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PULMONARY MANIFESTATIONS OF NEUROFIBROMATOSIS TYPE 1 – A LITERATURE REVIEW

Abstract: Introduction/Aim: Neurofibromatosis type 1 is an autosomal dominant disorder whose pulmonary manifestations remain underrecognized in clinical practice. Previous reviews have focused on diffuse lung disease and pulmonary arterial hypertension, without addressing the broader spectrum of complications or explaining the relationship between diffuse lung disease and tobacco smoking. The aim of this review is to synthesize the literature, identify opposing viewpoints, and formulate recommendations for clinical practice. **Methods**: PubMed and Google Scholar databases were searched for the period 2016–2026. Cohort studies, literature reviews, and case reports were included and analyzed according to methodological rigor and clinical relevance. **Results**: Six clinical categories of pulmonary manifestations of neurofibromatosis type 1 were identified. Diffuse lung disease occurs in 10–20% of adult patients and has been confirmed as a primary genetic entity that smoking modifies but does not cause. Pulmonary arterial hypertension carries a five-year survival rate below 50% and a limited response to standard therapy. Spontaneous pneumothorax is underrecognized as an initial manifestation of the disease. Intrathoracic meningoceles, vascular complications, and neurofibromas with malignant transformation complete the spectrum of manifestations that previous reviews have not systematically addressed. **Conclusion**: Pulmonary manifestations of neurofibromatosis type 1 are prognostically more significant than traditionally described. Routine evaluation using multidetector computed tomography of the lungs, spirometry, measurement of pulmonary diffusing capacity, and echocardiography is recommended. A multidisciplinary approach is essential for timely diagnosis and treatment of these patients.

Keywords: neurofibromatosis 1; neurofibroma; pulmonary diseases; interstitial lung disease; pulmonary hypertension

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Introduction

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is an autosomal dominant disorder with an incidence of 1:2,500–3,000 live births, occurring equally in both sexes and across all ethnic groups [1]. It is caused by loss of function of the NF1 tumor-suppressor gene on chromosome 17q11.2, which encodes neurofibromin, a negative regulator of the RAS/MAPK signaling pathway that controls cell growth, division, and survival [1]. The clinical picture is variable even within the same family, although the disease becomes almost fully expressed by the fifth year of life; in 30–50% of cases it arises through a new, de novo mutation, without a positive family history [1]. The most important prognostic consequence of this variability is a reduced life expectancy in affected individuals, on average by about ten years compared with the general population, attributed mainly to an increased risk of malignant tumors and vascular complications [2].

The characteristic clinical picture of NF1 that clinicians recognize includes café-au-lait macules, Lisch nodules of the iris, axillary and inguinal freckling, cutaneous and plexiform neurofibromas, optic nerve glioma, and bone dysplasia [1, 3]. However, the systemic manifestations of NF1 – involving the cardiovascular, endocrine, gastrointestinal, and respiratory systems – remain underrecognized in everyday clinical practice, even though it is often these that determine the outcome of the disease [1, 3, 4, 5]. Pulmonary manifestations of NF1 are particularly underrepresented: they occur in 10–20% of adult patients, yet clinicians often do not consider them until the disease has reached an advanced stage [2, 3].

The disease affects the lungs and thorax through several pathophysiologically distinct mechanisms. Neurofibromatosis-associated diffuse lung disease (NF-DLD) is characterized by cystic–emphysematous changes in the upper lung lobes and basal fibrotic reticulation. NF-DLD has been described in several cohort studies and case reports and is the subject of active scientific debate as to whether it arises as a primary genetic manifestation or as a consequence of smoking [3, 6, 7]. NF1-associated pulmonary arterial hypertension (PAH), classified in World Health Organization (WHO) group 5, has a five-year survival below 50% and a limited response to standard vasodilator therapy, making it the most severe pulmonary complication [2,6]. In addition to these well-studied entities, contemporary research continually broadens the spectrum of the disease. The literature review also identified spontaneous pneumothorax as an initial or recurrent manifestation of NF1 [8–13], thoracic neurofibromas with a risk of malignant transformation into a malignant peripheral nerve sheath tumor (MPNST) [14–16], meningoceles protruding into the thorax that must be differentiated from pleural effusion [17–19], and intercostal artery aneurysms with hemothorax [20, 21].

