INTERNAL MEDICINE

□ CASE REPORT □

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

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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 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/mm^3, hemoglobin levels of 14.0 g/dL, a platelet count of 18.1×10^4/mm^3, 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 a 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-

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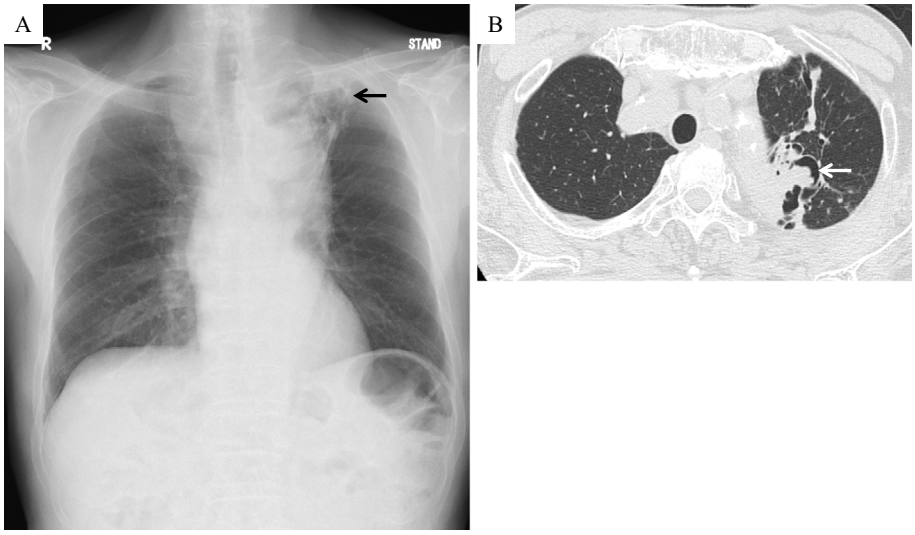

Figure 1. **(A) Chest radiography reveals a nodular lesion with inflammatory changes in the left upper lung field (black arrow), and (B) Chest radiography and computed tomography (CT) reveal multiple cavities with surrounding infiltration, and an intracavitary nodular lesion in the left upper lobe (white arrow).**

ter 3 months, we performed transbronchial lung biopsy (TBLB) from the left S^{1+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 S^{1+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 cavitary lesions (10), non-specific findings are commonly observed in clinical practice (11-13). However, pulmonary actinomycosis with fungus ball-like lesions that mimic pulmonary aspergilloma 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-

