J Infect Chemother 25 (2019) 1065–1069

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Case Report

Case of endobronchial metastasis from breast cancer accompanied with *Cunninghamella bertholletiae* tracheobronchial mycetoma☆

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ARTICLE INFO

Article history:
Received 26 February 2019
Received in revised form
9 May 2019
Accepted 27 May 2019
Available online 19 June 2019

Keywords:
Cunninghamella bertholletiae
Tracheobronchial mycetoma
Breast cancer
Endobronchial metastasis
Liposomal amphotericin B

ABSTRACT

Cunninghamella is a member of the class Zygomycetes. *Cunninghamella* species include ubiquitous filamentous fungi; infections caused by *Cunninghamella* species are less frequent but have higher mortality rates than infections caused by Mucorales group members such as *Rhizopus* and *Mucor*. Herein, we reported a rare fatal case of endobronchial metastasis from breast cancer accompanied with *Cunninghamella bertholletiae* tracheobronchial mycetoma.

A 73-year-old female with a history of right-sided breast cancer who had undergone mastectomy 11 years previously and had no recurrence presented to our emergency department with a 1-week history of left-sided back pain. Chest X-ray revealed left lung atelectasis; bronchoscopy revealed an endobronchial mass lesion in the left main bronchus. Pathological examination revealed fungal mycetoma but malignant lesions were not detected. Endobronchial and lung mycetoma caused by *Cunninghamella bertholletiae* were initially diagnosed; liposomal amphotericin B was administered, but her condition deteriorated. Rigid endoscopy showed growth of hemorrhagic tissue occupying the left main bronchus just under the carina. Pathological examination of the shaved lesion revealed metastasis from breast cancer covered with abundant necrotic tissue. No mold was observed in the necrotic tissue; this was probably due to liposomal amphotericin B treatment.

To our knowledge, this is the first case of endobronchial metastasis from breast cancer accompanied with *Cunninghamella bertholletiae* mycetoma. Distinguishing endobronchial metastases from breast cancer and atypical presentations of *Cunninghamella* endobronchial mycetomas can be very difficult. Repeated bronchoscopies maybe helpful in establishing an accurate diagnosis when clinical prognosis does not match the initial diagnosis.

1. Introduction

Cunninghamella bertholletiae is a member of the order Mucorales of the subphylum Mucormycotina. Mucorales are thermotolerant molds that are ubiquitous in nature and widely found in organic substrates, including bread, fruits, vegetable matter, soil, and animal excreta. Mucorales sometimes cause tissue infarctions and are associated with disseminated and frequently fatal infections [1]. A hallmark of invasive mucormycosis is the rapid development of tissue necrosis due to the invasion of blood vessels and subsequent thrombosis. In most cases, such infections are relentlessly progressive and result in death unless underlying risk factors are corrected, and effective antifungal therapy is

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https://doi.org/10.1016/j.jiac.2019.05.031
1341-321X/

instituted in combination with surgical excision. Based on the clinical presentation and anatomic predilection, invasive mucormycosis can be classified into six forms; (1) rhinocerebral syndrome, or as (2) pulmonary, (3) cutaneous, (4) gastrointestinal, (5) disseminated, and (6) uncommon presentations. The most common underlying risk factors for invasive mucormycosis are poorly controlled diabetes mellitus with metabolic acidosis, administration of high-dose systemic corticosteroids for solid-organ and hematopoietic stem cell transplantations, penetrating trauma or burns, persistent neutropenia, and the use of deferoxamine-based therapy for aluminum or iron chelation in patients receiving dialysis or extensive blood transfusions [1]. Herein, we report a rare fatal case of endobronchial metastasis from breast cancer accompanied with tracheobronchial mycetoma due to *C. bertholletiae*.

2. Case report

A 73-year-old female presented to our emergency department with a 1-week history of left-sided back pain. She had idiopathic thrombocytopenic purpura (ITP) since the age of 50 years and had undergone splenectomy at the age of 62 years, after which, her ITP was under control. She had also been diagnosed with right-sided stage IIIA breast cancer at the age of 70 years, and had undergone right-sided mastectomy and axillary lymph node dissection (level 2). She was recurrence-free on adjuvant letrozole therapy and was on follow-up in another hospital. She had no history of diabetes mellitus and underwent annual chest radiographs at the other hospital for suspected asbestosis. The findings on her chest radiographs remained unchanged until three months before she was referred to our hospital. At that time, the chest radiograph images showed pleural calcification near the left diaphragm and left mid-lung field (Fig. 1a).

