Respiratory Medicine 149 (2019) 9–15

Contents lists available at ScienceDirect

Respiratory Medicine

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

Review article

Neurofibromatosis type 1: State-of-the-art review with emphasis on pulmonary involvement

Sérgio Ferreira Alves Júnior[a], Gláucia Zanetti[a], Alessandro Severo Alves de Melo[b], Arthur Soares Souza Jr.[c], Luciana Soares Souza[c], Gustavo de Souza Portes Meirelles[d], Klaus Loureiro Irion[e], Bruno Hochhegger[f], Edson Marchiori[a,*]

[a] Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[b] Universidade Federal Fluminense, Rio de Janeiro, Brazil
[c] Faculdade de Medicina de São José do Rio Preto (Famerp) and Ultra X, São José do Rio Preto, SP, Brazil
[d] Universidade Federal de São Paulo (UNIFESP) and Grupo Fleury, São Paulo, SP, Brazil
[e] The University of Manchester, Manchester, United Kingdom
[f] Santa Casa de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil

ARTICLE INFO

Keywords:
Neurofibromatosis type 1
Interstitial lung disease
Computed tomography
Pulmonary hypertension
Pulmonary diseases

ABSTRACT

Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen's disease, is an autosomal dominant dysplasia of the ectoderm and mesoderm with a variable clinical expression, but near-complete penetrance before the age of 5 years. The estimated incidence is 1 in 3000 births. NF-1 is characterized by collections of neurofibromas, café-au-lait spots, axillary and inguinal freckling, and pigmented hamartomas in the iris (Lisch nodules). Pulmonary manifestations of NF-1, which usually include bilateral basal reticulations and apical bullae and cysts, are reported in 10–20% of adult patients. Clinically, neurofibromatosis-associated diffuse lung disease (NF-DLD) usually presents with nonspecific respiratory symptoms, including dyspnea on exertion, shortness of breath, and chronic cough or chest pain, at the time of diagnosis. Computed tomography (CT) is highly accurate for the identification and characterization of NF-DLD; it is the most reliable method for the diagnosis of this lung involvement. Various CT findings of NF-DLD, including cysts, bullae, ground-glass opacities, bibasilar reticular opacities, and emphysema, have been described in patients with NF-1. The typical CT pattern, however, is characterized by upper-lobe cystic and bullous disease, and basilar interstitial lung disease. Currently, the goal of NF-DLD treatment is the earliest possible diagnosis, focusing on symptom relief and interventions that positively alter the course of the disease, such as smoking cessation. The aim of this review is to describe the main clinical, pathological, and imaging aspects of NF-1, with a focus on pulmonary involvement.

1. Introduction

Neurofibromatosis type 1 (NF-1) is a genetic syndrome characterized by clinical manifestations of systemic and progressive involvement that mainly affect the skin, nervous system, bones, and eyes, and can affect any other organ [1,2]. Collections of neurofibromas, café-au-lait spots, axillary and inguinal freckling, and pigmented hamartomas in the iris (Lisch nodules) are the main features of NF-1 and represent some of the diagnostic criteria for this disease [1–4]. Less common features include bone deformities (pseudarthrosis, dysplasia), scoliosis, short stature, cognitive deficits, seizure disorders, peripheral neuropathies, and more serious manifestations, such as plexiform neurofibromas, malignant peripheral nerve sheath tumors (MPNSTs), and optic nerve and other central nervous system gliomas [3,5].

The thorax and lungs can be affected in several ways, including by the development of cutaneous and subcutaneous neurofibromas on the chest wall, kyphoscoliosis, ribbon deformity of the ribs, posterior vertebral scalloping, intrathoracic neurogenic neoplasms, meningoceles, bullous lung disease, pulmonary hypertension (PH), and interstitial lung disease [1,6,7]. The aim of this review is to describe the main clinical, pathological, and imaging aspects of NF-1, focusing on thoracic and pulmonary involvement.

* Corresponding author. Rua Thomaz Cameron, 438. Valparaiso, CEP 25685, 120.Petrópolis, Rio de Janeiro, Brazil.
E-mail addresses: sergio_faj@hotmail.com (S.F. Alves Júnior), glauciazanetti@gmail.com (G. Zanetti), alesevero@gmail.com (A.S. Alves de Melo), asouzajr@gmail.com (A.S. Souza), luciana.soaressouza@gmail.com (L.S. Souza), gmeirelles@gmail.com (G. de Souza Portes Meirelles), klaus.irion@btinternet.com (K.L. Irion), brunohochhegger@gmail.com (B. Hochhegger), edmarchiori@gmail.com (E. Marchiori).

https://doi.org/10.1016/j.rmed.2019.01.002
Received 11 August 2018; Received in revised form 4 January 2019; Accepted 11 January 2019
Available online 17 January 2019
0954-6111/

2. Epidemiology and genetic aspects

NF-1 traditionally exhibits autosomal dominant inheritance, being the most common of the phakomatoses (neurocutaneous syndromes) and the most common autosomal dominant disorder. It has a reported incidence of 1 in 3000 births; in 30–50% of cases, affected individuals have no family history of the disease, and NF-1 is caused by the spontaneous appearance of *de novo* mutations in (usually paternal) germ cells [4,8–11]. Penetrance is nearly complete before the age of 5 years, but the clinical expression of NF-1 is highly variable, even within the same family. Conversely, members of different affected families frequently show similarity in the distribution of lesions [2,12]. At least 1 million individuals worldwide are believed to be living with NF-1 [2]. The disease has no predilection for sex, and several studies have failed to establish any significant racial difference in its incidence [2,9].

NF-1 results from a mutation in the *NF1* tumor-suppressor gene, located on the long arm of chromosome 17 (at locus 17q11.2) and encoding a cytoplasmic protein called neurofibromin type 1. This protein is a negative regulator of the *Ras* proto-oncogene, and is predominantly expressed in neurons, Schwann cells, oligodendrocytes, and astrocytes [2,9,12].

