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Case report

# Combined pulmonary fibrosis and emphysema with myeloperoxidase-antineutrophil cytoplasmic antibody positivity that resolved upon smoking cessation

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ABSTRACT

Myeloperoxidase antineutrophil cytoplasmic autoantibody (MPO-ANCA) is well-known as a serological marker for small-vessel vasculitis. However, when a smoker with interstitial lung disease (ILD) exhibits serum ANCA positivity without systemic vasculitis, diagnosis is a matter of debate; the relationship between smoking and ANCA is unknown. We report a case of combined pulmonary fibrosis and emphysema (CPFE) with elevated MPO-ANCA. Surgical lung biopsy showed emphysema and fibrotic interstitial pneumonia without vasculitis. The MPO-ANCA level decreased after smoking cessation, and no vasculitis or progression was observed during 3 years of follow-up. This suggested that smoking cessation was related to normalization of MPO-ANCA and corresponding disease activity.

## 1. Introduction

Cigarette smoking has been related to various interstitial lung diseases, which are generally classified as smoking-related interstitial lung disease (SR-ILD) [1]. Combined pulmonary fibrosis and emphysema (CPFE) has also been reported as a subtype of SR-ILD [2].

Myeloperoxidase antineutrophil cytoplasmic autoantibody (MPO-ANCA) is a useful marker for the diagnosis of antineutrophil cytoplasmic antibody-associated vasculitis (AAV) and is known to be associated with pathogenesis and disease activity. One study reported that the positive and negative predictive value of ANCA for ANCA-associated systemic vasculitis is 79% and 63%, respectively [3]. In contrast, some studies have reported cases of IP with serum MPO-ANCA positivity and no vasculitis; most of these patients did not progress to AAV over the course of the disease [4,5]. These findings suggest that ANCA levels might be elevated in a non-specific manner.

Furthermore, elevated ANCA levels may be also observed as a result of various diseases, drug use, and occupational exposure; cigarette smoking has been a notable exception [6,7]. Although such reports have made clinicians attach less importance to serum ANCA, there have been several reports of patients previously diagnosed with ILD, including CPFE, that later developed AAV [8,9]. Thus, the meaning of elevated ANCA is sometimes unclear, but it is not negligible. To our knowledge, there have been no case report regarding the complications of SR-ILD with elevated MPO-ANCA levels that resolved only with smoking cessation. We herein report a case of unclassifiable idiopathic interstitial pneumonia (unclassifiable IIP) with prominent feature of CPFE with elevated MPO-ANCA levels that showed normalization only with smoking cessation.

## 2. Case report

A 57-year-old Japanese man who showed a chest radiographic abnormality without any symptoms during a medical checkup visited our clinic. He worked as a newspaper deliverer and had smoked 40 cigarettes daily for the past 40 years. Dust and bird exposure and family history were unremarkable. The patient showed no abnormal vital signs or findings in physical examination, including lung auscultation, skin and musculoskeletal assessments, and vasculitis was not suspected. The modified British medical council scale score was zero, and the six-

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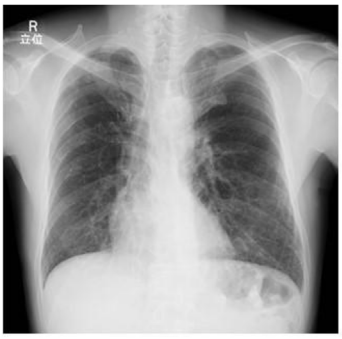


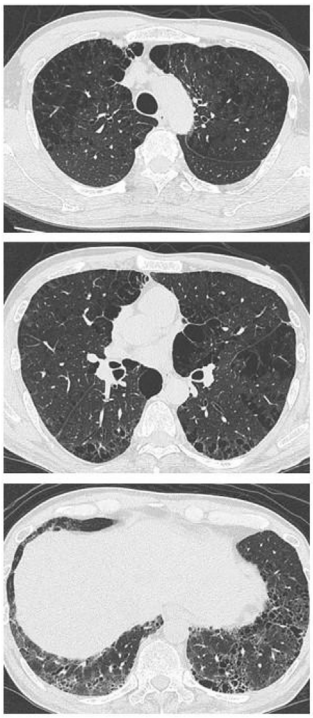

**Fig. 1.** Imaging findings at the initial examination. Chest radiography showed hyperlucency in both lungs and bilateral coarse reticular shadows in the lower lung field. On high-resolution CT, both centrilobular and paraseptal emphysema were seen in the upper lung zones on both sides and bilateral subpleural reticular and ground-glass opacities surrounding the emphysematous cysts were found in the lower lobes.

