Nontuberculous Mycobacterial Infection*

CT Scan Findings, Genotype, and Treatment Responsiveness

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Study objective: The purpose of this study was to compare the imaging findings of nontuberculous mycobacterial (NTM) infection in patients with normal and abnormal cystic fibrosis (CF) genotypes, and normal and abnormal α1-antitrypsin (AAT) phenotypes.

Design: A retrospective review of medical records and chest CT scans from 85 patients with microbiologically proven NTM infection was performed. All patients had undergone genotype analysis for CF mutations, and phenotypic evaluation for AAT status. Patients with homozygous CF or AAT were not included. Two independent observers assessed the patterns and distribution of disease, according to a standardized score sheet. In 52 patients, follow-up CT scans were obtained 1 to 46 months (mean duration, 8 months) following the initial CT scan. The CT scan findings on the follow-up scan were visually compared with those on the initial CT scan for progression or regression of abnormalities. Statistical analysis was performed to evaluate the relationship between the dominant CT scan pattern and CF/AAT status, and between CT scan pattern and radiologic change on follow-up.

Results: Fifteen patients (18%) were found to carry a single CF mutation, and an abnormal AAT phenotype was seen in 13 patients (15%). Three patients (3%) were found to have both a heterozygous CF mutation and a heterozygous AAT phenotype. On the initial CT scans, bronchiectasis and nodules were the most frequent findings of NTM infection in all three groups (p > 0.05). The prevalence of nodules was slightly lower in the CF group, and the prevalence of linear scarring was greater in the AAT group than in the normal group (p < 0.05). Among the 52 patients who had a follow-up CT scan, 8 (15%) had a CF mutation and 6 (12%) had an abnormal AAT phenotype. The extent and pattern of abnormality seen on the initial CT scan did not predict change on follow-up evaluation. After treatment, 40 patients (56%) with a normal CF genotype had decrease in disease extent, compared with 4 patients (25%) with a CF mutation (p < 0.05). Bronchiectasis was improved in approximately 35% of those with normal genotype, but in none of those with a CF mutation.

Conclusion: In patients with NTM infection, the CT scan findings show only minor differences according to phenotype and genotype. Initial CT scan findings do not predict change on follow-up CT scan evaluation. However, on follow-up CT scan, patients with CF mutations are less likely to improve, while those with AAT phenotype appear to have a radiographic outcome similar to those with normal phenotype.

Key words: α1-antitrypsin deficiency; cystic fibrosis; lung infection; mycobacteria

Abbreviations: AAT = α1-antitrypsin; CF = cystic fibrosis; MAC = Mycobacterium avium complex; NTM = nontuberculous mycobacterial

Pulmonary disease caused by nontuberculous mycobacterial (NTM) infection was previously thought to occur only in specific risk groups, such as patients with chronic lung disease or patients with deficiencies in cell-mediated immunity due to HIV or other causes. Recent data suggest that NTM infections are increasing in frequency,1 and there is

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Table 1—Distribution of Genotype and Phenotype in Patients With NTM Infection*

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Normal</th>
<th>CF</th>
<th>AAT</th>
<th>CF + AAT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>54 (65)</td>
<td>15 (18)</td>
<td>13 (15)</td>
<td>3 (3)</td>
<td>85</td>
</tr>
<tr>
<td>Follow-up</td>
<td>36 (60)</td>
<td>8 (15)</td>
<td>6 (12)</td>
<td>2 (4)</td>
<td>52</td>
</tr>
</tbody>
</table>

*Values are given as No. (%). Normal = normal CF genotype and AAT phenotype.

Materials and Methods

We reviewed the medical records and CT scan examinations of 85 patients presenting with microbiologically proven NTM infection that had been diagnosed between October 1991 and January 2002. NTM infection was diagnosed by cultures of sputum or BAL specimens. All patients met current American Thoracic Society criteria for the diagnosis of NTM infection. All patients had undergone genotype analysis for CF mutations, and phenotype evaluation for AAT status as part of their clinical evaluation at National Jewish. AAT phenotyping was performed using isoelectric focusing in polyacrylamide gel. DNA isolated from blood was tested for 86 CF mutations. Regions of the CFTR gene were amplified enzymatically and hybridized to specific CF mutation oligonucleotide probes. Results were characterized as positive or negative, and specimens with positive results were tested for specific mutation identity using either the same methodology or a solution-phase multiplex allele-specific primer extension with subsequent hybridization to a bead array and fluorescent detection. Patients with homozygous CF or AAT were not included in this study.