A central region of neurofibromin is structurally and functionally homologous to GTPase-activating proteins, which accelerate the hydrolysis of p21Ras-GTP (the active form) to p21Ras-GDP (the inactive form) by stimulating intrinsic p21Ras-GTPase activity. As p21Ras proteins play central roles in cell differentiation and growth, inactivation of the *NF1* gene favors the active state (p21Ras-GTP), resulting in the permanent stimulation of a cascade of signals and excessive cell division due to non-regulated activation of the MAP kinase pathway. This pathway could play a role in the development of benign neurofibroma-type tumors, MPNSTs, PH with hyperplasia of pulmonary artery smooth-muscle cells, and interstitial disease, such as hyperplasia/metaplasia of interstitial pulmonary fibroblastic cells [2,12].

3. Diagnosis

The diagnosis of NF-1 is based on the presence of two or more of the following seven criteria, determined by the clinical evaluation and family history of the patient: six or more café-au-lait spots (diameter > 5 mm before puberty and > 15 mm after puberty), two or more neurofibromas of any type or one plexiform neurofibroma, axillary freckling, two or more iris hamartomas (Lisch nodules), optic glioma, typical bone lesions (sphenoid dysplasia or tibial pseudarthrosis), and one or more first-degree relatives with NF-1. These diagnostic criteria were defined in 1987 by the United States National Institutes of Health and have been proven to be strong and reliable, as they have stood well over time [13–16]. Approximately 50% of patients meet the diagnostic criteria for NF-1 up to the age of 1 year, 97% meet the criteria by the age of 8 years, and virtually all patients fulfill them by the age of 20 years [16].

Café-au-lait spots (Fig. 1) are symmetrical flat areas of cutaneous hyperpigmentation (classically described as being light brown in color) with rounded edges, usually seen at birth. They are typically the initial clinical manifestation of NF-1 and tend to increase in size and number throughout childhood and puberty. By adulthood, about 95% of patients with NF-1 have café-au-lait spots [8,17]. In addition, 70% of patients with NF-1 show freckling in the intertriginous areas of the axilla and in the inguinal region [8].

Cutaneous and subcutaneous neurofibromas (Fig. 2) are other frequent skin manifestations of NF-1, usually developing in the late teens or early twenties but occasionally emerge in early childhood. They occur in more than 95% of patients, with variation in number and size among individuals and within families [8,15,16,18]. Lisch nodules, which are hamartomas of the iris pigment epithelium, are the most common ophthalmological feature of NF-1, although they are not pathognomonic. They appear as multiple pale, yellowish-brown, oval to round, dome-shaped papules projecting from the surface of the iris. Optic pathway gliomas, seen in about 15–20% of patients with NF-1, are usually low-grade astrocytomas that can grow in the optic nerve, optic chiasm, optic tract, and hypothalamus [8,15,19].

Cognitive problems are the most common neurological complications in individuals with NF-1. Severe intellectual disability with an intellectual quotient < 70 (mental retardation) is rare and only slightly more frequent than in the general population [8,15]. Epilepsy occurs in approximately 6–7% of individuals with NF-1 [15]. Plexiform neurofibromas are classic neurogenic tumors that occur outside the central nervous system and are the pathognomonic feature of NF-1. They can affect a range of organs and, given the rich distribution of peripheral nerves throughout the thorax, NF-1–related thoracic neurofibromas may involve the ribs, chest wall, lungs, and mediastinum [11]. They typically manifest at birth, increase particularly in the first decade of life, and can grow during adolescence and early adulthood. They differ from other neurofibromas in arising from multiple nerve fascicles; they grow along the length of the involved nerve (compromising long segments), infiltrate the nerve, and extend to surrounding structures [8,9]. Plexiform neurofibromas carry a lifetime risk of malignant transformation to MPNSTs, although such transformation is rare [8,20].

Mutational and molecular analyses are helpful in confirming the clinical diagnosis of NF-1, notably in patients with paucisymptomatic forms: segmental forms in pediatric cases (café-au-lait spots are often the only clinical findings in young children) and Legius syndrome. Such analyses are also useful for prenatal diagnosis. However, genetic testing is not routinely recommended to establish the diagnosis in the daily clinical care of patients with typical NF-1, and consultation with medical specialists is advised before the test is performed [15,16,21]. One limitation of genetic testing is the lack of genotype–phenotype correlation. Therefore, although useful for diagnostic confirmation, a positive test result cannot be used to predict the severity or outcome of the disease [15,16].

4. Thoracic involvement

4.1. Pulmonary involvement

Pulmonary manifestations of NF-1 observed in imaging examinations include nodular, bullous, cystic, and/or interstitial parenchymal lesions, and are reported in 10–20% of adults with the disease (Figs. 3 and 4) [12,22,23]. NF-1–associated interstitial lung disease is generally bilateral, symmetrical, and predominantly basal. Typically, it occurs in association with thin-walled bullae, which are located in the upper lung zones [4]. This combination has been considered to be the hallmark of NF-1, although it is not pathognomonic of the disease [24].

Although NF-1 is congenital, pulmonary fibrosis and neurofibromatosis-associated diffuse lung disease (NF-DLD) are traditionally not evident before the patient reaches adulthood, typically appearing in the third or fourth decade of life [12,25]. Chest CT rarely reveals the typical honeycombing pattern representative of advanced-stage fibrosis; it more frequently shows different forms of injury, such as linear opacities, predominantly peripheral lung base reticulations, and ground-glass opacities [12]. The existence of an interstitial pneumonia type that is truly specific to NF-1 remains under debate, as most studies have provided little evidence to establish a reliable association between NF-1 and pulmonary fibrosis, and fibrotic changes may be smoking-induced manifestations [3,12,23,26]. Interstitial lung disease in patients with NF-1 is pathologically similar to that seen in other diseases that produce interstitial fibrosis [27]. It is characterized in its initial stages by thickening and lymphoplasmocytic cellular infiltration of the alveolar wall, with enlargement and desquamation of alveolar lining cells [25,27]. Subsequently, this cellular response is replaced by fibrosis, resulting in destruction of the alveoli, confluence of air spaces, formation of bullae, and obliteration of blood vessels [27]. This histopathology, defined by the expansion of the alveolar septa by

