A Phaeohyphomycosis Case: A Rare Entity

Prikaz redkega primera feohifomikoze

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Ključne besede:
feohifomikoza; črna plesen; itrakonazol

Key words:
Phaeohyphomycosis; black mould; itraconazole

Citirajte kot/Cite as:
Zdrav Vestn 2014; 83: 826–730

Prispelo: 8. maj 2013,
Sprejeto: 1. okt. 2014

Abstract

Phaeohyphomycosis is the term used to describe infections with darkly pigmented moulds appearing as septate filaments in host tissues. The disease is a histopathological rather than a clinical entity. A 79-year-old patient presented with multiple ulcerated lesions and nodules on the face. Microbiological culture identified the fungal isolate as phaeohyphomycosis. In the histopathological examination, granuloma formation with neutrophils in the center was detected due to infection. Oral daily 400 mg itraconazole was administered for 6 months. Follow-up at 12 months demonstrated no signs of infection. Clinical manifestations of cutaneous phaeohyphomycosis vary significantly. Although optimal treatment options remain contraversial, this case of phaeohyphomycosis was successfully treated by itraconazole monotherapy.

Izvleček

Feohifomikoza je izraz za okužbe, ki jih povzročajo temno pigmentirane glive, ki v tkivu gostitelja tvorijo hife in/ali kvasovkam podobne celice. Ta bolezen je bolj histopatološki kot klinični pojav. 79-letna bolnica je ob pregledu imela na obrazu številne gnojne lezije in vozličaste tvorbe. Glivični izolat iz mikrobiološke kulture je bil opredeljen kot feohifomikoza. Pri histopatološkem pregledu je bila odkrita granulomska tvorba z nevtrofilci v centru zaradi okužbe. Bolnica je 6 mesecev prejemala itrakonazol peroralno, v odmerkih 400 mg na dan. Ob kontrolnem pregledu po 12 mesecih ni bilo nobenih znakov okužbe. Klinična slika kožne feohifomikoze je lahko zelo različna. Čeprav so mnenja glede najustreznejšega načina zdravljenja deljena, je bila v tem primeru feohifomikoza uspešno ozdravljena z monoterapijo z itrakonazolom.

Introduction

Dematiaceous or darkly pigmented fungi comprise a large, heterogeneous group of organisms that have been associated with a variety of clinical syndromes. These are uncommon causes of human disease, but can be responsible for life-threatening infections in both immunocompromised and immunocompetent individuals.[1] The main route of inoculation appears to be skin trauma; less frequent is through inhalation of spores. Lesions usually appear on exposed areas of the human body. There are several different presentations, depending on the route of acquisition. The disease is rare, and generally occurs in form of localized, subcutaneous or intramuscular infections.[2] Nosocomial outbreaks can follow contamination of medical equipment, fluids or drugs. The term phaeohyphomycosis was first coined by *Ajello* in 1974.[3] The diagnosis of cutaneous and subcutaneous phaeohyphomycosis rests on histopathologic examination of clinical specimens and extensive microscopic examination and identification of cultures obtained through biopsy material.[4] The term subcutaneous phaeohyphomycosis involves skin and subcutaneous tissue and it is characterized by nodular or cystic lesions or a pyogranuloma.[5] The most frequent causes of subcutaneous phaeohyphomycoses are *E. jeanselmei*, *Wangiella dermatitidis* and *Bipolaris* species. Other genera frequently related to human infections are *Alternaria*, *Curvularia,* and *Exserohilum*.[6]

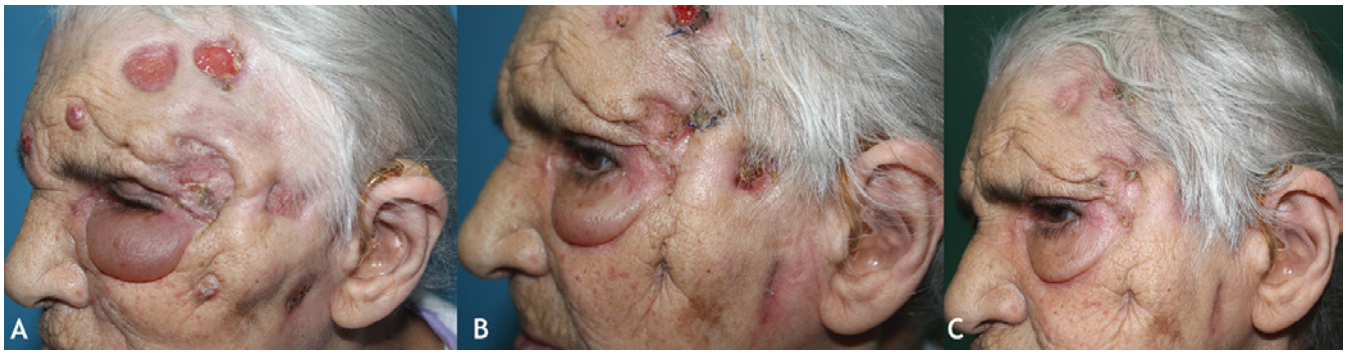


Figure 1: (A) Localized cutaneous or subcutaneous abscesses, periorbital edema, ulcerations following traumatic implantation. (B) Notice that edema was decreased. (C) Patient's photos at the end of the second month of treatment. Edema was markedly reduced, and ulcers were healed.

