Respiratory Medicine Case Reports 34 (2021) 101530

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Actinomyces meyeri pleural infection that was difficult to treat due to delayed culture: A case report and literature review of 28 cases

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ARTICLE INFO

Keywords:
Actinomyces meyeri
Pleural fluid
Penicillin allergy
Pleural infection
Actinomycosis

ABSTRACT

An eighty-three-year-old man suffered from cough, right chest pain, and progressive dyspnea for sixteen days. He had hypoxemia, high white blood cells and C-reactive protein, and moderate right-sided pleural effusion on radiographic imaging. A pleural fluid examination revealed exudate. He was diagnosed with pleural infection and treated with intravenous ampicillin/sulbactam. On the second day of hospitalization, the treatment was changed to levofloxacin and clindamycin due to drug eruption. He improved gradually and was prescribed only oral levofloxacin on the eighteenth day of hospitalization. However, improvements in inflammation and imaging findings were poor. *Actinomyces meyeri* resistant to fluoroquinolones was cultured from a pleural effusion sample on the twenty-sixth day of hospitalization. The treatment was changed to oral clindamycin, and his medical condition subsequently improved. We reviewed twenty-eight patients with *Actinomyces* pleural infection and thirty-eight patients with other pleural infection phenotypes from our hospital and published case reports. *Actinomyces* pleural infection is a long-term process and results in a large amount of pleural effusion compared to other pleural infection phenotypes. These results might be related to the fact that *Actinomyces* is a slow-growing organism.

1. Introduction

Actinomyces is an anaerobic gram-positive bacterium, commonly associated with cervicofacial, abdominopelvic, and thoracic granulomatous infection [1, 2], which can be chronic, and disseminated cases have been reported [2, 3]. *Actinomyces meyeri* usually involves the lungs and is a rare pathogen of pleural infection, including empyema and parapneumonic effusion. *Actinomyces* pleural infection is treated with long-term antibiotic therapy, such as penicillin, and chest drainage [4–6]. This is a case report of *Actinomyces meyeri* pleural infection that was difficult to treat due to the delayed culture of *A. meyeri* and a penicillin allergy. Furthermore, we reviewed the characteristics of twenty-eight patients with *Actinomyces* pleural infection through comparisons to those of patients with pleural infections due to other pathogens.

2. Case presentation

An 83-year-old man suffered from cough, right chest pain, and progressive dyspnea for sixteen days. The patient had a medical history of chronic obstructive pulmonary disease (COPD) with home oxygen therapy (HOT), chronic renal disorder, diabetes mellitus (DM), and cerebral infarction. He had a smoking history (30 pack-years), alcohol abuse history, and poor dental hygiene.

His vital signs on admission showed afebrile status, tachycardia at 105 beats per minute, and hypoxemia with an oxygen saturation of 88% with a 5 L nonrebreather mask. Physical examination revealed no abnormalities, except for inspiratory coarse crackles in the right lower lung. An arterial blood sample showed a $PaCO_2$ of 27.4 mmHg and a PaO_2 of 59.3 mmHg with a 5 L nonrebreather mask. The laboratory findings showed leukocytosis (13980/μL with 90.0% polymorphic nuclear leukocytes), increased C-reactive protein (CRP) (28.24 mg/dL),

Abbreviations: COPD, chronic obstructive pulmonary disease; HOT, home oxygen therapy; DM, diabetes mellitus; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase.

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https://doi.org/10.1016/j.rmcr.2021.101530
Received 15 July 2021; Received in revised form 15 September 2021; Accepted 19 October 2021
Available online 21 October 2021

Table 1
The laboratory findings of the patient.

Hematology		Biochemistry		Arterial blood gas (5 L/min mask)	
Hb	12.0 g/dL	Na	139 mmol/L	pH	7.301
Ht	34.4 %	K	4.3 mmol/L	$PaCO_2$	27.4 Torr
RBC	354 × 10^4/μL	Cl	108 mmol/L	PaO_2	59.3 Torr
WBC	13980/μL	BUN	55.0 mg/dL	HCO_3	27.4 mmol/L
Seg	90.0 %	Cr	3.23 mg/dL	BE	−11.6 mmol/L
Eo	0.0 %	TP	6.84 g/dL		
Baso	0.1 %	Alb	2.09 g/dL	**Pleural fluid**	
Mono	2.8 %	T-bil	0.3 mg/dL	Total cell count	2794/μL
Lymph	7.1 %	AST	25 IU/L	Neutrophils	55.0 %
Plt	33.7 × 10^4/μL	ALT	21 IU/L	Lymphocytes	43.5 %
PT-INR	1.15	LDH	163 IU/L	Eosinophils	1.0 %
APTT	29.0 sec	CK	162 IU/L	Macrophages	0.5 %
Fib	732 mg/mL	Glu	377 mg/dL	TP	4.82 g/dL
FDP	28.0 μg/mL	CRP	28.24 mg/dL	LDH	944 IU/L
D-dimer	2.12 μg/mL	PCT	1.19 ng/mL	Glu	285 mg/dL
		(1 → 3)-β-D-glucan	<6.0 ng/mL	ADA	34.9 U/L
		HbA1c	7.7 %		