Eighty-five patients (74 women and 11 men) with NTM infection were studied. They reflected a randomly selected subset of a larger retrospective cohort (Human Subjects approval 1439; the institutional review board approved the study). Patient ages at the time of diagnosis ranged from 35 to 84 years (average age, 63 years). Follow-up times ranged from 1 to 46 months; the average follow-up time was 8 months. Patients presented with typical symptoms of NTM infection, predominantly chronic cough and fatigue. Treatment was optimized utilizing in vitro susceptibility-testing results, severity of disease, and patient tolerance of medications. In keeping with American Thoracic Society recommendations, treatment was continued for at least 12 months after the last negative finding of a sputum culture.

A CF mutation was observed in 15 patients (18%), abnormal heterozygous AAT phenotype was seen in 13 patients (15%), and both a heterozygous CF mutation and an abnormal heterozygous AAT phenotype was observed in 2 patients (3%) (Table 1). The heterozygous genotypes of CF were ΔF508 (n = 10), w1282x (n = 3), R117H (n = 1), and D1152H (n = 1). The heterozygous phenotypes of AAT were MS (n = 4), MZ (n = 3), IM (n = 3), SZ (n = 2), and FM (n = 1). In the patients with both heterozygous CF mutation and abnormal heterozygous AAT phenotype, the abnormalities were ΔF508 and MG, ΔF508 and MS, and R117H and MS. There was no statistical difference in age or gender among patients in the affected groups.

The NTM organisms found in these patients were identified as Mycobacterium avium complex (MAC) [n = 73], Mycobacterium chelonae-abscessus (n = 22), Mycobacterium simiae (n = 5), Mycobacterium fortuitum (n = 4), Mycobacterium xenopi (n = 2), and Mycobacterium kansasii (n = 2) [Table 2]. The prevalence of these organisms was not different among those with abnormal genotype or phenotype. Twenty-one patients with MAC (29%) showed mixed infection with M chelonae (n = 9), M simiae (n = 3), M fortuitum (n = 3), M abscessus (n = 2), M kansasii (n = 2), and M xenopi (n = 1). Seventeen patients with M chelonae (88%) showed mixed infection with MAC (n = 9), M abscessus (n = 5), and M kansasii (n = 1). Four patients with M fortuitum (75%) showed mixed infection with MAC (n = 3). The prevalence of CF genotype and AAT phenotype was not different in those with mixed NTM infection compared with those infected with a single organism.

Contiguous 10-mm or 7-mm CT scans were performed through the chest. IV contrast material was not used unless there was a specific clinical indication. In most patients, additional high-resolution imaging was performed at 2-cm intervals. On the CT scan images, the patterns and distribution of disease were assessed according to a standardized score sheet by two indepen-

Table 2—Types of NTM Infection in Study Population, According to CF Genotype and AAT Phenotype*

<table>
<thead>
<tr>
<th>Organism</th>
<th>Normal (n = 54)</th>
<th>CF (n = 15)</th>
<th>AAT (n = 13)</th>
<th>CF + AAT (n = 3)</th>
<th>Total (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC</td>
<td>47 (87)</td>
<td>13 (87)</td>
<td>10 (77)</td>
<td>3 (100)</td>
<td>73 (86)</td>
</tr>
<tr>
<td>M chelonae-abscessus</td>
<td>13 (24)</td>
<td>4 (27)</td>
<td>4 (31)</td>
<td>1 (33)</td>
<td>22 (26)</td>
</tr>
<tr>
<td>M simiae</td>
<td>3 (6)</td>
<td>1 (7)</td>
<td>1 (8)</td>
<td>0 (0)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>M fortuitum</td>
<td>2 (4)</td>
<td>2 (13)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>M xenopi</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>M kansasii</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Values are given as No. (%). See Table 1 for abbreviation not used in the text.
dent observers who were blinded to the patients’ genotype or phenotype results. Features scored on CT scan included the following: presence or absence of bronchiectasis; nodules; consolidation; cavity; ground-glass opacity; linear scarring; volume loss; parenchymal calcification; emphysema; air-trapping; mediastinal or hilar lymph node enlargement or calcification; pleural effusion; pleural thickening or calcification; esophageal dilatation; esophageal wall thickening; and hiatal hernia. The predominant CT scan pattern was classified into one of the following five categories: (1) bronchiectasis/nodules; (2) airspace consolidation; (3) cavities; (4) others; and (5) mixed. Separate scores were recorded for each lung lobe. The lingular segment was included as a separate lobe for the purpose of this study.

