ABSTRACT • Aim: The purpose of this study was to identify the radiographic and CT scan findings in patients with Mycobacterium simiae pulmonary infections. Methods: A total of 40 patients with positive cultures for M. simiae were identified between January 2000 and August 2015. In our radiographic analysis, we included those with cultures that grew M. simiae as the only isolate. The patients’ chest X-rays and Computed Tomography scans were reviewed and Receiver Operating Characteristic (ROC) and inter- and intra-reader variability was recorded. Results: A total of 54 images were retrieved, 30 Chest X-rays and 24 CT scans. Out of the 9 patients who had chest X-rays, 3 (33.3%) patients had their x-rays read as normal while the rest 6 (66.6%) had abnormal findings. All patients had abnormal findings on their CT images. The most common radiographic findings were consolidations, bronchiectasis, nodules, ground glass opacities, and enlarged mediastinal lymph nodes. ROC scores demonstrated significant detection of nontuberculous mycobacteria (NTM) (p < 0.003) (95%; CI [0.589-0.864] and CI [0.566-0.844]) (p < 0.001) with good interobserver agreement (k = 0.63). Conclusion: M. simiae infection has various radiographic presentations. It is imperative that radiologists recognize its common radiographic features. Furthermore, M. simiae must be considered even in immunocompetent patients.

Keywords: lung, Mycobacterium simiae, chest X-ray, computed tomography

INTRODUCTION

The number of patients with pulmonary disease caused by nontuberculous mycobacteria (NTM) is rapidly increasing globally [1]. Poor resistance against infections, due to previous lung diseases, immune deficiency and immune-modulating treatment, increases the likelihood of patients developing pulmonary NTM disease. Additionally, co-morbidities such as chronic liver disease, diabetes mellitus, cardiac disease, and malignancy predispose to infection as well [2].

Advances in medical imaging and microbiological techniques, particularly molecular techniques, have enhanced our understanding of this disease, but many uncertainties remain, especially in radiological diagnosis. Consequently, radiographic abnormalities often seem to remain stable and progress very slowly. All of these factors contribute to the delay in diagnosis. However, recent position statements have suggested that patients that have suspected NTM and are classified as grade D should have a chest X-ray and CT scan [3] based on expert opinions and previous case studies.

Patients with chronic respiratory symptoms have M. simiae isolated from sputum and bronchoalveolar lavage specimens. This increase has been noted in Middle-Eastern countries and in other countries such as Israel and Australia [4-7]. Often M. simiae is considered to be of low virulence. However, radiologically it can be challenging. The aim of this study was to identify the radiographic and CT scan findings in patients with M. simiae pulmonary infection.

MATERIALS AND METHODS

Patient selection
Institutional review board approval was received for this study. We reviewed all consecutive cases with positive culture for NTM obtained between January 2000 and August 2015. There was a total of 40 patients where M. simiae was either the only species cultured or was detected amongst other species from respiratory samples. Speciation of the isolated NTM was carried out at the Mayo Clinic by using the Maldi-Tofassay or, if that failed, DNA sequencing was used.

The images retrieved dated from the initial day of admission till either the last day of the study if a positive culture persists or until the first negative culture was obtained. All patients (n = 40) met the diagnostic criteria of the American Thoracic Society inclusion criteria for NTM pulmonary disease [8]. However, in order to discard the possibility of regarding a case as a mere colonization, we included only those where M. simiae grew as the only isolate. Some patients had their diagnostic radiographs performed at other hospitals and the images were not available for review.

Of the patient population, 17 patients were included in the radiographic analysis (male: n = 10; female: n = 7). The mean age of patients at time of diagnosis was 60 (range, 21-84 years). Five patients had a chest X-ray, 8 patients had CT scan, and 4 patients had both X-ray and CT. A total of 54 cases were retrieved (30 chest X-rays and 24 CT scans). In the study population, only six patients had a single image with no follow-up imaging studies. The rest of the patients were followed up for an average of 15 months, with the shortest period being 1 month and the longest 55 months.

Imaging technique
Chest X-ray exams consisted of a single posterior-anterior view that was obtained using 70-80KVP along with a tube-to-distance of 6 feet. Unenhanced CT scans were acquired with either a Philips ICT scanner (8 patients) or a Siemens Somatom sensation scanner (4 patients).