Data on these manifestations are scarce in the literature; the available studies are mostly single-center and based on small samples, and knowledge is supplemented by case reports describing an increasingly broad clinical spectrum [2, 3, 6, 7]. The fragmentation of knowledge and the ongoing scientific debate about the standing of NF-DLD as a distinct clinical entity created the need to synthesize the available evidence. The aim of this review is to systematize and analyze the contemporary literature on the pulmonary manifestations of NF1, to identify opposing viewpoints, and to formulate recommendations for clinical practice based on the available scientific evidence.

Materials and Methods

The literature review was performed by searching the PubMed and Google Scholar databases for the period 2016–2026, including older seminal studies when necessary to understand a subject of active scientific debate. The search terms used were “neurofibromatosis type 1”, “NF1”, “pulmonary manifestations”, “diffuse lung disease”, “pulmonary hypertension NF1”, “intrathoracic neurofibroma”, “NF1 lung cysts”, “spontaneous pneumothorax NF1”, “intrathoracic meningocele NF1”, “NF1 vascular complications”, “von Recklinghausen lung”, and “MPNST thoracic”.

The search initially identified 86 articles. Inclusion criteria comprised articles in English, French, and Serbian describing the pulmonary manifestations of NF1, including cohort studies, review articles, and case reports published in peer-reviewed journals. Exclusion criteria were articles dealing exclusively with extrapulmonary manifestations of NF1, conference abstracts, letters to the editor, and articles without available full text. Studies were assessed according to methodological rigor, sample size, and relevance. After review of titles and abstracts, 42 articles that did not describe pulmonary manifestations of NF1 and 11 articles without available full text were excluded. The selection comprised 33 relevant articles. The results are presented in tabular form in three categories: cohort studies and review articles, case reports grouped by clinical category, and the differential diagnosis of other cystic/parenchymal lung diseases.

Results

The literature review identified six clinical categories of pulmonary manifestations of NF1: diffuse lung disease (NF-DLD), pulmonary arterial hypertension (PAH), spontaneous pneumothorax, intrathoracic neurofibromas and MPNST, intrathoracic meningoceles, and vascular complications.

Table 1 presents the cohort studies, literature reviews, and case series that form the basis of the current understanding of the pulmonary manifestations of NF1. Retrospective single-center cohort studies with relatively small samples predominate, reflecting the rarity of the disease itself. The key common finding of the cohort studies is the presence of parenchymal changes in 14–43% of NF1 patients, with a consistent pattern of apical cystic-emphysematous disease and basal fibrotic reticulation.

Table 1. Overview of studies on the pulmonary manifestations of NF1

Author, year	Study type	N	Population and method	Findings and conclusion
Reviron-Rabec et al., 2016 [2]	Literature review	–	Adults with NF1; PubMed review; focus on all pulmonary complications	Comprehensive description of NF-DLD, PAH, spontaneous pneumothorax, intrathoracic tumors, and meningoceles. PAH carries a poor prognosis; MEK inhibitors.
Alves Júnior et al., 2019 [3]	Literature review	–	All ages; PubMed/ Scopus review; focus on pulmonary manifestations of NF1	NF-DLD: apical cysts and bullae + basal reticulation. RAS/MAPK is the key mechanism; NF1 increases lung susceptibility to cigarette smoke; CT is the method of choice.
Alves Júnior et al., 2021 [22]	Retrospective cohort study	88	Adults with NF1; single center, Brazil; chest MDCT	Parenchymal changes in 42%: cysts, bullae, emphysema, GGO, basal reticulation. MDCT superior to radiography; no correlation of cysts with smoking – confirms the independence of NF-DLD.
Spinnato et al., 2019 [23]	Retrospective study	14	Children with NF1, Italy; age 3–17 years; lung MDCT	Cystic and emphysematous changes in 6/14 (43%) non-smokers; apical predominance. Strongest evidence that smoking is not the cause of NF-DLD; early MDCT screening justified.
Wang et al., 2022 [24]	Review with radiological atlas	–	All ages; MDCT, MRI, PET/CT; focus on radiological manifestations of NF1	Presented: intrathoracic neurofibromas, NF-DLD, paravertebral masses, meningoceles. MRI and MDCT are complementary; the radiologist must know the full spectrum of thoracic NF1 manifestations.
Ilić et al., 2016 [25]	Case series	5	Adults with NF1, Serbia; lung HRCT; presentation of parenchymal changes	Emphysema, cysts, GGO; one case with PAH. HRCT superior to conventional radiography; confirms NF-DLD as a clinical entity – Serbian literature.

