CASE REPORT

Smoking-related interstitial fibrosis (SRIF) and pulmonary hypertension

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SUMMARY

Smoking-related interstitial fibrosis (SRIF) is a relatively new term used to describe chronic interstitial fibrosis that can develop in smokers. The association of SRIF with pulmonary hypertension has not been described. We present a 55-year-old man with an extensive smoking history who presented for evaluation of insidious onset of dyspnoea on exertion and hypoxaemic respiratory failure. Physical examination was unremarkable. Pulmonary function testing demonstrated a marked reduction of the diffusion capacity with no obstruction or restriction. Ventilation perfusion scan showed no evidence of thromboembolic disease. High-resolution chest CT revealed minimal biapical pleural parenchymal scarring and subtle dependent atelectasis. Serological markers for connective tissue diseases were negative. Open lung biopsy was consistent with SRIF. Vascular intimal proliferation consistent with pulmonary hypertension was also noted. Right heart catheterisation yielded mild pulmonary hypertension and treatment was initiated with tadalafil and bosentan.

BACKGROUND

Smoking-related interstitial fibrosis (SRIF) is a term used to describe chronic interstitial fibrosis that can develop in smokers. It is essential to differentiate SRIF from other fibrotic interstitial lung diseases, especially usual interstitial pneumonia (UIP) and fibrosing non-specific interstitial pneumonia (NSIP) that are associated with a poor prognosis. To our knowledge, SRIF with pulmonary hypertension (PH) has not been described. We present a case of SRIF with PH. We discuss the unique pathological features of SRIF and PH in the setting of SRIF.

CASE PRESENTATION

A 55-year-old man with an extensive smoking history, presented for evaluation of dyspnoea on exertion (DOE) that had been progressing during the year prior to presentation. The patient stopped smoking 1 year before presentation, but without subjective improvement. He had occasional dry cough, moderate exertional dyspnoea and dizziness with exertion but no orthopnoea, no paroxysmal nocturnal dyspnoea, no wheezing, no fever, no night sweats or weight loss. The patient denied any skin rash, joint swelling or stiffness. No muscle pain, no dry mouth or difficulty in swallowing. The patient used to work as an arborist and occasionally sprayed insecticides but not on a routine basis. He has a cat but no birds. Vital signs were stable on 2 litres of oxygen per nasal cannula. Physical examination was normal without any crackles, oedema or

clubbing and a normal cardiac auscultation without any accentuation of the second heart sound.

INVESTIGATIONS

Blood count, complete metabolic panel and brain natriuretic peptide were normal. Pulmonary function testing (PFT) showed no obstruction. The forced expiratory volume/forced vital capacity (FEV1/FVC) was 73% predicted and both FEV1 and FVC were normal at 3.17 litres and 4.37 litres, respectively. Lung volumes were determined by plethysmography and were normal with no evidence of restriction or air trapping. The diffusion capacity (DLCO) was markedly reduced at 9.32 ml/min/mm Hg that represents 32% of predicted.

A high-resolution CT (HRCT) of the chest showed minimal biapical pleural parenchymal scarring.

With no evidence of honeycombing, bronchiectasis or diffuse interstitial opacities, there were subtle ground glass opacities in the dependent portions of the lungs appreciated only on the expiratory images likely representing atelectasis and there was no significant air trapping (figure 1).

Serological markers for connective tissue disease were negative and included antinuclear antibody, rheumatoid factor, aldolase, anti-RNP (ribonucleoprotein) antibody and anti Jo-1 antibody.

Erythrocyte sedimentation rate and C reactive protein were within normal limits. Antineutrophil cytoplasmic antibodies (ANCA) testing including anti-proteinase 3 (PR3) and anti-myeloperoxidase (MPO) were negative as well as the hypersensitivity pneumonitis panel.

Ventilation-perfusion scan was not consistent with thromboembolic disease. Transthoracic echocardiogram showed normal ejection fraction, trace tricuspid regurgitation and a calculated systolic pulmonary artery pressure of 38 mm Hg with normal right ventricular systolic function.