At our emergency department, her vital signs were as follows: consciousness, clear; blood pressure, 163/90 mm Hg; pulse rate, 82 beats/min; SpO2, 97% on ambient air; respiratory rate, 18 breaths/min with no effort; and body temperature, 36.0 °C. The respiratory sounds on the left side were weak. The chest radiograph at this stage revealed atelectasis of the left lung (Fig. 1b); chest computed tomography revealed that her left main bronchus was obstructed by a tumor (Fig. 1c). She was initially diagnosed with endobronchial lung cancer and obstructive pneumonia. The laboratory data are summarized in Table 1.

Sputum cytology was negative for malignant cells. She was admitted and administered sulbactam/ampicillin on suspicions of obstructive pneumonia. Her back pain resolved on day 2; sulbactum/ampicillin was continued until day 7. She underwent a diagnostic bronchoscopy on day 6, that revealed an endobronchial mass lesion almost obstructing the left main bronchus (Fig. 2a). No malignant lesion was seen on histopathology and cytology, and the lesion was noted to be entirely filled with necrotic tissue, inflammatory cells which included neutrophils and lymphocytes, and fungi-like particles on hematoxylin-eosin (HE) staining (Fig. 2b). The fungi-like particles were found to be mold on Grocott staining (Fig. 2c); which was isolated by culturing on Sabouraud Dextrose Agar, and was suggested Mucorales by the morphology. As determined using the National center for Biotechnology Information Basic Local Alignment Search Tool, sequencing of 18S rRNA showed 99% consistency with *C. bertholletiae*. Therefore, she was initially diagnosed with endobronchial mycetoma and lung infection caused by *C. bertholletiae*.

We administered liposomal amphotericin B (L-AMPHB) intravenously at a dose of 5 mg/kg/day for 4 weeks starting from day 14. Her renal function did not worsen during administration of L-AMPHB. However, the findings on the chest radiographs deteriorated. She was transferred to the Nara Medical University hospital, a tertiary emergency medical facility, on day 39 to undergo rigid endoscopy to relieve the bronchial obstruction. Rigid endoscopy showed that the left main bronchus just under the carina was obstructed by hemorrhagic tissue (Fig. 3a). Pathological examination of the shaved lesion showed a metastasis from breast cancer that was covered with abundant necrotic tissue (Fig. 3b and c). No molds were observed in the necrotic tissue on HE, periodic acid Schiff (PAS), or Grocott staining and culture. Since the endobronchial metastasis from breast cancer grew into the trachea with necrotic tissue causing obstruction, her respiratory condition worsened very rapidly before initiation of therapy. She died on day 54 because of the tracheal obstruction. Her family refused pathological autopsy.

3. Discussion

To our knowledge, this is the first reported case of endobronchial metastasis from breast cancer accompanied with tracheobronchial mycetoma due to *C. bertholletiae*. A search of the PubMed database revealed no reports of *C. bertholletiae* endobronchial mycetoma accompanying cancer. It was very difficult to identify whether the illness was caused by endobronchial metastasis from breast cancer, an atypical presentation of *C. bertholletiae* endobronchial mycetoma, or both. We speculate that the patient's clinical condition was influenced by the metastatic lesion as well as by the endobronchial fungal mycetoma. This was probably because of two distinct histopathological findings, one finding characteristic of *C. bertholletiae* tracheobronchial mycetoma in the first tissue sample, and another finding characteristic of breast cancer metastasis in the second tissue sample. We also speculate that endobronchial metastasis, and possibly lung metastasis existed at

