



## Case report

## IgG4-related disease presenting with combined pulmonary fibrosis and emphysema (CPFE)



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## ABSTRACT

A 64-year-old man was admitted to our hospital with an abnormal chest shadow. The patient was a current-smoker and had a past illness of autoimmune pancreatitis with a high serum level of IgG4, 348 mg/dL. Chest CT showed upper-lobe emphysema, and lower-lobe reticulation with honeycombing, suggestive of combined pulmonary fibrosis with emphysema (CPFE). Surgical lung biopsy was revealed a usual interstitial pneumonia pattern with marked infiltration of IgG4-positive plasma cells. The patient was diagnosed with IgG4 related disease (IgG4-RD) presenting with CPFE. Pulmonary manifestation was improved by corticosteroid therapy. IgG4-RD may be an underlying condition in patient with CPFE.

## 1. Introduction

Combined pulmonary fibrosis with emphysema (CPFE) is described as a syndrome characterized by exertional dyspnea, upper-lobe emphysema and lower-lobe fibrosis, preserved lung volume and severely diminished capacity for gas exchange [1]. It is considered a combined pattern, not believed to represent a distinctive idiopathic interstitial pneumonia (IIP) [2], and comprises a heterogeneous population of patients [3]. Although usual interstitial pneumonia (UIP) appears to be the most common imaging and/or pathologic findings in CPFE, various forms of fibrotic interstitial lung disease (ILD) with emphysema have been reported [3–6].

IgG4-related disease (IgG4-RD) is a recently recognized systemic fibroinflammatory disease characterized by an elevated serum level of IgG4, infiltration of IgG4-positive plasma cells and fibrosis, which affects various organs including the lungs [7–10]. ILD associated with IgG4-RD shows variable features on high-resolution CT (HRCT) and manifests histopathologically as nonspecific interstitial pneumonia

(NSIP) [11–13] and other forms of ILD, including UIP [14–18]. However, little information is available on the clinical characteristics of CPFE in IgG4-RD. We herein report a case of IgG4-RD presenting with CPFE.

## 2. Case report

A 64-year-old man was admitted to our hospital with an abnormal chest shadow in 2016. The patient was a current-smoker, who smoked with 1 pack per day for 34 years and the following previous conditions: a posterior mediastinum tumor of schwannoma diagnosed by surgical resection in 1994, an urticarial vasculitis that was treated with prednisolone for 3 years in 2011, and an autoimmune pancreatitis (AIP) diagnosed clinically with radiographical findings and high levels of serum IgG4, 435 mg/dL, in 2015. Chest computed tomography (CT) showed emphysema in bilateral upper lobes, and reticulation with honeycombing in bilateral lower lobes, suggestive of combined pulmonary fibrosis with emphysema (CPFE) (Fig. 1A and B). In addition,

**Abbreviations:** AIP, autoimmune pancreatitis; CPFE, Combined pulmonary fibrosis with emphysema; CT, computed tomography; CTD, connective tissue disease; DIP, desquamate interstitial pneumonia; DLco, diffusion capacity for carbon monoxide; FEV1.0, forced vital capacity in 1 second; FVC, forced vital capacity; GGO, ground-glass opacities; HE, hematoxylin-eosin; HRCT, high-resolution CT; IIP, idiopathic interstitial pneumonia; IgG4-RD, IgG4-related disease; IgG4-RLD, IgG4-related lung diseases; IL, interleukin; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; PFT, pulmonary function tests; RA, rheumatoid arthritis; TGF, tissue growth factor; UIP, usual interstitial pneumonia

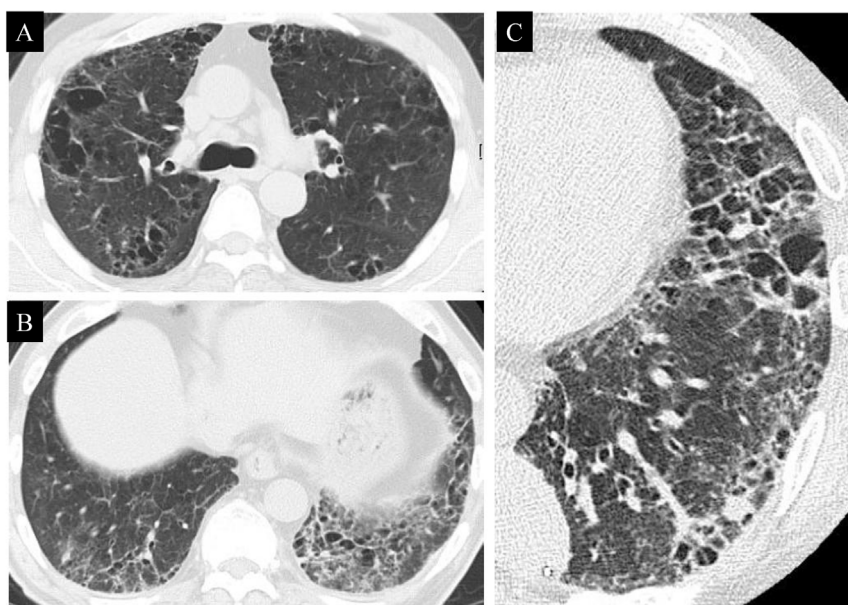
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**Fig. 1.** Chest computed tomography (CT) shows emphysema in bilateral upper lobes (A) and reticulation with honeycombing in bilateral lower lobes (B), suggestive of combined pulmonary fibrosis with emphysema (CPFE). In addition, high-resolution CT (HRCT) reveals the extent of ground-glass opacities (GGO) around emphysema and fibrotic lesion, multiple nodules, and thickening of bronchovascular bundles (C).