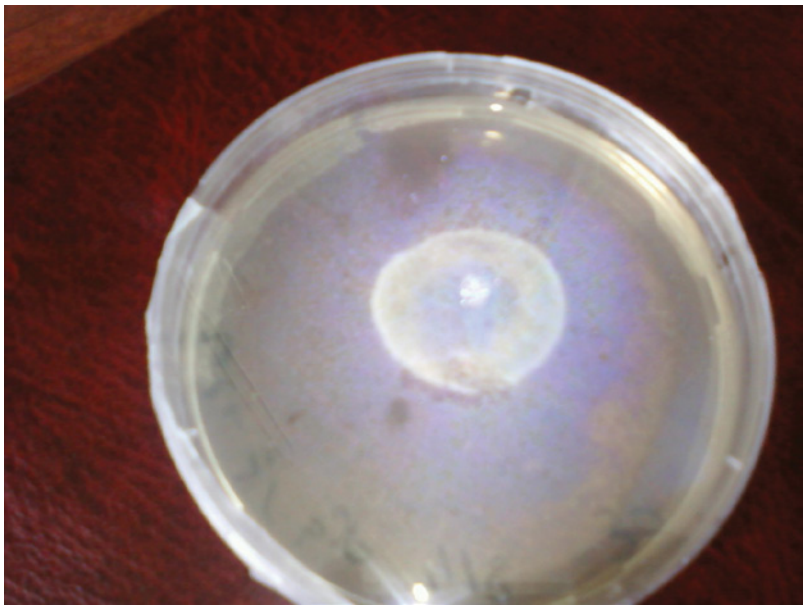
Case

A 79-year-old female patient was admitted to hospital with complaint of painful wounds on her forehead and face. She had a history of trauma. She had fallen when walking and her head hit the asphalt. She had lost consciousness and was hospitalized for 2 days in an intensive care unit. The patient was discharged from the intensive care unit when symptoms regressed. Local antibiotic therapy had been applied to the wounds but treatment was not successful and wounds and draining nodules became more extensive. She had no disease that could cause immunosuppression in her medical history. Dermatological examination of the patient revealed two ulcerated lesions measuring 4 cm in diameter lateral to the left of the forehead, prominent left upper eyelid edema leading to closure of the eye, right infraorbital edema with medium hardness, fistula on the forehead, and ulcerated lesion lateral to the left eye, measuring approximately 5 cm in diameter (Figure 1A).

Thickening of the subcutaneous tissue of the left fronto-parietal region was seen on MR imaging. Phaeohyphomycosis was detected based on the result of mycological culture medium (Figure 2). An incisional biopsy sample measuring $1 \times 0.8 \times 0.4$ cm was taken from the left side of the forehead and sent for pathological examination. The microscopic examination of the biopsy revealed an active chronic inflammation localized in subcutaneous fat tissue (Figure 3A-C). The inflammation had focal areas of granulomatous response and abscess formation. No specific etiological agent was found with PAS and EZN special stains.

Based on these findings, the patient was diagnosed with phaeohyphomycosis. The patient was treated with itraconazole 400 mg daily and discharged on the 20th day of treatment. The patient was followed monthly in our outpatient department; blood counts and transaminase levels were checked every month. At the end of the first month of treatment, edema began to decrease (Figure 1B). At the beginning of the third month of treatment, ulcerated lesions healed, edema markedly decreased and oozing stopped (Figure 1C). At the sixth month of itraconazole treatment, the lesions completely regressed and so the treatment was terminated (Figure 4).

Figure 2: A typical view of phaeohyphomycosis on culture medium.



Discussion

Dematiaceous fungal infections may cause clinically heterogeneous diseases. Chromoblastomycosis, mycetoma, and phaeohyphomycosis are possible presentations and are mostly defined based on histologi-

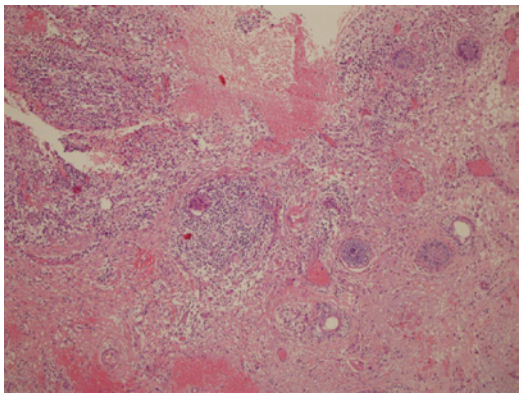


Figure 3A: The inflammation had focal areas of granulomatous response (HEx10).

