Respiratory Medicine Case Reports 24 (2018) 8–11

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

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

Daniela Rodrigues[a,*], Hugo Oliveira[b], Carina Andrade[b,1], Luísa Carvalho[c], Susana Guimarães[d], Conceição Souto Moura[d], Ana Paula Vaz[a]

[a] Pulmonology Department, Hospital Pedro Hispano, Rua Dr. Eduardo Torres 4464-513 Senhora da Hora, Matosinhos, Portugal
[b] Internal Medicine Department, Hospital Pedro Hispano, Rua Dr. Eduardo Torres 4464-513 Senhora da Hora, Matosinhos, Portugal
[c] Internal Medicine Department, Centro Hospitalar do Porto, Largo Prof. Abel Salazar 4099-001 Porto, Portugal
[d] Pathological Anatomy Department, Centro Hospitalar de São João, Alameda Prof. Hernâni Monteiro 4200–319 Porto, Portugal

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).

* Corresponding author.
E-mail address: danielar@portugalmail.pt (D. Rodrigues).
[1] Permanent address: Internal Medicine Department, Centro Hospitalar do Porto. Largo Prof. Abel Salazar 4099-001 Porto, Portugal.

https://doi.org/10.1016/j.rmcr.2018.03.008
Received 20 January 2018; Received in revised form 14 March 2018; Accepted 15 March 2018

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].

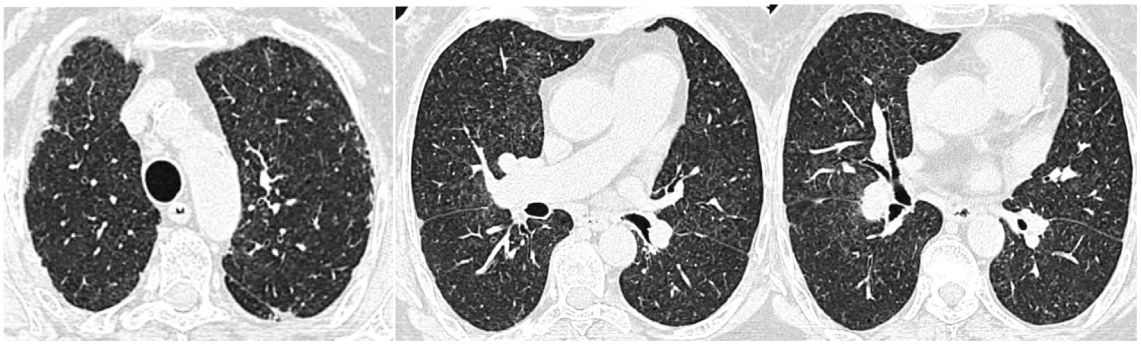

Fig. 2. Chest CT (axial reconstruction, pulmonary window) revealing patchy areas of centrilobular ground-glass micronodules.

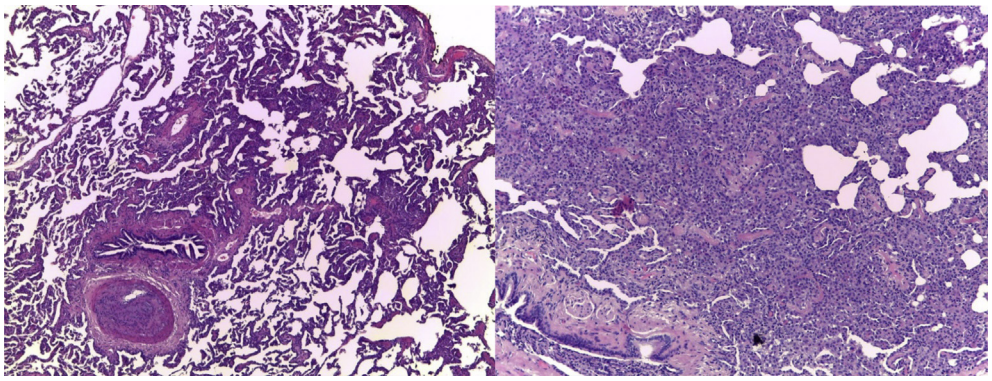

Fig. 3. (*Left*): Haematoxylin and Eosin (H&E) stain, 100× magnification. Arteriole with concentric and eccentric intimal thickening by fibrosis; pneumocyte hyperplasia and accumulation of macrophages, mostly along bronchovascular bundles.
(*Right*): Haematoxylin and Eosin (H&E) stain, 100× magnification. Intense macrophage accumulation in alveolar spaces, predominantly in the centrilobular regions.

Vasculopathy is a recognized but rare expression of the disease with an estimated prevalence of 0.4–6.4% [17]. Characteristically there is a proliferation of intima and media layers usually involving renal, mesenteric and aortic vessels [14,17]. The involvement of pulmonary arterial beds with associated pulmonary hypertension is unusual in NF1 [14,15,17].

