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Case report

Improvement in idiopathic nonspecific interstitial pneumonia after smoking cessation

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A B S T R A C T

Although cigarette smoking has been recognized as a risk factor for the development of several interstitial lung diseases, the relationship between smoking and nonspecific interstitial pneumonia (NSIP) has not yet been fully elucidated. We here present a case of fibrotic NSIP with mild emphysema in an elderly male with normal pulmonary function, whose symptoms, serum KL-6 level, and high-resolution computed tomography findings of interstitial changes markedly improved without medication following the cessation of smoking. Our case suggests that smoking may be an etiological factor in some patients with NSIP and that early smoking cessation before a clinically detectable decline in pulmonary function may be critical for smokers with idiopathic NSIP.

Introduction

Cigarette smoking has been recognized as a risk factor for the development of several interstitial lung diseases (ILDs), such as pulmonary Langerhans cell histiocytosis, respiratory bronchiolitis-associated ILD, and desquamative interstitial pneumonia (DIP) [1]. Although these diseases have a relatively good prognosis following smoking cessation, typically in combination with corticosteroid therapy, the causative role of smoking in fibrotic lung diseases remains controversial.

Nonspecific interstitial pneumonia (NSIP) is characterized by the temporally homogenous involvement of alveolar septa by inflammation and fibrosis, in contrast to the heterogeneity of usual interstitial pneumonia (UIP). Most patients with interstitial pneumonia showing a pathological NSIP pattern are of unknown etiology, and the clinical features of fibrotic NSIP resemble idiopathic pulmonary fibrosis (IPF)/UIP. Although the prognosis of fibrotic NSIP was documented to be better than that of IPF/UIP [2], the relationship between smoking and NSIP has not yet been fully elucidated.

In this report, we present a case of fibrotic NSIP with mild emphysema in an elderly male, whose symptoms, serum KL-6 level, and high-resolution computed tomography (HRCT) findings markedly improved without medication after smoking cessation.

Case report

A 66-year-old man who enjoyed karaoke visited our department because of respiratory difficulties during singing. He smoked a pack of cigarettes a day for 45 years. He had a history of essential hypertension and hyperlipidemia, but not pulmonary or autoimmune diseases or occupational exposure to fibrogenic substances. Chest CT revealed mild emphysema and faint interstitial changes in the lungs. Since neither obstructive nor restrictive impairments were detected on pulmonary function tests, we recommended that the patient quit smoking without medication. However, he was unable to quit, and the appearance of a dry cough, increment in serum KL-6, and gradual worsening of interstitial changes on CT were observed during the next one and a half years without a decline in pulmonary function. Therefore, the patient was admitted for further examinations including bronchoscopy.

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Physical examination indicated fine inspiratory crackles in both lungs. Laboratory values were as follows: white blood cell count, 8420/μl with normal differentiation; hemoglobin, 16.4 g/dl; platelet count, 21.4 × 10^4/μl; C-reactive protein, 0.25 mg/dl; serum KL-6, 930 U/ml (<500); anti-nuclear antibody, positive at 1:40 dilution based on the Japanese criteria with a homogenous and speckled pattern. No elevations were observed in specific autoantibodies (anti-DNA, anti-RNP, anti-SS-A, anti-SS-B, and anti-Scl-70 antibodies) for the corresponding connective tissue diseases.

Chest X-ray showed no obvious abnormal findings; however, HRCT demonstrated mild emphysema in the upper lung fields (Fig. 1a). HRCT also revealed ground-glass opacity and reticular patterns without honeycombing in the lower lung fields, which were consistent with an NSIP pattern. A crazy-paving pattern, which was previously reported to be frequent in non-smokers with NSIP [3], was not observed (Fig. 1b).

Pulmonary function testing showed that VC, FVC, FEV_1, and FEV_1/FVC were 3.04 L (90.7% of predicted), 2.84 L (86.9%), 2.30 L (86.8%), and 81.0% respectively. TLC, RV, and RV/TLC were 4.80 L (93.8%), 1.76 L (112%), and 36.7% (100%) respectively. DLCO was 14.64 mL/min/mmHg (88.9%) and DLCO/VA was 3.73/min/mmHg (84%).

