Drastically progressive lung cavity lesion caused by *Actinomyces odontolyticus* in a patient undergoing chemoradiotherapy: A case report and literature review

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**ARTICLE INFO**

**Keywords:** Pulmonary actinomycosis, Immunocompromised, Bronchoscopy, Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

**ABSTRACT**

Pulmonary actinomycosis reportedly forms 15% of all cases of actinomycosis, and pulmonary *A. odontolyticus* is particularly rare. A 60-year-old man with a hoarse voice was referred to our hospital. Lung squamous cell carcinoma was diagnosed at the clinical tumor-node-metastasis stage of cT2N2M0, and concurrent chemoradiotherapy was initiated. Further, a small cavity was also detected in the left upper lobe, but it was observed. During chemoradiotherapy, the small cavity lesion rapidly increased accompanying infiltration, and administration of short-term antibiotics did not improve the patient’s condition. Bronchoscopy did not show any diagnostic results. Although a rapidly progressive malignant lesion could not be excluded and surgical management was considered, resection could not be performed because of the tight adhesion of the mass. Therefore, bronchoscopy was performed again, and the bronchial lavage culture showed a positive smear for the *Actinomyces* species. Further, using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), the bacteria was identified as *A. odontolyticus*. After long-term administration of amoxicillin, the lung cavity with infiltration gradually improved. To the best of our knowledge, there have been nine cases of pulmonary *A. odontolyticus* (excluding those with only empyema or pleural mass without lung lesions), which can occur in immunocompetent patients with persistent lung shadow. None of the cases showed drastic deterioration; therefore, the present case is the first to highlight that *A. odontolyticus* possibly produce drastically progressive lung cavity lesion. Further, repeated bronchoscopy and MALDI-TOF MS could help to diagnose pulmonary actinomycosis.

1. Introduction

*Actinomyces* species are anaerobic gram-positive rods. Actinomycosis has been reported worldwide. Recently, the incidence of all types of actinomycosis has markedly declined. Total 15% of all cases of actinomycosis are of pulmonary actinomycosis [1]. Pulmonary actinomycosis is rare, mainly owing to *A. israelii* and *A. odontolyticus* being particularly rare [1–3]. *A. odontolyticus* was first isolated from dental caries in 1958 and is a commensal organism found in the mouth [4]. Actinomycosis is difficult to diagnose using bronchoscopy or sputum culture [1], and in many patients, surgery is required for diagnosis [5]. In addition, usually, pulmonary actinomycosis gradually grows with air-space consolidation, adjacent pleural thickening, or cavitation in the lung field [6]; hence, pulmonary actinomycosis is not likely to be a disease with a rapidly progressive clinical course. Therefore, patients with progressive pulmonary disease can be misdiagnosed and consequently treated inappropriately. Here we report a case of drastically progressive lung cavity lesion caused by *A. odontolyticus* in a patient undergoing chemoradiotherapy and present a literature review.

2. Case report

A 60-year-old man with a hoarse voice was referred to our hospital. He did not have any medical history but had been smoking for 40 pack-years. His physical examination revealed no apparent abnormalities except for hoarse voice. Left vocal cord paralysis was discovered, and chest X-ray revealed a mass in the left hilum (Fig. 1a).

Computed tomography (CT) revealed a mass with mediastinal...
lymphadenopathy in the left main bronchus and a small cavity in the left upper lobe. Bronchoscopy revealed a mass with distended vessels in the left main bronchus (Fig. 1b), and the mass was revealed to be lung squamous cell carcinoma. Positron emission tomography revealed high uptake of fluorodeoxyglucose in the mass in the left main bronchus \[\text{SUV}_{\text{max}} = 11.5\]; however, minor uptake was observed in the lung cavity \[\text{SUV}_{\text{max}} = 1.9\] (Fig. 1c and d). The patient was diagnosed with lung squamous cell carcinoma at the clinical tumor-node-metastasis stage of cT2N2M0 (stage 3A). Concurrent chemoradiotherapy, i.e., chemotherapy comprising weekly carboplatin and paclitaxel combined with radiation therapy (60 Gy; 30 fractions), was initiated. A small cavity located in the left upper lobe was not included in the radiation field.

During chemoradiotherapy, the small cavity lesion steadily increased (Fig. 2).

Two weeks after chemoradiotherapy was initiated, CT revealed increased cavity wall thickness and new infiltration. Although the patient had no fever or purulent sputum, bacterial infection was assumed, and administration of antibiotics (ampicillin/sulbactam, 1.5 g every 6 h) was initiated. All sputum cultures for bacteria, including acid-fast bacteria, were negative, and chest X-ray obtained 5 days later revealed enlargement of the cavity under the administration of antibiotics.

