

Is Phaeohyphomycosis an Emerging Fungal Infection in Iran? A Short Communication

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ARTICLE INFO	ABSTRACT
<p>Article type: Short Communication</p>	<p>Introduction: Phaeohyphomycosis is a rare opportunistic fungal infection that can be caused by dematiaceous fungi. The clinical manifestations of this disease are highly diverse and include cutaneous, subcutaneous, and systemic forms. However, the mortality rate of this infection depends on the immune status of patients. Although infections caused by black fungi have been on an increasing trend during the past decade, infections with dematiaceous fungi have rarely been reported in the Middle East. However, some fungal species are associated with a disseminated disease without the known clinical and pathologic risk factors. The analysis of DNA sequence is a highly effective method for differentiating various species among some genera, due to the variable cultural and morphological characteristics of DNA. Despite the presence of therapeutic methods, there are numerous reports regarding the high mortality rate of this infection. Published studies indicate no specific risk factors for phaeohyphomycosis and report the incidence of this disease in immunocompetent individuals. Moreover, selective treatment for these rare infections has not even been defined in clinical studies. However, the clinical syndromes associated with dematiaceous fungi should be considered in the Middle East, Iran.</p>
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Introduction

Phaeohyphomycosis is an opportunistic and rare fungal infection that can be caused by a group of pigmented filamentous fungi (dematiaceous) and their filamentous relatives. This disease could manifest in cutaneous, subcutaneous, and systemic forms, which, in some instances, may be severe or fatal (1). Dematiaceous fungi are pathogens (opportunistic pathogens) that

can invade into the deep tissue of the patients with underlying immunodeficiency. However, there are rare reports regarding the incidence of this infection in immunocompetent individuals (1).

Although hyaline fungi are the most commonly known causes of fungal infections among the fungal agents, melanized fungi have been recently reported significantly (2,3). Meanwhile, these fungi are often overlooked among the causative agents of

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fungal infections. These agents require strict isolation techniques because they are difficult to distinguish morphologically (4). The geographical conditions can impact the possible reservoirs of dematiaceous fungal infections due to black yeast-like fungi (5). There are no definitive guidelines for the determination of the antifungal susceptibility profiles of dematiaceous fungi. However, a few numbers of reports have addressed the clinical infections caused by these organisms. With this background in mind, the present study was conducted to investigate the importance of phaeohyphomycosis and the infected cases in Iran, located in the Middle East.

Evidence and Discussion

Phaeohyphomycosis can cause a wide spectrum of clinical manifestations in different hosts, ranging from cutaneous to disseminated infections (1). The immune status of the patients may be the most prominent factor for the mortality rate of this disease. However, some species of dematiaceous fungi are reportedly associated with a disseminated disease without the known clinical and pathologic risk factors (6). In some reports, the results of antifungal therapy are dismal with 100% mortality rate (1). Although the clinical manifestations of infection with dematiaceous fungi have been rarely reported in the Middle East, they have been on an increasing trend during the past decade, particularly in Iran (6-8).

To the best of our knowledge, ten cases of phaeohyphomycosis were reported in the various cities of Iran, including Tehran (9-11), Mashhad, Isfahan, Arak, Garmsar, Yazd between 2001 and 2018 (6-8,12-15. Table 1). The dematiaceous fungi was reported to affect the individuals of both genders at a ratio of 1:1, with the median ages of 27.2 and 47.8 years for the affected males (n=5) and females (n=5), respectively.

This disease had a mortality rate of 40% despite the administration of antifungal therapies (9-11). Out of the 10 cases, 1, 1, 2, 3, and 3 patients presented with rhinosinusitis, pulmonary involvement, subcutaneous masses, cutaneous lesions, and brain (cerebral) involvements, respectively. Two of the patients who acquired cerebral phaeohyphomycosis showed immune

dysfunction. However, no immune system disorder was reported in any of the patients with subcutaneous masses or rhinosinusitis and two patients with cutaneous lesions. Out of the three cutaneous infections reported in this literature, two cases were reported to have trauma, and no information about a history of trauma was presented for one case. Therefore, it seems most of the cutaneous forms caused by black fungi result from a systemic infection.