In 2011, Montani et al. published a report of 8 patients with NF1-related PH [18]. Like in our case, PH occurred late in the course of the disease. Dyspnea and right heart failure signs were the initial findings. At diagnosis, patients had severe hemodynamic impairment with low CI (median 2.3 L/min/m^2) and elevated indexed PVR (median 15.1 mmHg/L/min/m^2). All patients were in NYHA III with severe exercise limitation (median 6-min walked distance: 180 m).

PH late diagnosis in NF1 patients is probably related to the indolent nature of symptoms and brings into question the possible benefit of a systematic echocardiographic evaluation of patients with an established diagnosis of NF. However to date this strategy is still not recommended because of the very low incidence of PH in NF1 patients [15].

The available treatments for PH in NF have been showing discouraging results. An aggressive therapeutic approach similar to group 1 PH, based in a phosphodiesterase-5 inhibitor and an endothelin receptor antagonist, is currently advocated [18,19]. Usually there is a progressive course with development of cor pulmonale and progression to terminal right cardiac failure [15,20].

In addition to vascular findings, interstitial abnormalities have been also reported in NF1-related PH patients [4-14,20].

Considering again the sample of 8 N1-PH patients analysed by Montani [18], 5 had also interstitial findings (mainly lung cysts). Like in our case, in some of them the exuberance of vascular disease was disproportionate when compared to pulmonary involvement. Therefore, in our case, considering the subtlety of interstitial findings, PH was thought to belong more probably to group 5 than to group 3.

Since the last 50 years, the hypothesis of a NF1-related interstitial disease has aroused interest in the scientific community [4–13]. In fact, since then and even nowadays, there has been some divergence between the published studies.

Ryu et al. studied 156 patients with NF with chest radiography and found evidence of interstitial involvement in only 3 patients (1.9%). Interstitial findings (cysts, reticular opacities and ground-glass infiltrates) were attributed to other known conditions of the patients, refusing the existence of a characteristic interstitial pattern in NF1 [11]. However, in this study, there was no evaluation with HRCT or lung biopsy.

Tobacco smoke has been suggested as a potential confounding factor since the reported bubbles and ground-glass opacities may occur in smoking emphysema and RB-ILD and not secondarily to NF [21]. In this regard, some studies also hypothesize that NF1 can potentially increase lung susceptibility to smoke injury [21,22].

Zamora et al. reviewed 64 literature reports of DLD in patients with NF1. The mean age of patients was 50 years and 69% were male. HRCT was performed in only 8 patients and revealed the presence of ground-glass opacities (37%), bibasilar reticular opacities (50%), bubbles (50%) and cysts (25%). However the information on smoking history was only available in 16 patients and only four were non-smokers (one evaluated with HRCT) [10].

In 2011 Oikonomou et al. evaluated 6 non-smoking NF1 patients with HRCT. Small thin-walled cysts not associated with emphysema and micronodular ground-glass infiltrates were observed in all patients. Despite the absence of histological support, it was stated that the changes described in this and other related studies were not associated with smoking and may constitute specific manifestations of NF1 [22]. One year later, Nardecchia et al. reported another case of a 16-year old non-smoker NF1 patient who presented bilateral apical lung bullae. In this case, surgical lung biopsy was performed, revealing emphysematous abnormalities [23].

Solid data about histological features in these patients is lacking, preventing the ascertainment of a potential “NF1 pattern”. In one of Montani's NF1-PH patients, the pathological assessment of lung tissue revealed, as in our case, marked intimal hyperplasia in arterial beds and numerous macrophages and giant cells within alveolar spaces. However, those interstitial findings could also be related to the patient previous smoking habits [18].

In this case we believe that pulmonary lung biopsy strongly suggests the presence of a DLD with accumulation of macrophages in centrilobular regions in a patient with no environmental exposure.

The pertinence of this report seems to us to go beyond its rarity, in that it allows to reflect on two controversial manifestations of NF1: pulmonary hypertension, whose mechanisms still need further research in order to find an effective therapeutic target, and DLD, whose existence as a NF1-related entity has been discussed for decades and still lacks a formal extended investigation supported by all the current diagnostic tools.

Compliance with ethical standards

- There was no funding for this work.

- The authors declare that they have no conflict of interest.
- This article does not contain any study with human participants or animals performed by any of the authors.

Informed consent

- Written informed consent for publication of this case report, accompanying images and any additional related information was obtained from the next of kin of the deceased participant (daughter).

References

[1] A.C. Hirbe, D.H. Gutmann, Neurofibromatosis type 1: a multidisciplinary approach to care, Lancet Neurol. 13 (2014) 834–843.
[2] M.H. Shen, P.S. Harper, M. Upadhyaya, Molecular genetics of neurofibromatosis type 1, J. Med. Genet. 33 (1996) 2–17.

