Pulmonary Actinomycosis Mimicking Pulmonary Aspergilloma and a Brief Review of the Literature

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Abstract

Pulmonary actinomycosis is a rare pulmonary infection that often exhibits unspecific symptoms and radiological findings. We herein report a case of pulmonary actinomycosis that mimicked pulmonary aspergilloma in an immunocompetent patient.

Key words: pulmonary actinomycosis, fungus ball-like lesion, aspergilloma, Aspergillus antigen test, polymerase chain reaction


Introduction

Actinomycosis is a chronic purulent and granulomatous disease that is caused by infection with the Actinomyces species. Although this disease can develop at various sites in the human body, the most common type is cervicofacial actinomycosis (1). In contrast, pulmonary actinomycosis is relatively rare (2) and its symptoms and radiological findings are often unspecific, which can make it difficult for even experienced physicians to diagnose this disease. We herein report a rare case of pulmonary actinomycosis that was difficult to differentiate from pulmonary aspergilloma due to the presence of fungus ball-like lesions and false-positive results from serum Aspergillus antigen tests.

Case Report

A 78-year-old man visited our hospital to undergo the evaluation of abnormal lung shadows, which had been discovered when investigating a cough with purulent sputum that had persisted for several months. At the admission, his body temperature was 36.5°C, his heart rate was 71 beats/min, and his blood pressure was 143/80 mmHg. The patient’s oxygen saturation was 97% while breathing ambient air, and the findings of a physical examination were generally normal. Laboratory tests revealed a white blood cell count of 4,700/mm3, hemoglobin levels of 14.0 g/dL, a platelet count of 18.1×104/mm3, C-reactive protein levels of 0.05 mg/dL, and an erythrocyte sedimentation rate of 7 mm/h. The levels of tumor markers (cytokeratin 19 fragment, carcinoembryonic antigen, and pro-gastrin-releasing peptide) and serum β-D-glucan were within the normal ranges. A QuantiFERON TB-2G test yielded a negative result. The patient was negative for serum Aspergillus antibodies, but a Platelia™ Aspergillus galactomannan assay was positive (1.1; cut-off index: 0.5). Sputum cultures were negative for bacteria, fungi, and mycobacteria. A sputum polymerase chain reaction (PCR) to detect mycobacteria also yielded a negative result. Chest radiography and computed tomography (CT) revealed multiple cavities with surrounding infiltration, and an intracavitary nodular lesion in the left upper lobe (Fig. 1).

Based on these findings, we suspected pulmonary aspergilloma and followed the patient at our outpatient clinic. Af-
ter 3 months, we performed transbronchial lung biopsy (TBLB) from the left S1+2 because of slightly increased signs on chest imaging. A microscopic examination of the collected tissue revealed filamentous Gram-positive organisms that resembled *Actinomyces* species, despite the negative culture results. The patient was subsequently hospitalized and treated with intravenous ampicillin (3,000 mg/day) for 2 weeks. His condition improved, and he was discharged with a prescription for oral amoxicillin (1,500 mg/day). Unfortunately, despite continuous treatment with amoxicillin for 6 months, we did not observe any improvement in the chest CT findings. We therefore repeated the TBLB from the left S1+2, and again detected filamentous organisms during a microscopic examination. Furthermore, a PCR of the lung tissue specimens, which was performed as previously described (3), was positive for the *Actinomyces* 16S rRNA gene (Fig. 2A). As the fungus ball-like lesions were still present after 9 months of daily antibiotic treatment, we performed left upper lobectomy. The resected material and histopathological findings from the cavity lesion are shown in (Fig. 2B-D). A microscopic examination of the resected tissue revealed filamentous organisms and Gram-negative rods, and a culture test was positive for *Fusobacterium nucleatum*. The patient is currently in a good condition and has not experienced any recurrence of the actinomycosis after surgery.

