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Case report

Desquamative interstitial pneumonia in a non-smoker with neurofibromatosis type 1 (Von Recklinghausen syndrome)

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Accepted 26 December 2019

SUMMARY

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with multiple systemic manifestations. Pulmonary involvement has been reported in the form of interstitial fibrosis, emphysema, pulmonary hypertension and thoracic neoplasm. We report a case of desquamative interstitial pneumonia in a non-smoker with NF1.

BACKGROUND

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that occurs in 1 per 3000 individuals, caused by a mutation of the NF1 gene that encodes the protein neurofibromin, which has a role in tumour suppression.¹ Inactivation of the gene leads to loss of function and subsequent development of many different tumours.¹ It is clinically characterised by cutaneous café-au-lait spots, freckling, hyperpigmentation, peripheral neurofibromas and iris hamartomas. Pulmonary involvement can occur in the form of interstitial fibrosis, emphysema, pulmonary hypertension and thoracic neoplasm. We report the first case of desquamative interstitial pneumonia (DIP) in a non-smoking patient with NF1.

CASE PRESENTATION

A young man, in his early 40s, non-smoker with a history of NF1 presented with a 1-year history of cough and gradually worsening dyspnoea on exertion. His dyspnoea did not respond to inhaled bronchodilators or antibiotics. However, it improved significantly with a week course of prednisone, given for gouty arthritis, but returned once the prednisone was stopped.

His medical history included oesophageal varices, gastro-oesophageal reflux disease, hypothyroidism, hypertension, gout, cholelithiasis and he had had a splenectomy for an enlarged spleen at the age of 9. He also carried a history of emphysema of unclear origin and spontaneous pneumothorax at the age of 12. The patient worked in information technology and never had environmental exposure to toxic fumes, smoke or dust. Physical examination was notable for diffuse bilateral crackles, multiple cutaneous café-au-lait spots, neurofibromas and axillary freckles. There was no clubbing, rashes, ulcerations or arthropathy.

INVESTIGATIONS

The CT of the chest showed diffuse peripheral ground glass opacities as shown in [figure 1](#). Pulmonary function tests revealed moderate restriction with total lung capacity 4.60L (60% predicted). Diffusing capacity of carbon monoxide was substantially reduced with an absolute value of 13.27 mL/min/mm Hg (44% predicted). Alpha-1-antitrypsin was normal and autoimmune markers were all negative. Trans-thoracic echocardiography and right heart catheterisation were normal. The patient desaturated to 92% from 98% on room air after 420 m on a 6 min walk test and his dyspnoea went from 2 to 6 on the Borg Scale. Bronchoalveolar lavage (BAL) cytology was markedly hypercellular with increased macrophages. Video-assisted thoracoscopic surgery was performed and lung wedge biopsies were obtained from the left upper and lower lobes. Cultures sent from the BAL did not grow bacteria, fungi or any other microbes.

Pathologic findings

Both left upper and lower lobe biopsies showed numerous histiocytes within the airspaces and the alveolar interstitium was mildly thickened by chronic inflammatory infiltrates ([figure 2](#)) consistent with a diagnosis of DIP. Emphysematous cysts were also present. The pulmonary arteries and veins showed moderate-to severe concentric and eccentric intimal thickening ([figure 3](#)).

TREATMENT

Prednisone was restarted at 40 mg daily for 1 month followed by slow taper over 5 months.

OUTCOME AND FOLLOW-UP

He remained clinically asymptomatic and radiologically stable after 1-year follow-up.

DISCUSSION

Interstitial lung disease has been reported in NF1 with an incidence of 5.5%–23%.^{2,3} Ground glass opacities, cystic lesions and emphysematous changes are the most common described radiological findings, but the association of these findings to NF1 is controversial since all those reported patients had history of smoking.^{3,4} There are limited data of cases of NF1 with interstitial lung disease documented with tissue biopsy in the literature. The histopathological patterns reported include



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To cite: Ferrer G, Saleh AO, Tazelaar HD, *et al.* *BMJ Case Rep* 2020;**13**:e227379. doi:10.1136/bcr-2018-227379

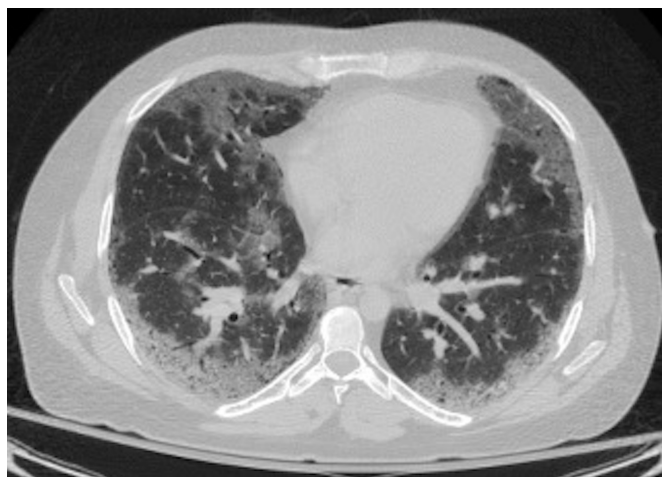


Figure 1 CT scan of the chest showing diffuse peripheral ground glass opacities bilaterally.

non-specific interstitial pneumonia (NSIP),² chronic eosinophilic pneumonia⁵ and DIP.⁶ To the best of our knowledge, there have been no reports of DIP-pattern of injury in non-smoker patients with NF1.