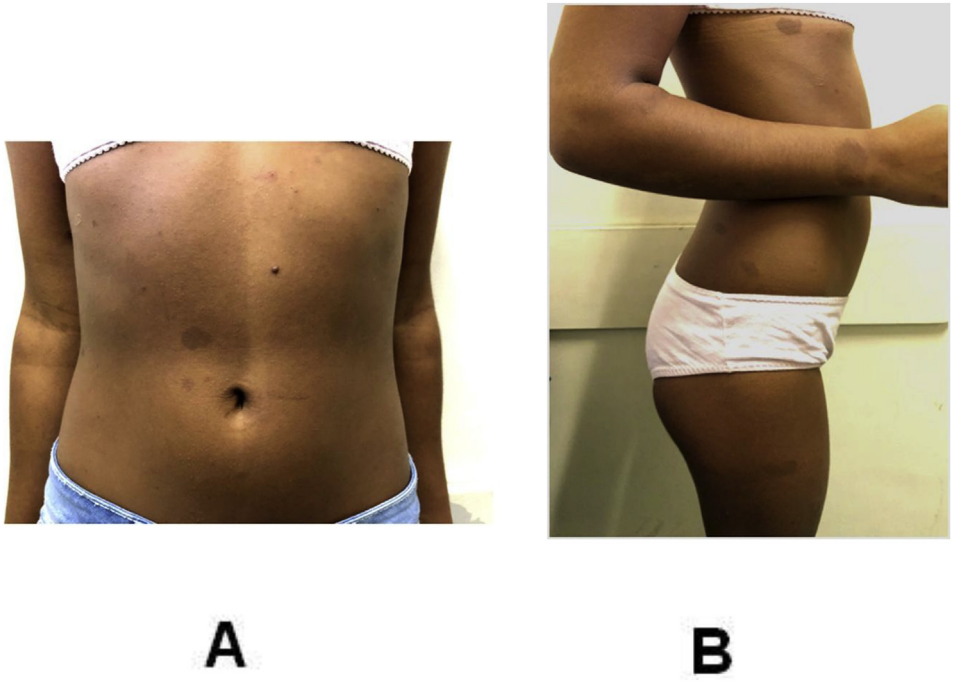

Fig. 1. A 12-year-old girl with neurofibromatosis type 1. Ectoscopic examination (a and b) shows multiple light-brown macules with rounded edges representing typical café-au-lait spots, coexisting with hypopigmented macules on the skin surface. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

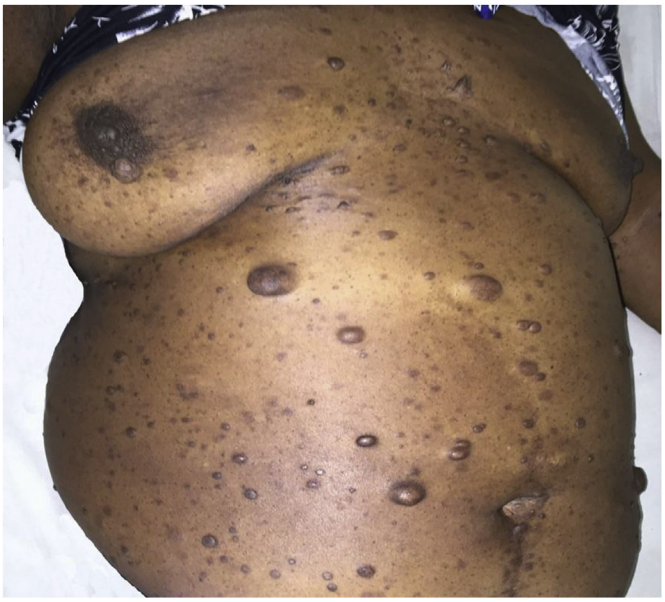

Fig. 2. A 70-year-old woman with neurofibromatosis type 1. Ectoscopic examination shows multiple pedunculated cutaneous neurofibromas on the skin surface.

lymphocytic inflammatory cells, with variable and increased amounts of interstitial smooth muscle and fibrosis, is consistent with a non-specific interstitial pneumonia pattern. Massaro and Katz [27] also reported increased numbers of intra-alveolar eosinophils and desquamated pneumocytes, rather than pigmented macrophages, as would be expected in desquamative interstitial pneumonia or respiratory bronchiolitis, entities linked to smoking. Thus, these findings support the hypothesis that NF-DLD (interstitial/cystic) is a distinct manifestation of NF-1, rather than a disease related purely to smoking. However, NF-1 may increase the sensitivity of the lungs to cigarette smoke, increasing the severity of NF-DLD in smokers and causing early development of emphysema-like changes in these patients [4,26].

Centrilobular nodules and parenchymal cysts show an apical predominance, with some subpleural cysts capable of simulating paraseptal emphysema. In the advanced stages of NF-1, the lesions are clustered, potentially leading to erroneous diagnosis of centrilobular emphysema [4,12]. Also, in advanced-stage disease, damage from diffuse cystic disease may progress to chronic respiratory failure, and may even lead to more serious complications, such as spontaneous pneumothorax or PH, mostly secondary to hypoxemia [12,28,29].

PH associated with NF-1 (PH-NF1) is a rare, but severe, complication of NF-1. It is classified as pre-capillary group 5 PH, defined as “PH with unclear and/or multifactorial mechanisms” [12,30]. PH-NF1 is characterized by female predominance, diagnosis at an advanced age, association with parenchymal lung disease in two-thirds of cases, and a poor long-term prognosis. Severe PH-NF1 is generally associated with lung lesions, mostly cysts or bullae in the upper lobes, diffuse ground-glass opacities (sometimes with a mosaic pattern), and reticular opacities. However, parenchymal lung disease is absent in one-third of PH-NF1 cases, and the severity of PH is disproportionate to the degree of NF-DLD in other cases, supporting the hypothesis of a specific vascular disease, rather than disease secondary to hypoxemia [12,30–33].