### Discussion

*Actinomyces* are filamentous Gram-positive obligate anaerobic rods (4). Although *Actinomyces* reside in the oropharynx and gastrointestinal tract, and are normally avirulent in healthy individuals (5, 6), *Actinomyces*-associated diseases can occur in individuals with particular host characteristics [e.g., aspiration, alcohol abuse, periodontal disease, chronic obstructive pulmonary disease (COPD), and diabetes mellitus] (7). Pulmonary actinomycosis is relatively rare (8), and is thought to result from the aspiration of *Actinomyces* into the lungs (9). Although chest imaging of pulmonary actinomycosis most commonly reveals fibrotic infiltrates that are confined to a single lobe with small cavity lesions (10), non-specific findings are commonly observed in clinical practice (11-13). However, pulmonary actinomycosis with fungus ball-like lesions that mimic pulmonary aspergillosis is extremely rare, with only 16 reported cases (Table (14-21)). According to these reports, all of the cases occurred in adults (mean age: 45.5±14.3 years), and 14 of the 16 cases occurred in men. Hemoptysis was observed in 13 cases, persistent cough was observed in 6 cases, and 7 cases exhibited underlying diseases (diabetes, n=4; COPD, n=1; alcohol abuse, n=1; and bronchial asthma, n=1; 4 cases did not exhibit an underlying disease).

The mechanism by which fungus ball-like lesion are induced by *Actinomyces* remains unclear. For example, Hirukawa et al. reported that the cavity in their case was not pathologically connected to the bronchiole (20). Mabeza et al. reported that the disease progressed slowly, with little regard for anatomic boundaries, that it crossed the interlobar fissures, and that it may be related to the bacteria’s proteolytic enzymes (8). However, in the present case, the surface of cavity was covered by the bronchial epithelium, and an intracavitary nodule was composed of fibrous and inflammatory granulomatous tissue, Gram-negative rods and Gram-positive filamentous rods. Fibrous and chronic inflammatory changes were observed in the area of infiltration surrounding the cavity, but bacteria were not. These findings indicate that *Actinomyces* colonization and gradual proliferation in the pre-existing cavity might induce chronic inflammatory reac-

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**Figure 1.** (A) Chest radiography reveals a nodular lesion with inflammatory changes in the left upper lung field (black arrow), and (B) Chest radiography and computed tomography (CT) reveal multiple cavities with surrounding infiltration, and an intracavitary nodular lesion in the left upper lobe (white arrow).
The rate of mixed infections are common. Moreover, only 3 of the previous cases involving actinomycotic intracavitary lesions exhibited positive culture results (Table). Thus, most cases were diagnosed based on the histopathological examination of the involved tissues. In the present case, culture tests of the lung tissues that were collected during the TBLB and lobectomy yielded negative results; however, the PCR results were positive for *Actinomyces*. In line with a previous report that described the usefulness of a PCR and rRNA gene sequencing in the diagnosis of pulmonary actinomycosis (25), the present case confirms that a PCR and histopathological testing can facilitate the diagnosis of this disease.

In the present case, *Fusobacterium nucleatum* was isolated from the resected tissue. There are some case reports described co-isolation of *Actinomyces* species with other bacteria, such as *Fusobacterium* species, *Escherichia coli* and *Streptococcus constellatus* (26-29). Although the role of co-isolated organisms in the clinical course of actinomycosis remains unclear, the concomitant bacteria will accelerate the consumption of oxygen, making it more conducive for the growth of anaerobes (30). However, contamination by *F. nucleatum* from the oral cavity might be considered since the patient in the current study had a history of cerebral infarction.

The treatment for pulmonary actinomycosis includes antimicrobial therapy with or without surgery. Although the treatment is tailored to each patient, the main component is high-dose intravenous penicillin for 2-6 weeks (generally 18-24 million units of penicillin per day) followed by oral penicillin V (or amoxicillin) for 6-12 months (8). Among
the cases that are listed in Table, 6 cases had information on the type and duration of antimicrobial therapy after the diagnosis, and 4 cases received antibiotic treatment for ≥6 months. In the present case, the cavity lesions persisted, despite the continuous administration of amoxicillin for >12 months. Thus, in cases of pulmonary actinomycosis that exhibit fungus ball-like lesions, a longer duration of antimicrobial treatment may be necessary.