Jutant et al., 2020 [6]	Multicenter prospective study	58	Adults with NF1 + PAH; 7 referral PAH centers, France	PAH occurs late (5th–6th decade), female predominance (76%), high mPAP, NSIP pattern. Limited response to standard vasodilator therapy; 5-year survival < 50%; early transplant assessment necessary.
Avanesov et al., 2021 [7]	Retrospective cohort study	71	Adults with NF1; single center, Hamburg; MDCT + PET/CT; subgroups by smoking status	Cysts 14%, emphysema 35%, combined 8%. Centrilobular emphysema correlates with smoking, cystic changes do not. NF-DLD independent of NF1 mutation type; MDCT mandatory in follow-up.

Note: NF1 – neurofibromatosis type 1; NF-DLD – diffuse lung disease; PAH – pulmonary arterial hypertension; MDCT – multidetector computed tomography; HRCT – high-resolution CT; MRI – magnetic resonance imaging; GGO – ground-glass opacity; NSIP – nonspecific interstitial pneumonia; mPAP – mean pulmonary artery pressure; MEK – mitogen-activated protein kinase kinase

Table 2 presents case reports grouped into six clinical categories, illustrating the clinical spectrum of NF1 pulmonary manifestations beyond NF-DLD and PAH. Particularly notable are reports documenting pleuroparenchymal fibroelastosis, a previously undescribed complication (Nainani, 2025) as the second case in the world literature, as well as reports indicating NF1 as a cause of spontaneous pneumothorax diagnosed before the manifestations of NF1 itself (Lorentzen, 2021).

Table 2. Case reports of NF1 pulmonary manifestations by clinical category

Author, year	Patient and clinical presentation	Treatment	Outcome / clinical significance
Spontaneous pneumothorax			
Sherfinski & Cooper, 2022 [8]	M, 34 y. Apical bullae; prior bleb repair in adolescence; NF-DLD	Surgical intervention	Recurrence 20 y after the first; progressive NF-DLD course; importance of long-term follow-up
Lorentzen et al., 2021 [9]	Adult, M. Apical bullae and cysts; NF-DLD; pneumothorax as the initial presentation	Chest tube; pleurodesis	NF1 diagnosed only because of the pneumothorax; highlights NF1 in the differential diagnosis of pneumothorax
Paoloni-Giacobino et al., 2024 [11]	Adult. Cystic lesions; recurrent pneumothorax; novel causative NF1 mutation	Conservative + follow-up	Broadens genotype–phenotype correlation for pneumothorax in NF1; unique genetic contribution

Author, year	Patient and clinical presentation	Treatment	Outcome / clinical significance
Simamora et al., 2026 [12]	Adult, M. Bilateral cysts and bullae; NF-DLD; chest tube without lung re-expansion	Pleurodesis	Persistent pneumothorax as a complication of NF-DLD; a particular therapeutic challenge
Pulmonary arterial hypertension (PAH)			
Santos & Pereira, 2022 [26]	Adult, F. Dilated PA, right-sided strain, high PAP; no significant parenchymal disease	Triple oral PAH therapy (ERA + PDE5i + prostanoid)	No response to triple therapy; referred for transplantation; illustrates the poor prognosis of PAH-NF1
Yagi et al., 2025 [27]	Adult. PAH without significant parenchymal disease; high PAP on echocardiography; novel NF1 mutation	PAH-specific therapy	Vascular mechanism of PAH independent of parenchymal disease; novel NF1 mutation
Diffuse lung disease (NF-DLD)			
Nainani et al., 2025 [28]	M, 28 y. Subpleural fibroelastosis (PPFE) of the upper lobes; bilateral cysts; recurrent pneumothorax	Pneumothorax intervention; transplant assessment	PPFE – only the 2nd case in the world literature as an NF1 complication; transplant list
Sarkar et al., 2024 [29]	Elderly, M. Bilateral cysts, emphysema, bullae, basal reticulation; superimposed bacterial pneumonia	Antibiotic therapy; HRCT follow-up	NF-DLD as a diagnostic pitfall alongside pneumonia; illustrates the association between smoking and NF-DLD
Intrathoracic tumors and MPNST			
Zhang et al., 2021 [14]	Adult. Giant MPNST mass of the posterior mediastinum; superficial benign neurofibromas	Surgical resection	Simultaneous malignant and benign components; MPNST resectable; no recurrence short-term
Pascoe et al., 2019 [15]	Adult. Mediastinal plexiform mass + endobronchial neurofibromas; bronchial compression	Bronchoscopic intervention; surgical evaluation	Endobronchial neurofibromas – a rare and specific NF1 manifestation; bronchoscopy necessary
Laatfa & Lachraf, 2025 [16]	M, 13 y. Mediastinal mass + multiple cystic lesions of both lungs	Surgical resection (intraoperative complication)	Fatal intraoperative outcome; a warning about intrathoracic NF1 involvement in pediatrics
Petković et al., 2022 [30]	Adult. CT: MPNST of the thigh + bilateral lung metastases + spleen + brain	Chemotherapy; palliative	NF1 MPNST with multiorgan metastases; fatal outcome