Physical examination revealed no apparent abnormality, even in the oral cavity, and the following observations were noted: heart rate, 88 beats/min and regular; blood pressure level, 102/72 mmHg; oxygen saturation level, 97% on room air; and body temperature, 36.5 °C. Laboratory testing revealed a white blood cell count of 4800/mm³ with a neutrophil percentage of 70.9% and C-reactive protein level of 2.66 mg/dL. Procalcitonin level, interferon-gamma release assay findings, Mycobacterium avium complex-specific glycopeptidolipid core antigen antibody level, Aspergillus galactomannan antigen level, and β-D-glucan level were all within normal ranges. The second bronchoscopy was performed for diagnosis; although the mass in the left main bronchus identified as lung squamous cell carcinoma was diminished, there were no apparent findings indicating bacterial infection. However, garenoxacin, 400mg once daily, was administered owing to the rapid progression of the disease and the consideration of bacterial infection. The bronchial lavage culture was negative for bacteria, and the bronchial tissue showed no evidence of malignancy. Further, Mycobacterium
szulgai was cultured; however, considering the clinical course, as described later, the organism was not considered to be the causative organism.

Although the administration of garenoxacin was continued, the lung cavity with infiltration drastically increased (Fig. 2). Because the presence of a rapidly progressive malignant lesion could not be excluded, surgical management was considered for the diagnostic therapy. However, resection could not be performed because of the tight adhesion of the mass. Therefore, the third bronchoscopy was performed. The bronchial lavage culture showed a positive smear for the organism.

Summary of pulmonary Actinomyces odontolyticus (excluding those with only empyema or pleural mass without lung lesions).

| Authors          | Age (y), sex | Presentation                  | Comorbidities or immunocompromised factors | Diagnostic method                  | Antibiotics for long-term administration | Outcome         |
|------------------|--------------|--------------------------------|-------------------------------------------|-------------------------------------|------------------------------------------|-----------------|
| Takiguchi et al. | 64, female   | Lung abscess                   | Periodontal disease                       | Percutaneous needle aspiration      | Sultamicillin tosilate                   | Recovery        |
| Baron et al.     | 61, female   | Lung abscess                   | Rheumatoid arthritis with prednisone therapy | Thoracoscopic aspiration           | Penicillin                              | Recovery        |
| Dontfraid F. et al. | 52, female  | Pneumonia with soft-tissue abscesses | Alcoholism and periodontal disease        | Cutaneous drainage                  | Amoxicillin                             | Recovery        |
| Bassiri et al.   | 61, male     | Pneumonia                      | Lung transplantation with prednisone, cyclosporine, and azathioprine | Bronchoscopy                        | Penicillin                              | Recovery        |
| Iancu et al.     | 37, female   | Lung abscess                   | B cell lymphoma with prednisone therapy   | Thoracotomy                         | Penicillin and metronidazole            | Deceased        |
| Verrot et al.    | 52, female   | Pneumonia                      | Bronchiectasis                            | Surgery                             | Imipenem and minocycline               | Recovery        |
| Susaki et al.    | 51, male     | Pneumonia                      | Dental caries                              | Sputum                              | Penicillin                              | Recovery        |
| Gray et al.      | 11, female   | Pneumonia                      | Bronchiectasis                            | Bronchoscopy                        | Penicillin                              | Recovery        |
| Erro Ilariurren et al. | 43, male | Pneumonia                      | Bronchial asthma with oralization         | Bronchoscopy                        | Amoxicillin-clavulanic acid             | Recovery        |

Present case 60, male Pneumonia Lung squamous cell carcinoma undergoing chemoradiotherapy

Bronchoscopy Amoxicillin Recovery

3. Discussion

We reported a drastically progressive lung cavity lesion caused by A. odontolyticus in a patient undergoing chemoradiotherapy. In this case, diagnosis of drastically progressive lung cavity lesion and its distinction from the diagnosis of rapidly progressive malignant tumor was difficult; however, repeated bronchoscopy and MALDI-TOF MS identified A. odontolyticus, which contributed to the appropriate treatment.

