Lack of Evidence for an Association Between Neurofibromatosis and Pulmonary Fibrosis*

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Study objectives: To reassess the association between neurofibromatosis and pulmonary fibrosis.

Design: Retrospective single-center study with analysis of patients’ chest radiographs, CT scans, and medical records.

Setting: Tertiary care, referral medical center.

Patients: One hundred fifty-six adult patients with neurofibromatosis seen over a 6-year period between 1997 and 2002.

Results: A review of chest radiographs revealed abnormal findings in 70 patients (44.9%). The most common radiographic abnormalities were extrapulmonary nodules or masses seen in 22 patients (14.1%), followed by skeletal abnormalities in 16 patients (10.3%). Bilateral interstitial infiltrates were noted in only three patients (1.9%), all of whom had potential causes other than neurofibromatosis for their lung infiltrates, including smoking-related interstitial lung disease, rheumatoid lung disease, and recurrent pneumonias, and a history of ARDS. CT scans were available in two of these patients and revealed nonspecific patterns of abnormalities with no honeycombing. Six patients had bullae or cystic airspaces demonstrated on chest radiography or CT scan; all of these findings occurred in the context of smoking-related emphysema. Combined together, bilateral interstitial lung infiltrates or cystic airspaces were demonstrated in five patients (3.2%) by chest radiography, and in eight patients (5.1%) by chest radiography or CT scanning; one patient had both findings on the CT scan.

Conclusions: We found little evidence to support an association between neurofibromatosis and pulmonary fibrosis or any other form of parenchymal lung disease. Interstitial lung disease and bullae described in association with neurofibromatosis in previous reports may have, in part, represented smoking-induced manifestations.

Key words: genetics; interstitial lung disease; pulmonary fibrosis

Abbreviations: HRCT = high-resolution CT; NF = neurofibromatosis; NF1 = neurofibromatosis type 1; NF2 = neurofibromatosis type 2

The neurofibromatoses (NFs) are among the most common neurogenetic disorders. They represent a group of autosomal-dominant diseases that have widespread effects on neuroectodermal and mesodermal tissues.1–4 The most common manifestation is a benign peripheral nervous system tumor. The following two distinct forms of NF are recognized: NF type 1 (NF1); and NF type 2 (NF2). The NF1 gene has been localized to chromosome 17q11.2 and the NF2 gene has been shown to reside on chromosome 22q12.2.1–4 NF1 and NF2 genes appear to function as tumor-suppressor genes, and their respective gene products have been named neurofibromin and merlin (or schwannomin), respectively.1–4

Thoracic manifestations of NF are varied, and include intrathoracic neurogenic tumors, meningiomas, kyphoscoliosis, and pulmonary fibrosis.5 Bullous lung disease has also been described in patients with NF, sometimes coexisting with pulmonary fibrosis.6,7 In several surveys,8,9 pulmonary fibrosis (sometimes called fibrosing alveolitis) or interstitial lung disease has been reported to occur in 10 to 20% of adults with NF. In addition, multiple case re-
ports\textsuperscript{7,10–18} have described the association between NF and interstitial lung disease. In contrast, a population-based study\textsuperscript{19} of 135 patients with NF1 in southeast Wales yielded no cases of parenchymal lung disease as a complication of the underlying disease. In the current study, we sought to reexamine the association between pulmonary fibrosis and the various types of NF.

**Materials and Methods**

We conducted a computer-assisted search of the Mayo Clinic database to identify patients with NF who were seen at our institution over a 6-year period between January 1, 1997, and December 31, 2002. This search was limited to adults (≥ 21 years of age) since pulmonary fibrosis associated with NF has previously been reported only in adults with this disorder.