Intrathoracic meningoceles			
Chen et al., 2024 [17]	Adult. Bilateral intrathoracic meningoceles; initially mistaken for pleural effusion	Conservative	MRI of the spinal canal is key to diagnosis; biopsy contraindicated – risk of CSF fistula
Elsayed et al., 2022 [19]	Adult. Cystic intrathoracic mass; MRI + histopathological verification	Surgical resection; histological analysis	The only histopathologically verified series of meningoceles in NF1; MRI is key to differential diagnosis
Vascular complications			
Panesar et al., 2024 [20]	Adult, M. Acute hemothorax; CTA: intercostal artery aneurysm	Surgical hemostasis; chest tube	Hemothorax as a presentation of NF1 vasculopathy; vascular NF1 complications underrecognized
Kanda et al., 2026 [21]	Adult. CTA: ruptured intercostal artery aneurysm; patient on sunitinib for GIST	Endovascular treatment	Sunitinib as a precipitating factor for rupture; NF1 vasculopathy + GIST – a complex clinical interaction

Note: NF-DLD – diffuse lung disease; PAH – pulmonary arterial hypertension; PPFE – pleuroparenchymal fibroelastosis; MPNST – malignant peripheral nerve sheath tumor; GIST – gastrointestinal stromal tumor; ERA – endothelin receptor antagonists; PDE5i – phosphodiesterase-5 inhibitors; CTA – CT angiography; PA – pulmonary arteries; PAP – pulmonary artery pressure; M – male; F – female; MRI – magnetic resonance imaging.

Table 3 presents the differential diagnosis of NF-DLD relative to other cystic and parenchymal lung diseases. NF-DLD is distinguished from the other listed entities by the combination of apical cysts and bullae with basal reticulation in the presence of clinical signs of NF1, without a specific biological marker that would unambiguously confirm it.

Table 3. Differential diagnosis of NF-DLD and other cystic/parenchymal lung diseases

Disease	CT cyst distribution	Demographics	Diagnostic marker	Difference from NF-DLD
NF-DLD (NF1)	Apical cysts and bullae; centrilobular emphysema; basal reticulation	Both sexes; 5th decade; more often smokers	Clinical signs of NF1: café-au-lait macules, neurofibromas, Lisch nodules	Reference disease; diagnosis based on clinical NF1 signs plus typical CT findings; no specific biological marker
LAM	Diffuse, uniform, round cysts; even distribution throughout both lungs	Women of reproductive age; association with TSC	TSC1/TSC2 mutation; elevated VEGF-D; extrapulmonary LAM	No sex predilection in NF1; cysts are apical and non-uniform; no TSC mutation or VEGF-D elevation

