ERJ Express. Published on July 26, 2006 as doi: 10.1183/09031936.06.00044006

Neurofibromatosis-Associated Lung Disease:

A Case Series and Literature Review

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Short title: Neurofibromatosis-Associated Lung Disease

ABSTRACT: An association of neurofibromatosis with diffuse lung disease (NF-DLD) has been described, but its true prevalence and characteristics remain unclear. The objective of this study is to define diffuse lung disease in patients with neurofibromatosis.

We report a retrospective case series and literature review in a tertiary care academic medical center. Medical records, chest radiographs and high-resolution computed tomography (HRCT) scans were reviewed.

Fifty-five adult patients with neurofibromatosis were identified. Three of these fifty-five patients had NF-DLD. A literature review revealed sixteen articles reporting sixty-one additional cases, yielding a total of 64 cases. The mean age was fifty years. Men outnumbered women; most reported dyspnea. Twelve of sixteen with documented smoking histories were ever smokers. Eight patients had HRCT scan results demonstrating ground glass opacities (37%), bibasilar reticular opacities (50%), bullae (50%), cysts (25%), and emphysema (25%). None had honeycombing. Fourteen patients had surgical biopsy results which showed findings of interstitial fibrosis (100%) and interstitial inflammation (93%).

In conclusion, NF-DLD is a definable clinical entity. It is characterized by upper lobe cystic and bullous disease and lower lobe fibrosis. Its relationship to smoking remains unclear.

KEYWORDS: cystic lung disease**,** High Resolution Computed Tomography, interstitial lung disease, neurofibromatosis, pulmonary fibrosis,

INTRODUCTION

Von Recklinhausen's disease or neurofibromatosis type 1 (NF) is an autosomal dominant dysplasia of ectoderm and mesoderm with a variable clinical expression characterized by collections of neurofibromas, café-au-lait-spots and pigmented hamartomas in the iris (Lish nodules) (1). Neurofibromatosis has a prevalence of 1 in 3000. In 30–50% of cases of NF there is no family history of the disease. These sporadic cases probably arise from (usually paternal) germ cell mutations (1).

In NF, the thorax and lungs can be affected in several ways: cutaneous and subcutaneous neurofibromas on the chest wall, kyphoscoliosis; ribbon deformity of the ribs; thoracic neoplasms; and interstitial lung disease (1). Sporadic cases of NF-DLD have been published in case reports, but the overall prevalence and clinical characteristics of NF-DLD remain unclear. A recent article has questioned the association of NF with diffuse interstitial lung disease (2). This article reports 3 patients with NF-DLD seen at our institution. We also summarize the clinical and radiographic characteristics of cases of NF-DLD reported in the literature.

METHODS

Medical records of all adult patients (>25 years old) with NF seen at the University of California San Francisco between 1980 and 2004 were reviewed for evidence of diffuse lung disease. NF was defined according to published diagnostic criteria (3). Only adult cases of NF-DLD were included in this manuscript as it has been reported previously that NF-DLD does not occur in children. Primary radiographic data were obtained on identified cases of NF-DLD and reviewed by an experienced pulmonary radiologist (WRW). A literature review was performed using PubMed (keywords "neurofibroma", "fibrosis", "scar", "pulmonary", "interstitial lung

disease", and "lung"), by searching references of published articles and through input from experts in the field. Articles reporting cases of NF-DLD were included in this review.

Data from newly identified cases were combined with data abstracted from identified articles. Variables extracted were: age, gender, dyspnea, cough, chest pain, smoking status, pulmonary function pattern (obstructive or restrictive), diffusing capacity for carbon monoxide (DLCO, normal or decreased), high resolution computed tomography (HRCT) patterns (ground glass, linear densities, nodular densities, bullae and honeycombing), surgical lung biopsy (yes or no), and histopathological patterns (fibrosis, inflammation, and honeycombing). For some variables of interest, only aggregate data were available. Statistics were calculated for each variable: age was reported as mean (because of aggregate data, the standard deviation could not be determined). All other variables were reported as percentages. Cases of known non-smokers were compared to cases of known smokers using univariate linear regression for continuous variables and Fisher's exact test for dichotomous variables. Statistical analyses were performed using SAS version 9.1 (Cary, NC).