high-resolution CT (HRCT) revealed the extent of ground-glass opacities (GGO) around emphysema and interstitial fibrotic change, multiple nodules and thickening of bronchovascular bundles (Fig. 1C).

Laboratory examinations showed high serum IgG, 1802 mg/dL, and IgG4 levels, 348 mg/dL. Serum KL-6 and surfactant protein-D levels were elevated to 751 U/mL and 221 ng/mL, respectively. The test results for the autoantibodies were all negative except for anti-nuclear antibody, titer 1: 80; speckled, homogeneous, nucleolar pattern. Arterial blood gas analysis was normal: pH, 7.441; PaCO<sub>2</sub>, 38.2 Torr and PaO<sub>2</sub>, 81.0 Torr. However, the six-minute walk test showed a desaturation of minimal SpO<sub>2</sub> to 85%. Pulmonary function tests (PFT) revealed the preserved lung volumes: forced vital capacity (FVC), 3.49 L (92.2%); forced vital capacity in 1 second (FEV<sub>1.0</sub>), 2.54 L (81.4%); and FEV<sub>1.0</sub>/FVC, 81.4%, and showed a reduced diffusion capacity: diffusion capacity for carbon monoxide (DLco) was 60.8%. There was no evidence of pulmonary hypertension: the estimated systolic pulmonary artery pressure was 22 mmHg by echocardiography. Bronchoalveolar lavage fluid revealed the following: total cell counts,  $0.65 \times 10^5$  cells/mL; macrophage, 79.4%; lymphocytes, 5.6%; neutrophils, 1.2%; eosinophils, 13.8% and CD4/8 ratio, 0.62. Transbronchial lung biopsy was did not provided a definitive diagnosis.

Therefore, we performed video-assisted thoracoscopic lung biopsy of right S<sup>3</sup> and S<sup>5</sup>. Histopathological examination revealed a patchy distribution and involvement of the subpleural and paraseptal fibrosis with airspace enlargement and honeycombing (Fig. 2A), suggesting a usual interstitial pneumonia (UIP) pattern. However, intriguingly, there was marked lymphoplasmacytes infiltration with lymphoid aggregates in the alveolar septa and bronchovascular bundles, especially in dense fibrotic lesions (Fig. 2B and C). The immunohistochemical staining revealed that most of the infiltration plasma cells were positive for IgG and IgG4 (Fig. 2D and E). The ratio of IgG4/IgG-positive plasma cells was approximately 65% and IgG4-positive plasma cells were > 10 in the high-power field although there were no key morphological features of IgG4-related disease (IgG4-RD), such as storiform fibrosis and obliterative phlebitis. Based on these examinations, we diagnosed the patient as having IgG4-RD presenting with CPFE.

Corticosteroid therapy, as prednisolone 40mg/day, was started and the patient's pulmonary manifestation was improved. After 6 months of treatment, the patient had normalization of serum IgG4 levels to 68.9 mg/dL and had an improved chest CT features. The improvement was characterized by the disappearance of GGO around emphysema and interstitial fibrotic changes, loss of multiple nodules, and decreased