In 52 patients, follow-up CT scans were obtained 1 to 46 months (mean, 8 months) after the initial CT scan, following appropriate individual optimized therapy based on drug susceptibility, tolerance, and sensitivity. The CT scan findings on the follow-up scan were visually compared with those on the initial CT scan. The overall change seen on follow-up CT scans was evaluated by the consensus of two observers. \( \chi^2 \) testing, with Fisher exact test where appropriate, was performed to evaluate the relationship between the dominant CT scan pattern and CF/AAT status, and between CT scan pattern and radiologic change on follow-up, using a statistical software package (JMP; SAS Institute Inc; Cary, NC).

**Results**

CT scan findings were abnormal in all subjects. CT scan findings are provided in Table 3. The most significant initial CT scan findings were bronchiectasis, nodules, consolidation, and cavities (Table 3). The predominant CT scan pattern at presentation was bronchiectasis with nodules, which was found in 160 observations (94%) [Fig 1]. The predominant sites of NTM infection were the lingula in 72 observations (42%), the right middle lobe in 69 observations (41%), the right upper lobe in 67 observations (39%), the basal segments of the right lower lobe in 39 observations (22%), the superior segment of the right lower lobe in 26 observations (15%), the basal segments of the left lower lobe in 24 observations (14%), and the superior segment of the left lower lobe in 15 observations (9%).

When the CT scan findings were classified according to genotype and phenotype, bronchiectasis and nodules were the most frequent CT scan findings of NTM infection in all three groups (\( p > 0.05 \)). The prevalence of nodules was slightly lower in the CF group. The prevalence of linear scarring was greater in the AAT group (\( p < 0.05 \)) [Fig 2]. However, the prevalence of all other CT scan features was similar in those with different genotype and phenotype (Table 3).

Among the 52 patients who underwent follow-up CT scans, 8 (15%) had a CF mutation and 6 (12%) had an abnormal AAT phenotype (Table 1). The two patients with a combined abnormality of CF genotype and AAT phenotype were excluded from analysis because of the small numbers of patients in this group.

On follow-up CT scan, NTM infection was improved in 52 of 104 readings (50%), and was worse in 26 readings (25%), with a mixed pattern of response in 26 readings (25%) [Table 4]. On review of specific CT scan features, there was a wide variation in response, with bronchiectasis increased in 22 readings (21%), and decreased in 29 readings (28%). Nodules progressed in 25 readings (24%), and improved in 45 readings (43%). Consolidation progressed in 25 readings (24%), and improved in 34 readings (33%).

**Table 3—Initial CT Findings (170 Readings)*

<table>
<thead>
<tr>
<th>Findings</th>
<th>Normal (n = 108)</th>
<th>CF (n = 30)</th>
<th>AAT (n = 26)</th>
<th>CF + AAT (n = 6)</th>
<th>Total (n = 170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>104 (96)</td>
<td>28 (93)†</td>
<td>26 (100)</td>
<td>6 (100)</td>
<td>164 (96)</td>
</tr>
<tr>
<td>Nodule</td>
<td>106 (98)</td>
<td>26 (87)†</td>
<td>25 (96)</td>
<td>6 (100)</td>
<td>163 (96)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>59 (55)</td>
<td>14 (47)</td>
<td>11 (42)</td>
<td>2 (33)</td>
<td>76 (45)</td>
</tr>
<tr>
<td>Cavity</td>
<td>46 (43)</td>
<td>8 (27)</td>
<td>10 (38)</td>
<td>2 (33)</td>
<td>66 (39)</td>
</tr>
<tr>
<td>GGO</td>
<td>17 (16)</td>
<td>6 (20)</td>
<td>4 (15)</td>
<td>0 (0)</td>
<td>27 (16)</td>
</tr>
<tr>
<td>Linear scarring</td>
<td>65 (63)</td>
<td>18 (60)</td>
<td>23 (88)†</td>
<td>6 (100)</td>
<td>115 (68)</td>
</tr>
</tbody>
</table>

*Values are given as No. (%). GGO = ground-glass opacity. See Table 1 for abbreviation not used in the text.
†\( p < 0.05 \) (compared with Normal).
readings (33%). Cavitation progressed in 10 readings (10%), and improved in 17 readings (16%). Ground-glass opacity progressed in 7 readings (7%), and improved in 12 readings (12%). Linear scarring progressed in 16 readings (15%), and improved in 5 readings (5%) [Table 5]. The extent and pattern of abnormality on the initial CT scan did not predict a change on the follow-up evaluation.

There was a significant difference between the patients with heterozygous CF and patients in the other groups in the prevalence of improvement on follow-up scans. Forty of 72 readings (56%) with normal genotype and 6 of 12 readings (50%) with AAT group showed a decrease in disease extent, compared with 4 of 16 readings (25%) with CF mutations (p < 0.05) [Table 4]. Patients with a CF mutation were less likely to improve, while those with AAT phenotypes appeared to have a similar outcome to those with normal phenotypes.

