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Pulmonary infection caused by *Exophiala dermatitidis* in a patient with multiple myeloma: A case report and a review of the literature

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ABSTRACT

Exophiala dermatitidis is a dematiaceous fungus that is increasingly being identified as a cause of fungal infection especially in patients with immunodeficiency. To date, however, the factors predisposing *E. dermatitidis* and its optimal treatments have not been fully addressed. Here, we report the first patient with untreated multiple myeloma who developed *E. dermatitidis* pulmonary infection. We also review recent clinical reports describing the features of *E. dermatitidis* infection.

1. Introduction

Exophiala dermatitidis (formerly *Wangiella dermatitidis*) is a dematiaceous fungus that is found in soil and dead plant material worldwide, and sometimes causes phaeohyphomycosis [1]. This fungus plays a significant role as a respiratory pathogen in patients with cystic fibrosis. It is also an increasingly common cause of systemic or visceral infection, particularly in patients with compromised immunity [2]. However, because *E. dermatitidis* infections are still relatively rare, the underlying risk factors remain unknown. Sporadic cases of systemic or visceral *E. dermatitidis* infection have been reported but, to our knowledge, no cases of *E. dermatitidis* infection associated with multiple myeloma have been reported. Here, we report a patient with untreated multiple myeloma who developed *E. dermatitidis* pulmonary infection. We also review recent clinical reports describing the features of *E. dermatitidis* infection.

2. Case

A 65-year-old man, whose medical history only included hypertension, developed back pain and was treated with pain relief medication by his primary care physician for 1 month. He had worked in the silviculture industry in rural areas for many years. Routine lumbar X-ray scans at day-14 revealed multiple compression fractures and the possibility of bone metastasis was strongly suspected. Therefore, he was referred to a central hospital. Computed tomography (CT) of the chest at day-10 revealed a solitary nodule with spicula, prompting suspicion of lung cancer (Fig. 1). Accordingly, he underwent bronchoscopic examination at day-7. Bronchioalveolar lavage (BAL) and biopsy did not detect any malignant findings, but a specimen sent for culture yielded a growth of black fungi. No other microorganisms were cultured from the specimen. For further investigation, he was referred to our hospital (day 0).

On examination, he appeared to be in good health, was afebrile, and had no symptoms other than back pain. The full blood count showed the following: leukocyte count, 6200/μL; hemoglobin, 9.5 g/dL; and platelet count, 213,000/μL. Peripheral blood smear revealed marked rouleaux formation. The biochemical profile was almost normal except for mild renal insufficiency (creatinine, 1.55 mg/dL) and elevated protein levels (total protein, 9.0 g/dL) with an IgGκ light chain monoclonal spike on protein electrophoresis. The C-reactive protein and 1,3-β-D glucan levels were 0.12 mg/dL and <3.7 pg/dL, respectively. A bone marrow aspirate showed that $>20\%$ of the total cell population were plasma cells. These findings, together with the evidence for monoclonal gammopathy and osteomyelitic lesion, resulted in the diagnosis of multiple myeloma (symptomatic myeloma).

Subculture of the fungi obtained at the former hospital on Sabouraud agar produced large gray–black colonies with a wool-/cotton-like structure (Fig. 2a). Arcian blue staining and microscopic examination revealed the fungi had septate hyphae branching at acute angles (Fig. 2b). The segment of ribosomal DNA gene with internal transcribed spacer (ITS) was amplified

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from extraction of genomic DNA by polymerase chain reaction methods using ITS1 and ITS4 primers and the isolate was finally identified as *E. dermatitidis* by sequencing of ribosomal DNA ITS region [3]. The obtained sequences were compared to all known sequences in the Genbank by use BLAST. It displayed over 99% sequence homologies in the ITS region with *E. dermatitidis* (Accession number JX473286.1). Therefore, the patient was ultimately diagnosed with *E. dermatitidis* pulmonary infection and multiple myeloma.

Antifungal susceptibility testing revealed that the minimum inhibitory concentrations of amphotericin B, fluconazole, itraconazole, voriconazole, minozazole, 5-fluorocytosine, and micafungin against this isolate were 2, >64, 2, 1, 1, 4, and >16 μg/mL, respectively. Therefore, he was initially treated with voriconazole (300 mg every 12 h on day 1 and then 200 mg every 12 h thereafter) for about 4 weeks (up to day $+30$). Despite this treatment, the size of lung lesion did not significant change on follow-up CT. Consequently, he underwent surgical resection of the lung lesion at day $+37$ to avoid possible clinical deteriorations caused by starting chemotherapy to treat the myeloma. Histopathologic examination and culture study of the surgical specimen confirmed *E. dermatitidis* infection. Following resection, he received steroid-based combined chemotherapy without relapse of infection, which achieved remarkable improvements in clinical findings in relation to the multiple myeloma.