renal dysfunction, and hemoglobin A1c at 7.7% (Table 1). A moderate amount of right-sided pleural effusion was present on the radiograph (Fig. 1), and chest computed tomography (CT) showed right loculated pleural effusion and emphysematous changes in both lungs (Fig. 2). A chest drainage tube was inserted, and pleural fluid analysis was performed. The pleural fluid examination revealed a high white blood cell count, at 2794/μL, with 55.0% neutrophils and 43.5% lymphocytes. High protein and lactate dehydrogenase (LDH) in the pleural fluid indicated exudative effusions. Gram staining of pleural fluid was negative.

He was diagnosed with pleural infection and treated empirically with ampicillin/sulbactam 3.0 g IV every 8 hours. However, drug eruption appeared two days after starting the antibiotic. He was diagnosed with a penicillin allergy, and the treatment was changed to clindamycin and levofloxacin. He improved gradually, and the pleural fluid was reduced. Therefore, the chest drain tube was removed, clindamycin was stopped, and 250 mg of oral levofloxacin daily was prescribed on the eighteenth day of hospitalization. However, the improvement of empyema stopped (Fig. 3). On the twenty-sixth day of hospitalization, *A. meyeri* was cultured from pleural effusion fluid on Gifu anaerobic medium semisolid agar; other bacteria were not cultured. He was diagnosed with complex complicated parapneumonic effusion based on Light's classification [7]. Drug-susceptibility testing revealed that the cultured *A. meyeri* was resistant to tosufloxacin and sensitive to clindamycin. The treatment was changed to 900 mg of oral clindamycin daily, and his CRP level decreased to within normal limits; a chest radiograph showed complete resolution of the pleural effusion. He had received clindamycin therapy for 3 months, and there has been no evidence of recurrence thus far. We obtained informed consent from the patient's family for the publication of this report.

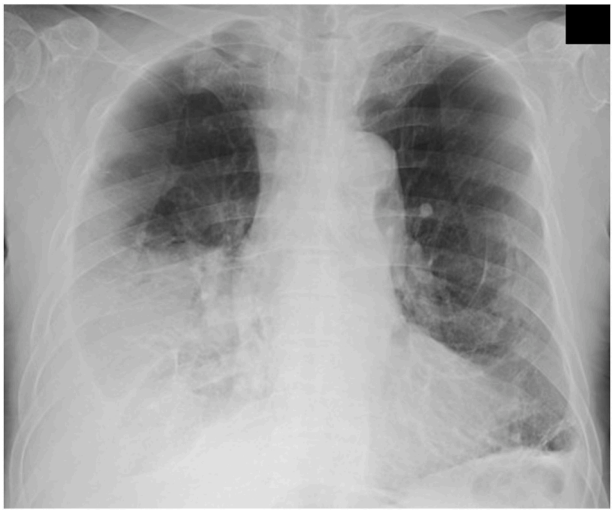

Fig. 1. A chest radiograph showing right pleural effusion.

3. Discussion

This is a case report of a rare pleural infection caused by *A. meyeri* in a patient with a penicillin allergy. The treatment was difficult due to the delayed culture of *A. meyeri*. *Actinomyces* is a gram-positive anaerobic bacteria [4–6, 8] and a slow-growing organism that can be cultured for up to three weeks [8]. Therefore, patients with *Actinomyces* pleural infection need to be treated without information regarding the causative pathogen for a long time until *Actinomyces* is cultured, and they might receive ineffective antibiotics, similar to our case. Previous studies have reported the following other features of *Actinomyces* infections [1]: there is typically slow progression of disease [2,9]; drug-susceptibility testing can indicate *Actinomyces* susceptibility to β lactams, clindamycin, and other agents, whereas fluoroquinolones perform poorly [8, 10]; and there are risk factors of pulmonary actinomycosis, such as being a middle-aged or elderly male, having a history of alcoholism, having poor dental hygiene, and having structural lung diseases [6, 11, 12]. Our patient showed similar risk factors. However, *Actinomyces* pleural infection is rare and does not have specific reported clinical findings [1, 4–6, 13]. If the characteristics of *Actinomyces* pleural infection are known, patients might be able to avoid treatment with ineffective antibiotics. Therefore, we reviewed the data of patients with *Actinomyces* pleural infection and compared the data to those for other pathogens.