Disease	CT cyst distribution	Demographics	Diagnostic marker	Difference from NF-DLD
PLCH	Upper lobes; bizarrely shaped cysts with nodules; nodules dominate early	Male predominance; smokers > 95%	CD1a+ Langerhans cells on BAL or biopsy	Almost exclusively smoking-related; nodules early in the course; clinical NF1 signs absent; CD1a negative in NF1
BHD syndrome	Subpleural, basal, elliptical cysts; no apical predominance	Both sexes; autosomal dominant inheritance	FLCN gene mutation; skin fibrofolliculomas; association with renal carcinoma	Cysts are basal and subpleural versus apical in NF1; skin lesions differ; confirmed by genetic analysis
Emphysema (smoking-related)	Centrilobular (upper lobes) or panacinar; no true cyst walls	Smokers; older age	Spirometry: obstructive pattern; absence of cyst walls on CT	No true cyst walls, unlike NF-DLD; smoking is a confounding factor in NF1
LIP	Perivascular cysts and GGO; diffuse distribution	Women; autoimmune diseases (Sjögren, SLE); HIV infection	Hypergammaglobulinemia; biopsy: diffuse lymphocytic infiltration of the interstitium	Perivascular distribution versus apical cysts in NF1; clinical NF1 signs absent; autoimmune or infectious background
Intrathoracic meningocele	Paravertebral smooth cystic mass; not a parenchymal change	Adults with NF1; association with scoliosis and bone dysplasia	MRI: connection with the spinal canal; CSF signal on diffusion MRI	Not a parenchymal lung disease; spinal-canal MRI is key to diagnosis; biopsy contraindicated – risk of CSF fistula

Note: NF-DLD – NF1-associated diffuse lung disease (reference disease, bold); LAM – lymphangioleiomyomatosis; PLCH – pulmonary Langerhans cell histiocytosis; BHD – Birt–Hogg–Dubé syndrome; LIP – lymphocytic interstitial pneumonia; CT – computed tomography; GGO – ground-glass opacity; BAL – bronchoalveolar lavage; VEGF-D – vascular endothelial growth factor D; FLCN – folliculin gene; TSC – tuberous sclerosis; CSF – cerebrospinal fluid; MRI – magnetic resonance imaging; SLE – systemic lupus erythematosus

Discussion

This review systematizes the pulmonary manifestations of neurofibromatosis type 1, examines their pathophysiological basis and key unresolved questions – above all the relationship between diffuse lung disease and smoking – and proposes an evidence-based diagnostic and therapeutic approach.

Pathophysiological basis of NF1 pulmonary manifestations

Loss of neurofibromin function leads to hyperactivation of the RAS/MAPK signaling pathway in tissues rich in this protein – neurons, Schwann cells, and pulmonary mesenchymal cells [1, 3]. The resulting uncontrolled proliferation of mesenchymal cells of the pulmonary interstitium leads to pathological collagen deposition, destruction of the alveolar septa, and cystic–emphysematous changes, as well as fibrotic reticulation in the basal parts of the lungs [3]. In parallel, the same mechanism in the walls of the pulmonary arterioles – proliferation of intimal and smooth-muscle cells – causes PAH even without severe parenchymal disease, as documented by Jutant et al. in 58 patients with PAH-NF1, one-third of whom had minimal parenchymal disease but severe hemodynamic compromise [6]. In 71 patients studied with multidetector computed tomography (MDCT), Avanesov et al. confirmed that cystic changes occur independently of the specific NF1 mutation type and suggested that loss of any neurofibromin function is sufficient for the development of the pulmonary phenotype [7].

Beyond these primary mechanisms, NF1 vasculopathy also affects medium and large vessels, causing intercostal artery aneurysms with potential hemothorax, as illustrated by the reports of Panesar et al. (2024) and Kanda et al. (2026) [20, 21]. Intrathoracic meningoceles arise from protrusion of arachnoid cysts through widened intervertebral foramina – a consequence of NF1-induced mesodermal dysplasia – and may be misdiagnosed as pleural effusion or tumor masses [17, 18, 31].

NF-DLD as a distinct clinical entity

Whether NF-DLD is a primary entity caused by the genetic defect or a consequence of smoking remains a subject of active scientific debate [3, 29]. In a case report of an elderly man with NF-DLD and pneumonia, Sarkar et al. (2024) note that NF-DLD as a separate entity has been disputed and often attributed to smoking [29]. Aziz et al. (2025) document the characteristic CT appearance of cystic–emphysematous disease in NF1 and emphasize that smoking is a confounding factor that may worsen or mask NF-specific changes [32].