Extending beyond the frequent reporting of nodular and cystic lesions in smokers, Oikonomou et al. [23] reported the CT finding of upper-lobe-predominant cystic lesions in all of six non-smokers with NF-1, and centrilobular nodules in five of the six patients. Given that none of these six patients was ever a smoker, the observed cystic changes cannot be attributed to emphysema. The random distribution of the cystic changes, the cysts’ thin but well-defined walls, and the absence of any centrilobular artery in their centers also do not support the diagnosis of emphysema [23].

In 2007, Zamora et al. [4] carried out an extensive literature review in which 64 cases of NF-DLD were analyzed by chest radiography (available in 63 cases) and/or chest CT (available in 8 cases), with the aims of estimating the frequency and describing the pattern of pulmonary radiological findings. Chest CT revealed bullae (50%), bibasilar reticular abnormalities (50%), ground-glass opacities (37%), emphysema (25%), and cysts (25%), but not honeycombing [4]. The review showed no significant difference in age, pulmonary function pattern, or radiographic abnormalities between non-smokers and smokers. Emphysema was not seen in any of the 4 non-smoking patients and was seen in 2 of the 12 smokers. The remaining cases had no smoking

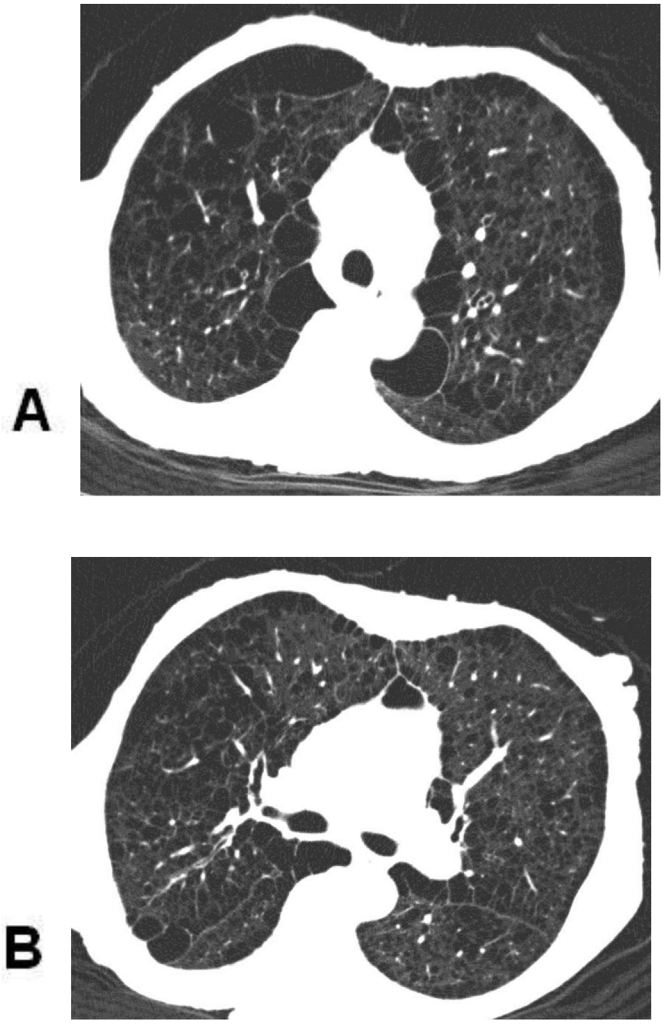

Fig. 3. A 64-year-old female smoker with neurofibromatosis type 1. Axial high-resolution CT images obtained with lung window settings at the levels of the upper lobes (a) and the tracheal bifurcation (b) show numerous large subpleural bullae and emphysema with predominance in the upper lobes. Note also bilateral, variably sized, thin-walled cysts distributed without peripheral–central predominance. Multiple cutaneous neurofibromas are visible in the thoracic wall.

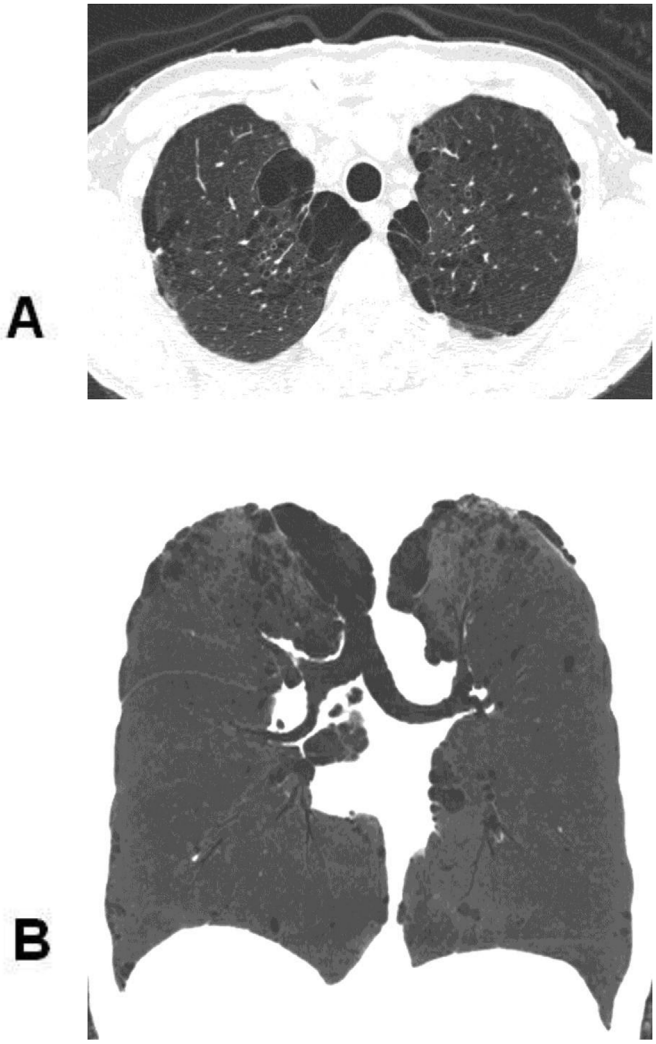

Fig. 4. A 55-year-old non-smoking woman with neurofibromatosis type 1. Axial high-resolution CT image obtained with lung window settings at the level of the upper lobes (a) and coronal reformatted minimum intensity projection image (b) shows upper- and peripheral-dominant distribution of centrilobular and paraseptal emphysema and some bilateral subpleural bullae. Some scattered thin-walled cysts are also visible in the upper zones. Multiple cutaneous neurofibromas are visible in the thoracic wall.

history available [4].