We retrospectively collected the data of forty-one patients with pleural infection for whom pathogens were cultivated from pleural effusion samples at the Respiratory Disease Center of Fukujuji Hospital from January 2012 to December 2018. *Actinomyces* were cultured in three out of 41 patients (7.3%), and other pathogens, such as the *Streptococcus anginosus* group (n = 11, 26.8%), *Streptococcus pneumoniae* (n = 3, 7.3%), *Streptococcus mitis* (n = 3, 7.3%), *Staphylococcus aureus* (n = 2, 4.9%), anaerobic bacteria (n = 13, 31.7%), and others (n = 5, 13.2%) were cultured from the rest of the patients. Seven patients (18.4%) presented coinfections. *Actinomyces* pleural infection was not as rare as 7.3% and was similar to the rate of *S. pneumoniae* pleural infection. In addition, the data of nineteen adult patients with *Actinomyces* pleural infection were collected from PubMed and the Japan Medical Abstracts Society, using the keywords "actinomyces empyema", "actinomyces pleural effusion", and "actinomyces pleuritis" in English and Japanese only [4–6, 11–32]. Cases with no *Actinomyces* identified in the pleural effusion and no English abstracts were excluded. The data of

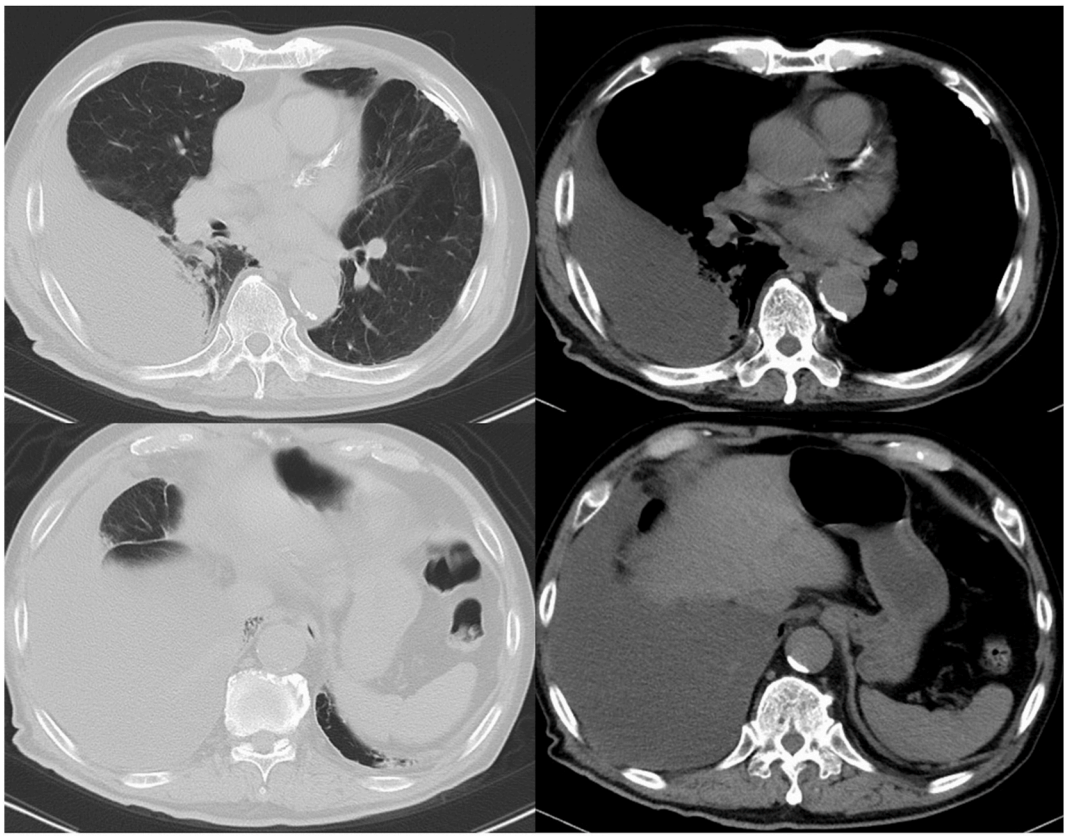

Fig. 2. A chest computed tomography scan showing right pleural effusion, without pulmonary lesions or gas bubbles throughout.