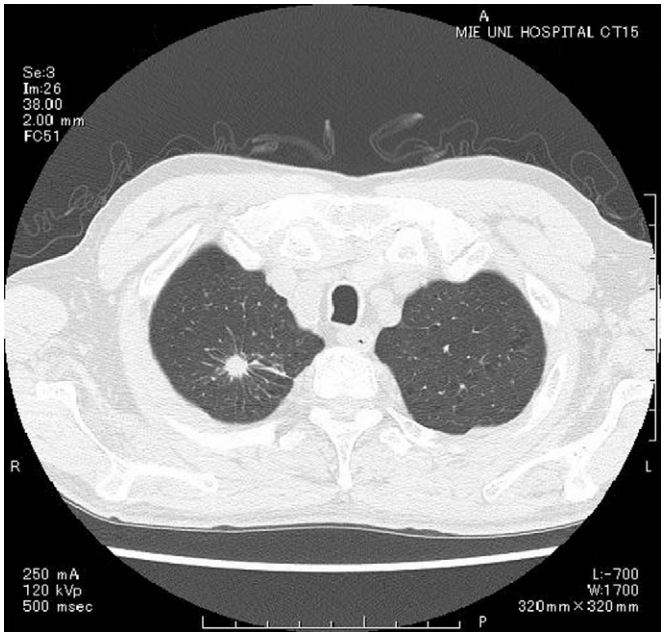

Fig. 1. Computed tomography of the chest at the initial visit. A solitary nodule with spicula was observed in the right upper lobe.

3. Discussion

E. dermatitidis is a melanized yeast-like organism belonging to the dematiaceous family of fungi, which are ubiquitous in nature and are increasingly being recognized as a cause of human disease [1,2]. In humans, *E. dermatitidis* infections can be separated into three types: (1) superficial infections; (2) cutaneous and subcutaneous disease; and (3) systemic or visceral disease [4]. Superficial infections are often related to trauma or operation, whereas non-superficial infections generally occur in patients with predisposing factors. For example, an association with cystic fibrosis is well documented. However, because of the rarity of human infections, the definitive risk factors have not yet been established [5]. In a literature review of 37 patients with *E. dermatitidis* infections from 1960 to 1992 conducted by Matsumoto et al. [4], 19 had an associated disease or predisposing condition, and 20 had evidence of systemic disease, including 12 with fatal disseminated infections. To our knowledge, 30 cases, including our current case, were reported between 1993 and 2011 [2,5–32]. Of these, 24 (80%) had invasive (i.e., non-superficial) infections; these 24 cases are summarized in Table 1. Considering the cases reported to date, the incidence of *E. dermatitidis* infection is certainly increasing. As in the previous review [4], the majority of the invasive cases (17/24 cases; 71%) identified in the present review had predisposing factors, including peritoneal dialysis, leukemia, steroid use, human immunodeficiency virus infection, cancer, bronchiectasis, and diabetes mellitus. Changes in immune status can influence the progression of infectious disease, such as *E. dermatitidis* infection. However, an association between *E. dermatitidis* infection and multiple myeloma has not been described until now. Our case suggests that immunodeficiency caused by multiple myeloma may be a risk factor for invasive infection with *E. dermatitidis*.

The route of infection is also obscure in most cases, usually because of the absence of identifiable cutaneous or subcutaneous lesions. It is possible that the fungus is either inhaled into the