In 2015, Ueda et al. [3] reviewed chest CT images of 88 patients with NF-1; 44 (51%) were positive for subcutaneous nodules, 34 (39%) for skin nodules, 20 (23%) for scoliosis, 16 (18%) for emphysema, 13 (15%) for cysts, 13 (15%) for mediastinal masses, 8 (9%) for nodules, and 8 (9%) for ground-glass nodules. No patient had interstitial pneumonia. This series showed an upper-lobe-dominant distribution of cysts, in agreement with all previous reports and with no significant difference in the rate of cysts between smoking and non-smoking patients, suggesting that smoking does not affect the appearance of cysts in patients with NF-1 [3]. Furthermore, it showed an upper- and peripheral-dominant distribution of emphysema. Although 2 of 16 emphysema cases were never-smokers, the study findings implied that emphysema is strongly affected by a history of smoking, as reported previously by Ryu et al. [26]. Still, one can say that the association between smoking and emphysema in patients with NF-1 remains unclear [3].

A pulmonary association that is uncommon, but worth noting, is that between NF-1 and lung cancer. Two predominant theories have been postulated to explain this association: the development of tumors from previous scar tissue or bullae secondary to interstitial fibrosis, and the deletions on chromosome 17p, where the p53 tumor suppressor gene is located [34,35]. Our review of the literature yielded reports on only a few scattered cases of NF-1 with lung cancer. Adenocarcinoma was the most frequent histological diagnosis, followed by other types of non-small cell cancer, small cell cancer, poorly differentiated cancer, and carcinosarcoma [36]. Hence, NF-1 should be considered as an underlying risk factor for the development of lung cancer, although additional studies with larger cohorts are required.

4.2. Mediastinal involvement

Neurogenic tumors growing in the posterior mediastinum are frequently seen in patients with NF-1 [12,18]. Plexiform neurofibromas usually appear as well-delimited, smooth, round or elliptical masses in the paravertebral region or along the path of the vagus, phrenic, recurrent laryngeal, or intercostal nerve [11] (Fig. 5).

Plexiform neurofibromas are usually extensive fusiform or infiltrating masses that tend to surround mediastinal vessels with loss of normally visible fat planes and can result in diffuse mediastinal widening. They demonstrate variable contrast material enhancement and may calcify. Both types can remodel, erode, invade, or even destroy

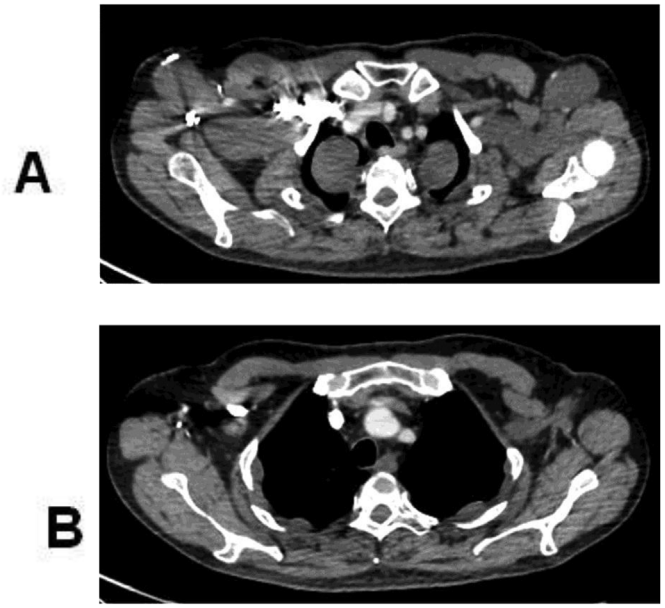

Fig. 5. A 56-year-old man with neurofibromatosis type 1. Contrast-enhanced axial (a and b) high-resolution chest CT images obtained with mediastinal window settings demonstrate multiple hypodense, well-delimited round masses in the intercostal spaces, protruding to both lungs. These masses did not enhance with contrast and were ultimately diagnosed as neurofibromas. Other similar lesions are visible in the deep axillary region.

adjacent bone structures, thereby simulating more aggressive lesions [11,12]. Of particular concern is that these lesions can apply pressure to mediastinal structures, such as the trachea, esophagus, nerves, or blood vessels. The symptoms are mainly those of compression, with chest pain and cough being the most frequent. Digestive and other respiratory symptoms, or even superior vena cava syndrome, can also be present in rare cases [12].

Intrathoracic meningocele associated with NF-1 is a relatively rare entity, and an estimated 60–85% of all thoracic meningoceles are associated with NF-1. These cystic formations of the posterior mediastinum originate by saccular protrusion of the meninges into the thoracic cavity through a pathologically dilated intervertebral foramen or a bone defect in a thoracic vertebra. The accepted etiopathogenesis in patients with NF-1 is that of dural dysplasia and intervertebral foraminal enlargement. Most patients become symptomatic between 30 and 50 years of age, and the disease has a slight female predominance [37–39]. Lateral or anterior thoracic meningoceles are unilobed cystic formations of variable dimensions, filled by cerebrospinal fluid, which appear on CT images as well-circumscribed paravertebral masses with low attenuation due to their liquid content. Meningoceles usually occur in association with scoliosis of the thoracic spine (typically on the convex side of the scoliotic curve), expand the intervertebral foramen, and occasionally exhibit peripheral enhancement by iodinated contrast [11,37]. Magnetic resonance imaging (MRI) findings are usually diagnostic, showing meningoceles with the same signal intensity as the cerebrospinal fluid in all sequences and defining better relationships between the cystic lesion and the spinal canal, nerve root, and spinal cord compared with evaluation by CT [11,37]. Thoracic meningoceles should be differentiated from solid tumors, especially mediastinal tumors that usually arise from the posterior mediastinum, such as neurofibroma, neuroblastoma, ganglioneuroma, and posterior mediastinal cystic hygroma [38].