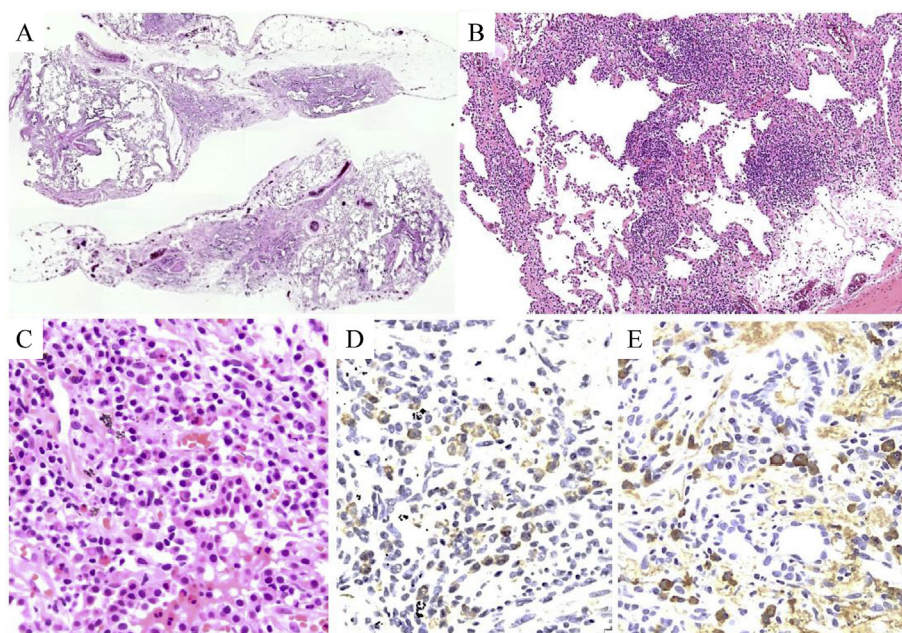
thickening of bronchovascular bundles (Fig. 3A–C). Furthermore, the pulmonary function test showed improvement in FVC to 3.60 L (104.0%) and in DLco to 67.2% after 6 months of treatment.

### 3. Discussion

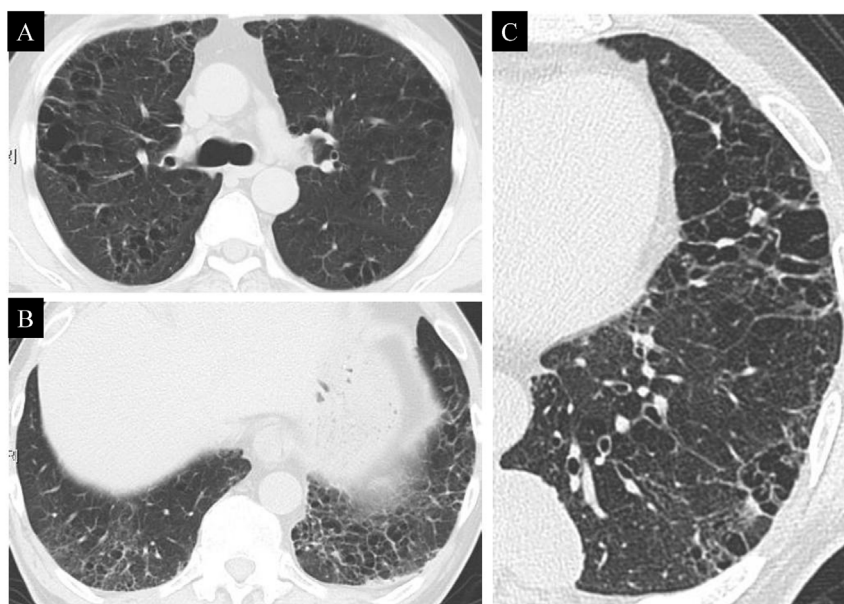
In the present case, where the patient exhibited clinical features of CPFE, it was interesting to determine the definitive diagnosis of IgG4-RD histopathologically. Although previous studies reported that high levels of serum IgG4 or IgG4-positive cell infiltration into alveolar interstitium were often shown in many different diseases other than IgG4-RD [11,19,20], our case had AIP as an extrathoracic lesion of IgG4-RD and fulfilled not only the comprehensive diagnostic criteria of IgG4-RD [9], but also the recent diagnostic criteria of IgG4-related respiratory disease [21]. Furthermore, the corticosteroid therapy improved the chest radiological features and pulmonary function. Therefore, we suggested that the pulmonary manifestation of CPFE was associated with IgG4-RD in this case.

CPFE has been recognized as a unique entity that is characterized by upper-lobe emphysema and lower-lobe fibrosis [1]. Patients with this entity have the common clinical features, such as smoking, male-dominance, the distinct physiologic profile characterized by preserved lung volumes and markedly reduced diffusion capacity [1,4–6]. Since a consensus definition of CPFE does not currently exist, all patients with coexisting emphysema and pulmonary fibrosis are included in this entity broadly [4–6]. Thus, CPFE comprises a heterogeneous population of patients [3], not believed to represent a distinctive IIPs [2]. Furthermore, it has been reported in individuals with asbestos or other mineral exposures [4,6], hypersensitivity pneumonia [23] and various connective tissue diseases (CTDs), especially rheumatoid arthritis (RA) and systemic sclerosis [24]. However, there have been few cases of IgG4-RD presented with CPFE.