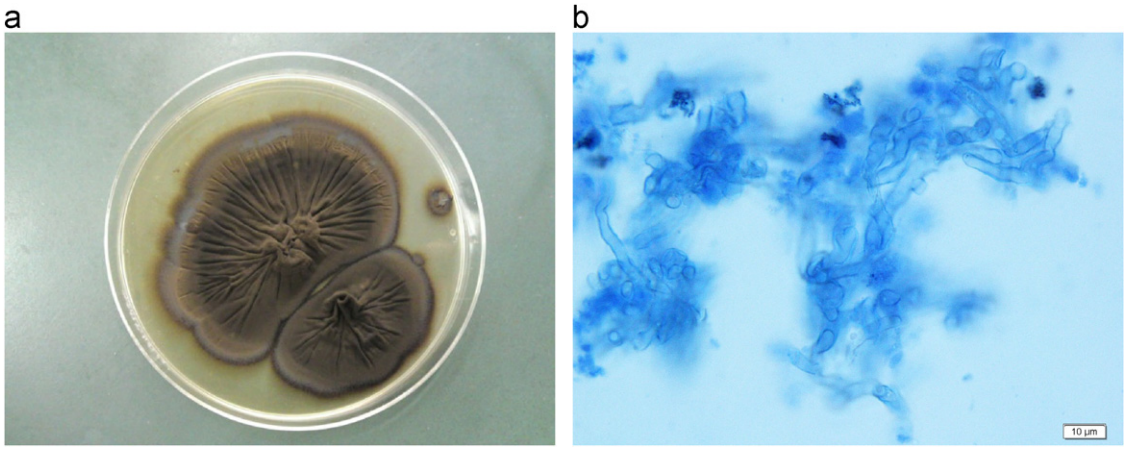

Fig. 2. Macroscopic and microscopic finding of the fungi obtained by the former hospital. (a) Subculture of the fungi on Sabouraud agar. Gray–black colonies with a wool-/cotton-like appearance were obtained. (b) Microscopic appearance of the specimen. Numerous fungal septate hyphae can be seen branching at acute angles (Arcian blue stain. Original magnification, $\times 200$).

Table 1
Summary of cases with invasive/non-superficial *Exophiala dermatitidis* infection reported since 1993.

No.	Age/sex	Manifestation	Predisposing factor	Diagnostic method	Treatment	Outcome	Region	Reference
1	24/M	Brain abscess*	None	Biopsy, culture	MCZ, 5-FC, AMPH-B, ketoconazole	Dead	Japan	Hiruma et al. [6]
2	39/M	Peritonitis*	Peritoneal dialysis	Culture	Catheter removal, FLCZ	Survived	Singapore	Lye [7]
3	3/M	Fungemia*	Acute leukemia	Culture	Catheter removal, AMPH-B, 5-FC	Survived	Germany	Blaschke-Hellmessen et al. [8]
4	70/M	Brain abscess*	None	Biopsy, culture	AMPH-B, Op	Dead	Singapore	Ajanee et al. [9]
5	58/F	Phaeohyphomycosis	RA, steroid	Biopsy, culture	ITCZ, Op	Survived	UK	Woollons et al. [10]
6	3/M	Fungemia*	HIV infection	Culture	Catheter removal, AMPH-B, ITCZ	Survived	USA	Nachman et al. [11]
7	28/M	Meningitis, brain abscess*	None	Biopsy	AMPH-B, Op	Dead	Korea	Chang et al. [16]
8	53/F	Peritonitis*	Peritoneal dialysis	Culture	Catheter removal, FLCZ	Survived	Greece	Vlassopoulos et al. [17]
9	29/F	Pneumonia*	Cystic fibrosis	Culture	AMPH-B, ITCZ, VRCZ	Survived	Canada	Diemert et al. [18]
10	62/M	Lymphadinitis	Acute leukemia	Biopsy, culture	AMPH-B, ITCZ	Survived	Taiwan	Liou et al. [19]
11	39/F	Invasive stomatitis*	Acute leukemia	Biopsy, culture, PCR	ITCZ, AMPH-B	Survived	Japan	Myoken et al. [20]
12	55/F	Peritonitis*	Peritoneal dialysis	Culture	Catheter removal, AMPH-B	Survived	UK	Greig et al. [21]
13	58/F	Fungemia*	Lung cancer	Culture	Catheter removal, AMPH-B	Survived	Taiwan	Tseng et al. [22]
14	54/F	Pneumonia*	Bronchiectasis	Culture	MCZ, nebulized AMPH-B	Survived	Japan	Mukaino et al. [2]
15	54/F	Pneumonia*	DM, systemic cancer	Biopsy, culture, PCR	FLCZ, ITCZ, AMPH-B	Dead	Netherlands	Tai-Aldeen et al. [24]
16	81/F	Pneumonia*	None	Biopsy, culture, PCR	FLCZ, ITCZ	Survived	Japan	Ozawa et al. [25]
17	8/M	Systemic phaeohyphomycosis*	None	Biopsy	AMPH-B, VRCZ	Dead	Turkey	Albaz et al. [26]
18	3/M	Brain abscess, meningitis*	None	Biopsy, culture, PCR	AMPH-B, FLCZ, ITLC	Dead	China	Chang et al. [27]
19	11/F	Liver chirosis*	None	Biopsy, culture, PCR	VRCZ, liver transplantation	Survived	Korea	Hong et al. [28]
20	24/F	Systemic phaeohyphomycosis*	None	Biopsy, culture, PCR	AMPH-B, VRCZ	Survived	Turkey	Oztas et al. [29]
21	16/F	Pneumonia*	Cystic fibrosis	Culture	ITCZ, VRCZ	NS	USA	Griffard et al. [30]
22	86/F	Lung nodule*	Dementia	Biopsy, culture	VRCZ	Survived	USA	Bulloch [5]
23	17/M	Phaeohyphomycosis	None	Biopsy	ITCZ, Op	Survived	Argentine	Russo et al. [32]
24	65/M	Lung nodule*	Multiple myeloma	Biopsy, culture, PCR	VRCZ, Op	Survived	Japan	Our case