RESULTS

Three patients with NF-DLD were identified among 55 cases of NF seen at our institution between 1980 and 2004 (prevalence = 5.5%). These cases are described below and summarized in Table 1.

Case 1. A 66-year-old Caucasian man with NF was referred for evaluation of severe dyspnea. He could walk no more than 50 feet without stopping. He was a former smoker. Chest exam revealed diffuse inspiratory crackles. There was no clubbing. Pulmonary function testing is

shown in Table 1. HRCT of the chest showed diffuse and numerous small rounded thin-walled lung cysts with an upper lobe predominance. (Figure 1)

Case 2. A 53-year-old Caucasian man with NF was referred for evaluation for lung transplantation. He had chronic cough and dyspnea. He was a former smoker. The chest exam was normal. Pulmonary function testing is shown in Table 1. HRCT revealed bilateral asymmetric bullous disease with an apical predominance. (Figure 2)

Case 3. A 70-year-old African-American woman with NF was referred for evaluation of chest pain. She had never smoked. The chest exam was normal. No pulmonary function testing was performed. HRCT showed scattered small round lung cysts in both lungs, with an apical predominance. (Figure 3)

Literature Review

The literature review revealed 529 articles, which were reviewed by one of the authors (AZ). Sixteen articles were identified reporting 61 cases of NF-DLD. Combined with three newly identified cases reported here, a total of 64 cases of NF-DLD have now been reported. (Table 2) .The mean age is 50 years (range 23 to 72). Forty-four cases were men (69%) and 20 (31%) were women. Common symptoms include dyspnea (80%) and cough (32%). Only 5% presented with chest pain and 11% were asymptomatic.

Pulmonary function results were available in 30 cases and in all cases but one (3%) the function was abnormal. 43% of patients had an obstructive pattern, 37% had a restrictive pattern

and 17% had a mixed pattern. When measured (n=18), DLCO was almost always decreased (94% of cases).

Chest radiography readings were available in 63 cases. HRCT was available in 8 cases. (Table 3) On chest radiography, bullous lung disease was present in 73% of cases, almost always in the upper lobes (93%). Basilar linear densities were present in 62% and radiographic honeycombing in 13%. HRCT was available in 8 cases and revealed emphysema (25%), cyst (25%), ground glass abnormality (37%), bullae (50%) and reticular abnormalities (50%).

Sixteen cases had smoking histories available. Of these, four (25%) were non-smokers. When data were analyzed by smoking status, non-smokers were more likely to be women (100% vs 25%, $p = 0.01$). There were no statistically significant differences in age, pulmonary function pattern or radiographic abnormalities between non-smokers and smokers. (Table 4)

Surgical lung biopsy results were available in 14 cases. All 14 biopsies showed fibrosis and 13 showed interstitial inflammation (93%). Honeycomb cysts were present in 3 cases (23%).

DISCUSSION

Neurofibromatosis-associated interstitial lung disease was first described in 1963 by Davies, and over the ensuing decades, other reports have described the association between NF and ILD (4-17). In some patients, the finding of lung disease was incidental, but most subjects reported dyspnea on exertion. Pulmonary function tests show either an obstructive or a restrictive defect, and a decreased DLCO is almost always present.

Radiographic studies of neurofibromatosis patients using conventional chest radiography commonly report large apical asymmetric thin-walled bullae (73%), sometimes occupying a

substantial portion of hemithorax and associated with areas of hypovascularity, and bibasilar, subpleural reticular abnormality (61%). Honeycombing mimicking idiopathic pulmonary fibrosis (IPF) is rare, but has been described (16). Limited data are available regarding HRCT appearance in NF-DLD. Five cases with HRCT imaging are reported in the literature and here we report 3 additional cases. Our three cases revealed cystic changes and bullae, changes distinct from but easily confused with emphysema.

There remains debate as to whether NF-DLD is a primary manifestation of NF. Riccardi and colleagues did not observe pulmonary parenchymal disease in over 200 patients with various forms of neurofibromatosis, although HRCT scan was not performed in these patients (1). Therefore, cases of NF-DLD may have been missed. Ryu and colleagues reviewed 70 patients with NF and found 12 with evidence of NF-DLD (2). Ten (6 by chest radiography and 4 by CT) had emphysema, cystic airspace disease or bullae. All were current or former smokers. Because all of these cases had a history of smoking, the authors suggest that these ten cases may simply represent smoking-related emphysema. Three cases had reticular opacities. These cases had other potential causes of their diffuse lung disease: residual scarring from ARDS, rheumatoid arthritis related ILD and smoking-related ILD (e.g., desquamative interstitial pneumonia).