Bronchiectasis was improved in 23 of the 72 readings (32%) in those with normal genotype and phenotype, and in 6 of 12 readings (50%) in the AAT group (Fig 3). But none of those with a CF mutation showed this improvement (p < 0.05) [Fig 4]. Nodules were improved in 37 of 72 readings (51%) in those with normal genotype and phenotype, compared with 4 of 16 readings (25%) in the CF mutation group and in 4 of 12 readings (33%) in the AAT group (p < 0.05 for each group). Cavitation was improved in 17 of 72 readings (24%) in the normal genotype group, but no patient with heterozygous CF and AAT deficiency showed improvement in cavitation (p < 0.05 for each group) [Table 5]. There was no difference in the prevalence of improvement of other CT scan features in the three groups.

**Discussion**

In our study of patients with NTM infection, patients with an abnormal mutation of the CF gene were less likely to have improvement in the overall extent of disease, and, specifically, in the extent of bronchiectasis, nodules, and cavities, were all less likely to improve than those with a normal genotype. In those with abnormal AAT phenotype, the extent of nodules and cavities were less likely to improve compared with those with a normal phenotype (p < 0.05). The extent and pattern of abnormality seen on the initial CT scan did not predict the genotype or phenotype and did not change on the follow-up evaluation.

The retrospective nature of this study, combined with the highly individualized therapy necessitated by both NTM infection and the clinical approach at National Jewish, made antibiotic treatment outcomes difficult to assess. However, we analyzed the cohort according to a matrix of standard therapy (*ie*, clarithromycin/azithromycin, rifabutin, and ethambutol), standard therapy plus the addition of an IV antibiotic (*ie*, amikacin), standard therapy plus the addition of an inhaled antibiotic (*ie*, amikacin or Tobramycin), nonstandard therapy, and finally non-standard therapy plus amikacin. These five categories captured the regimens for the cohort. Of those patients with MAC, 38% were receiving standard therapy, 28% were receiving standard therapy plus amikacin, 9% were receiving standard therapy plus an inhaled antibiotic (*ie*, amikacin or Tobramycin), nonstandard therapy, and finally non-standard therapy plus amikacin. Of the patients with

<table>
<thead>
<tr>
<th>Changes</th>
<th>Normal (n = 72)</th>
<th>CF (n = 16)</th>
<th>AAT (n = 12)</th>
<th>CF + AAT (n = 4)</th>
<th>Total (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall improvement</td>
<td>40 (56)</td>
<td>4 (25)†</td>
<td>6 (50)</td>
<td>2 (50)</td>
<td>52 (50)</td>
</tr>
<tr>
<td>Overall progression</td>
<td>14 (19)</td>
<td>8 (50)</td>
<td>2 (17)</td>
<td>2 (50)</td>
<td>26 (25)</td>
</tr>
<tr>
<td>No change</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mixed response</td>
<td>18 (25)</td>
<td>4 (25)</td>
<td>4 (33)</td>
<td>0 (0)</td>
<td>26 (25)</td>
</tr>
</tbody>
</table>

*Values are given as No. (%). See Table 1 for abbreviation not used in the text.
†p < 0.05 (compared with Normal).
rapidly growing mycobacteria infection, 22% were receiving standard therapy, 45% were receiving standard therapy plus IV amikacin, and 22% were receiving standard therapy plus an inhaled antibiotic.

NTM infection, long believed to be commensal organisms, are increasingly recognized as being responsible for clinically important disease. Most of the previous descriptions of NTM infection have emphasized its occurrence in subjects with predisposing chronic lung disease, such as COPD, prior tuberculosis, bronchiectasis, pneumoconiosis, diabetes mellitus, scoliosis, pectus excavatum, malignant disease, and immunodeficiency states, particularly AIDS. However, there is an increasingly recognized group of subjects who develop NTM infection without any predisposing lung disease. The majority of these patients are older women, who are not immunocompromised in any overt way.2–5 In keeping with this newly recognized group, the population in our study was 87% women and had a mean age of 63 years.