4.3. Skeletal involvement

Musculoskeletal thoracic involvement in NF-1 comprises focal thoracic scoliosis, posterior vertebral scalloping, enlargement of neural foramina (Fig. 6), and characteristic rib deformities due to bone dysplasia or erosion by adjacent neurofibromas [11].

Muniz et al. [40] studied 141 chest radiographs of NF-1 individuals and found that the following findings were very frequent: rib erosion (19.8%), pectus excavatum (12.0%), kyphoscoliosis (3.5%), and posterior mediastinal masses (7.1%). The spinal column and ribs are the components of the skeletal system most commonly affected by NF-1 [41]. Thoracic spinal curvature affects approximately 10% of patients with NF-1, appearing early in childhood and often requiring corrective surgery. Scoliosis associated with NF-1 more commonly involves the lower cervical and upper thoracic spine, and may be idiopathic or dystrophic. Dystrophic scoliosis typically involves four to six segments, causes distortion of the vertebral bodies and ribs, and is rapidly progressive. Scoliosis with rotation may also occur, producing a reduction in lung volume, which, if severe, may result in respiratory failure [8,15]. Pectus excavatum and carinatum occur in up to 30% of patients

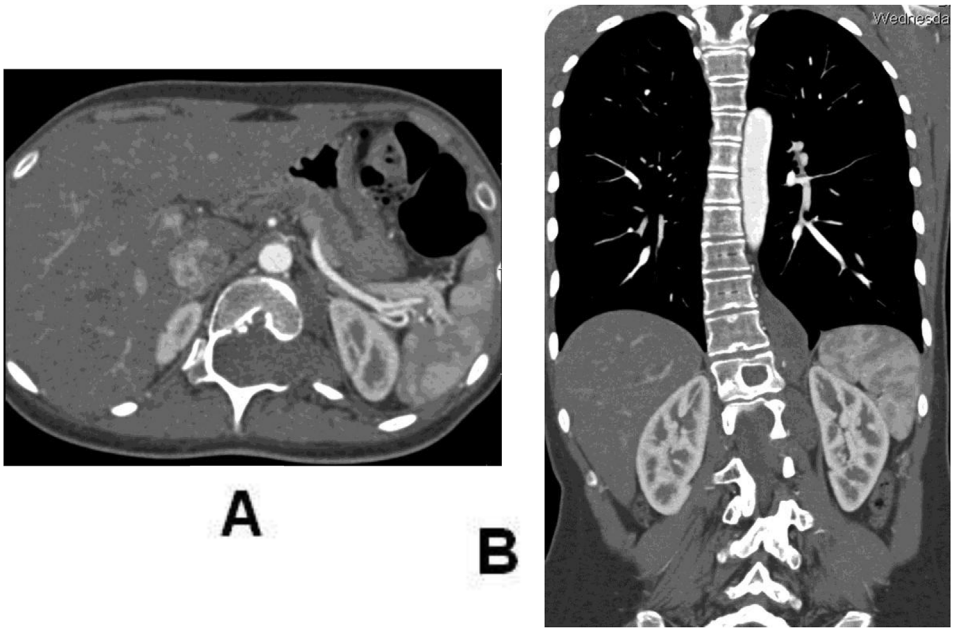

Fig. 6. A 19-year-old woman with neurofibromatosis type 1 presenting with left lumbar pain. Contrast-enhanced thoracoabdominal CT images with axial (a) and coronal (b) reconstruction demonstrate an elliptical, hypodense, well-delimited, non-enhancing mass (plexiform neurofibroma) extending through an enlarged thoracic neural foramen to the left paravertebral region of the inferior region of the posterior mediastinum. Note also the presence of scoliosis.

with NF-1, but they do not contribute to respiratory symptoms or complications [8]. Posterior vertebral scalloping most commonly occurs due to dural ectasia (caused by mesodermal dysplasia of the meninges), but may also be secondary to neurofibromas or thoracic meningoceles. It is observed on lateral radiographs of the spine and on coronal sections of spinal CT and MRI images as an exaggeration of the normal concavity of the posterior surface of one or more vertebral bodies [42]. Costal arch irregularities may occur due to a primary dysplastic defect in bone formation or by erosion of an intercostal neurofibroma. In patients with NF-1, ribs corresponding to abnormal and dysplastic vertebral bodies often have a “twisted ribbon” appearance on images. In the initial description of the radiographic appearance of NF-1, such deformities were attributed to the pressure exerted by intercostal neurofibromas. Now, it is known that some patients exhibiting such changes do not present intercostal neurofibromas. Respiratory symptoms are not associated directly with these defects [40,43].

5. Management and treatment

Given that NF-1 is a genetic syndrome, effective clinical monitoring of these patients with evaluation by a multidisciplinary team is the basis of treatment [16]. The management of patients with NF-1 is focused on the age-specific monitoring of disease manifestations and the education of patients regarding the disease, its possible complications, and the importance of regular clinical follow-up. Individuals with NF-1 need to be encouraged to seek medical help if they experience any unusual symptoms and to ask whether these symptoms are related to NF-1, increasing knowledge about their condition. An important fact reflecting the need for such patient awareness and regular follow-up is that severe disease complications, such as MPNST, are most likely to become symptomatic in the inter-appointment period in patients of all ages [15,44].