Initial bronchoscopy with transbronchial biopsy was not diagnostic. Subsequently, video-assisted thoracoscopy was performed for right lung wedge biopsy revealing evidence of interstitial fibrosis and interalveolar septal thickening with scant interstitial inflammation. Vascular intimal proliferation consistent with early pulmonary hypertension was also noted. Pigmented macrophages were seen in abundance in the alveolar spaces consistent with respiratory bronchiolitis (RB) and some emphysematous changes (figures 2–4).

The right heart catheterisation showed mean right atrial pressure of 4 mm Hg, pulmonary artery pressure of 48/14 with a mean of 30 mm Hg, pulmonary capillary wedge pressure of 5 mm Hg and

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Figure 1 A high-resolution CT of chest, inspiratory (on the left) and expiratory phases (on the right), showing subtle ground glass opacities in the dependent portions of the lungs on the expiratory phase.

the cardiac output measurement via the Fick method was 5.14 l/min. Vasoreactivity test using inhaled nitric oxide was negative. The 6 min walk test showed moderate functional impairment with a distance 59% of predicted and an oxygen desaturation from 94% to 87%. Evaluation for other causes of pulmonary hypertension was unrevealing. The patient had an overnight pulse oximetry study which showed no evidence of nocturnal hypoxaemia. Hepatitis panel was negative and HIV testing was negative as well.

DIFFERENTIAL DIAGNOSIS

On the basis of initial presentation with DOE and only isolated reduction in DLCO on pulmonary function testing with no obstruction or restriction, the initial differential diagnosis was mainly between early interstitial lung disease (ILD) and pulmonary vascular disease.

Upon physical examination there were no clubbing or basilar crackles. Findings on HRCT of the chest were very minimal to explain such a reduction in DLCO or to suggest a specific ILD. Serological assessments for connective tissue disease and hypersensitivity pneumonitis panel were negative.

Pulmonary vascular diseases can include thromboembolic disease, vasculitis and pulmonary hypertension. The ventilation perfusion scan was negative for thromboembolic disease, ANCA testing was negative. On cardiac catheterisation there was an evidence of mild pulmonary hypertension and the findings on biopsy were consistent with SRIF.

TREATMENT

The patient continued to receive supplemental oxygen and selective pulmonary artery vasodilator therapy was initiated

with tadalafil and bosentan for treatment of PH, as he was New York Heart Association functional class III.

DISCUSSION

Smoking-related interstitial lung diseases include respiratory bronchiolitis-associated ILD (RB-ILD), desquamate interstitial pneumonia (DIP) and pulmonary Langerhans' cell histiocytosis (PLCH). Smokers also may be at an increased risk for developing idiopathic pulmonary fibrosis, ILD in rheumatoid arthritis, acute eosinophilic pneumonia and pulmonary haemorrhage in Goodpasture syndrome.¹

Katzenstein *et al* examined 23 lobectomy specimens that were excised for primary pulmonary neoplasms. Twelve cases (all smokers) had significant fibrosis, but nine cases did not fit with a recognised interstitial lung disease. Patient ages of these nine cases ranged from 52 to 69.

Five were men and four were women, five were current smokers and four were ex-smokers.

These cases had a characteristic mixture of uniform-appearing collagen-type alveolar septal fibrosis combined with emphysema and RB and the term 'smoking-related interstitial fibrosis' (SRIF) was used to describe these findings.²

The most important characteristic that differentiates SRIF from other fibrosing ILD (mainly UIP and fibrosing NSIP) is the uniform pattern of fibrosis and lack of temporal heterogeneity compared with the former and lack of cellular inflammatory infiltrate and the presence of pigmented macrophages compared with the latter. In addition, the presence of emphysematous changes is not a characteristic finding in smoking-related ILD such as RB-ILD and DIP.³

Figure 2 Interalveolar septal thickening, emphysematous changes and intra-alveolar pigmented macrophages are the characteristic findings in smoking-related interstitial fibrosis (H&E stain, ×4).

Figure 3 Medial thickening with narrowing of the arteriolar lumens are the first step in developing grade I pulmonary hypertension. (H&E, ×10).

Figure 4 Interalveolar septal thickening and blood vessels medial proliferation with intra-alveolar pigmented macrophages. (Movat's stain, $\times 10$).