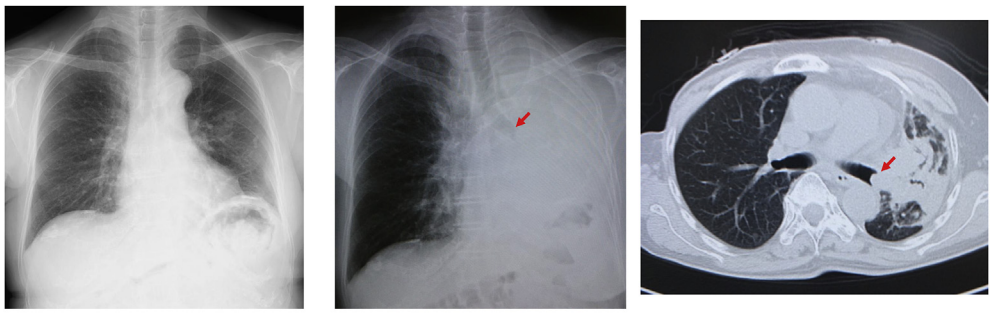
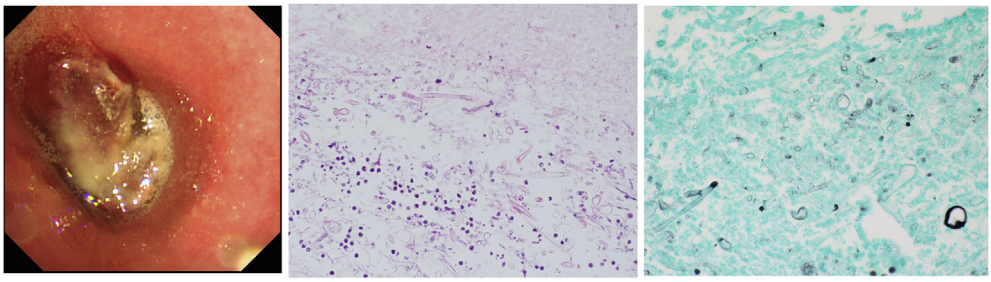


Fig. 1. Chest X-ray and computed tomography (CT) findings. (a) Chest X-ray image obtained 3 months before admission showed pleural calcification near her left diaphragm and left mid-lung field. (b) Chest X-ray, and (c) CT images obtained on admission revealing obstruction of the left main bronchus by the tumor and atelectasis of the lung (red arrow).

Table 1
Laboratory findings on admission.

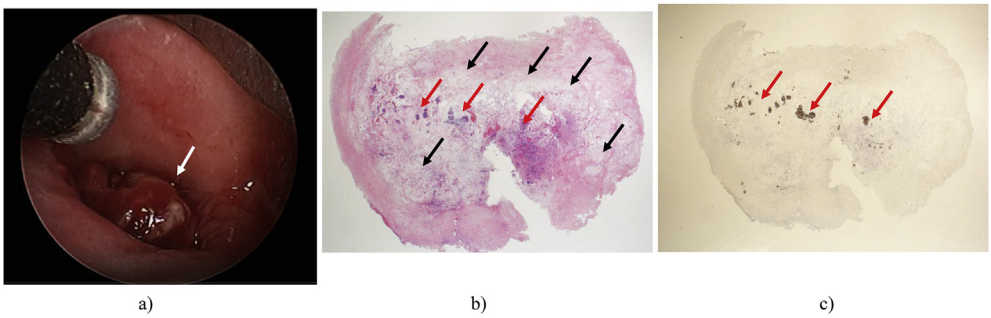
【Peripheral Blood】			【Biochemistry】			【Electrolyte】		
WBC	11600	/μL	CRP	0.17	mg/dL	Na	141.1	mEq/L
Stab	0	%	TP	6.23	g/dL	K	3.81	mEq/L
Seg	59.7	%	Alb	3.98	g/dL	Cl	105.8	mEq/L
Lym	27.2	%	AMY	44	U/L	Ca	9.25	mEq/dL
Mono	8.7	%	AST	13	U/L	【Tumor marker】		
Eos	2.8	%	ALT	9	U/L	CEA	7.28	ng/mL
Baso	1.6	%	CK	217	U/L	CYFRA	2.8	ng/mL
Hb	12.7	g/dL	LDH	128	U/L	sIL-2R	481	U/mL
Plt	14.8×10^4	/μL	ALP	173	U/L	ProGRP	48.3	pg/mL
【Coagulation test】			γ - GTP	52	U/L	【Infection marker】		
PT-INR	0.99		ChE	217	U/L	Aspergillus precipitating antibody		negative
APTT	29.4	sec	Glu	110	mg/dL	Aspergillus antigen		negative
			UA	3.98	mg/dL	(1,3) β-D glucan	8.3	pg/mL
			BUN	10.7	mg/dL			
			Cre	0.46	mg/dL			

Red: abnormal data



a) b) c)

Fig. 2. Bronchoscopy findings. a) Bronchoscopy revealing almost complete obstruction of the left main bronchus by the white colored endobronchial mass. b) hematoxylin-eosin staining of the endobronchial mass lesion. c) Grocott staining of the endobronchial mass lesion.