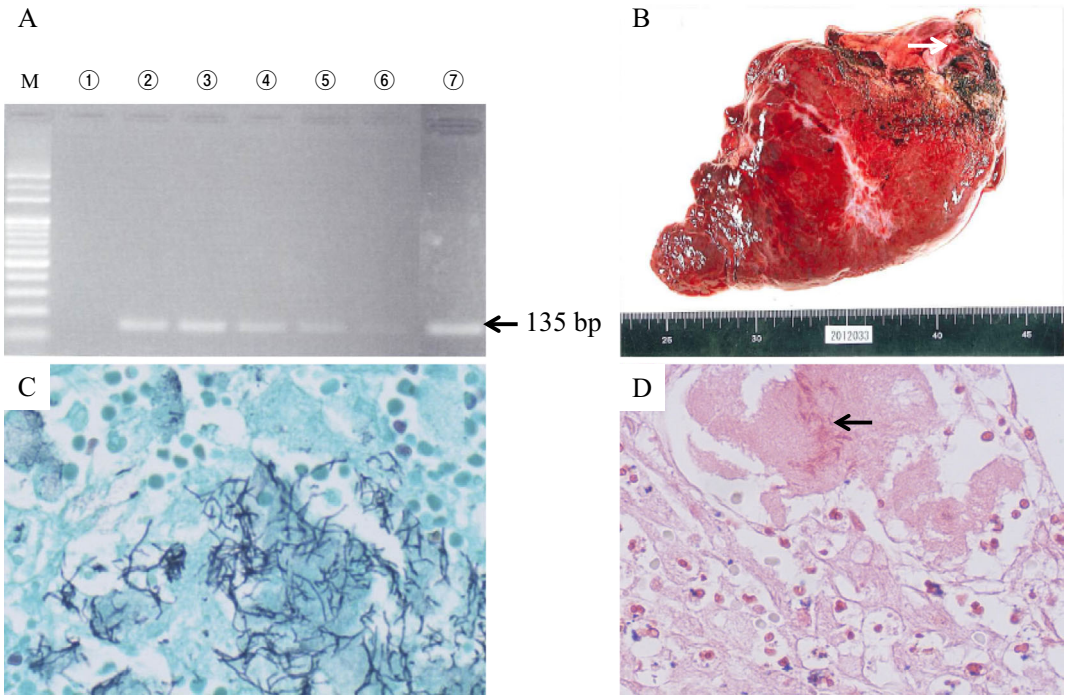

Figure 2. **(A) The polymerase chain reaction to test for the *Actinomyces* 16S rRNA gene (M: 100 bp marker, ①: negative control (methicillin-resistant *Staphylococcus aureus*), ②: positive control (*Actinomyces odontolyticus*), ③: positive control (*Actinomyces meyeri*), ④-⑦: the lung tissue samples that were collected during the transbronchial lung biopsy (④⑤: 3 months; ⑥⑦: 7 months after the initiation of amoxicillin treatment). All of the patient samples were positive for the *Actinomyces* 16S rRNA gene (B) A macroscopic view of the resected lung reveals a cavity of approximately 5 cm in diameter (white arrow) (C) A histological examination of the cavitary lesion revealed filamentous bacteria (Grocott staining) and (D) Gram-negative rods (Gram staining) (black arrow).**

tions and the enlargement of cavity.

In the present case, we initially suspected pulmonary aspergilloma based on the radiological findings and the positive results of serum *Aspergillus* antigen testing. The patient was not using any antibacterial drugs, for example piperacillin/tazobactam, which could have elicited false-positive results. In this context, although it exhibits variable sensitivity, the serum galactomannan (GM) antigen test has been widely used for the auxiliary diagnosis of aspergillosis (22). No previous reports have described cross-reactivity between actinomycosis and aspergillosis in the GM antigen test. Furthermore, *Actinomyces* may elicit a false-positive result for *Bifidobacterium* (which belong to the same class as *Actinomyces*) on GM antigen tests because of a cross-reaction between the bacterial lipoglycan and the GM (23).

A definitive diagnosis of actinomycosis is generally confirmed by isolating the pathogen(s) from the involved organs. It is difficult to isolate this anaerobe from clinical samples because the specimen that is used for the identification of *Actinomyces* must be collected under strictly anaerobic conditions, and because mixed infections are common. The rate of *Actinomyces* isolation using culture tests is only approximately 7% (24). 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 the 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

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

Case	Age	Sex	Underlying disease	Symptoms	Site of the lesion	Radiographic findings	Method for definitive diagnosis	Duration of antimicrobial therapy after diagnosis	reference
1	49	M	Alcohol abuse	Cough	Right lower lobe	Mass-like lesions within a cavity and consolidations	BAL	1 year of oral amoxicillin	17
2	72	M	None	Hemoptysis	Right lower lobe	Cavity and surrounding small granular shadows	VATS	2 months of oral amoxicillin and clavulanate potassium	18
3	60	M	None	Anorexia, general malaise	Left upper lobe	Mass-like lesions within a cavity and pleural thickening with infiltration	Lobectomy	None	19
4	40	M	Diabetes	Hemoptysis	Left upper lobe	Infiltration	Lobectomy	2 weeks of i.v. penicillin G, 6 months of oral penicillin	16
5	42	M	None	Hemoptysis, purulent expectoration	Right upper lobe	Consolidation with an air meniscus	Lobectomy	Unknown	14
6	43	M	Diabetes	Hemoptysis, anorexia, weakness, dyspnea chest pain	Left upper lobe	Fibroatelectatic retraction	Lobectomy	Unknown	14
7	64	M	Diabetes	Hemoptysis	Left lower lobe	Opacity and bronchostenosis	Lobectomy	Unknown	14
8	65	M	Diabetes, COPD	Hemoptysis, purulent expectoration, dyspnea	Right upper lobe	Cavity partially filled with secretion	Lobectomy	Unknown	14
9	30	F	Unknown	Hemoptysis, cough	Left lower lobe	Fibroatelectatic retraction	Lobectomy	Unknown	15
10	26	M	Unknown	Hemoptysis, cough	Left lower lobe	Cavity and irregular consolidations	Lobectomy	Unknown	15
11	37	F	Unknown	Hemoptysis	Right upper lobe	Cavity and irregular consolidations	Lobectomy	Unknown	15
12	57	M	Unknown	Hemoptysis	Right upper lobe	Irregular consolidations	Lobectomy	Unknown	15
13	26	M	Unknown	Hemoptysis, cough	Left lung (lobe is unknown)	Cavity and irregular consolidations	Lobectomy	Unknown	15
14	39	M	Unknown	Hemoptysis, cough	Left lower lobe	Irregular consolidations and thickening of bronchial walls	Lobectomy	Unknown	15
15	43	M	None	Hemoptysis, fever	Left upper lobe	Consolidation with a cavity	Lobectomy	6 months of oral amoxicillin and clavulanate potassium	20
16	35	M	Bronchial asthma	Cough, fever	Right upper lobe	Irregular consolidations	Lobectomy	6 months of oral amoxicillin	21

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

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).

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