Three independent lines of evidence support the independence of NF-DLD: Alves Júnior et al. (2019) document the characteristic CT appearance of NF-DLD in 6 asymptomatic non-smokers [3]; the study by Massaro and Katz found an absence of pigmented macrophages – a histological marker of smoking-related lung disease – in the lung tissue of NF1 patients with diffuse changes; and Avanesov et al. (2021), in a cohort study of 71 patients, showed that the only parameter statistically associated with smoking was centrilobular emphysema, whereas cystic lesions were independent of smoking status [7]. The current consensus accepted by Alves Júnior (2019) and Reviron-Rabec et al. (2016) is that NF-DLD is primarily caused by NF1, while

smoking accelerates progression and increases the risk of complications but is not the underlying cause of the changes [2, 3].

In a pediatric cohort study of 14 children aged 3–17 years, Spinnato et al. (2019) documented cystic–emphysematous changes in 6/14 (43%) who were non-smokers, providing perhaps the strongest evidence in favor of a primary NF1 etiology of NF-DLD [23]. This finding is particularly important because it eliminates smoking as a cause in the pediatric population.

Pulmonary arterial hypertension

PAH in NF1 differs pathophysiologically from idiopathic group 1 PAH because it is caused by RAS/MAPK-mediated proliferation of intimal and smooth-muscle cells of the pulmonary arterioles rather than by primary bone morphogenetic protein receptor involvement [2, 6]. In a multicenter study of 58 patients with PAH-NF1, Jutant et al. (2020) document a relatively late onset (5th–6th decade), a female predominance (76%), severe hemodynamic dysfunction, and five-year survival below 50% [6]. Santos and Pereira (2022) present a case of a female patient in whom triple oral PAH therapy failed to achieve a therapeutic response [26]. Yagi et al. (2025) describe PAH with a novel NF1 mutation and emphasize a vascular mechanism that develops independently of the degree of parenchymal disease [27]. Reviron-Rabec et al. (2016) recommend early assessment for possible lung transplantation [2]. MEK inhibitors (selumetinib, mirdametinib) represent a potential direction for future research, for which there is currently insufficient clinical evidence in the treatment of NF1-associated pulmonary hypertension.

Spontaneous pneumothorax

Spontaneous pneumothorax as a manifestation of NF-DLD is represented in the more recent literature far more often than earlier reviews suggested. Case reports from the period 2021–2026 document various clinical scenarios: pneumothorax as the initial presentation of NF1 [9], primary spontaneous pneumothorax in a young patient [10], recurrent pneumothorax with a novel NF1 mutation [11], persistent pneumothorax as a therapeutic challenge [12], and rare causes of spontaneous pneumothorax [13]. This entity should be included in the differential diagnosis of every spontaneous pneumothorax, especially in younger patients, since NF1 can sometimes be diagnosed on the basis of this complication.

Intrathoracic tumors and MPNST

Intrathoracic plexiform neurofibromas present as paravertebral masses in the posterior mediastinum, but they may also have endobronchial extension [15], spread

into the lung parenchyma [31], or present as giant tumor masses [14]. Malignant transformation into MPNST occurs in 8–13% of patients with plexiform neurofibromas and carries a poor prognosis. The case report by Petković et al. (2022) illustrates an MPNST of the thigh with pulmonary, splenic, and cerebral metastases and a fatal outcome [30]. The case report by Laatfa and Lachraf (2025) – a fatal intraoperative outcome in a 13-year-old child with a mediastinal mass and cystic lesions – demonstrates the manifestation of NF1 in pediatric patients [16]. NF1 vasculopathy also affects neurofibromas, sometimes causing severe vascular hemorrhage, as in the large solitary neurofibroma described by Terzić et al. [33].

Intrathoracic meningoceles

Intrathoracic meningoceles arise from protrusion of arachnoid cysts through widened intervertebral foramina due to NF1-associated mesodermal dysplasia. Chen et al. (2024) present bilateral meningoceles initially misdiagnosed as pleural effusion; therefore, magnetic resonance imaging of the lungs and thorax with visualization of the spinal canal must be included in the diagnostic algorithm for every paravertebral cystic finding in an NF1 patient [17]. Mousavi et al. (2026) and Elsayed et al. (2022) present the operative challenge and histopathological diagnosis [18, 19]. It is important to emphasize that meningoceles do not require biopsy when magnetic resonance imaging is performed for diagnostic purposes, because biopsy may cause a CSF fistula.