Bronchoalveolar lavage (BAL) (recovery rate; 63/150) revealed high total cellularity (36 × 10^4 cells/ml) consisting of 22% lymphocytes, 2% neutrophils, and 2% eosinophils. BAL lymphocytosis was suggestive of NSIP and transbronchial biopsies of the right lung (rS9) showed lymphocyte infiltration with no evidence of infection. However, the specimens obtained were insufficient to allow for a definitive diagnosis. The patient then underwent thoracoscopic biopsy.

The main finding of the surgical biopsy specimen (rS9) was irregular interstitial fibrosis with mild chronic inflammation, which ranged from the peripheral to the central part of lobule (Fig. 1c). The patchy distribution of fibrotic changes seen in some subpleural regions was similar to UIP, while the fibrotic process was temporally homogenous. The lung architecture was relatively preserved and honeycombing was not observed. These pathological findings were consisted with that of fibrotic NSIP, and centrilobular emphysema in the non-fibrotic lesion and focal intraluminal accumulation of macrophages suggested superimposed smoking effects (Fig. 1d,e).

Clinical, radiological, and pathological information established the diagnosis of idiopathic NSIP. Although we planned to treat the patient with prednisolone plus an immunosuppressive agent, he refused the medication due to an improvement in his cough following the complete cessation of smoking after the surgical biopsy. Moreover, ground-glass opacity and reticular patterns on HRCT were found to have gradually improved without medication during the next 4 months (Fig. 1f) and KL-6 was reduced to 392 U/ml. No evidence of exacerbation was detected during the 15-month follow-up.

Discussion

Possible pathogenic factors implicated in smoking with interstitial fibrosis may include oxidative stress [4], decreased HDAC2 activity [5], VEGF expression [6], and the up-regulation of TNF-α [7]. However, the impact of the cessation of smoking during the clinical course of NSIP remains to be established. To the best of our knowledge, this is the first reported case of fibrotic NSIP that markedly improved without medication after the complete cessation of smoking, which suggested that smoking may be an etiological factor in some patients with NSIP. The association of emphysema with NSIP, as shown in our case, and differences in the morphological features on HRCT between non-smokers and smokers may support this hypothesis [3].

Differential diagnosis of this case includes DIP, combined pulmonary fibrosis and emphysema (CPFE), and smoking-related interstitial fibrosis (SRIF). DIP usually responds to corticosteroid therapy. However, some cases progress to fibrosis, despite treatment [8]. In contrast, spontaneous improvement without treatment was observed in 22% of patients with DIP, although the involvement of smoking cessation was not described [9]. Previously, Kawabata et al. reported that distinct lobular distribution and