We identified 163 adults with NF who underwent chest radiography during their clinical evaluation at our medical center. Of these 163 patients, we were able to retrieve chest radiographs for 156 for current review by a chest radiologist (GLA); these 156 patients formed the final study group. Seven patients for whom we were unable to retrieve the chest radiographs had reportedly had normal results by previous interpretation. Forty-one of these 156 patients (26.3\%) also had undergone CT scans of the chest, which were reviewed and evaluated by the chest radiologist (GLA). In those patients with more than one chest radiograph or CT scan available, the most recent study was chosen for review. Demographic data, clinical features, and laboratory results were extracted from the medical records. Radiographic abnormalities were categorized as nodules (< 3 cm in diameter) or masses (≥ 3 cm in diameter), focal or diffuse infiltrate, emphysematous changes, and pleural findings. The pulmonary origin vs extrapulmonary origin of the abnormality was noted.

All patients in this study fulfilled the criteria outlined by the National Neurofibromatosis Foundation Clinical Care Advisory Board in 1997 for the diagnosis of NF1 or NF2.\textsuperscript{20} The diagnosis of NF1 required at least two of the following clinical features: (1) six or more café-au-lait macules having a diameter of > 5 mm in prepubertal individuals, and > 15 mm in postpubertal individuals; (2) two or more neurofibromas of any type or one plexiform neurofibroma; (3) freckling in the axillary or inguinal regions; (4) optic glioma; (5) two or more Lisch nodules (ie, iris hamartomas); (6) a distinctive bony lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis; and (7) a first-degree relative with NF1 based on the above criteria. The diagnosis of definite NF2 required the presence of (1) bilateral vestibular schwannomas or (2) a family history of NF2 (first-degree family relative) plus either a unilateral schwannoma in a person < 30 years old or any two of the following: meningioma; glioma; schwannoma; or posterior subcapsular cataracts. This study was approved by the Mayo Foundation Institutional Review Board. Patients who did not authorize the use of their medical records for research were excluded from this study.

**Results**

Demographic and clinical characteristics of the 156 patients included in this study are outlined in Table 1. The median age of these adults with NF was 43 years, and approximately two thirds of them were nonsmokers. The number of patients with NF1 exceeded that of patients with NF2 by a ratio of 5.5:1. The primary indications for referral (or self-referral) of these patients to our institution included neurologic manifestations in 56 patients (35.9\%), dermatologic manifestations in 15 patients (9.6\%), malignant tumor in 12 patients (7.7\%), orthopedic problem in 1 patient (0.6\%), medical problems unrelated to NF in 60 patients (38.5\%), and comprehensive assessment of NF in 12 patients (7.7\%). The indication for chest radiography was chest symptoms in 30 patients; these symptoms included cough, dyspnea, chest pain, and palpitations. In the remaining 126 patients, chest radiography was performed as a screening examination in a comprehensive or preoperative evaluation. Conventional CT scans were available in 41 patients, with high-resolution images available in 2 patients. The indication for CT scanning was the evaluation of an abnormality seen on chest radiography in 20 patients (49\%), staging of a malignant tumor in 11 patients (27\%), suspected pulmonary embolism in 4 patients (10\%), and further evaluation of chest symptoms in 6 patients (15\%).

The most common abnormalities detected on chest radiography were extrapulmonary nodules/masses and skeletal abnormalities (Table 2), which

### Table 1—Demographic and Clinical Data*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>43</td>
</tr>
<tr>
<td>Range</td>
<td>21–83</td>
</tr>
<tr>
<td>Male sex</td>
<td>70 (44.9)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>14 (9.0)</td>
</tr>
<tr>
<td>Previous</td>
<td>35 (22.4)</td>
</tr>
<tr>
<td>None</td>
<td>107 (68.6)</td>
</tr>
<tr>
<td>Type of neurofibromatosis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>132 (84.6)</td>
</tr>
<tr>
<td>2</td>
<td>24 (15.4)</td>
</tr>
</tbody>
</table>

*Values are given as No. (%), unless otherwise indicated.