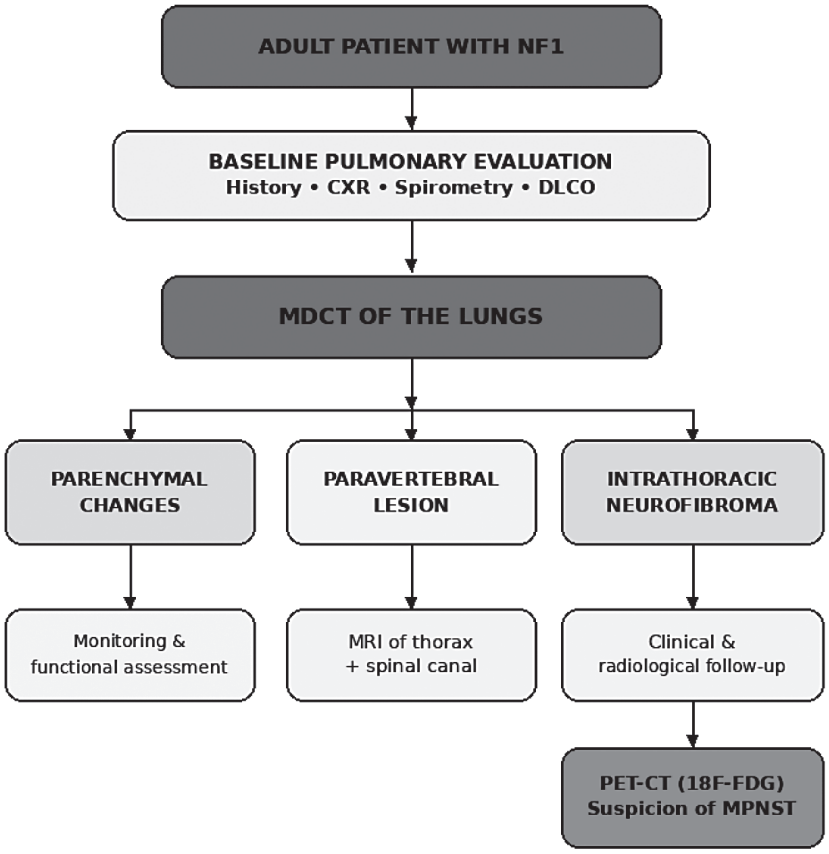
Differential diagnosis of cystic lung diseases in NF1

Cystic changes in NF1 require a systematic differential-diagnostic approach (Table 3). The key feature of NF-DLD is the combination of apical cysts and bullae with basal reticulation in the presence of clinical signs of NF1. Alves Júnior et al. (2019) emphasize that CT is the superior diagnostic tool, but that the final diagnosis of NF-DLD remains a clinical correlation, since there is no specific histological or serological biomarker for this disease [3].

Diagnostic approach and recommendations

Based on the review of available studies, a diagnostic algorithm is proposed for patients with NF1 (Figure 1).

Figure 1. Proposed diagnostic algorithm for adult patients with NF1.



Based on the synthesis of available data, we propose that the baseline pulmonary evaluation at the time of NF1 diagnosis in all adult patients include history-taking, chest radiography, spirometry, and the pulmonary diffusing capacity. A reduced pulmonary diffusing capacity is an early marker of parenchymal disease, often preceding the appearance of structural changes on CT [7].

According to the proposed algorithm, lung MDCT is the method of choice for detecting pulmonary changes. Characteristic findings are bilateral apical cysts and bullae, centrilobular emphysema in the upper lobes, and basal reticulonodular infiltration [7, 22]. MDCT is a superior diagnostic tool to radiography [22].

Depending on the MDCT findings, the diagnostic algorithm branches in three directions. For parenchymal changes, monitoring and functional assessment with spirometry and measurement of the pulmonary diffusing capacity are indicated. For a paravertebral lesion, magnetic resonance imaging of the thorax with visualization of

the spinal canal is necessary to exclude an intrathoracic meningocele before planning a biopsy [17, 18, 19]. For an intrathoracic neurofibroma, clinical and radiological follow-up is indicated, and in the case of rapid growth of the lesion, onset of pain, or neurological deficits, positron emission tomography is recommended to assess the risk of malignant transformation [24].