Several observations, however, suggest that NF-DLD is a distinct clinical entity. First, of the 16 cases of NF-DLD with recorded smoking histories, 4 (25%) were non-smokers (4, 11, 14). Second, the radiographic appearance on HRCT in our three cases (which constitute approximately 40% of reported HRCT cases) is atypical for smoking-related disease; the borders of the cysts and bullae are thicker and more sharply defined than is seen in smoking-related emphysema. Ground glass opacites, a hallmark of smoking-related ILD, was only seen in 3 patients (18, 19). Third, surgical lung biopsy reports do not describe the intra-alveolar

accumulation of pigmented macrophages one would expect in DIP or RB-ILD (9). Instead, the alveolar septa demonstrate lymphoplasmocytic inflammation and fibrosis consistent with non-specific idiopathic pneumonia (NSIP) pattern.

There is biological rationale for a relationship between NF and ILD. Patchefsky has suggested that the pulmonary parenchymal disease in NF is attributed to a mesenchymal defect resulting in primary deposition of collagen (13). Consistent with this suggestion, the pathologic features of the pulmonary parenchymal lesions, at autopsy or lung biopsy, reveal areas of normal lung alternating with patchy interstitial fibrosis, septal thickening, and cellularity. Moreover, perhaps there is a fibrotic environment in this patients as Fabricant and coworkers have found that nerve growth factor is increased in the serum of patients with NF (20). This factor activates fibroblasts directly, differentiating them into the more pro-fibrogenic myofibroblasts. This may contribute to the pathogenesis of lung fibrosis in NF (21).

The occurrence of NF-DLD in non-smokers, the presence of cysts distinct from smoking related emphysema on HRCT, and the histopathological pattern of NSIP, all support the association of cystic lung disease as a distinct manifestation of NF. However, it has been suggested that NF may increase the sensitivity of the lungs to cigarette smoke, causing the early development of emphysema-like changes. This suggests smoking may indeed be a risk factor for the development and severity of NF-DLD (2, 17).

In summary, we believe the currently available data suggest that NF-DLD is a distinct clinical entity, characterized by upper lobe cystic and bullous disease and basilar fibrosis. To properly and definitively address the association of NF, diffuse lung disease, and cigarette smoking, a cross-sectional cohort study in which patients with NF undergo HRCT and careful medical histories is needed. It is hoped that a better understanding of NF-DLD, together with an

increased understanding of the pathobiology of NF, will lead to future therapies for this rare but highly morbid condition.

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FIGURE LEGENDS:

Figure 1:

High resolution computed tomography from patient 1 shows diffuse, numerous, small round lung cysts involving the upper lobes and superior segment of the left lower lobe. In distinction to centrilobular emphysema, the cysts have well-defined walls