Oral insanitation, diabetes, and frequent alcohol consumption are reportedly the risk factors of pulmonary actinomycosis; however, no baseline diseases are found in 30% of them [7]. Of note, immunosuppression, such as that caused by acquired immune deficiency syndrome, cancer chemotherapy, or chronic steroid therapy, has not been reported as the risk factor for pulmonary actinomycosis [8,9]; however, underlying lung disease reportedly increases the prevalence of pulmonary actinomycosis [10]. Emphysema is reported to be associated with increased activity of proteolytic enzymes, which are activated because of inflammation and oxidative stress occurring in chronic obstructive pulmonary disease (COPD) [11]. Also, inflammation and chronic colonization of Haemophilus influenzae in sputum of patients with COPD were reported to be associated with the degree of emphysema and bronchiectasis on CT [12]. Therefore, in the present case, having emphysematous lesions might have predisposed the patients to bacterial infections, and these lesions possibly contributed to the infection by A. odontolyticus. Although the lung cavity lesion was not included in the radiation field, local immunosuppression might have affected the course of pulmonary actinomycosis because of the presence of lung squamous cell carcinoma and the administration of chemoradiotherapy.

Pulmonary actinomycosis is reportedly difficult to culture owing to the lack of culturing techniques, prevalence of previous antibiotic therapy in the patient, and bacterial overgrowth even when clinical suspicion is high, thereby resulting in a culture rate of <50% [1,9]. First, A. odontolyticus is part of the normal oropharyngeal flora, and positive sputum culture cannot establish the diagnosis of pulmonary actinomycosis [3]. Generally speaking, it is difficult to prevent the cross contamination of oral bacteria during bronchoscopy, and in this case, it was impossible to rule out coinfection by other bacteria in addition to A. odontolyticus. However, incubation of the bronchial lavage led to a significant number of A. odontolyticus colonies, and long-term administration of antibiotics was effective for treating the lung cavity lesion. Therefore, we believe that A. odontolyticus was the causative organism in this case. Pulmonary actinomycosis is most commonly misdiagnosed as a malignant disease or tuberculosis [13]; moreover, nocardiosis, histoplasmosis, blastomycosis, mixed anaerobic infections, bronchogenic carcinoma, lymphoma, mesothelioma, and pulmonary infarction are among the entities confused with pulmonary actinomycosis [14]. A quarter of cases were misdiagnosed as malignancy, and surgery was performed [1]. In the present case, although surgical resection was difficult, repeated bronchoscopy yielded the specimen. In addition, MALDI-TOF MS was effective in detecting the causative organism. Thus, MALDI-TOF MS would be a new tool for the diagnosis of this infectious disease [5,15].

In the present case, short-term administration of antibiotics could not improve the patient’s condition; however, this does not necessarily indicate that the bacteria were resistant to the antibiotics. Infection caused by Actinomyces species is usually recommended to be treated using penicillin injection for 2–6 weeks followed by oral penicillin for 6–12 months [1,13]. In fact, in the present case, long-term administration of antibiotics improved the radiological findings.

To the best of our knowledge, there have been nine patients with pulmonary A. odontolyticus (excluding those with only empyema or pleural mass without lung lesions) [2,3,16–22]. A summary of the reported cases is presented in Table 1.

Considering the reported cases, an immunocompetent patient can also suffer from pulmonary A. odontolyticus. Aspiration of oropharyngeal
or gastrointestinal secretions into the respiratory tract, or in rare cases, hematogenous dissemination due to disruption of the gastrointestinal tract mucosal barrier caused by periodontal disease, dental procedure, bacterial suppuration, surgery, or trauma is considered to cause pulmonary actinomycosis [1,13]. Although there was no apparent periodontal disease, dental caries, or Actinomyces bacteremia in the present case, similar cases have previously been reported [19,21]. Although one patient died likely due to lymphoma, pulmonary A. odontolyticus usually has a good prognosis. None of the cases, including immunocompromised ones, showed drastic deterioration. Therefore, the clinical course of the disease in our patient was rare; however, our case suggests that we should be aware that pulmonary A. odontolyticus could rapidly become exacerbated.

In conclusion, pulmonary A. odontolyticus is rare but can occur in immunocompetent patients with persistent lung shadow. Further, it should be noted that A. odontolyticus may produce drastically progressive lung cavity lesion. Repeated bronchoscopy and MALDI-TOF MS could help to diagnose pulmonary actinomycosis.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Patient consent for publication
Consent for publication has been obtained.

Declaration of competing interest
The authors have no conflict of interest.

Acknowledgements
The authors thank T. Takuwa, A. Fukuda (Department of Thoracic Surgery, Saiseikai-Noe Hospital), M. Kamata, and Y. Itsuno (Department of Radiation Therapy, Saiseikai-Noe Hospital) for their clinical support. The authors also thank Enago (www.enago.jp) for the English language review.