PFT results were available for eight of the nine SRIF cases reported by Katzenstein *et al*, six individuals had evidence of obstruction (4 with normal DLCO and 2 with reduced DLCO) and two with normal spirometry and reduced DLCO. Three of the nine cases showed non-specific areas of fibrosis or scarring on CT examinations while no interstitial abnormalities were noted in the other six cases.²

Our case showed no evidence of obstruction or restriction on PFT but did have a marked reduction in DLCO. HRCT of chest showed minimal non-specific changes.

The relationship between smoking and pulmonary fibrosis has been noted in various studies.

Cottin *et al* described the coexistence of diffuse fibrosing interstitial pneumonia, mostly UIP and emphysema in a syndrome they termed combined pulmonary fibrosis and emphysema (CPFE). The patients with CPFE had mixed fibrotic and emphysematous changes on HRCT, mixed pattern on PFT with marked reduction in DLCO which was associated with a high prevalence of PH.⁴

In a study of RB, Fraig *et al*⁵ noted interstitial fibrosis in more than 40% of smokers.

Yousem⁶ reported pathological changes identical to SRIF but they were referred to as RB-ILD with fibrosis in four lobectomy specimens of smokers with lung cancer, also in nine patients with ages ranging from 32 to 68 years who underwent surgical lung biopsy because of respiratory symptoms.²

The nine cases reported by Yousem⁶ were unique in that they had clinical symptoms, radiological changes on chest CT and mixed obstructive and restrictive pattern on PFTs (which were available in only 4 patients) with predominant obstruction and marked reduction of DLCO.

Kawabata *et al* described interstitial fibrosis associated with emphysematous changes in about 17% of 572 lobectomy specimens from cigarette smokers. The term airspace enlargement with fibrosis was used to describe these changes which overlap with SRIF.^{2,7}

In a recent study, SRIF was induced in mice via 6-month cigarette smoking. Specific microRNAs (miRNAs), which are small regulatory noncoding RNA molecules, were found to be significantly changed both in lung and plasma with lung changes occurring earlier than those in the plasma. These findings may suggest that circulating miRNAs can be a future potential biomarker for SRIF.⁸

Since SRIF is newly described, there is no consensus regarding the coexistence of PH. The cause of the reduction in DLCO

in such cases may be because of the combination of both pathologies. PH would be considered the culprit of a depressed DLCO in the absence of gross changes on chest imaging or when PFTs are free of either significant obstruction or restriction.

Notably, PH had higher prevalence in cases of CPFE; these patients had clinically significant fibrosis associated with emphysema.

Whether to classify pulmonary hypertension in the setting of SRIF as WHO group I (Idiopathic) versus WHO group III (PH associated with hypoxaemia) is challenging but an important determination, as the former is amenable to selective pulmonary artery vasodilator therapy. We feel that if SRIF was mainly a pathological finding, such as in the nine cases reported by Katzenstein *et al*, with no gross changes on imaging or marked PFTs abnormalities and evaluation for other causes of PH is negative, PH in such setting can be considered WHO Group I or idiopathic pulmonary arterial hypertension. However, if changes of SRIF were severe enough to result in imaging abnormalities and clear PFTs changes, such as in the nine cases reported by Yousem, concomitant PH would be categorised as WHO Group III.

In conclusion, it is important to recognise SRIF as a clinical and pathologic entity. SRIF should be differentiated from UIP or fibrosing NSIP (non-specific interstitial pneumonia) as these portend a poor prognosis. SRIF cases need long-term follow-up in order to better understand the disease progression and outcome. The coexistence of PH with SRIF remains uncertain and needs further study.

Learning points

- ▶ Smoking-related interstitial fibrosis (SRIF) is a new term used to describe chronic interstitial fibrosis that can develop in smokers.
- ▶ It is important to be aware of SRIF and differentiate this process from usual interstitial pneumonia or fibrosing non-specific interstitial pneumonia which can carry poor prognosis.
- ▶ The most important characteristic that differentiates SRIF from other fibrosing interstitial lung disease is the uniform fibrosis combined with the presence of numerous pigmented macrophages and emphysematous changes.
- ▶ The coexistence of pulmonary hypertension in the setting of SRIF is uncertain and needs further investigation.
- ▶ We would consider screening patients with SRIF for pulmonary arterial hypertension if the degree of dyspnoea/hypoxaemia, reduced diffusion capacity or functional status is out of proportion to the degree of interstitial involvement.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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