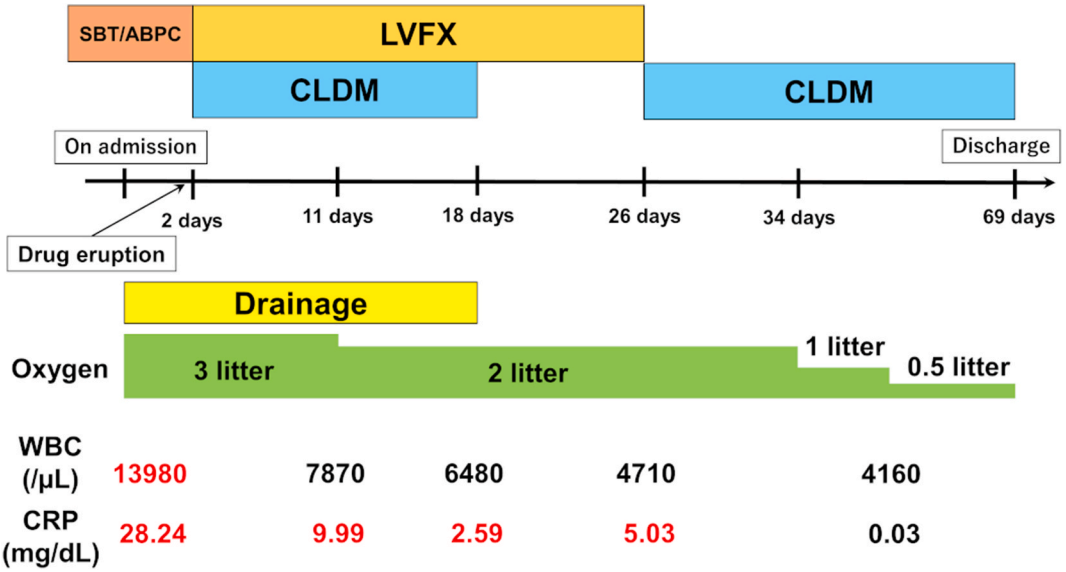

Fig. 3. The clinical course of the patient. SBT/ABPC ampicillin/sulbactam; LVFX levofloxacin; CLDM clindamycin; WBC white blood cell; CRP C-reactive protein.

those patients and our three patients were combined for analysis, and finally, the characteristics were compared between the twenty-eight patients with *Actinomyces* pleural infection (the *Actinomyces* group) and our thirty-eight patients with other-pathogen pleural infection (the other pathogens group) (Table 2). All data were analyzed and processed using EZR, version 1.35. Student's t tests, Mann–Whitney U tests, and Fisher's exact tests were used to compare groups. The level of statistical significance was set at $p = 0.05$ (2-tailed).

Among the *Actinomyces* group, the *Actinomyces* species were *A. meyeri* (n = 10, 35.7%), *Actinomyces israelii* (n = 10, 35.7%), *Actinomyces naeslundii* (n = 2, 7.1%), *Actinomyces odontolites* (n = 1, 3.6%), and *Actinomyces* spp. (n = 6, 21.4%). One patient showed both *A. meyeri* and *A. israelii*. Eight patients (28.6%) presented coinfections with other anaerobic bacteria. The median age in the *Actinomyces* group was 57.0 years (interquartile range (IQR): 43.5–68.3 years), which was lower than that in the other pathogens group (median (IQR): 63 years (59.3–73.0), $p = 0.008$). The number of patients with alcohol abuse in the *Actinomyces* group was higher than that in the other pathogens group

Table 2
The characteristics of the 23 cases of *Actinomyces* empyema from the literature review compared to the other-pathogen cases.

