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Case report

Interstitial lung disease and pre-capillary pulmonary hypertension in neurofibromatosis type 1

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A B S T R A C T

Although previously reported, the existence of a neurofibromatosis (NF)-associated diffuse lung disease (DLD) still lacks solid evidence. We report a case of a 68-year-old non-smoking female with NF1, pre-capillary pulmonary hypertension (PH) and an interstitial lung pattern. Initial findings included progressive dyspnea, hypoxemia and sparse centrilobular ground-glass micronodules on high-resolution computed tomography (HRCT). Further study demonstrated a severe defect in diffusing capacity for carbon monoxide (DLCO), macrophages on bronchoalveolar lavage and pre-capillary PH on right cardiac catheterization. Surgical biopsy revealed macrophage accumulation along bronchovascular bundles and alveolar spaces and type II pneumocytes hyperplasia. Given the absence of environmental exposure or new drugs, a NF-DLD was hypothesized. Pre-capillary PH was disproportionate to interstitial findings, so it was attributed to a NF1-vasculopathy. Treatment with triple sequential combined therapy was unsuccessful culminating in death 18 months later. This case adds HRCT and anatomopathological data suggesting NF-DLD as a distinct manifestation of the disease.

1. Introduction

Neurofibromatosis type 1 (NF1) is a relatively common single-gene disorder, with an estimated incidence of 1 in 2500–3000 individuals [1].

Cutaneous, musculoskeletal and neurological involvement is frequent [1,2]. In the spectrum of thoracic manifestations [3], abnormalities in pulmonary vasculature and parenchyma are rarely seen [2,3].

For several decades there have been reports of NF-DLD [4–11] however that association still lacks robust evidence. To date, more than 60 cases have been described [4–13], but few included HRCT scans or lung biopsy [5,10–13]. HRCT findings reported in NF include upper lobe predominant cysts and bullae, ground-glass opacifications and basilar reticular abnormalities. Histological data is even poorer, regarding the paucity of anatomopathological reports in published series [5,10–12].

Pulmonary hypertension (PH) is another rare NF1 manifestation, resulting from an underlying vasculopathy whose mechanisms are not fully understood [14,15].

The authors present a rare case of a non-smoking female with NF1 presenting a pre-capillary PH and centrilobular ground-glass micronodules in HRCT, in which histological documentation of DLD was obtained. The actual existence of an NF-DLD is subject of debate in the scientific community. We believe that the presented case provides additional data favoring the existence of NF-DLD as a distinct clinical entity.

2. Case report

A 68-year-old female presented with progressive exertional dyspnea for a year. She worked as a quality controller in the denim industry. There was history of dyslipidemia, multinodular goiter and osteoporosis. Chronic medication was Pytavastatine, Alendronic Acid and Colecalciferol.

There was no smoking or other known environmental exposure.

Physical examination showed one cafe au lait spot on an ankle and four on the trunk, multiple cutaneous neurofibromas and axillary freckles (Fig. 1).

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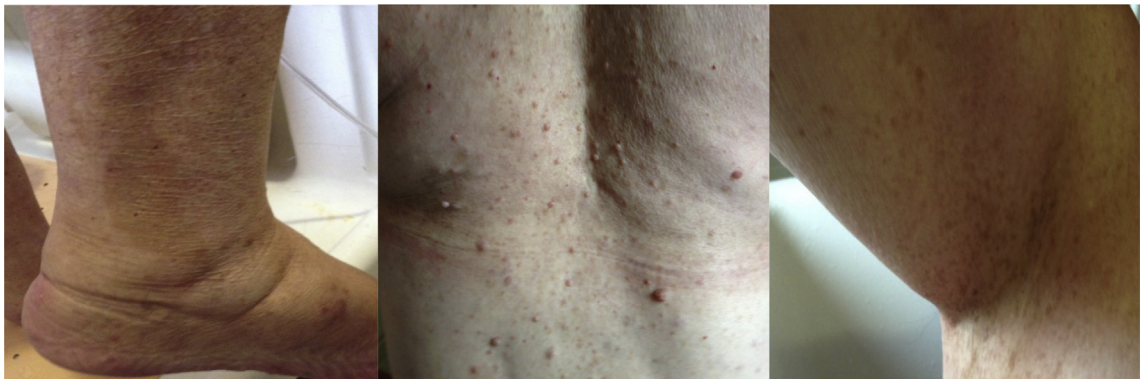

Fig. 1. Café au lait spot (left), cutaneous neurofibroma (center) and axillary freckles (right).

Cardiopulmonary auscultation was normal. Arterial blood gas analysis revealed hypoxemia (pa02 = 55 mmHg) and CT-angiography had no signs of pulmonary embolism but indicated a sparse ground-glass centrilobular micronodular infiltrate. Initial transthoracic echocardiogram showed preserved global systolic function and minimal tricuspid insufficiency, with pulmonary artery systolic pressure (PASP) of 32 mmHg; autoimmune study was normal and HIV serology was negative.