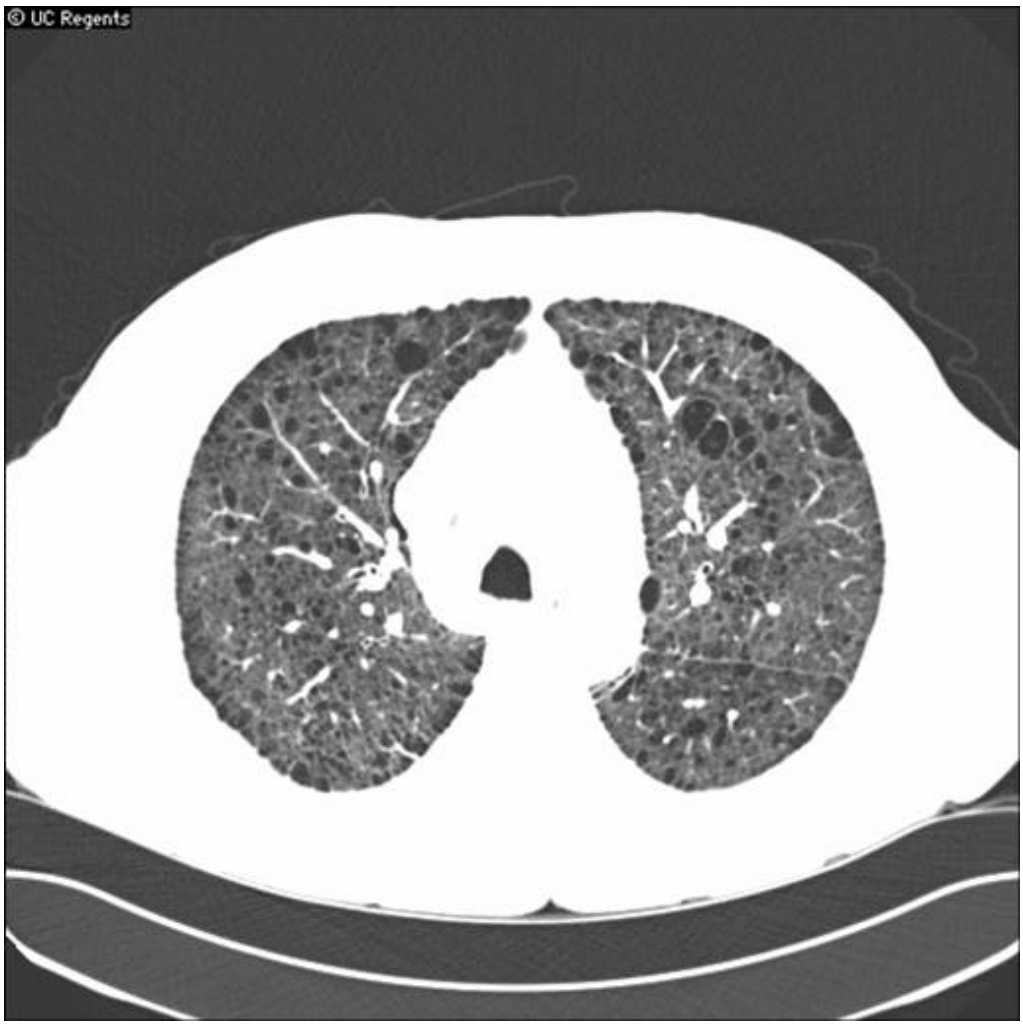

Figure 2:

High resolution computed tomography from patient 2 shows bilateral asymmetric bullous disease.