References
[1] G.F. Mabeza, J. Macfarlane, Pulmonary actinomycosis, Eur. Respir. J. 21 (2003) 545–551.
[2] A.G. Bastiri, R.E. Girgis, J. Theodore, Actinomyces odontolyticus thoracopulmonary infections. Two cases in lung and heart-lung transplant recipients and a review of the literature, Chest 109 (1996) 1109–1111.
[3] Y. Takiguchi, T. Terano, A. Hiraí, Lung abscess caused by actinomyces odontolyticus, Intern. Med. 42 (2003) 723–725.
[4] I. Batty, Actinomyces odontolyticus, a new species of actinomycote regularly isolated from deep carious dentine, J. Pathol. Bacteriol. 75 (1958) 455–459.
[5] F. Valour, A. Senechal, C. Dupieux, J. Karsenty, S. Lustig, P. Breton, et al., Actinomycotic etiology, clinical features, diagnosis, treatment, and management, Infect. Drug Resist. 7 (2014) 183–197.
[6] J.S. Kwong, N.L. Muller, J.D. Godwin, D. Aberle, M.R. Gymaloski, Thoracic actinomycosis: Ct findings in eight patients, Radiology 183 (1992) 189–192.
[7] Y. Kobashi, K. Yoshida, M. Miyashita, Y. Niki, T. Matsushima, Thoracic actinomycosis with mainly pleural involvement, J. Infect. Chemother. 10 (2004) 172–177.
[8] S.I. Chaudhry, J.S. Greenspan, Actinomycosis in HIV infection: a review of a rare complication, Int. J. STD AIDS 11 (2000) 349–355.
[9] D.F. Bennhoff, Actinomycosis: diagnostic and therapeutic considerations and a review of 32 cases, The Laryngoscope 94 (1984) 1198–1217.
[10] K.P. Schaaf, H.J. Lee, Actinomycite infections in humans—a review, Gene 115 (1992) 201–211.
[11] N. Angelis, K. Porpodis, P. Zarogoulidis, D. Spyratos, I. Kioumis, A. Papaiwannou, et al., Airway inflammation in chronic obstructive pulmonary disease, J. Thorac. Dis. 6 (Suppl 1) (2014) S167–S172.
[12] E. Tufvesson, H. Markstad, G. Bozovic, M. Ekberg, L. Björner, Inflammation and chronic colonization of haemophilus influenzae in sputum in COPD patients related to the degree of emphysema and bronchiectasis in high-resolution computed tomography, Int. J. Chronic Obstir. Pulm. Dis. 12 (2017) 3211–3219.
[13] R.A. Smego Jr., G. Foglia, Actinomycosis, Clin. Infect. Dis. 26 (1998) 1255–1261, quiz 63–3.
[14] P. Ray, J. Mandal, V. Gautam, K. Singh, D. Gupta, A case of pulmonary actinomycosis caused by actinomyces odontolyticus from India, Indian J. Med. Res. 122 (2005) 547–548.
[15] S. Schubert, M. Kostrzewa, MalDI-TOF ms in the microbiology laboratory: current trends, Curr. Issues Mol. Biol. 23 (2017) 17–20.
[16] E.J. Baron, J.M. Angevine, W. Sundstrom, Actinomycotic pulmonary abscess in an immunosuppressed patient, Am. J. Clin. Pathol. 72 (1979) 637–639.
[17] F. Donzelaid, P. Rampal, Bilateral pulmonary infiltrates in association with disseminated actinomycosis, Clin. Infect. Dis. 19 (1994) 143–145.
[18] D. Iancu, A. Chu, P.E. Schoch, B.A. Cunha, Actinomycosis odontolyticus pulmonary infection, Am. J. Med. 107 (1999) 293–294.
[19] D. Verrot, P. Didier, J.R. Harle, Y. Peloux, L. Garbes, A. Arnaud, et al., Pulmonary actinomycosis caused by actinomyces odontolyticus? Rev. Med. Interne 14 (1993) 179–181.
[20] K. Suzuki, S. Bandoh, J. Fujita, N. Kanaji, T. Ishii, A. Kubo, et al., A case of pulmonary actinomycosis, who expectorated sulfur granules, caused by actinomyces odontolyticus and actinomyces meyeri, Nihon Kokyuki Gakkai Zasshi 43 (2005) 231–235.
[21] A. Gray, P. Do, The case of the unwanted crystal: a case of pediatric pulmonary actinomycoses odontolyticus, Clin Case Rep 6 (2018) 1230–1231.