* Systemic or visceral disease. RA, rheumatoid arthritis; HIV, human immunodeficiency virus; DM, diabetes mellitus; PCR, polymerase chain reaction; MCZ, miconazole; AMPH-B, amophotericin B; FLCZ, fluconazole; 5-FC, 5-fluorcytosine; Op, operation; ITCZ, itoraconazole; NS, not stated; UK, United Kingdom; USA, United States of America; VRCZ, voriconazole.

lungs with dust, or is ingested with food and enters the digestive tract, followed by retrograde passage into the biliary tract and the blood stream [29]. Central venous catheters also act as portals for fungal entry [8,11,22]. Additionally, this fungus was reported to be abundant in public steam baths and in water reservoirs, and a contaminated water supply was considered to be the most likely source of an *Exophiala* outbreak [26]. The present patient worked in silviculture, so it is possible that he was exposed to *E. dermatitidis* during the course of his employment. From these findings, it seems that the risk of infection may depend on the patient's history of contact with the fungus as well as the patient's immune status.

However, invasive *E. dermatitidis* infection occurred in several patients with no risk factors or known immunodeficiency [6,9,16,25–29,32]. Of the nine cases with no predisposing factors, eight were from Asian countries. Additionally, all four central nervous system infections reported to date occurred in Asia. This could imply that immunologic differences in the host or differences in exposure to the fungal propagules play a significant role in disease progression [25].

Another factor that should be considered is the overall prognosis. Indeed, 25% of the invasive cases (6/24) identified in our literature review were fatal. Based on these data and those reported in the earlier literature review [4], invasive *E. dermatitidis* infection is generally associated with a high mortality rate. However, comparing the two reports, it seems that the mortality rate has decreased over time, even for invasive infection, although not for central nervous system infection. Because of the rarity of this infection, no large-scale controlled studies have been done to examine the efficacy of specific antifungal agents. Nevertheless, newer antifungal agents and combination therapy may further improve the management of this disease [26,29]. Although clinical experience of treating this infection is relatively limited, recent reports, as well as our case, have documented beneficial effects of voriconazole *in vitro* [5]. Unsurprisingly, it is difficult to treat the infection after it has become fulminated, which means that appropriate therapy should be started as soon as possible. In previous report, the initial small localized lesions were amenable to surgical excision [26,29]. If central venous catheter was inserted, it should be removed to prevent systemic infection [21]. In the present patient, because the lung lesion did not change in size after treatment with voriconazole for 1 month and he needed prompt chemotherapy to treat his multiple myeloma, we opted for surgical resection of the lesion, based on the previous reports [26,29]. In general, hematologic malignancies require highly immunosuppressive therapy. Steroids are a key component of the treatment regimen for lymphoid neoplasms, including multiple myeloma. Therefore, surgical resection or debridement with antifungal agents is strongly recommended to prevent disseminated disease.

In conclusion, this is the first reported case of pulmonary *E. dermatitidis* fungal infection in a patient with multiple myeloma. This report should increase the awareness of *E. dermatitidis*, particularly its pathogenicity, in immunodeficient patients. With the more frequent use of immunosuppressive agents, the incidence of *E. dermatitidis* infection is likely to increase. Although

the optimal treatment remains unknown, the cases accumulated to date indicate that appropriate antifungal therapy, surgical debridement, and careful immunological interventions are necessary for a positive outcome. Because of the high mortality rate, it is vital that this still life-threatening fungal infection is promptly diagnosed and treated.

Conflict of interest

There are none.

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