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CASE REPORT

Bullous lung disease and neurofibromatosis type-1

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ABSTRACT: ***Bullous lung disease and neurofibromatosis type-1. E. Nardecchia, L. Perfetti, M. Castiglioni, D. Di Natale, A. Imperatori, N. Rotolo.***

Lung interstitial diseases and bullae are described as possible complications of neurofibromatosis type-1 (NF-1), a genetic disorder inherited as a autosomal-dominant trait. We report the case of a 16-year-old male non-smoker with NF-1, who presented with pneumothorax caused by ruptured lung bullae. The case of this young patient, successfully treated by video-assisted thoracoscopic resection of bullae, supports the concept that pulmonary alterations may be part of the NF-1 syndrome, rather than as an unrelated complication.

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Keywords: Neurofibromatosis, Pneumothorax, Emphysema, Lung bullae.

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Introduction

Von Recklinghausen's disease (VRD), also known as neurofibromatosis-1 (NF-1) is an autosomal-dominant disease that occurs with a prevalence of 1:2500-3000, independently from ethny and gender. Approximately 50% of cases are due to mutation of chromosome 17. Clinically, NF-1 is recognised by the presence of numerous "café-au-lait" skin macules, but 25% of affected patients develop multiple cutaneous and central nervous system (CNS) tumors that are histologically characterized as neurofibroma, pheochromocytoma or fibrosarcoma [1, 2].

To establish the diagnosis of NF-1, molecular definition of the disease is not necessary. Clinical criteria for the diagnosis of NF-1 were defined in 1997 and confirmed in 2007 [3]; two or more of the following criteria must be met:

- six or more *café-au-lait* spots >5 mm in diameter before puberty, or >15 mm after puberty;
- two or more typical neurofibromas of any type, or one plexiform neurofibroma;
- frackles/hyperpigmentation spots in area inaccessible to sunlight (axilla, groin);
- two ore more iris hamartomas (Lisch nodules);
- typical bone abnormalities (see below);
- first-degree relative meeting the above criteria.

The thoracic manifestations of NF-1 are most commonly cutaneous, but they can also be skeletal and pulmonary [4]. The most common thoracic skeletal manifestations of NF-1 involve the spine and ribs. Characteristic deformities of the ribs include well-marginated erosions of one or more ribs, and the separation of adjacent ribs due to plexiform neurofibromas. Spinal abnormalities can present as kyphoscoliosis, posterior scalloping of the vertebral bodies and enlargement of neural foramina [2]. Lung manifestations, that usually include interstitial lung disease (ILD) and thin-walled bullae, are reported in as many as 10-20% of adult patients with NF-1. Although these findings may be incidental, sometimes patients present with dyspnea that may also result from lung mesenchymal abnormalities [5]. Pulmonary fibrosis is usually bilateral and simmetric, predominantly basal [6]. Typically, ILD occurs in association with bullae that are thin-walled, located in the upper lobes, and usually asymmetric [1, 6].

Case report

A 16-year-old male non-smoker, with ectomorph body build, affected by VRD was referred to our hospital complaining of chest pain and palpitations. His vitals signs and haemoglobin oxygen saturation were normal. Chest X-ray examination showed left pneumothorax (fig. 1). The patient past medical history was unremarkable, except for the diagnosis of VRD made in 2004. This diagnosis was based on physical examination, which revealed multiple (>6) large *café-au-lait* macules on the chest skin and in cutaneous areas of the abdomen usually not exposed to sunlight (fig. 2). Other clinical manifestations of VRD (CNS, skeletal, neurological) were absent. The pneumothorax