DIP is characterised by diffuse involvement of the lung by numerous histiocytes filling the airspaces with a sheet-like configuration and slight thickening of the alveolar septa. A histopathological pattern that is typical for DIP, commonly associated with smoking, has also been described in autoimmune disorders, after occupational exposures and drugs.⁷ The absence of any drug or environmental exposures in the history of this patient argue in favour that his interstitial lung disease with the DIP-pattern is most likely associated with the NF1. Further, increased levels of circulating monocytes and increased expression of inflammatory cytokines are observed in NF1 patients providing evidence of chronic inflammation associated with NF1.⁸ The mechanism of DIP in NF1 is unclear but it has been proposed that the connection between NF1 and interstitial lung disease could be linked to a mesenchymal defect in NF1³ leading to deposition of collagen. Patients with NF1 have also been noted to have increased levels

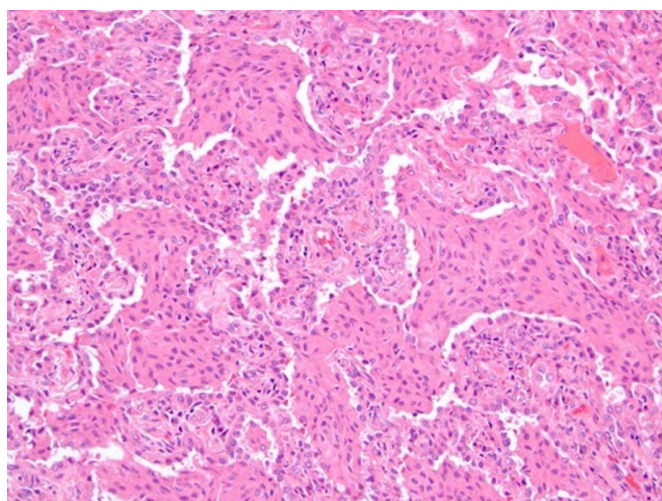


Figure 2 Pathology slide of lung biopsy showing numerous histiocytes within the airspaces and the alveolar interstitium was mildly thickened by chronic inflammatory infiltrates.

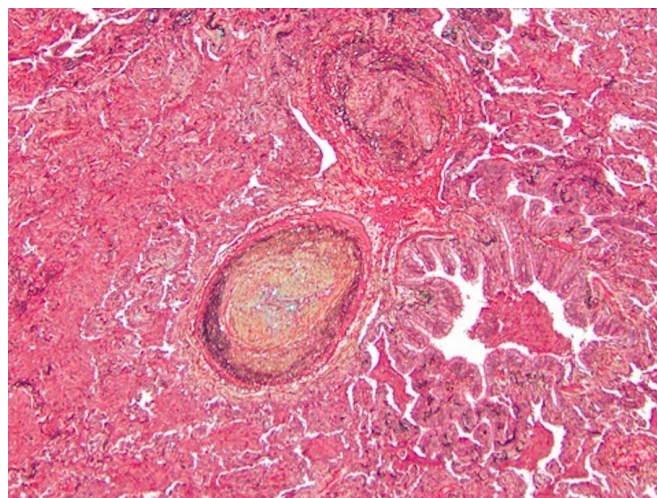


Figure 3 Pathology slide of lung biopsy showing pulmonary arteries and veins with moderate-to-severe concentric and eccentric intimal thickening.

of nerve growth factor which may have a pro-fibrogenic effect on lung tissue.⁹

Pulmonary hypertension has also been described as a complication in patients with NF1, sometimes leading to right ventricular failure and death.^{10–12} Neoangiogenesis of the large, medium-sized and small vessel leading to pulmonary vasculopathy with intimal vascular smooth muscle cell (VSMC) proliferation and fibrosis is the possible pathogenic mechanism.² In addition to the DIP-pattern, pulmonary hypertensive changes were histologically seen in the biopsy from this patient, but there was no evidence of pulmonary hypertension on right heart catheterisation. Though these vascular changes might be secondary to the presence of interstitial disease, neurofibromin has clearly been established as a critical regulator of endothelial cell (EC), VSMC and bone marrow cell function. Excessive and chronic infiltration of macrophages into the neointima promoting EC senescence and increased VSMC proliferation may explain the endothelial changes found in our patient and the association between NF1 and pulmonary hypertension.⁸

In summary, we report the first case of a non-smoker patient with NF1 with interstitial lung disease with DIP-pattern and pulmonary hypertensive vasculopathy.

Learning points

- ▶ Interstitial lung disease has been reported in neurofibromatosis type 1 (NF1) with an incidence of 5.5%–23%, though in most cases smoking has been a confounding factor in the reported cases.
- ▶ Pulmonary hypertension has also been described in patients with NF1 and can lead to right ventricular failure.
- ▶ Histopathological pattern that is typical for desquamative interstitial pneumonia, commonly associated with smoking, has also been described in autoimmune disorders, occupational exposure and drugs.

Contributors GF performed substantial contributions to conception and design of the manuscript and has provided final approval of the version to be published. HDT contributed to review and confirmation of the interpretation of pathology results. AOS drafted, revised and submitted the manuscript. AVA performed substantial contributions to interpretation of the pathology results and contributions to the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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