All CT data were reconstructed using sharp algorithm dedicated to lung imaging. On the Philips ICT scanner, CT technique was as follows: 80 mm collimation, 100KVP, 200 mA, 1.5-mm intervals. On the Siemens Somatom sensation scanner, CT technique was as follows: 20 mm collimation, 120KVP, 200 mA, 1.5-mm intervals. All images were reconstructed at 1.5 mm thickness. The scan data were displayed on two monitors (with 1536 x 2048 image matrices, 3 megapixel viewable gray-scale, using BARCO luminescence) of a picture archiving and communication system, or PACS (AGFA version 6.5.3.562). Both mediastinal (window width, 150 HU; window level, 88HU) and lung (window width, 1500 HU; window level, - 600 HU) window scans could be viewed and image brightness manually adjusted when being reviewed.

Review of radiographs and CT scans
Two radiologists reviewed initial and follow-up radiographs and CT scans (mean years of experience: 10 years; minimum 5 years, maximum 15 years). The radiologists were given a mixture of cases including patients with TB, NTM infection, and normal studies.

They were unaware of any clinical information. They assessed the images separately then reached final decisions by consensus. A total of six lobes were assessed for any abnormal findings. The lingula was counted as a lobe.

Chest X-rays were assessed for the following: bronchiectasis, cavitary lesions, nodules, atelectasis, pleural effusions, pleural thickening, reticulonodular opacities, and volume loss/decrease.

CT images were assessed for the following: consolidations, bronchiectasis, nodules, cavities, ground glass opacity, linear scarring, volume loss, parenchymal calcification, emphysema, air-trapping, mediastinal or hilar lymph node (LN) enlargement or calcification, pleural effusions, pleural thickening/calcification, esophageal dilatation, esophageal wall thickening, and hiatal hernias. Consolidations were described as lobular, segmental, or peribronchial. Bronchiectasis was also described as cylindrical, cystic, or varicose. As for the nodules, they were described as either tree-in-bud pattern or peribronchovascular. In the presence of cavities, we accounted for their number, their diameters measured and reported in millimeters, and wall thickness was commented on whether it was thick or thin walled.

ROC analysis
A total of 60 cases were randomly allotted, divided equally between the three groups. Of the 60 cases, 22 exhibited no pathology, 13 demonstrated tuberculosis, and 25 with NTM. Truth was determined by the cardiothoracic radiologist reports as well as confirmation with CT and culture.

Chart review
The medical records were reviewed for the following information, when present: smoking history, pre-existing lung disease, immunodeficiency, purified protein derivative (PPD) result, history of tuberculosis (TB) treatment, and human immunodeficiency virus (HIV) status. Concerning their smoking history, 9 (53%) were past smokers, 6 (35%) never smoked, and we had data missing for 2 (12%) patients. Six (35%) patients had pre-existing lung disease while 11 (65%) patients did not. There was a single case of asthma, 2 cases of bronchiectasis, and 3 cases of chronic obstructive pulmonary
disease (COPD). One patient had another risk factor namely immunodeficiency, for he had acute myeloid leukemia (AML). Two of the 3 cases of patients with COPD and the patient with AML had a history of recurrent pneumonias. PPD testing was done for all patients, 13 patients were negative while 4 were positive for latent TB. None of those patients with latent TB took treatment medications prior to their admission. All patients were HIV negative except for one patient who was already diagnosed prior to presentation.

**Statistical analysis**

Pathology compared between normal, tuberculosis and NTM using a two-tailed independent t-test. The ROC analysis utilized the Dorfman-Berbaum-Metz (DBM) approach while using random readers and fixed cases [9]. The analysis treated cases as fixed because the limited image sample size should not be taken as representative of all images. Results were considered statistically significant at \( p \leq 0.05 \). In each case series inter- and intra-observer agreements were calculated using Cohen’s kappa analysis. A \( k \) value 0.60-1, 0.41-0.60, 0.21-0.40 and less than 0.20 was considered excellent, moderate, fair and poor agreement respectively.

**RESULTS**

The chest X-ray findings are summarized in table I. Nine patients had chest X-rays, 6 (66.6%) of which had abnormal findings. Both lungs were concomitantly affected in 3 patients. Bronchiectasis and pleural effusions were identified in 2 patients each. Reticulonodular opacities, emphysematous changes (Fig. 1a), and infiltrates were visualized in one patient each. A single patient had a consolidation visualized in the left lower lobe. None of the patients had cavitary lesions, nodules, atelectasis, pleural thickening, or volume loss in the lung visualized on their chest X-rays.