In conclusion, we believe that this case provides useful information regarding the diagnosis of pulmonary actinomycosis. In this context, pulmonary actinomycosis and pulmonary aspergilloma exhibit similar clinical and radiological findings, which can make it difficult to differentiate between the diseases. Molecular methods may therefore be useful for diagnosing pulmonary actinomycosis.

The authors state that they have no Conflict of Interest (COI).

References


### Table. Sixteen Cases of Actinomycosis with Fungus Ball-like Lesions in Pulmonary Cavities.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying disease</th>
<th>Symptoms</th>
<th>Site of the lesion</th>
<th>Radiographic findings</th>
<th>Method for definitive diagnosis</th>
<th>Duration of antimicrobial therapy after diagnosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49M</td>
<td>26</td>
<td>Alcohol abuse, cough</td>
<td>Right lower lobe</td>
<td>Mass-like lesions within a cavity and consolidations</td>
<td>BAL</td>
<td>1 year of oral amoxicillin</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>72M</td>
<td>None</td>
<td>None, cough</td>
<td>Right lower lobe</td>
<td>Cavity and surrounding small granular shadows</td>
<td>VATS</td>
<td>2 months of oral amoxicillin and clavulanate potassium</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>60M</td>
<td>None</td>
<td>Anorexia, general malaise</td>
<td>Left upper lobe</td>
<td>Mass-like lesions within a cavity and pleural thickening with infiltration</td>
<td>Lobectomy</td>
<td>None</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>40M</td>
<td>Diabetes</td>
<td>Diabetes, cough</td>
<td>Left upper lobe</td>
<td>Infiltration</td>
<td>Lobectomy</td>
<td>2 weeks of i.v. penicillin G, 6 months of oral penicillin</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>42M</td>
<td>None</td>
<td>Diabetes, purulent expectoration</td>
<td>Right upper lobe</td>
<td>Consolidation with an air meniscus</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>43M</td>
<td>Diabetes</td>
<td>Diabetes, cough</td>
<td>Right lower lobe</td>
<td>Fibroatelectatic retraction</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>64M</td>
<td>Diabetes</td>
<td>Diabetes, cough</td>
<td>Right lower lobe</td>
<td>Cavity partially filled with secretion</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>65M</td>
<td>Diabetes, COPD</td>
<td>COPD, cough, dyspnea</td>
<td>Right upper lobe</td>
<td>Cavity and bronchostenosis</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>36F</td>
<td>Unknown</td>
<td>Unknown, cough</td>
<td>Left lower lobe</td>
<td>Fibroatelectatic retraction</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>26M</td>
<td>Unknown</td>
<td>Unknown, cough</td>
<td>Left lower lobe</td>
<td>Cavity and irregular consolidations</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>37F</td>
<td>Unknown</td>
<td>Unknown, cough</td>
<td>Right upper lobe</td>
<td>Cavity and irregular consolidations</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>57M</td>
<td>Unknown</td>
<td>Unknown, cough</td>
<td>Right upper lobe</td>
<td>Irregular consolidations</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>26M</td>
<td>Unknown</td>
<td>Unknown, cough</td>
<td>Left lung (lobe is unknown)</td>
<td>Cavity and irregular consolidations</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>39M</td>
<td>Unknown</td>
<td>Unknown, cough</td>
<td>Left lower lobe</td>
<td>Irregular consolidations and thickening of bronchial walls</td>
<td>Lobectomy</td>
<td>Unknown</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>43M</td>
<td>None</td>
<td>Diabetes, cough, fever</td>
<td>Left upper lobe</td>
<td>Consolidation with a cavity</td>
<td>Lobectomy</td>
<td>6 months of oral amoxicillin and clavulanate potassium</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>35M</td>
<td>Bronchial asthma</td>
<td>Bronchial asthma, cough</td>
<td>Right upper lobe</td>
<td>Irregular consolidations</td>
<td>Lobectomy</td>
<td>6 months of oral amoxicillin</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease, BAL: bronchoalveolar lavage, VATS: video-assisted thoracoscopic surgery, i.v.: intravenous

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