Since routine radiological screening is not recommended by most NF-1-management guidelines, neither MRI of the neuro axis, nor routine images of the chest and abdomen should be performed to identify asymptomatic tumors or to be use as basal exams. Imaging surveillance of patients with NF-1 is guided by positive findings of physical examination [9,15,45]. Currently, no effective medical treatment is available to reverse or prevent lesions characteristic of NF-1. Genetic counseling and regular clinical follow-up for the early detection of treatable complications are employed in current practice [44,46]. Targeted treatment depends on and is specific to each manifestation of the syndrome that a patient develops. Therefore, for each involvement found in NF-1 patients an expectant or surgical management may be chosen. Effective medical treatments for NF-1–related neurogenic tumors are lacking. Dombi et al. [47] reported early-phase data suggesting that children with NF-1 and inoperable plexiform neurofibromas benefited from long-term treatment with selumetinib. Fischer-Huchzermeyer et al. [48] suggested that MPNSTs might be treated successfully by combined therapy with all-trans retinoic acid and MEK inhibitors. Pre-conception genetic counseling is essential for adult patients and is recommended for all individuals with NF-1 [15,17].

6. Conclusion

NF-1 is the most common multisystem neurocutaneous syndrome. It may present with various phenotypes and a wide variety of clinical and imaging manifestations. NF-1 should be suspected in the presence of classic diagnostic lesions, such as café-au-lait spots, skin-fold freckling, neurofibromas, iris hamartomas (Lisch nodules), and typical bone lesions. In affected patients, although interstitial lung disease can develop into pulmonary fibrosis, as well as to cystic, emphysematous, or bullous lesions, our literature review showed that the strongest and most reliable pulmonary association is between cystic lung disease and NF-1, allowing characterization of NF-DLD as a distinct clinical entity. Still, whether emphysematous, bullous, and fibrotic changes can be attributed essentially to lung involvement of NF-1 or to variable degrees of smoke-induced alteration remains under debate. Recognition of the various clinical and imaging features of NF-1 and, more specifically, NF-DLD is pivotal in making a presumptive associative diagnosis, as well as in defining the extent of pulmonary involvement; it also aids decision making about disease management.

Contributions of each author

Dr. Alves Júnior: contributed to data interpretation, and preparation and revision of the manuscript.

Dr Zanetti: contributed to CT scan evaluation, literature review, and revision of the manuscript.

Dr Alves de Melo: contributed to the collection of the data and preparation of the manuscript.

Dr Souza Jr: contributed to literature review and final review of the manuscript.

Soares Souza: contributed to the data interpretation, literature review, and revision of the manuscript.

Dr Meirelles: contributed to CT scan evaluation, and final review of the manuscript.

Dr Irion: contributed to literature review and revision of the manuscript.

Dr Hochhegger: contributed to the design of study, CT scan evaluation, and final review of the manuscript.

Dr Marchiori was the principal investigator and is the guarantor of the entire manuscript. He contributed to the coordination and design of the study, data interpretation, and preparation and revision of the manuscript.

Conflicts of interest

All authors inform that there are none conflicts of interest.

References

[1] V.M. Riccardi, Von recklinghausen neurofibromatosis, N. Engl. J. Med. 305 (27) (1981) 1617–1627.
[2] J.R. Antônio, E.M. Goloni-Bertollo, L.A. Trídico, Neurofibromatosis: chronological history and current issues, An. Bras. Dermatol. 88 (3) (2013) 329–343.
[3] K. Ueda, O. Honda, Y. Satoh, et al., Computed tomography (CT) findings in 88 neurofibromatosis 1 (NF1) patients: prevalence rates and correlations of thoracic findings, Eur. J. Radiol. 84 (6) (2015) 1191–1195.
[4] 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 (1) (2007) 210–214.
[5] 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.
[6] G.F. Louza, G. Zanetti, E. Marchiori, Neurofibromatosis type I with pulmonary involvement, Arch. Bronconeumol. 54 (2) (2018) 106–107.
[7] A. Fernández Plaza, A. Sánchez González, Diffuse cystic lung disease as a manifestation of neurofibromatosis, Radiologí 56 (4) (2014) 376–377.
[8] N.P. Hirsch, A. Murphy, J.J. Radcliffe, Neurofibromatosis: clinical presentations and anaesthetic implications, Br. J. Anaesth. 86 (4) (2001) 555–564.
[9] C. Vijapura, E. Saad Aldin, A.A. Capizzano, B. Policeni, Y. Sato, T. Moritani, Genetic syndromes associated with central nervous system tumors, Radiographics 37 (1) (2017) 258–280.
[10] J.H. Tonsgard, Clinical manifestations and management of neurofibromatosis type 1, Semin. Pediatr. Neurol. 13 (1) (2006 Mar) 2–7.
[11] B.J. Fortman, B.S. Kuszyk, B.A. Urban, E.K. Fishman, Neurofibromatosis type 1: a diagnostic mimicker at CT, Radiographics 21 (3) (2001) 601–612.
[12] L. Reviron-Rabec, B. Girerd, A. Seferian, et al., Pulmonary complications of type 1 neurofibromatosis, Rev. Mal. Respir. 33 (6) (2016) 460–473.
[13] National Institutes of Health consensus development conference statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987, Neurofibromatosis 1 (3) (1988) 172–178.
[14] 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 (2) (2012) 152–157.
[15] R.E. Ferner, S.M. Huson, N. Thomas, et al., Guidelines for the diagnosis and management of individuals with neurofibromatosis 1, J. Med. Genet. 44 (2) (2007) 81–88.