The CT findings are summarized in tables II and III. All patients had abnormal findings on their CT images. Of the 12 patients who had CT images, 7 patients (58%) had both lungs concomitantly affected. Unilateral lung infection was detected in a total of 5 (41.6%) patients; left and right lungs were involved in 3 patients (25%) and 2 patients (17%), respectively.

The most commonly involved lobe was the right upper lobe (66.67%) [patients], followed by the left lower and right middle lobes (50%), the lower right lobe and the lingula (41.67%). The least common lobe affected was the left upper lobe which was involved only in 3 patients (25%).

Consolidation was visualized in 5 patients. It was lobular shaped in 1 patient while the rest were segmental. Bronchiectasis was noted in 5 patients all of which had cylindrical type (Fig. 2a). However, one patient had cylindrical type bronchiectasis which on follow-up had evolved into having a cystic component as well. Nodules were visualized in 6 cases, most commonly as a tree-in-bud pattern (66.67%) (Figs. 2b & 3b), followed by peribronchovascular, and nonspecific (16.67%) each.

Over a follow-up of 18 months, one patient had 2 CT scans in which 5 thin walled cavities were visualized in total. Two cavities (8 mm & 17 mm in diameter) were detected on the first CT and 3 cavities (9, 10, & 20 mm in diameter) on follow-up (Fig. 3a). Other findings include: ground glass opacity and enlarged mediastinal lymph nodes (41.67%), bilateral apex linear scarring (16.67%), emphysema (16.67%) (Fig. 1b), and hilar lymphadenopathy (16.67%).

**TABLE II. SUMMARY OF LOBES AFFECTED AS SEEN ON CT**

<table>
<thead>
<tr>
<th>Lobe affected</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper lobe</td>
<td>8</td>
</tr>
<tr>
<td>Left lower lobe</td>
<td>6</td>
</tr>
<tr>
<td>Right middle lobe</td>
<td>6</td>
</tr>
<tr>
<td>Right lower lobe</td>
<td>5</td>
</tr>
<tr>
<td>Lingula</td>
<td>5</td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>3</td>
</tr>
</tbody>
</table>

**TABLE III. SUMMARY OF CT FINDINGS**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>5</td>
</tr>
<tr>
<td>Lobular</td>
<td>1</td>
</tr>
<tr>
<td>Segmental</td>
<td>4</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>5</td>
</tr>
<tr>
<td>Cavitation</td>
<td>1</td>
</tr>
<tr>
<td>Ground glass opacity</td>
<td>5</td>
</tr>
<tr>
<td>Linear scarring</td>
<td>2</td>
</tr>
<tr>
<td>Emphysema</td>
<td>2</td>
</tr>
<tr>
<td>Enlarged mediastinal lymph nodes</td>
<td>5</td>
</tr>
<tr>
<td>Hilar lymph node calcification</td>
<td>2</td>
</tr>
<tr>
<td>Nodules</td>
<td>6</td>
</tr>
<tr>
<td>Tree in bud pattern</td>
<td>4</td>
</tr>
<tr>
<td>Bronchovascular</td>
<td>1</td>
</tr>
<tr>
<td>Non specific</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure 1. A 70-year-old male with *M. simiae* pulmonary disease
a. PA chest radiograph showing right upper lobe emphysematous changes (arrows) and left upper lobe fibrosis from previous surgery and loss of volume.  b. Axial thick section (4mm) CT scan showing similar changes to corresponding chest radiograph.

Figure 2. A 61-year-old female with *M. simiae* pulmonary disease
a. Axial thick-section (4 mm) CT scan shows abnormal dilatation of the bronchial tree in keeping with bronchiectasis (arrow) in the right middle lobe  b. CT shows multiple small nodules and branching centrilobular nodules, so called tree-in-bud (arrow) in the right lower lobe.

Figure 3. A 55-year-old female with *M. simiae* pulmonary disease
a. Axial thick-section (4mm) CT scan obtained at the level of the great vessels shows multiple thin-walled cavities in both lung apices.  b. CT shows multiple small nodules and branching centrilobular nodules, so called tree-in-bud (arrows) in the upper right and lower right lobes.
None of the patients had lung volume loss, parenchymal calcification, air trapping, pleural thickening or calcification on their CT scans.