	Actinomyces (n = 28)	Other pathogens[a] (n = 38)	*p*-value
Age, median (IQR), years	57.0 (43.5–68.3)	68.0 (59.3–73.0)	0.008
Sex (Male/Female)	21/7	33/5	0.333
Comorbidity, n (%)[a]	19 (73.1)	30 (83.3)	0.360
Respiratory disease as an underlying disease, n (%)[a]	5 (19.2)	16 (44.4)	0.057
Immune suppression, n (%)[a]	7 (27.0)	12 (33.3)	0.781
Smoking history, n (%)[b]	16 (100)	30 (83.3)	0.408
Alcohol abuse, n (%)[c]	11 (78.6)	12 (38.7)	0.023
Duration from symptom onset to hospital admission, median (IQR), day[d]	25.5 (13.3–45.0)	9.5 (4.0–14.3)	<0.001
Radiological findings			
Pleural effusion in half or more of thorax on chest radiograph, n (%)[e,b]	15 (75.0)	16 (43.2)	0.023
Pleural effusion			
LDH, median (IQR), IU/L[f]	1045 (879–20265)	3817 (1586–11844)	0.646
TP, median (IQR), g/dL[f]	3.70 (2.90–4.76)	3.86 (3.07–4.56)	1.000
Multiple pathogens cultured, n (%)	8 (25.0)	7 (18.4)	0.382
Treatment			
A chest drainage tube inserted, n (%)	21 (75.0)	31 (81.6)	0.555
Duration of antibiotic therapy, median (IQR), weeks	16 (6–24)	4 (3–7)	<0.001
Thoracotomy, n (%)	6 (15.8)	3 (7.9)	0.153
Intrapleural urokinase, n (%)	1 (3.6)	7 (18.4)	0.125

LDH lactate dehydrogenase, TP total protein.
a; *Actinomyces* n = 26, other pathogens n = 36, b; *Actinomyces* n = 17, other pathogens n = 36, c; *Actinomyces* n = 14, other pathogens n = 31, d; *Actinomyces* n = 20, other pathogens n = 36, e; *Actinomyces* n = 20, other pathogens n = 37, f; *Actinomyces* n = 11, other pathogens n = 27.
[a] *Streptococcus milleri* group (n = 11, 26.8%), *Streptococcus pneumoniae* (n = 3, 7.3%), *Streptococcus mitis* (n = 3, 7.3%), *Staphylococcus aureus* (n = 2, 4.9%), anaerobic bacteria (n = 13, 31.7%), and others (n = 5, 13.2%).
[b] The measurement of pleural effusion was calculated as the length from lung base to the top of the pleural effusion divided by the length from lung base to the top of the apex on the midclavicular line on chest radiographs.

(n = 11 (78.6%) vs n = 12 (38.7%), $p = 0.023$). However, there were no significant differences in the ratios of males (males n = 21 (75.0%) vs n = 33 (86.8%), $p = 0.333$) or the rates of underlying pulmonary disease (n = 5 (19.2%) vs n = 16 (44.4%), $p = 0.057$), which were both reported as risk factors for pulmonary actinomycosis. We evaluated pleural effusion by calculating the length from the lung base to the top of the pleural effusion divided by the length from lung base to the top of the apex on the midclavicular line on the chest radiograph. The rate of pleural effusion involving half or more of the thorax on chest radiographs was higher in the *Actinomyces* group than in the other pathogens group (n = 15 (75.0%) vs n = 16 (43.2%), $p = 0.023$). Furthermore, the duration from symptom onset to hospital admission was longer in the *Actinomyces* group than in the other pathogens group (median (IQR) 25.5 days (13.3–45.0 days) vs 9.5 days (4.0–14.3 days), $p < 0.001$). These results might be related to the fact that *Actinomyces* is a slow-growing organism [8] and that actinomycosis has a slow disease progression [9]. We suspected that *Actinomyces* would induce weak symptoms in the early stage and gradually induce stronger symptoms with growth. The characteristics in the *Actinomyces* group were similar to those of pneumonia and lung abscess caused by actinomycetes [8].

This investigation had several limitations. This review was conducted retrospectively in a single-center hospital, and some medical data were not recorded. There was publication bias because the data of many of the patients with *Actinomyces* pleural infection were from published reports. Moreover, the detailed measurement of pleural effusion is difficult. Some medical data, such as the duration from symptom onset to hospital visit, were not described in detail. Some patients in the other pathogens group might have been infected with *Actinomyces* but were not diagnosed because *Actinomyces* is a difficult species to culture, while all cases of other phenotypes in our study had negative *Actinomyces* results on anaerobic culture. The review was approved by the Institutional Review Board of the Fukujuji Hospital.

4. Conclusion

A. meyeri pleural infection in a patient with a penicillin allergy was difficult to treat due to the delayed culture of *A. meyeri*. Furthermore, we demonstrated that *Actinomyces* pleural infection is a long-term process, resulting in a large amount of pleural effusion compared to other pleural infection phenotypes. When a patient with a severe pleural infection shows slow progression, *Actinomyces* infection should be considered.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

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