minute walk test showed normal distance of 520 m without desaturation. The pulmonary function test revealed normal values for VC (3.70 L; 102.5% of the predicted value), FEV1 (3.12 L; 105% of the predicted value), and FEV1/FVC (84%). We found moderate reduction in diffusing capacity for carbon monoxide (13.01 mmoL/min/kPa—66.2% of the predicted value). Blood gas examination revealed normoxia (87.5 mmHg) and negative results for urine blood and protein. The other laboratory tests showed elevated levels of Krebs Von den Lungen-6 (KL-6) [825 U/ml] and MPO-ANCA [31.7 RU/mL] (Normal range; < 20 RU/mL). Chest radiography showed hyperlucency in both lungs and bilateral coarse reticular shadows in the lower lung field. (Fig. 1). On high-resolution CT, both centrilobular and paraseptal emphysema were seen in the upper lung zones on both sides, and bilateral subpleural reticular and ground-glass opacities surrounding the emphysematous cysts were found in the lower lobes. (Fig. 1). There was no obvious honeycombing. A month later, bronchoalveolar lavage (BAL) was performed. The total cell count in the BAL fluid was $1.75 \times 10^5$/ml. The cell fraction contained 72% lymphocytes and 28% macrophages. The lymphocyte CD4/CD8 ratio was 1.24. The patient was offered rheumatological consultation for the ANCA positivity, but the findings were negative for systemic vasculitis. In the differential diagnosis based on clinical and radiological information, we considered SR-ILDs, such as idiopathic pulmonary fibrosis (IPF), and CPFE, lung-limited AAV, and unclassifiable IIP. Video-assisted thoracoscopic lung biopsy at right segments 2, 5, and 8 was performed one month later. The histopathological examination showed emphysema and inflammatory cell infiltration with airway-centered respiratory bronchitis on segment 2. Some part of segment 8 showed a nonspecific interstitial pneumonia (NSIP) pattern, while others showed a usual interstitial pneumonia (UIP) pattern, such as few fibroblast foci with chronic fibrosis and abrupt changes in normal lesions with microscopic honeycombing (Fig. 2). There were no signs of vasculitis, granuloma, and other causes of ILD.

After multidisciplinary discussion (MDD) based on the clinical, radiological, and pathological findings, we diagnosed unclassifiable IIP with prominent feature of CPFE, based on the American Thoracic Society/European Respiratory Society 2013 statement of IIPs [10]. The patient received follow-up examinations without any medication, and the MPO-ANCA positivity was resolved (15.2 RU/mL) only with smoking cessation for four months, with no progression of ILD noted over the 3-year follow-up period without re-elevation of MPO-ANCA. This finding suggests an association between smoking and MPO-ANCA positivity (see Table 1).

Treatment with an anti-fibrotic agent or lung transplantation was planned if the disease showed a progressive course, but the patient showed no change in the lung condition over 3 years of follow-up examinations after smoking cessation, and the MPO-ANCA status was within a normal range at 3 months after the VATS operation (Table 2 and Fig. 3).

## 3. Discussion

SR-ILD is a broad concept of ILD that includes IPF, CPFE, respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), and desquamative interstitial pneumonia (DIP) [10]. CPFE is typically associated with a poor prognosis when it presents with IPF; however, the prognosis and disease behavior of CPFE without IPF have remained unknown [11].

ANCA was first described in patients with segmental necrotizing glomerulonephritis by Davies et al. [12]. Since then, many studies have presented measurement methods for this marker and described the high accuracy of its positive predictive value. However, the value of lung-limited AAV is obscure [3]. Notably, one study reported that 7.2% of patients with IPF tested positive for ANCA (4% MPO and 3.2% PR3) at the initial evaluation, without any signs of vasculitis; 11% of these patients later developed ANCA positivity (5.7% MPO, 5.3% PR3) [8]. A clinical diagnosis of microscopic polyangiitis (MPA) developed in 25% of those patients with a positive MPO-ANCA [8]. ILD was sometimes the initial manifestation of MPA [13]. In the differential diagnosis of this case, IPF, CPFE, and potential development of AAV, several choices were considered for treatment, including smoking cessation, lung transplant, anti-fibrotic medication, or immunosuppressant administration. Even if AAV does not develop in patients with ANCA positivity, one report stated that the presence of MPO-ANCA positivity itself was an unfavorable prognostic factor in patients with IP [14]. Thus, surgical biopsy and MDD was a reasonable diagnostic strategy.