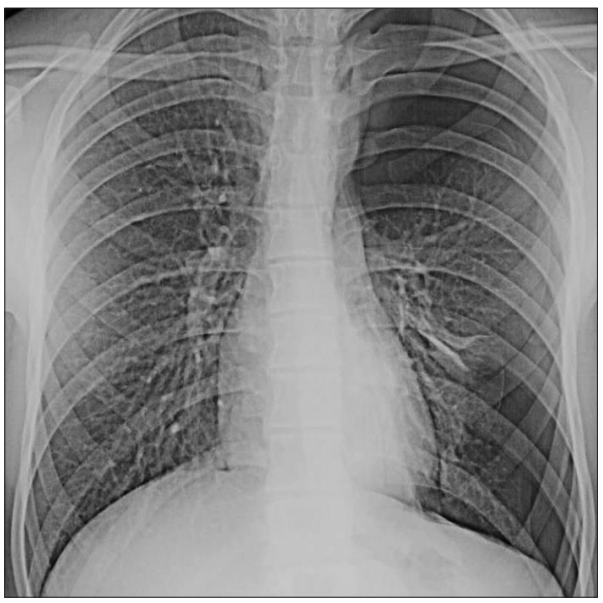

Fig. 1. Chest X-ray exam on admission, showing left-sided pneumothorax.

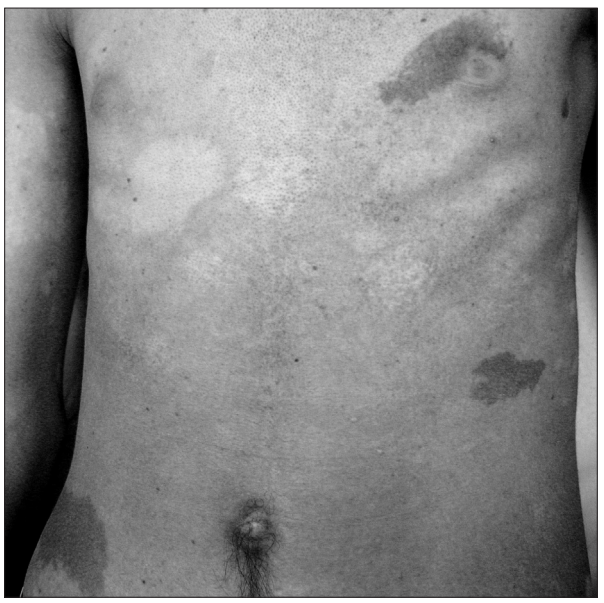

Fig. 2. *Café-au-lait* cutaneous macules on the chest and abdomen.

was treated by tube drainage of the left pleural space. Since pulmonary air leakage persisted for several days, high-resolution computed tomography (HRCT) of the chest was obtained. Chest scans revealed bilateral apical lung bullae, with diameter up to 1.5 cm (fig. 3). Surgical treatment of persistent pneumothorax was decided. With a left 3-port video-thoracoscopic approach, the apical lung bullae were resected and successful pleurodesis was obtained by partial parietal pleurectomy. Histological examination of the resected pulmonary bullae revealed emphysematous parenchyma with sub-pleural bullae. The post-operative course was uneventful and after seven days the patient was discharged in good condition. At 30-day follow-up the patient was asymptomatic.

Discussion

NF-1 is a neurogenetic disorder with widespread involvement of neuroectodermal and mesodermal tissues [7, 8]. Lung involvement consisting of ILD and/or bullae is not infrequent in the context of NF-1. The association between NF-1 and ILD was first reported in 1963 by Davies [9], and several authors described coexisting lung diseases in 10-20% of patients with NF-1 [5, 9]. A review of the pertinent literature revealed many different types of lung lesions detected by radiological imaging in VRD patients, as summarized in table 1. Associated pulmonary manifestations most commonly include bilateral fibrosis with basal predominance, associated or not with thin-walled bullae that typically occur in the upper lobes [1, 2, 5, 9-16]. Less frequently intra thoracic tumour and cystic disorders have been described [1, 2, 5]. However, it is uncertain whether the development of ILD is a peculiar phenotypic manifestation of NF-1. A recent article questioned such association, reporting that the evidence supporting a causative relationship between NF-1 and interstitial diseases is poor, and suggested that the latter are mainly smoking-induced manifestations [15]. However, Zamora *et al*. proposed that NF-1 in association with ILD represents a distinct clinical entity [1]. The pathogenesis of ILD in patients with NF-1 is uncertain. Patchefsky *et al*. suggested that pulmonary fibrosis in NF-1 may be determined by increased deposition of collagen in the lung, causing a fibrotic environment [12]. Fabricant *et al*. postulated a similar pathogenetic mechanism, attributing the cause of ILD to myofibroblast activation by increased nerve growth factor levels in NF-1 patients [17].