a) b) c)

Fig. 3. Rigid endoscopy findings. a) Rigid endoscopy revealing growth of the endobronchial mass and its location in the main bronchus under the carina (white arrow). b) Hematoxylin-eosin staining of the endobronchial mass lesion showing an endobronchial metastasis from breast cancer (red arrow) surrounded by abundant necrotic tissue (black arrow). c) Estrogen receptor staining of the endobronchial mass lesion, which revealed that it was breast cancer (red arrow).

the peripheral part of the bronchus when the first bronchoscopy was performed, and that the mold was attached to the surface of the metastasis, which progressed into the mycetoma. The second pathological examination revealed abundant necrotic tissue surrounding the metastasis from breast cancer. Although no findings indicative of mold were observed, this was consistent with both, cancer necrosis and mold mycetoma. The efficacy of L-AMPHB was probably responsible for these findings.

Roden et al. reviewed the epidemiology and outcomes of mucormycosis in 929 reported cases [2]. They reported that unlike other mold fungi, Mucolares change their phenotypes according to the host conditions. They described that rhinocerebral syndrome, a cutaneous pattern, and pulmonary involvement were the most common in patients with diabetes, without any underlying conditions, and with malignancies or bone marrow and solid organ transplants, respectively. Moreover, among the 154 patients with malignancies, mucormycosis was reported in only 7 patients with non-hematological malignancies.

In this case, the patient was initially diagnosed with *C. bertholletiae* tracheobronchial mycetoma. However, the clinical manifestation was not characteristic of *C. bertholletiae* infection. Clinical manifestations of pulmonary mucormycosis are generally similar to those of invasive aspergillosis. Patients having pulmonary mucormycosis present with fever, cough, pleuritic chest pain, and rapidly progressive dyspnea. In such cases, regular chest radiographs show a multitude of patterns, including (in descending order of frequency) lobar consolidation or nonspecific infiltrates, cavities, masses, nodules, and wedge-shaped infarcts of the lung [1]. However, disease progression was not so fulminant in this case. Some atypical presentations of pulmonary mucormycosis have been reported, including chronic infections in relatively immunocompetent hosts, with symptoms lasting for several months, multiple mycotic pulmonary artery aneurysms and pseudoaneurysms, bronchial obstructions, asymptomatic solitary nodules, and even normal chest radiograph findings [3].

He et al. reported 12 cases of tracheobronchial mucormycosis that were treated in their institution and reviewed 48 cases that were previously reported in English literature [4]. Most patients had underlying medical conditions; diabetes mellitus and renal insufficiency were the most common predisposing factors. Some degree of immunosuppression was observed in 31.7% patients and 6.7% had solid malignancies. Fever, cough, dyspnea, hemoptysis, and chest pain were the most common symptoms. However, 5.1% of patients were asymptomatic. Most cases were diagnosed using bronchoscopic biopsy. In only one reported case in literature, *Cunninghamella* species were isolated from endobronchial mycetomas [5]. In that case, lobectomy was performed without major complications after administering oral itraconazole for 6 weeks. Our patient could not undergo operation because her general condition was considerably poor.

We chose L-AMPHB 5 mg/kg/day for treating the *C. bertholletiae* mycetoma. No prospective randomized trials have been conducted for defining the optimal antifungal therapy for mucormycosis. The Clinical and Laboratory Standard Institute (CLSI) has developed a reproducible procedure for antifungal susceptibility testing of Mucorales species as described in the M38-A2 broth microdilution document [6]. However, minimal inhibitory concentration (MIC) distributions, clinical breakpoints, and epidemiological cutoff values are not available for Mucorales species. Some studies have reported that posaconazole has good anti-fungal activity in vitro and in vivo [1,3,7–10]; however, posaconazole is not available in Japan. Petrikkos reported that L-AMPHB 5–15 mg/kg/day is the therapy of choice in most zygomycosis cases [11]. Espinel-ingroff et al. reported the MIC distributions of antifungal agents from 32 *C. bertholletiae* clinical isolates; the MIC distribution of amphotericin B ranged from 0.25 μg/mL to 8.0 μg/mL [8]; this value was higher than that for most non-dermatophytic opportunistic filamentous fungi, which have MIC distributions ranging between 0.5 and 2.0 μg/mL according to the CLSI M38-A2 [6]. Roden et al. [2] reported that infection with *Cunninghamella* species was one of the independent risk factors for mortality among patients with mucormycosis. Furthermore, the high MIC distribution in *Cunninghamella* may be related to high mortality; high doses of L-AMPHB could increase nephrotoxicity. A phase II clinical trial is needed to address the validation of high doses of L-AMPHB (10 mg/kg/day) in mucormycosis [12]. However in this case, there was no need to treat with high doses of L-AMPHB because abundant necrotic tissue was seen on rigid endoscopy, which meant L-AMPHB was apparently effective in treating the *C. bertholletiae* mycetoma.