When combining normal and abnormal images in the reading session, it resulted in significant reader sensitivity and specificity with mean ROC values demonstrating increased reader confidence range by reader 1 (95%; CI [0.722-0.873]) and reader 2 (95%; CI [0.648-0.813]) ($p < 0.0001$) (Fig. 4). We further extrapolated the data that evaluated the sensitivity and specificity of NTM on its own with significant reader confidence by reader 1 (95%; CI [0.589-0.864]) and reader 2 (95%; CI [0.566-0.844]) ($p < 0.003$) (Fig. 5).

Moreover, detection and agreement in patients with NTM yielded good ($p < 0.001$) interobserver agreement ($k = 0.63$) and there was a strong positive relationship between NTM and patients with chest pathology overall ($r = 0.61, p < 0.001$).

**DISCUSSION**

The true virulence of NTM is controversial. Even in the presence of a positive culture, it is difficult to distinguish between colonization and invasive pulmonary disease. Nevertheless, studies have shown that NTM are indeed pathogenic. Transbronchial lung biopsies carried out in patients with *Mycobacterium avium* complex (MAC) infection demonstrated lung tissue invasion. Extensive epithelioid granuloma formation, destruction of bronchial cartilage and smooth muscle layers, and ulceration of bronchial mucosa were visualized [10-12]. Furthermore, Moore studied serial computed tomographies [8] for patients with an atypical *Mycobacterium* infection. Upon follow-up, the most common manifestation, namely bronchiectasis was noted in new lung areas and progression of existing bronchiectasis was visualized [13].

NTM pulmonary infection has two distinct radiologic manifestations: the cavitary form (classical infection) and bronchiectatic form (nonclassical infection). The cavitary form of the disease is prevalent in elderly men with an underlying chronic disease; usually chronic obstructive pulmonary disease (COPD). The characteristic radiologic findings include upper lobe cavitary formation and nodules [14-17]. The bronchiectatic form is prevalent in elderly women without an underlying disease. The characteristic radiologic findings include bronchiectasis, bronchiolitis, and small nodules. The middle lobe and lingula are most commonly affected [18-22]. Despite the nonspecific imaging features, they are useful in ruling out or ruling in an NTM infection when put in clinical context. This is echoed by our readers’ significant high sensitivity and low specificity as well as good inter- and intra-reader variability in identifying images of NTM infected individuals.

Our radiological imaging results showed that we had normal chest radiographs in 33.3% of the patients who had a chest X-ray. This is comparable to the findings by Shitrit et al. in which 38% of their patients had normal chest X-ray readings [2]. The right upper lobe was the most commonly involved lobe in our study. According to Moaz et al. the lower/middle lobes (55%) were more affected than the upper lobes (45%) [23]. However, the right upper lobe was affected more than its left counterpart; 25% and 20% respectively. In our study, the most common radiographic findings were consolidations, bronchiectasis, nodules, ground glass opacities, and enlarged mediastinal lymph nodes. It is comparable to other studies which reported nodular lesions (100%) and bronchiectasis (85%) as the most common findings [6,24]. However, unlike Baghaei et al. where cavitation (88.5%) was amongst the most common findings, we had only one single patient who had a total of 5 cavities over a follow-up duration of 18 months.
Miller Jr WT claimed that radiographic findings of NTM pulmonary infections are not influenced by a specific mycobacterial species [18]. This was corroborated by Jeong et al., whereby irrespective of which mycobacterial species caused the infection, the most common findings were the same [25]. In contrast to a report by Ellis and Hansell in which radiographic features of NTM infections were variable according to the isolated species [26]. Some differences are subtle while others are blatant. Nevertheless, the question remains whether these differences are significant. Further studies are needed to address this matter. This is particularly important as the clinical manifestations of various NTM mycobacterial infections are variable and not all laboratories have the ability to identify the species, especially that such infections are prevalent in some developing countries with limited resources. Moreover, treatment is species specific since the organisms tend to have different susceptibility profiles.

Our study has its limitations including patient selection bias in a tertiary care medical center with patient referral mostly from the city area. Another limitation is that the number of immunocompromised patients was limited. These patients might have a different radiographic pattern. Finally, our case load was small to run further statistical analyses.

*M. simiae* infection has various presentations on imaging which makes it difficult to diagnose. Therefore, a radiologist’s role is pivotal in recognizing its common radiographic features and to include NTM infection, and specifically *M. simiae* infection in the differential diagnosis in the endemic countries. Finally, it is imperative to recognize that *M. simiae* can affect immunocompetent patients.

REFERENCES