### Table 2—Chest Radiographic Findings*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapulmonary nodules/masses</td>
<td>22 (14.1)</td>
</tr>
<tr>
<td>Skeletal abnormalities</td>
<td>16 (10.3)</td>
</tr>
<tr>
<td>Focal atelectasis or infiltrate</td>
<td>14 (9.0)</td>
</tr>
<tr>
<td>Pulmonary nodules/masses</td>
<td>8 (5.1)</td>
</tr>
<tr>
<td>Emphysematous changes</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>Pleural thickening or small effusion</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Bilateral interstitial infiltrates</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Normal</td>
<td>86 (55.1)</td>
</tr>
</tbody>
</table>

*Values are given as No. (%).
were found in 14.1% and 10.3% of patients, respectively. One or both of these findings were noted in 37 patients (1 patient had both). Extrapulmonary nodules or masses usually represented paravertebral or chest wall neurofibromas and cutaneous neurofibromas. Skeletal abnormalities included scoliosis and rib anomalies. All but 2 of these 37 patients (95%) had NF1.

The most common parenchymal abnormality found on chest radiographs was focal atelectasis or infiltrate, which was found in 9.0% of patients. The infiltrate usually consisted of a few strands of fibrotic-appearing linear opacities. Intrapulmonary nodules/masses were detected in eight patients (5.1%), including three patients with metastatic neurofibrosarcoma to the lung and one smoker with metastatic lung cancer (adenocarcinoma). In the remaining four patients, the lung nodules were small and undetermined in character.

Emphysematous changes were detected by chest radiography in six patients (3.8%). Two of these patients were current smokers, three were previous smokers, and the remaining patient was a 74-year-old nonsmoker manifesting hyperinflation on a chest radiograph with no associated respiratory symptoms. Two of these patients had cystic airspaces or bullae detected by chest radiography. Four additional patients had emphysematous changes detected by CT scan, among whom one was a current smoker and the remaining three were previous smokers. In 6 of these 10 patients with emphysema, cystic airspaces or bullae (i.e., a cystic airspace with a diameter of >1 cm) were seen by chest radiography or CT scan. All six patients had a history of smoking. No other NF patient had similar cystic or bullous changes.

Bilateral interstitial infiltrates were seen in three patients (1.9%) by chest radiography. A summary of these patients is provided in Table 3. Two of these patients had a CT scan study available for current review. One patient (a 55-year-old ex-smoker with a 50-pack-year history and NF1) had emphysematous changes predominantly in the upper lung zones (Fig 1, top, A) with scattered cystic airspaces in the lower lung zones (Fig 1, bottom, B). Reticular and ground-glass opacities were present in the periphery of the lower lung zones. The second patient (a 72-year-old ex-smoker with NF1, rheumatoid arthritis, large granular lymphocytic leukemia, and recurrent pneumonias) had coarse reticular opacities predominantly in the periphery of the lower lobes (Fig 2). The third patient was a 57-year-old nonsmoker with NF1, who had received a cadaveric renal transplant, and had a history of ARDS, which had been managed with prolonged mechanical ventilatory support, and recurrent pneumonias. Diffuse interstitial infiltrates were present on her chest radiograph but no CT scan study was available. No other NF patient had evidence of interstitial lung disease by chest radiography or CT scanning.

Three patients had undergone lung resection. This included a lower lobectomy for squamous cell lung cancer in a 65-year-old woman (current smoker), along with a 42-year-old man and a 45-year-old woman, both of whom had undergone wedge resections of metastatic neurofibrosarcoma. The histopathologic examination of the resected lung specimen demonstrated the surrounding lung parenchyma to be unremarkable with no evidence of interstitial fibrosis; CT scan studies in all three patients revealed no evidence of interstitial lung disease. No NF patient underwent a bronchoscopic or surgical lung biopsy for suspected interstitial lung disease.