The subsequent investigation included respiratory functional tests that revealed reduced DLCO (2.15 mmol/min/kPa, 33.5%) and 6MWT with O_2 supplementation at 2L/min that showed a significant desaturation (walked distance: 240 m/61%, desaturation from 97 to 81%).

HRCT revealed patchy areas of centrilobular ground-glass micronodules (Fig. 2).

Bronchoalveolar lavage (BAL) citoimunologic study revealed increased monocytes/macrophages (97%). A transthoracic lung biopsy was also performed but it didn't allow a definitive diagnosis.

Concomitantly, the presence of cafe au lait spots, axillary freckles and cutaneous neurofibromas lead to the suspicion of NF1. Further investigation revealed multiple bilateral Lisch nodules. The conjugation of established well-defined clinical criteria (two or more Lisch nodules, two or more neurofibromas and axillary freckling) allowed a definitive diagnosis of NF1, which was complemented by genetic study (with identification of one of the known NF1-related somatic mutations - exon53:c.7846C > T).

In the meantime, there was a progressive clinical worsening with development of cor pulmonale. Right heart catheterization was performed and confirmed pre-capillary PH (mean PASP: 41 mmHg; pulmonary wedge pressure: 9 mmHg; pulmonary vascular resistance (PVR): 10.73UWood; cardiac index (CI) = 2,39L/min/m^2). Pre-capillary PH could fit in group 5, secondary to NF, but at this time there were doubts about the presence of a diffuse lung disease (DLD), so surgical lung biopsy was requested.

The material obtained was reviewed in the Pathology Department of Royal Brompton Hospital in London. There was marked thickening of the intima of arteries and some arterioles as a manifestation of vascular disease. It was also visible an accumulation of macrophages along bronchovascular bundles but also at alveolar spaces and hyperplasia of type II pneumocytes (Fig. 3).

With regard to interstitial findings, the diagnosis of respiratory bronchiolitis (RB-ILD) was considered, however there was no smoke exposure history. As in other previous publications, the presence of interstitial abnormalities in the context of NF1 was hypothesized.

The patient was diagnosed as having a DLD with a mild radiologic appearance, disproportionate to pulmonary vascular disease so that pre-capillary PH was interpreted in the context of NF.

She was referred to a PH treatment center in class III of New York Heart Association (NYHA). The patient began Iloprost in January 2014; Bosentan and Sildenafil were added a month later and Iloprost was changed to Epoprostenol IV 6 months later. There was no response to triple therapy and the patient experimented progressive deterioration culminating in death 18 months after treatment beginning.

3. Discussion

NF1 is a common neurogenetic disease of autosomal dominant inheritance affecting ectodermal and mesodermal tissues [1,10]. Half of the cases are familiar and the other half result from spontaneous mutations. The disease is caused by a mutation in a gene on the long arm of chromosome 17 (NF1 gene) encoding Neurofibromin, a GTPase-activator protein that produces a downregulation of proto-oncogenes. As a result, there is a disproportional cell proliferation leading to an increased risk of neoplasms [2].

NF diagnosis is based on well-defined clinical criteria, requiring the fulfillment of at least two items in order to assert the diagnosis [1].

Although the mutation in NF1 gene has complete penetrance, the disease itself is highly variable in its clinical manifestations and degrees of severity [1,16].

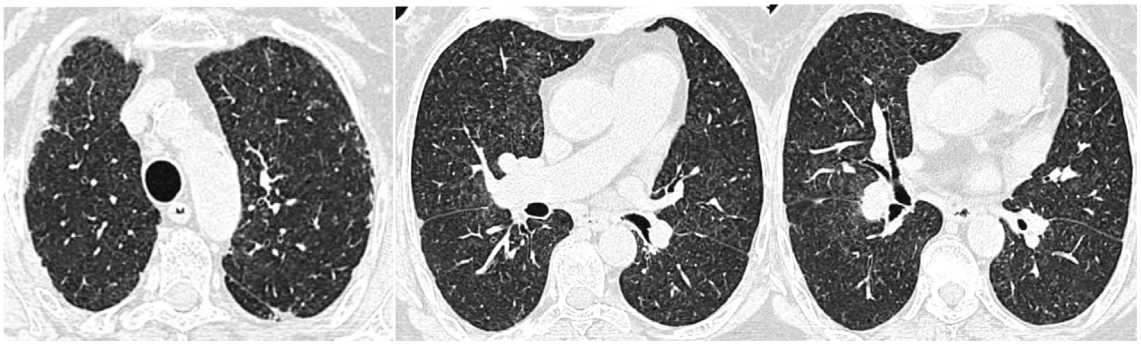

Fig. 2. Chest CT (axial reconstruction, pulmonary window) revealing patchy areas of centrilobular ground-glass micronodules.