The typical CT scan abnormalities in this group of nonimmunocompromised subjects with NTM infection, include diffuse bronchiectasis with centrilobular nodules, multifocal consolidation, and cavitation. These findings are similar to those found in other studies.2,6,7 In our institution, a high prevalence of CF mutation and AAT phenotype was found in patients with NTM infection. Eighteen percent of those with NTM infection had a heterozygous CF mutation, and 15% had a heterozygous AAT phenotype. The background prevalence of heterozygous CF mutation in the general North American population is approximately 1 in 25 to 1 in 35 white individuals (3 to 4%).17 The prevalence of heterozygous abnormal AAT phenotype is 5%.18 Given these findings, it was important to determine whether the CT scan pattern of abnormality could be used to predict abnormal genotype or phenotype, and whether the genotype or phenotype can predict radiologic progression or regression of disease.

The reported prevalence rate of NTM infection in CF patients ranges from 4 to 20%19–22 and may depend in part on the definition of NTM infection as opposed to colonization. In general, apart from increased age,19,20 patients with CF who have NTM infection do not differ from those without CF. In the report by Oliver et al,22 the overall prevalence of NTM infection in CF patients mutation is 13% (range by center, 7 to 24%). This prevalence is quite similar to that found in our study. Our study suggests that even patients with the heterozygous CF muta-

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22036/)
tion may be predisposed to NTM infection. The radiologic pattern of disease appears to be similar in those with normal and abnormal genotypes. According Oliver et al., the characteristic high-resolution CT scan findings of NTM infection are more prevalent in subjects with CF with repeated positive culture findings, and these findings may progress over even a relatively short period of 12 to 15 months. We speculate that the presence of the CF mutation may predispose patients to impaired mucociliary clearance, with resultant difficulty in clearing the NTM infection. The presence of irreversible bronchiectasis in >90% of our patients with the CF mutation may also partially explain the failure of improvement in this group.

Previous studies of CT scan findings in patients with homozygous AAT deficiency have shown areas of low density (emphysema), attenuation of pulmonary vasculature, bulla formation, and bronchial wall thickening and/or dilatation. The prevalence of bronchiectasis in these patients is 43%. Linear scarring was more frequent in patients with AAT phenotype (88%) compared with those with normal phenotype (63%) and CF mutation (60%; p < 0.05). We have seen similar basal long lines quite frequently in patients with homozygous AAT deficiency, and they have been reported by others. These long linear abnormalities may represent interlobular septa outlining hyperinflated lobules. To our knowledge, the prevalence of NTM infection in patients with homozygous or heterozygous AAT deficiency has not previously been reported. The overall rate of radiologic improvement in those patients with the abnormal AAT phenotype appeared to be similar to those with normal phenotype, although the extent of nodules and cavities was less likely to improve compared with patients with normal phenotype (p < 0.05).

An interesting and previously unreported finding of our study is the fact that the bronchiectasis associated with NTM infection is reversible in up to 30% of patients with normal genotypes. The reversible bronchiectasis was generally cylindrical in type, which is in keeping with previous reports that cylindrical bronchiectasis may be reversible after treatment for pulmonary infections. It is possible that this “bronchiectasis” may represent reactive bronchial dilation rather than true bronchiectasis. The fact that the bronchiectasis found in patients with CF mutations was not reversible suggests that these patients might have had structural bronchial abnormalities that were unrelated to the superimposed NTM infection. However, it is interesting that the initial prevalence of bronchiectasis was equally high in the three groups.

It is clear that this retrospective study is bound by certain limitations. Because treatment was individually tailored, it was not possible to determine whether treatment might have had a differential effect on outcome. The number of cases with heterozygous CF mutation and AAT phenotype was relatively small, perhaps leading us to miss some differences between the populations. Because our institution is a national referral center for mycobacterial diseases, the extent of the CT scan abnormalities reported here may differ substantially from that found in the community. Referral bias might have led us to see patients with more severe disease, perhaps including a greater proportion of patients with abnormal genotypes and phenotypes. Because of our study design, we are unable to estimate the true prevalence of NTM infection in subjects with abnormal genotypes and phenotypes. Also, it is possible that some of the patients with heterozygous CF or AAT deficiency may have had underlying bronchiectasis or other abnormalities prior to the
onset of NTM infection. However, our findings suggest that CF genotype and AAT phenotype should be regarded as potential risk factors for NTM infection, and that the presence of the abnormal CF genotype may be a predictor of poorer prognosis. A prospective study would be required to further evaluate this possibility.

We conclude that the initial CT scan pattern does not predict the response to treatment in patients with NTM infection. NTM infection is quite frequently associated with heterozygous CF genotype and normal AAT phenotype. The differences in initial CT scan findings between these groups are relatively minor. However, on follow-up CT scans, patients with CF mutation are less likely to improve, while those with an abnormal AAT phenotype appeared to have a similar outcome to those with normal phenotype. Bronchiectasis in patients with NTM infection improves with treatment in many of those with normal genotype, but not in those with CF mutations.

**References**