Echocardiography is proposed for all NF1 patients with dyspnea, reduced exercise tolerance, or signs of right-sided cardiac strain, given the poor prognosis of PAH-NF1 and the limited therapeutic response [6, 26].

Therapeutic approach and recommendations

- Smoking cessation is an important preventive measure because of the known harmful effects of smoking and its possible modifying influence on the NF1 pulmonary phenotype [3, 7].
- Supportive therapy for NF-DLD includes oxygen therapy in chronic respiratory failure, bronchodilators in obstructive ventilatory impairment, and pulmonary rehabilitation. No specific pharmacotherapy exists [2, 3].
- PAH-NF1 should be treated in specialized centers. Standard PAH therapy has limited effect [6, 26, 27], but should be applied in the absence of alternatives. MEK inhibitors (selumetinib, mirdametinib) theoretically address the RAS/MAPK signaling pathway and represent a potential direction for future research, for which there is currently insufficient clinical evidence in the treatment of PAH-NF1. Lung transplantation should be considered early [2].
- Spontaneous pneumothorax requires the standard approach (chest drainage, pleurodesis), but the clinician must be aware of the recurrence potential in NF-DLD [8–13].
- Intrathoracic neurofibromas require surgical resection for symptomatic or rapidly growing masses, with multidisciplinary oncological evaluation [14, 15, 32]. In asymptomatic patients, intrathoracic meningoceles are monitored conservatively [17, 18, 19].

Study limitations

This literature review has several methodological limitations that should be considered when interpreting its conclusions. First, the available cohort studies on the pulmonary manifestations of NF1 are mostly retrospective, single-center, and based on relatively small samples, which limits the generalizability of the findings. Second, there are no unified, internationally accepted diagnostic criteria for NF-DLD, so that prevalence across studies ranges from 10 to 20%, and comparison of results between

studies is hampered by the heterogeneity of the diagnostic methods used. Third, smoking as a confounding factor was not consistently controlled in all the analyzed studies, which complicates interpretation of the findings on the association between NF-DLD and smoking – the central subject of active scientific debate. Fourth, a significant part of the data on the rarer manifestations – spontaneous pneumothorax, intrathoracic meningoceles, and vascular complications – comes exclusively from case reports, which by their nature do not allow conclusions about prevalence or causal relationships. Fifth, a systematic review methodology (the PRISMA protocol) was not applied, which places this work in the category of a narrative review with a risk of selective literature selection. These limitations indicate the need for multicenter prospective cohort studies with standardized diagnostic criteria for NF-DLD, as well as for an NF1 patient registry that would allow monitoring of the course of all pulmonary manifestations.

Conclusion

This literature review confirms that the pulmonary manifestations of neurofibromatosis type 1 are more diverse and clinically more significant than traditionally described. In addition to diffuse lung disease and pulmonary arterial hypertension as well-known entities, spontaneous pneumothorax, intrathoracic neurofibromas with malignant transformation into a malignant peripheral nerve sheath tumor, intrathoracic meningoceles, and vascular complications require a systematic approach.

The available data strongly support the concept of NF-DLD as a primary pulmonary manifestation of NF1, while smoking likely represents an important modifier of the pulmonary phenotype and disease progression. NF1-associated pulmonary arterial hypertension carries a poor prognosis, with five-year survival below 50% and a limited response to standard vasodilator therapy. Inhibitors of the mitogen-activated protein kinase signaling pathway represent a biologically justified therapeutic option that requires further clinical investigation.

Routine screening of all adult patients with neurofibromatosis type 1 is recommended: spirometry and measurement of the pulmonary diffusing capacity as a baseline, multidetector computed tomography of the lungs at the first evaluation and in symptomatic patients, echocardiography to screen for pulmonary arterial hypertension, and magnetic resonance imaging of the thorax in the case of a paravertebral lesion. A multidisciplinary team including the primary-care physician, pulmonologist, cardiologist, radiologist, and oncologist is a prerequisite for optimal diagnostic work-up and treatment of these patients.

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