**DISCUSSION**

Although previous studies had described up to a 23% prevalence of parenchymal lung disease detected among patients with NF, we found little evidence to support a true association between NF and pulmonary fibrosis. We identified only three

| Table 3—Summary of Three Patients With Bilateral Interstitial Infiltrates on Chest Radiographs* |
|---|---|---|---|---|
| Patient/Age, yr/Sex | Smoking Status | Type of NF | CT Scan Findings | Coexisting Disorders |
| 1/53/F | Ex-smoker, 50 pack-yr | 1 | Emphysema, scattered cystic spaces, peripheral ground-glass and reticular densities | Emphysema |
| 2/72/M | Ex-smoker, 25 pack-yr | 1 | Reticular densities, ground-glass opacities | Rheumatoid arthritis, congestive heart failure, large granular lymphocytic leukemia, recurrent pneumonias |
| 3/57/F | Never | 1 | Not available | Cadaveric renal transplant, previous adult respiratory distress syndrome, recurrent pneumonias |

*F = female; M = male.
patients (1.9%) with bilateral interstitial infiltrates seen on chest radiography. All three patients had potential causes other than NF for their interstitial lung infiltrates, including smoking-related interstitial lung disease, rheumatoid lung disease, previous ARDS, and recurrent pneumonias. A CT scan was available in two of the three patients and revealed nonspecific abnormalities that were not characteristic of usual interstitial pneumonia, which is most commonly manifested as subpleural honeycombing in the lower lung zones.\textsuperscript{21,22} The association of pulmonary fibrosis (or fibrosing alveolitis) with NF has been described in multiple reports over the past 40 years.\textsuperscript{6–18} As of 1977, 31 such cases had been described in the English language medical literature.\textsuperscript{9} For example, Massaro and Katz\textsuperscript{6} were able to survey 88 patients with NF and identified 20 patients (23%) who had evidence of parenchymal lung disease by chest radiography (19 patients) or histopathology (6 patients). The age of these 20 patients ranged from 34 to 60 years. Most of these patients were men, a situation that is likely explained by the origin of this report being a Veterans Administration hospital. No information was given regarding tobacco, drug, or other inhalational exposures for these patients. Radiographic findings consisted of diffuse interstitial infiltrates and/or apical bullae. Histopathologic findings were described as alveolitis, interstitial fibrosis, and bullae.

Webb and Goodman\textsuperscript{9} reviewed chest radiographs of 70 consecutive patients with NF and identified 7 patients (10%) with radiographic findings of pulmonary fibrosis or bullae. These seven patients ranged in age from 39 to 72 years and included three women. Bilateral linear or small nodular opacities with a basilar predominance were seen in six patients; five of these patients also had upper lobe bullae, and honeycombing was seen in three patients. One remaining patient had upper lung bullae only. Pulmonary function test results had been obtained in three patients, revealing an obstructive pattern in two patients and a mixed obstructive-restrictive defect in the remaining patient. The smoking history for these patients was not included in this report. The combination of diffuse interstitial infiltrates and bullae on chest radiography was reported to be characteristic of NF.

Burkhalter and colleagues\textsuperscript{16} retrospectively reviewed the chest radiographs of 45 consecutive patients with NF ranging in age from 10 to 68 years, including 26 women. Three of these patients (7%), ranging in age from 38 to 46 years, had interstitial

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{HRCT scan of the chest of a 53-year-old ex-smoker with NF1 and bilateral interstitial lung infiltrates detected on chest radiography. \textit{Top, A:} this HRCT scan image demonstrates the changes in centrilobular emphysema and bullae in the upper lung zones. \textit{Bottom, B:} this image from the same HRCT scan demonstrates scattered cystic spaces present in the lower lung zones along with ground-glass opacities and reticular densities in the periphery.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{HRCT of the chest of a 72-year-old ex-smoker with NF1. This patient also had rheumatoid arthritis, large granular lymphocytic leukemia, and recurrent pneumonias. This image demonstrates nonspecific abnormalities consisting of coarse reticular densities and small areas of consolidation in the periphery of the lower lung zone.}
\end{figure}
infiltrates and/or bullae identified on chest radiography. Two patients had smoked previously.