IgG4-related lung diseases (IgG4-RD) show a greater variety of pulmonary and pleural lesions [16,17,24,25]. The pulmonary parenchymal involvement has been occurred in 5–18% of patients with IgG4-RD [17]. Although IgG4-RD is associated with a variety of pulmonary abnormalities, Inoue et al. showed that it could be categorized into four major categories of CT features which are as follows: solid nodular type, round shaped GGO type, alveolar interstitial type, and bronchovascular type [26]. Each feature of these findings corresponded pathologically to IgG4-related sclerosing inflammation [24,26]. More importantly, in the present case, some of these radiological features



**Fig. 2.** Histopathological findings of video-assisted thoracoscopic lung biopsy specimen from the right S<sup>3</sup> and S<sup>5</sup>. The specimens showed patchy distribution and involvement of the subpleural and paraseptal fibrosis with airspace enlargement and honeycombing (A:  $\times 4$ , hematoxylin-eosin [HE] stain). There is a dense lymphoplasmacytes infiltration with lymphoid aggregates in the alveolar septa and bronchovascular bundles (B:  $\times 40$ , HE stain). Plasma cell infiltration is prominent (C:  $\times 200$ , HE stain), and the immunohistochemical staining with IgG (D:  $\times 200$ ) and IgG4 (E:  $\times 200$ ) shows an IgG4/IgG-positive cell ratio of approximately 65%.



**Fig. 3.** Chest computed tomography (CT) after 6 months of corticosteroid therapy shows significantly improvement of ground-glass opacities (GGO) and/or consolidation around emphysema and fibrotic change in upper lobes (A) and in lower lobes (B). High-resolution CT (HRCT) reveals that the extent of GGO disappearance, loss of multiple nodules, and the decrease in the thickening of bronchovascular bundles (C).

suspected to indicate IgG4-RD were coexisted with the pulmonary manifestation of CPFE.

Most patients with CPFE have demonstrated UIP as the underlying histological pattern for their ILD [3–6]. Meanwhile, ILD in IgG4-RD often shows a pattern previously classified as NSIP [11–13] and other forms of interstitial fibrosis including UIP, organizing pneumonia, lymphoid interstitial pneumonia and desquamative interstitial pneumonia (DIP) [14–18]. The present case showed a histopathologically UIP pattern with emphysema, but was atypical for idiopathic pulmonary fibrosis (IPF) due to the extensive inflammatory cell infiltration, including the presence of IgG4-positive plasma cells.

The pathogenetic mechanism in IgG4-RD is still unknown, but autoimmunity and infectious agents are suggested to have potential immunologic triggers in IgG4-RD [7]. Some cytokines including interleukin (IL) –4, 5, 10, and 13 and tissue growth factor (TGF)  $\beta$  contribute to elevated serum IgG4, and the progression of fibrosis that is characteristic IgG4-RD [7]. On the other hands, cigarette smoking is

an established environmental factor for CPFE [4,5]. Regarding the relationship between smoking and IgG4-RD, Yamakawa et al. described a case report of DIP, which was smoking-related ILD, complicated with IgG4-RD. They speculated on the pathogenetic relationship between smoking and IgG4 immunity and/or an allergic response [18]. In the present case, interestingly, the radiological manifestation of CPFE was revealed histopathologically fibrotic interstitial pneumonia with a remarkable infiltration of IgG4-positive plasma cells, especially in dense fibrotic lesions. These findings were suggested that both exposure to smoking and an underlying sclerosing inflammation caused by IgG4-RD might promote the disease progression.

There is no specific effective treatment for CPFE at present. In addition to the smoking cessation, an inhaler bronchodilator may be effective in CPFE with airflow obstruction. Furthermore, anti-fibrotic agents, such as pirfenidone and nintedanib, may be useful in CPFE with IPF, but the evidence for the effect of these treatments is insufficient [4–6]. In contrast, corticosteroids therapy has been shown to be

effective in both pulmonary and extrapulmonary lesions of IgG4-RD, but there is no current consensus on the regimen [16,17,27]. In addition, long-term follow-up data on IgG4-RD after the corticosteroid therapy are still lacking. In the present case, GGO, nodules, and consolidation, which existed around emphysema and/or pulmonary fibrosis, were disappeared by corticosteroids therapy, but the bilateral pulmonary fibrosis was still present. Therefore, this case requires careful follow-up over the long term.

In conclusion, we herein described a case of IgG4-RD presenting with CPFE. IgG4-RD may be underlying in patients with clinical manifestations of CPFE, especially those that have some radiological features suspected to indicate IgG4-RD, such as the extended GGO, multiple nodules, and thickening of bronchovascular bundles. Although the relationship between CPFE and IgG4-RD is still unclear, IgG4-positive plasma cells may play an important role in the pathogenesis of smoking-related ILD and fibrosis.

### Conflict of interest disclosure

The authors have no conflicts of interest to declare.

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