[3] S.E. Rossi, J.J. Erasmus, H.P. McAdams, L.F. Donnelly, Thoracic manifestations of Neurofibromatosis-I, AJR Am. J. Roentgenol. 173 (1999) 1631–1638.
[4] P.B.D. Davies, Diffuse pulmonary involvement in vonRecklinhausen's disease: a new syndrome, Thorax 18 (1963) 198.
[5] D. Massaro, S. Katz, M.J. Matthews, G. Higgings, Von Recklinghsusen's neurofibromatosis associated with cystic lung disease, Am. J. Med. 38 (1965) 233–240.
[6] S.S. Sagel, J.V. Forrest, F.B. Askin, Interstitial lung disease in neurofibromatosis, South. Med. J. 68 (1975) 647–649.
[7] W.R. Webb, P.C. Goodman, Fibrosing alveolitis in patients with neurofibromatosis, Radiology 122 (1977) 289–293.
[8] S.A. Davis, R.L. Kaplan, Neurofibromatosis and interstitial lung disease, Arch. Dermatol. 114 (1978) 1368–1369.
[9] J.L. Burkhalter, J.U. Morano, M.B. McCay, Diffuse interstitial lung disease in neurofibromatosis, South. Med. J. 79 (1986) 944–946.
[10] A.C. Zamora, H.R. Collard, P.J. Wolters, W.R. Webb, T.E. King, Neurofibromatosis-associated lung disease: a case series and literature review, Eur. Respir. J. 29 (2007) 210–214.
[11] J.H. Ryu, J.G. Parambil, P.S. McGrann, G.L. Aughenbaugh, Lack of evidence for an association between neurofibromatosis and pulmonary fibrosis, Chest 128 (2005) 2381–2386.
[12] P. Nalepa, M. Wolnicka, Neurofibromatosis type 1 with interstitial pulmonary lesions diagnosed in adult patient. A case study and literature review, Pneumonol. Alergol. Pol. 80 (2012) 152–157.
[13] M.Y. Shino, S. Rabbani, J.A. Belperio, J.P. Lynch 3rd, S.S. Weigt, Neurofibromatosis-associated diffuse lung disease: case report, Semin. Respir. Crit. Care Med. 33 (5) (2012) 572–575.
[14] J.M. Friedman, J. Arbiser, J.A. Epstein, D.H. Gutmann, S.J. Huot, A.E. Lin, B. McManus, B.R. Korf, Cardiovascular disease in neurofibromatosis 1: report of the NF1 cardiovascular task force, Genet. Med. 4 (2002) 105–111.
[15] L. Gumbiene, Z. Petrulioniene, K. Rucinskas, V. Maneikiene, P. Serpytis, A. Dranenkiene, A. Laucevicius, Pulmonary hypertension: a fatal complication of neurofibromatosis type 1, Respir. Care 56 (2011) 1844–1848.
[16] L. Reviron-Rabec, B. Girerd, A. Seferian, K. Campbell, S. Brosseau, E. Bergot, M. Humbert, G. Zalcman, D. Montani, Pulmonary complications of type 1 neurofibromatosis, Rev. Mal. Respir. 33 (2016) 460–473.
[17] G.S. Oderich, T.M. Sullivan, T.C. Bower, P. Gloviczki, D.V. Miller, D. Babovic-Vuksanovic, T.A. Macedo, A. Stanson, Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results, J. Vasc. Surg. 46 (2007) 475–484.
[18] D. Montani, F. Coulet, B. Girerd, M. Eyries, E. Bergot, H. Mal, G. Biondi, C. Dromer, T. Hugues, C. Marquette, C. O'Connell, D.S. O'Callaghan, L. Savale, X. Jaïs, P. Dorfmüller, H. Begueret, L. Bertoletti, O. Sitbon, C. Bellanné-Chantelot, G. Zalcman, G. Simonneau, M. Humbert, F. Soubrier, Pulmonary hypertension in patients with neurofibromatosis type I, Medicine (Baltim.) 90 (2011) 201–211.
[19] P.B. Poble, J.C. Dalphin, B. Degano, Severe dyspnea in a patient with neurofibromatosus type 1, Resp Med Case Rep 22 (2017) 74–76.
[20] B. Martignac, F. Gagnadoux, W. Trzepizur, N. Beneton, F. Vinchon, A. Paris, D. Montani, F. Goupil, Atteinte pulmonaire sévère au cours de la neurofibromatose de type 1 [Severe pulmonary involvement in the course of type 1 neurofibromatosis], Rev. Mal. Respir. 31 (2014) 621–623.
[21] A. Yokoyama, N. Kohno, K. Sakai, K. Kondo, Y. Hirasawa, K. Hiwada, Distal acinar emphysema and interstitial pneumonia in a patient with von Recklinghausen's Disease: five-year observation following quitting smoking, Intern. Med. 36 (1997) 413–416.
[22] A. Oikonomou, K. Vadikolias, T. Birbilis, D. Bouros, P. Prassopoulos, HRCT findings in the lungs of non-smokers with neurofibromatosis, Eur. J. Radiol. 80 (2011) e520–e523.
[23] E. Nardecchia, L. Perfetti, M. Castiglioni, D. Di Natale, A. Imperatori, N. Rotolo, Bullous lung disease and neurofibromatosis type-1, Monaldi Arch. Chest Dis. 77 (2012) 105–107.