Thus, parenchymal lung involvement has been detected by chest radiography in 7 to 23% of adult patients with NF in the three largest surveys. 6,9,16 This involvement has been characterized as diffuse interstitial lung disease or fibrosing alveolitis, and bullae. In the current study, bilateral interstitial lung disease or cystic airspaces were demonstrated in five patients (3.2%) by chest radiography. Interestingly, histopathologic descriptions for cases of fibrosing alveolitis have included the presence of many mononuclear cells, some of which were pigmented, in the intraalveolar spaces. 6,9,12 This description is suggestive of respiratory bronchiolitis-associated interstitial lung disease or desquamative interstitial pneumonia, which are two forms of smoking-related interstitial lung diseases. 23,24 Indeed, de Scheerder and colleagues 14 reported a case of desquamative interstitial pneumonia and lung cancer occurring in a 40-year-old smoker with NF. Unfortunately, many of the reports linking NF with interstitial lung disease did not provide information regarding smoking history of the affected patients. 6,8,9,11,12,15,17

The CT scan appearance of lung involvement in NF has been described in five cases. 15,18,25 The abnormalities seen on CT scans have varied, and include linear opacities in the lung bases with neither a peripheral nor a central predominance, 15 subpleural honeycombing, 25 diffuse reticular and ground-glass opacities, 18 and bullous formation in the apices. 15 Thus, a variety of abnormalities have been described on lung CT scans. Similarly, no characteristic pattern was seen by CT scan of the chest in our two patients with interstitial infiltrates. Although the histologic findings in patients with interstitial lung disease associated with NF have previously been characterized as indistinguishable from those of idiopathic pulmonary fibrosis, there is little evidence that these patients truly had usual interstitial pneumonia, the histopathologic pattern that defines idiopathic pulmonary fibrosis.

All of our patients who had bullous changes or cystic airspaces in the lung parenchyma had smoked cigarettes, and these changes occurred in the context of smoking-induced emphysema. It appears plausible that the bullous lung disease reported in patients with NF may have been smoking-related rather than a manifestation of NF. Two of the largest surveys, 6,9 describing the association of NF with parenchymal lung disease did not include information regarding the smoking habits of the study subjects.

Some of the radiologic and histopathologic features described in patients with NF and interstitial lung disease could be explained on the basis of smoking-related interstitial lung diseases. For example, desquamative interstitial pneumonia is usually associated with patchy ground-glass opacities seen on CT scans, and some of these patients may also have cystic changes. 26 Similar findings were noted in one of our patients (ie, patient 1 in Table 3).

Our results cast doubt on a true association between NF and parenchymal lung disease. In the current study, parenchymal abnormalities of either the bilateral interstitial lung infiltrates or cystic airspaces were demonstrated by chest radiography or CT scanning in 8 of 156 patients (5.1%), with 1 patient having both findings. Bilateral interstitial lung infiltrates were noted in patients with other potential causes for interstitial lung disease, and cystic airspaces were found in patients with smoking-related emphysema. If pulmonary nodules are discovered in an NF1 patient, one must consider the possibility of metastatic neurofibrosarcoma in the differential diagnosis. However, we recognize the limitations of the current study, including the retrospective design and the use of chest radiography as the main detection tool. In addition, there may have been selection bias associated with the referral basis of our clinical practice (eg, the travel factor). A more accurate assessment of this issue could be performed in a prospective study using high-resolution CT (HRCT) scanning in screening these patients for parenchymal lung disease. Nonetheless, previous studies had used chest radiography in documenting the association between NF and parenchymal lung disease; our results using the same tool does not confirm previous observations.

In summary, we find little evidence to suggest an association between NF and pulmonary fibrosis or any other form of parenchymal lung disease. Interstitial lung disease and bullae in patients with NF that had been described in previous reports may have been smoking-related phenomena and not directly related to NF.

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