In our case, the patient had a pre-existing clinical diagnosis of NF-1, documented by *café-au-lait* macules on the chest and lower abdomen skin, and presented with pneumothorax caused by ruptured lung bullae. His chest HRCT showed bilateral apical lung bullae, without signs of fibrosis, and histology of the resected bullous parenchyma revealed emphysematous lung. Differently from previous reports of lung bullous disease associated with VRD, that occurred after the fourth decade of life [11, 13, 14, 16], the case here described occurred in a non-smoker young male, and supports the concept that NF-1 with bullous

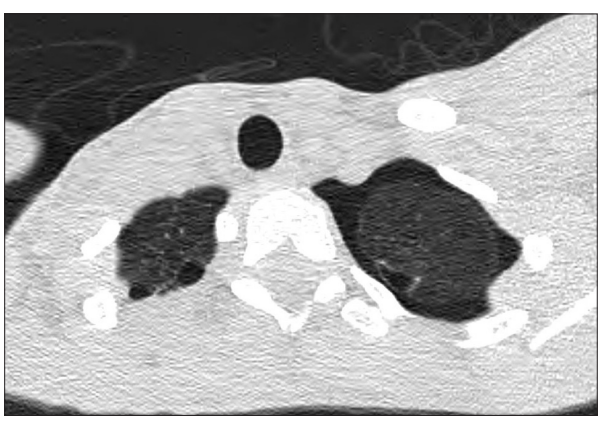

Fig. 3. High resolution computed tomography scan of the chest, showing pulmonary bullous disease bilaterally, and left-sided pneumothorax.

Table 1. - Chest radiographic findings of lung abnormalities associated with NF-1

Author	Cases of thoracic abnormalities in VRD* patients	Radiographic appearance	Predominant lung site	Respiratory symptoms
Davies PDB, 1963 [9]	9	Mottled opacities	Lower lobe	Breathlessnes, dyspnoea
Israel-Asselain R, 1965 [10]	2	Reticular/linear opacities Nodular opacities	Upper lobe Lower lobe	Dyspnoea, cough
Massaro D, 1966 [11]	20	Bullae Mottled and linear infiltrate	Upper lobe Diffuse	Not Available
Patchefsky A, 1973 [12]	1	Diffuse interstitial infiltrations	Lower lobe	Dyspnoea
Volpini E, 1995 [13]	1	Severe bullous emphysema	Upper lobe	Breathlessnes
Yokoyama A, 1997 [14]	1	Bullae and acinar emphysema	Upper lobe	No
Rossi SE, 1999 [2]	Not Available	Thin-walled bullae Lung fibrosis	Upper lobe Lower lobe	Not Available
Ryu JH, 2005 [15]	22	Pulmonary nodules Cystic airspace Bullae Interstitial infiltrate	Not Available	Not Available
Zamora AC, 2007 [1]	64	Thin-walled bullae Linear opacities Bullous emphysema Thin-walled cyst	Upper lobe Lowe lobe Upper lobe Upper lobe	Dyspnoea, cough, chest pain
Oikonomou A, 2010 [5]	6	Thin-walled cyst	Upper lobe	No
Zanobetti M, 2012 [16]	1	Small thin-walled cyst	Lower lobe	Dyspnoea, cough

* VRD = Von Recklinghausen's disease.

lung disease may be a distinct clinical entity, unrelated to smoking [1, 5, 9].

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