In this case, bronchoscopy did not provide any evidence of malignancy; therefore, endobronchial metastasis from breast cancer could only be diagnosed after performing rigid endoscopy, in which a larger tissue sample was taken. It was very difficult to accurately diagnose whether it was mycosis or malignancy. Marchioni et al. reported the occurrence of endobronchial metastases from extrapulmonary solid tumors, in which breast cancer was the most common primary neoplasm, followed by colorectal, renal, gastric, and prostate cancers [13]. According to the literature, in 48 of 52 cases, endobronchial metastases from breast cancers were recognized after primary cancer diagnosis. The temporal latency between the occurrence of endobronchial metastasis and primary breast cancer ranged from 17.66 to 154.48 months. This range is consistent with the latency period observed in this case.

In conclusion, to our knowledge, this was the first case of endobronchial metastasis from breast cancer accompanied with *C. bertholletiae* mycetoma. Distinguishing between endobronchial metastases from breast cancer and atypical presentations of *Cunninghamella* endobronchial mycetomas is very difficult. Our findings show that repeated bronchoscopies might be necessary to obtain an accurate diagnosis in cases where the clinical prognosis does not match the initial diagnosis.

Conflicts of interest

None.

Acknowledgements

We wish to thank Editage Insights for English language editing. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Kontoyiannis DP, Lewis RE. Invasive zygomycosis: update on pathogenesis, clinical manifestations, and management. Infect Dis Clin N Am 2006;20:581–607.
[2] Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634–53.
[3] Hamilos G, Samonis G, Kontoyiannis DP. Pulmonary mucormycosis. Semin Respir Crit Care Med 2011;32:693–702.
[4] He R, Hu C, Tang Y, Yang H, Cao L, Niu R. Report of 12 cases with tracheobronchial mucormycosis and a review. Clin Res J 2017. https://doi.org/10.1111/crj.12724 [Epub ahead of print].
[5] Dillard TA, Ortega I. Multiple endobronchial mycetomas with varied appearances and mixed fungal flora. J Bronchol Interv Pulmonol 2013;20:147–9.
[6] Clinical and laboratory standards Institute reference method for broth dilution antifungal susceptibility testing of filamentous fungi; approved standard-second edition M38-A2 vol. No. 1628. 2008.
[7] Espinel-Ingroff A, Chakrabarti A, Chowdhary A, Cordoba S, Dannaoui E, Dufresne P, et al. Multicenter evaluation of MIC distributions for epidemiologic cutoff value definition to detect amphotericin B, posaconazole, and itraconazole resistance among the most clinically relevant species of Mucorales. Antimicrob Agents Chemother 2015;59:1745–50.

[8] Spellberg B, Edwards Jr J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18:556–69.
[9] Pastor FJ, Ruíz-Cendoya M, Pujol I, Mayayo E, Sutton DA, Guarro J. In vitro and in vivo antifungal susceptibilities of the Mucoralean fungus *Cunninghamella*. Antimicrob Agents Chemother 2010;54:4550–5.
[10] Sayan M, Arpag H, Tokur M, Bahar AY. Pulmonary mucormycosis mimicking an endobronchial mass. Asian Cardiovasc Thorac Ann 2018;26:242–4.
[11] Petrikkos GL. Lipid formulations of amphotericin B as first-line treatment of zygomycosis. Clin Microbiol Infect 2009;15:87–92.
[12] ClinicalTrials.gov. Pilot study of high dose liposomal amphotericin B efficacy in initial zygomycosis treatment (AMBIZYGO). 2014. http://clinicaltrials.gov/ct2/show/NCT00467883. [Accessed 29 March 2018].
[13] Marchioni A, Lasagni A, Busca A, Cavazza A, Agostini L, Migaldi M, et al. Endobronchial metastasis: an epidemiologic and clinicopathologic study of 174 consecutive cases. Lung Cancer 2014;84:222–8.