[16] K.P. Boyd, B.R. Korf, A. Theos, Neurofibromatosis type 1, J. Am. Acad. Dermatol. 61 (1) (2009) 1–16.
[17] C. Lu-Emerson, S.R. Plotkin, The neurofibromatoses. Part 1: NF1, Rev. Neurol. Dis. 6 (2) (2009) E47–E53.
[18] T. Arazi-Kleinmann, Y. Mor, N. Brand, et al., Neurofibromatosis diagnosed on CT with MR correlation, Eur. J. Radiol. 42 (2002) 69–73.
[19] J.W. Chan, Neuro-ophthalmic features of the neurocutaneous syndromes, Int. Ophthalmol. Clin. 52 (3) (2012) 73–85.
[20] M. Farid, E.G. Demicco, R. Garcia, et al., Malignant peripheral nerve sheath tumors, Oncol. 19 (2) (2014) 193–201.
[21] E. Pasmant, B. Parfait, A. Luscan, et al., Neurofibromatosis type 1 molecular diagnosis: what can NGS do for you when you have a large gene with loss of function mutations? Eur. J. Hum. Genet. 23 (5) (2015) 596–601.
[22] P.D.B. Davies, Diffuse pulmonary involvement in von Recklinghausen's disease: a new syndrome, Thorax 18 (1963) 198.
[23] A. Oikonomou, K. Vadikolias, T. Birbilis, D. Bouros, P. Prassopoulos, HRCT findings in the lungs of non-smokers with neurofibromatosis, Eur. J. Radiol. 80 (3) (2011) e520–e523.
[24] W.R. Webb, P.C. Goodman, Fibrosing alveolitis in patients with neurofibromatosis, Radiology 122 (2) (1977) 289–293.
[25] A.S. Patchefsky, W.G. Atkinson, W.S. Hoch, G. Gordon, H.I. Lipshitz, Interstitial pulmonary fibrosis and von Recklinghausen's disease. An ultrastructural and immunofluorescent study, Chest 64 (4) (1973) 459–464.
[26] 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 (4) (2005) 2381–2386.
[27] D. Massaro, S. Katz, Fibrosing alveolitis: its occurrence, roentgenographic, and pathologic features in von Recklinghausen's neurofibromatosis, Am. Rev. Respir. Dis. 93 (6) (1966) 934–942.
[28] S. Ayed Della, A. Kotti, H. BenSik Ali, S. Ayed, M. Fekih Hassen, S. Elatrous, Pneumothorax spontané et maladie de Recklinghausen: À propos d'un cas, Rev. Pneumol. Clin. 68 (2012) 202–204.
[29] R. Bouchentouf, A rare aetiology of lung cystic lesions: neurofibromatosis type 1, Tunis. Med. 94 (5) (2016) 412–413.
[30] E.M. Jutant, B. Girerd, X. Jaïs, et al., Pulmonary hypertension associated with neurofibromatosis type 1, Eur. Respir. Rev. 27 (149) (2018 Aug 29).
[31] D. Montani, F. Coulet, B. Girerd, et al., Pulmonary hypertension in patients with neurofibromatosis type I, Medicine (Baltim.) 90 (3) (2011) 201–211.
[32] D. Rodrigues, H. Oliveira, C. Andrade, et al., Interstitial lung disease and pre-capillary pulmonary hypertension in neurofibromatosis type 1, Respir. Med. Case Rep. 24 (2018) 8–11.
[33] U. Chaddha, I. Puscas, A. Prosper, S. Ganesh, B. Yaghmour, A 63-year-old woman with neurofibromatosis type 1 and pulmonary hypertension with worsening hypoxemia, Chest 152 (4) (2017) e89–e93.
[34] E. Shimizu, T. Shinohara, N. Mori, et al., Loss of heterozygosity on chromosome arm 17p in small cell lung carcinomas, but not in neurofibromas, in a patient with von Recklinghausen neurofibromatosis, Cancer 71 (3) (1993) 725–728.
[35] A. Hsu, S. Han, Synchronous neuroendocrine tumor and non-small-cell lung cancer in neurofibromatosis type 1, Clin Case Rep 3 (12) (2015) 990–996.
[36] A. Oikonomou, D. Mikroulis, P. Mintzopoulou, L. Lukman, P. Prassopoulos, Lung cancer associated with neurofibromatosis type I, Case Rep Radiol 2013 (2013) 869793.
[37] G.C. Andrade, O.P. Braga, M.K. Hisatugo, M.A. De Paiva Neto, E. Succi, F.M. Braga, Giant intrathoracic meningoceles associated with cutaneous neurofibromatosis type I: case report, Arq Neuropsiquiatr 61 (3) (2003) 677–681.
[38] T. Zuo, Z. Ni, M. Zhou, C. Huang, Z. Tang, Z. Yang, Large intrathoracic meningocele in a patient with neurofibromatosis type 1, Asian Cardiovasc. Thorac. Ann. 22 (2) (2014) 219–221.
[39] D.G. Cho, Y.J. Chang, K.D. Cho, J.T. Hong, Collaborative treatment of huge intrathoracic meningoceles associated with neurofibromatosis type 1: a case report, J. Cardiothorac. Surg. 10 (2015 Nov 10) 161.
[40] M.P. Muniz, A.S. Souza, D.A.B. Criado, et al., Type 1 neurofibromatosis: radiological findings of the chest, Radiol. Bras. 43 (3) (2010) 167–170.
[41] S.E. Rossi, J.J. Erasmus, H.P. McAdams, L.F. Donnelly, Thoracic manifestations of neurofibromatosis-I, AJR Am. J. Roentgenol. 173 (6) (1999) 1631–1638.
[42] S.L. Wakely, The posterior vertebral scalloping sign, Radiology 239 (2) (2006) 607–609.
[43] J.C. Hunt, D.G. Pugh, Skeletal lesions in neurofibromatosis, Radiology 76 (1961) 1–20.
[44] A.F. Espig, A.A. Slomp, A.Q. Campagnolo, et al., Neurofibromatosis type 1: update, Rev. Bras. Ciência Mov. 6 (2008) 243–249.
[45] R. Listernick, R.E. Ferner, G.T. Liu, D.H. Gutmann, Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations, Ann. Neurol. 61 (3) (2007) 189–198.
[46] A. Casal, N. Rodríguez-Núñez, A. Martínez-Alegría, S. Candamio, J. Álvarez, L. Valdés, Neurofibromatosis type I with lung involvement in a cancer patient, Pulmonology 24 (4) (2018) 269–271.
[47] E. Dombi, A. Baldwin, L.J. Marcus, et al., Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas, N. Engl. J. Med. 375 (26) (2016) 2550–2560.
[48] S. Fischer-Huchzermeyer, A. Dombrowski, G. Wilke, et al., MEK inhibitors enhance therapeutic response towards ATRA in NF1 associated malignant peripheral nerve sheath tumors (MPNST) in-vitro, PLoS One 12 (11) (2017) e0187700.