bilateral, upper lobe-predominant, and peripheral consolidative and ground-glass opacities [12]. For the treatment of CEP, corticosteroid therapy usually yields a marked improvement of symptoms and radiographic changes [13], although a relapse may occur while the corticosteroid dose is tapered. Some reports suggest that treatment with inhaled steroids may be of some value in this condition [14].

In our patient, both the radiological findings and clinical course were consistent with CEP. The level of peripheral blood eosinophils was moderately high on admission and increased further over the next 2 days. However, the patient did not match the typical picture of the CEP population in that he was an elderly man without an atopic history. The condition of pSS in the present case was stable; his dry eye symptoms were well controlled with eye drops and oral aerosolized drugs. There was also no clinical impression that the use of several antibacterial agents prescribed by general physicians caused the exacerbation of the patient's respiratory status.

Another interesting aspect of our patient's case was the complications of gallbladder cancer with multiple liver metastases. It has been reported that T-cell lymphoma, lung cancer, prostate cancer, gastric cancer, colon cancer, esophageal cancer, malignant pleural mesothelioma and breast cancer, excluding gallbladder cancer, were complicated with eosinophil pneumonia [15, 16]. It was also reported that the activation of eosinophil-specific chemoattractants, including RANTES, eotaxin, and IL-5 released from Th2 lymphocytes in the lungs, is involved in eosinophil accumulation in the lungs [13, 17, 18]. The involvement of cytokines such as interleukin (IL)-3, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) produced by malignant cells in the development of eosinophil pneumonia was also reported [19]. It is thus possible that our patient developed CEP as a paraneoplastic syndrome via the activation of some cytokines and chemokines induced by the gallbladder cancer. If a similar patient's lung shadow worsens as prednisolone is tapered, the serum levels of such cytokines should be investigated to clarify the relevance of the tumor.

In summary, we treated an elderly patient with CEP that might have been related to his pSS and gallbladder cancer. The present case suggests the necessity of a systemic work-up in cases of pSS, particularly in elderly patients with an atypical pulmonary obstacle pattern.

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