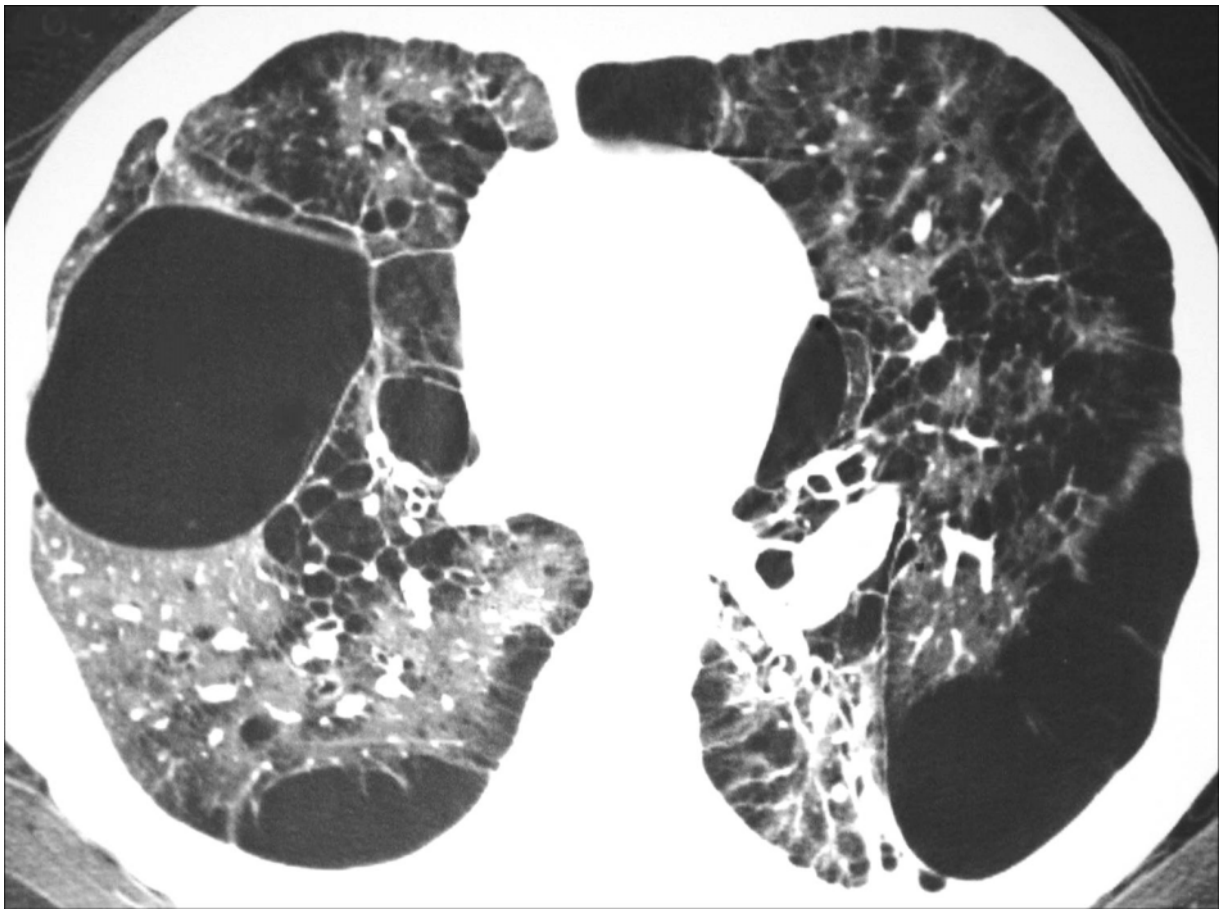

Figure 3:

High resolution computed tomography from patient 3 shows scattered small round lung cysts in both upper lobes.