Despite the use of amphotericin B therapy alone or along with voriconazole, posaconazole, and itraconazole, some of the patients passed away.

The microscopic examination using direct potassium hydroxide preparation and stained histopathology slides in all the specimens showed phaeoid filamentous moulds with branched and septate hyphae. The low number of reported cases in this area could have at least two reasons. First, climate conditions and local geography can affect the growth rate of these fungi. Second, the isolation and identification of these organisms due to the lack of equipment can be extremely difficult.

The analysis of DNA sequence is the most effective method for differentiating various species among some genera, due to the variable cultural and morphological characteristics and weak sporulation of DNA among some species (16). In the present review, two out of the three causative agents of cutaneous lesions were not identified at the species level.

Moreover, similar to previous reports, *Rhinochrysiella mackenziei* was the most common cause of cerebral phaeohyphomycosis in this area, except for a case caused by *Nattrassia mangiferae*. There are limited data on the antifungal susceptibility of dematiaceous fungi, and the treatment of choice for this rare infection has not been determined yet in similar clinical studies (17).

Among the cases presented in the reviewed literature, three subjects were treated with itraconazole, two cases were cured, and one patient passed away. Nevertheless, successful treatment could be accomplished by the use of itraconazole 400 mg/day, along with amphotericin B.

Table 1: Cases of phaeohyphomycosis caused by dematiaceous fungi reported from Iran, the Middle East

Case no. Ref.]	Species of dematiaceous fungi	City/ isolation year	Age/ gender	Type of lesion (involved organ)	Underlying disease	Fungal therapy	Outcome
1 (9)	<i>Nattrassia mangiferae</i>	Tehran/2004	17/Male	Cerebral	Systemic lupus erythematosus	Amphotericin B(300 mg/d)	Died
2 (10)	<i>Dematiaceous fungus (not identified at the species level)</i>	Tehran /2018	26/Female	Cutaneous	Inherited CARD9 deficiency	Amphotericin B (0.5 mg/kg/d) and voriconazole (400 mg/day)	Died
3 (11)	<i>Exophiala dermatitidis</i>	Tehran /2011	54/Female	Nail	Nothing	Amphotericin B (0.5 mg/kg/d) and voriconazole (400 mg/day)	Cured
4 (7)	<i>Chaetomium species</i>	Mashhad /2013	66/Female	Cyst on the neck	A history of thyroidectomy	Ketoconazole (200 mg twice a day)	Cured
5 (6)	<i>Neoscytalidium dimidiatum</i>	Mashhad /2013	20/Male	Maxillary sinus	Nothing	Nothing	Cured
6 (12)	<i>Alternaria malorum</i>	Isfahan/2012	27/Male	Sub-cutaneous necrotic lesions	Nothing	Amphotericin B (5 mg/kg/day) and itraconazole (400 mg/day)	Cured
7 (13)	<i>Rhinoctadiella mackenziei</i>	Isfahan/2017	67/Female	Brain	Diabetes mellitus and Behcet's disease	Amphotericin B (5 mg/kg/d) and posaconazole (200 mg daily)	Died
8 (8)	<i>R. mackenziei</i>	Arak /2014	54/Male	Brain	Nothing	Amphotericin B (0.5 mg/kg/d) and itraconazole (200 mg twice a day)	Died
9 (14)	<i>Cladosporium bantianum</i>	Garmsar /2001	18/Male	Rhinocerebral and chest	Wegener's granulomatosis	Amphotericin B (1 mg/kg/d)	Cured
10 (15)	<i>Dematiaceous fungus (not identified at the species level)</i>	Yazd /2016	26/Female	Cutaneous	Nothing	Itraconazole (200 mg/day)	Cured

Conclusion

Phaeohyphomycosis can be considered an emerging fungal infection in this part of Middle East. However, it is required to perform further studies to identify the clinical manifestations of this infection and determine the best antifungal treatment. The clinical syndromes associated with dematiaceous fungi should be also considered in the Middle East, Iran.

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