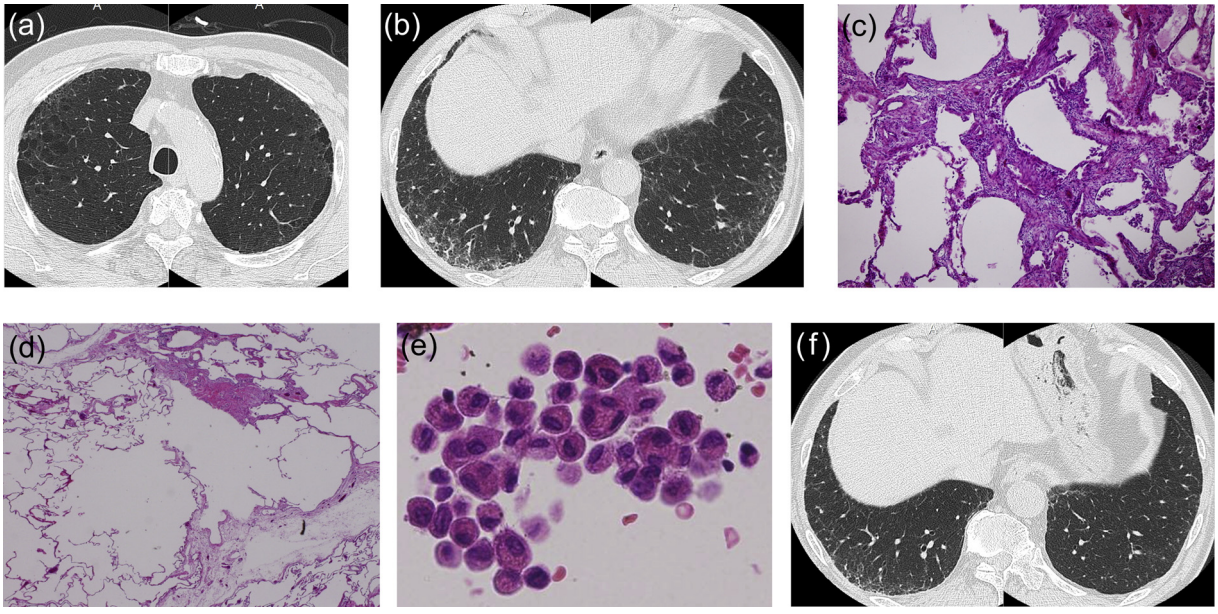

Fig. 1. HRCT images (a-b, before surgical biopsy: f, 4 months after the cessation of smoking) and pathological findings (c-e). (a) the upper zones of the lungs showing paraseptal and centrilobular emphysema. (b) the lower zones of the lungs showing ground-glass opacity and reticular patterns. (c) irregular interstitial fibrosis with mild chronic inflammation. (d) emphysema in the non-fibrotic lesion. (e) intraluminal accumulation of macrophages. (f) marked improvements in ground-glass opacity and reticular patterns.

architectural destruction with thin-walled cyst formation are characteristic features of DIP. They also found a marked increase in the number of BAL eosionophils in patients with DIP, although the significance of BAL eosinophilia is not yet fully understood [8]. Our patient did not exhibit these findings. Moreover, the prominent accumulation of intraalveolar macrophages with diffuse distribution throughout the pulmonary acini, which is a hallmark of DIP, was not observed in the biopsy specimen.

CPFE is a newly defined syndrome, in which upper lobe emphysema (>10% of the lung volume) coexists with significant pulmonary fibrosis in the lower lobe defined by honeycombing, reticular opacities, and/or traction bronchiectasis on HRCT. CPFE has been receiving considerable attention because pulmonary hypertension and severe reductions in diffusion capacity are highly prevalent in CPFE. Although the pathology of CPFE is heterogenous including DIP, organizing pneumonia, and unclassifiable interstitial pneumonia, UIP is the most common pattern and biopsy-proven NSIP has not yet been reported [10]. The HRCT findings of our case were milder in both emphysematous and interstitial changes than typical CPFE. However, this case may have progressed to a type of CPFE if the patient continued to smoke.

Katzenstein et al. recently documented clinically occult SRIF in lobectomy specimens. This distinct form of fibrosis is composed of thick hyalinized collagen bundles, often with variable numbers of hyperplastic smooth muscle fibers without significant inflammation [11]. The pathological findings of our patient were not consistent with these criteria.

Drug-induced NSIP is rare and NSIP may also be caused by the inhalation of high levels of mold and/bacteria [12]. However, in our case, no changes in drug ingestion, living environment, or habits were reported during the clinical course, except for the complete cessation of smoking.

The diagnosis of idiopathic NSIP in this patient was appropriate from the above-mentioned points of issue. The reason why similar cases have not been reported previously in spite of its relatively high incidence rate may be that the definite diagnosis of NSIP by surgical biopsy was not made before relatively advanced morphological abnormalities were confirmed by HRCT. We performed surgical biopsy in this patient with mild interstitial changes and normal pulmonary function. Early smoking cessation before a clinically detectable decline in pulmonary function may be critical for smokers with idiopathic NSIP.

Conclusion

In summary, our case suggests smoking-related pathogenesis in some patients with idiopathic NSIP; however, the presence of unknown factors that trigger the onset of the disease during a long smoking habit remains elusive. More molecular biological research is needed to obtain insights into the pathogenic factors induced by smoking in order to clarify differences in mechanisms between NSIP, UIP, SRIF, and other fibrotic lung diseases.

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