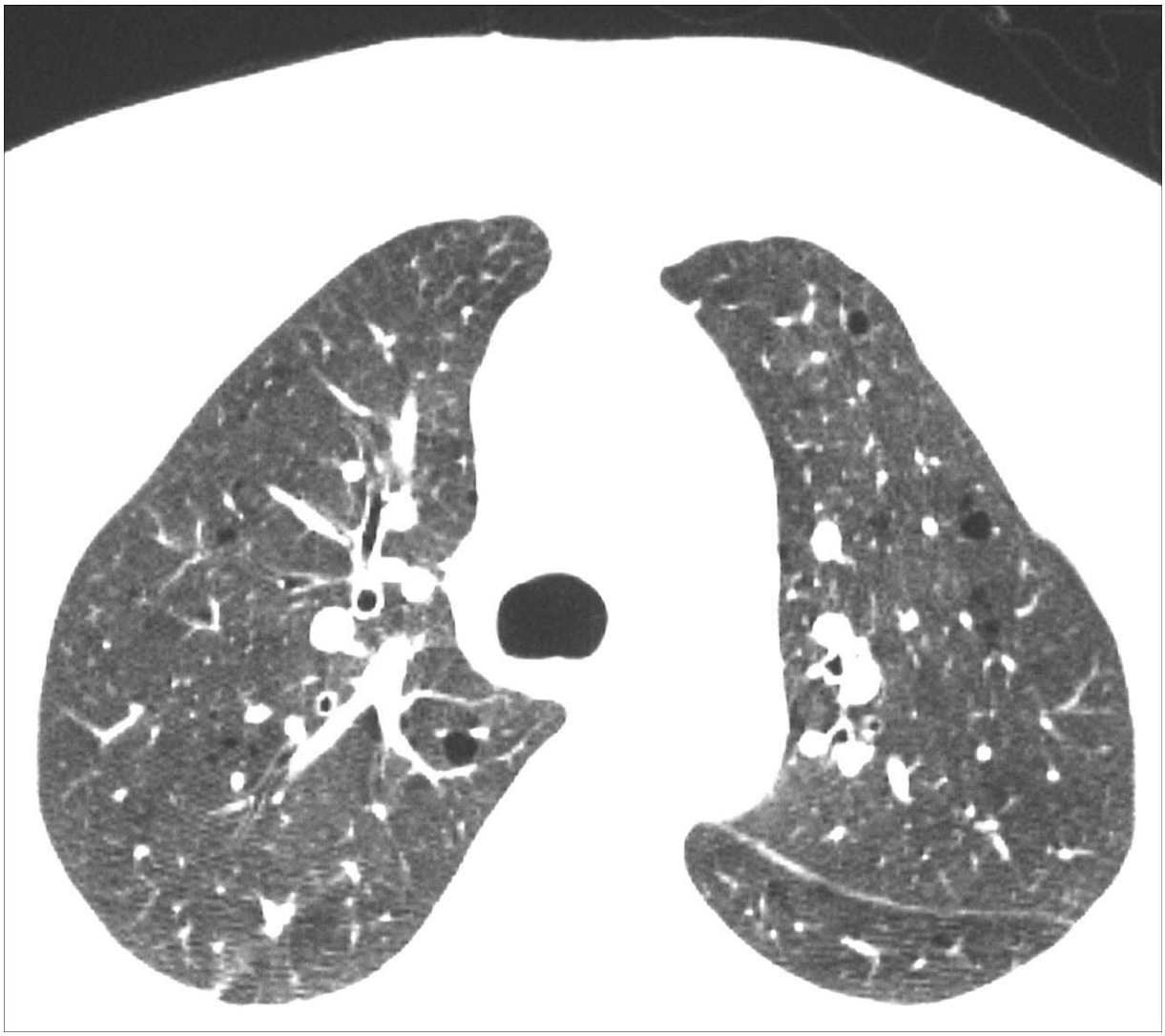

Table 1

New Cases of NF-DLD

	Clinical			Pulmonary Function				High Resolution Computed Tomography
No.	Age	Gender	Smoke	FVC(%)	FEV1(%)	Ratio	DLCO(%)	
1	66	Male	Former	4.7 (98)	2.9 (78)	0.61	8.24 (24)	Upper lobe predominance of thin-walled cysts (Figure 1)
2	54	Male	Former	4.2 (95)	1.3 (41)	0.43	5.7 (15)	Bilateral asymmetric bullae (Figure 2)
3	70	Female	Never	N/A	N/A	N/A	N/A	Scattered upper lobe cysts (Figure 3)

Abbreviations: FVC: Forced Vital Capacity, FEV1: Forced Expiratory Volume in the 1st second), DLCO: diffusing capacity for carbon monoxide.

Table 2

Demographic, Clinical and Laboratory Data

Variable	Number (%)
Demographics (n=64)	
Age, yr*	50, range 23-72
Male/ Female	44 /20
Symptoms (n=35)	
Dyspnea	28 (80)
Cough	11 (32)
Chest Pain	2 (5)
Asymptomatic	4 (11)
Pulmonary Function Pattern (n= 30)	
Normal	1 (3)
Obstructive	13 (43)
Restrictive	11 (37)
Mixed	5 (17)
Low DLCO (n=18)	17 (94)

Abbreviations: DLCO: diffusing capacity for carbon monoxide

Table 3

Radiographic Data

Modality	Number (%)
Chest radiograph (n=63)	
Mottled	20 (32)
Linear densities	38 (61)
Nodular densities	13 (13)
Bullae	46 (73)
Bullae upper localization	41 (93)
Honeycombing	7 (12)
HRCT (n=8)	
Ground glass	3 (37)
Reticular abnormality	4 (50)
Bullae	4 (50)
Emphysema	2 (25)
Cyst	2 (25)
Honeycombing	0 (0)

Abbreviations: HRCT: high resolution computed tomography

Table 4

Comparison of smokers and non-smokers

Variable	Smokers	Non-smokers	P value
Demographic	**N = 12**	**N = 4**	
Age (years)	52.4+9.2	46.75 + 20.5	0.4
Gender Male/Female	9/3 75/25	0/4 0/100%	0.01
Pulmonary Function Testing	**N = 7**	**N = 2**	
Obstructive pattern	7 (100)	2 (100)	0.5
Chest radiograph	N = 12	N = 3	
Linear densities	10 (90)	2 (50)	0.4
Bullae	11 (91)	0 (0)	1.0
High Resolution Computed Tomography	**N = 6**	**N = 2**	
Ground Glass Opacities	3 (50)	0 (0)	0.5
Reticular	3 (50)	1(50)	1.0
Bullae	3(50)	1(50)	1.0
Cyst	1(20)	1(50)	1.0
Emphysema	2(50)	0(00)	1.0