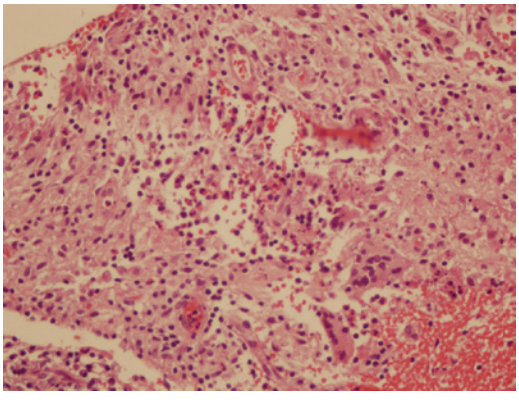


Figure 3B: Neutrophils in the center of the granuloma (HEx40).

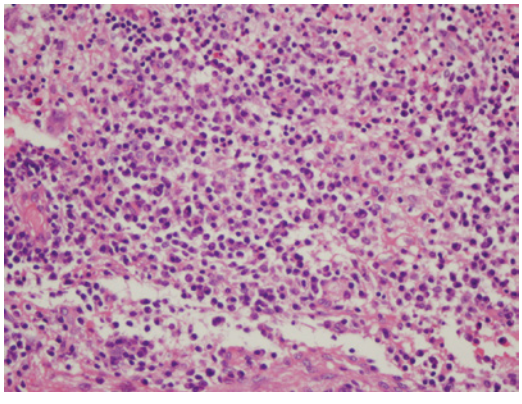


Figure 3C: The inflammation was rich in plasmocytes (HE x60).

cal findings.[7] More than 130 fungal species belonging to 70 diverse genera have been reported as causative agents in human and animal phaeohyphomycoses.[5,8,9]

Phaeohyphomycosis is a histopathological rather than a clinical entity.[10] This condition encompasses a group of disorders with superficial, cutaneous, subcutaneous, or systemic involvement.[7] Patients with phaeohyphomycosis are usually old, similar to our patient.[5,9] The majority of the cases of cutaneous or subcutaneous phaeohyphomycois have been reported in patients with systemic diseases or in those who were immunosupressed owing to Cushing's disease, kidney transplants, hematological malignancy, and AIDS. Healthy people are rarely affected.[11] Our patient did not have any disease that could cause immunosuppression.

The pathogen probably originates from an exogenous source by implantation, and occasionally fragments of plant tissue can be found in the lesions. However there was no plant tissue present in the histopathological examination of our case. The majority of cases of localized cutaneous/subcutaneous infections result from traumatic inoculation, such as cuts, abrasions or splinters, and there is little tendency for lymphatic or hematogenous dissemination.[12,13] Hence, lesions are mostly observed on the extremities. In our case, fungal elements may have been implanted in the subcutaneous tissue after accidental fall.

Lesions have been characterized as either localized eruptions or ulcerated, crusted plaques and papules, or as papulo-nodular, ulcerative or vegetative lesions, occurring singly or as multiple lesions on exposed parts of the body.[11] The overlying epidermis is not conspicuously thickened. There is no tendency towards lymphatic spread, and dissemination is exceedingly uncommon. Draining sinus formation may occur in immunocompromised or elderly patients as in our case.[2] At first, our patient presented with prominent left upper eyelid and mild right infraorbital edema. There could be two possible mechanisms for that edema: it resulted either from impaired or obstructed lymphatic transport leading to the pathological accumulation of protein-rich lymphatic fluid in the interstitium and it could be due to increased capilliary permeability occuring in infections or as a result of fungal agents or inflammatory damage to the capillary walls.[1,2]

The diagnosis of phaeohyphomycosis is based on the clinical presentation, fungal isolation from culture, and histopathological demonstration of tissue invasion by fungi. In tissue, fungi usually have a characteristic appearance of irregularly swollen or toruloid hyphae with yeast-like structures, with no grains or muriform cells. Serologic tests have not been used as diagnostic tools in phaeohyphomycosis.[6]

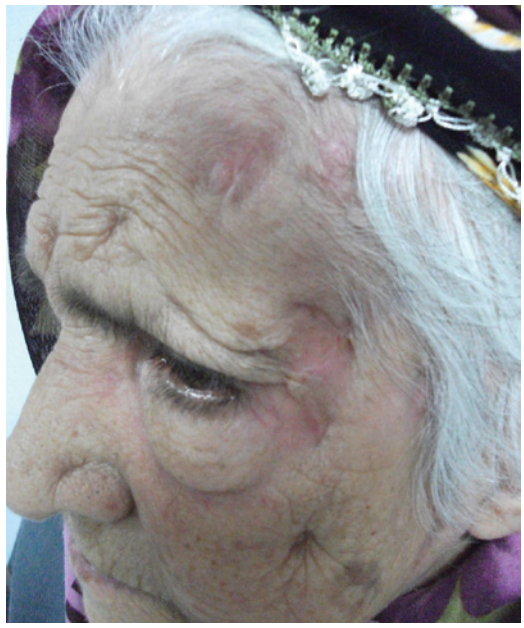


Figure 4: All the lesions were healed at the end of six months of treatment.

Surprisingly little is known regarding the pathogenetic mechanisms by which these fungi cause disease, particularly in immunocompetent individuals. One of the likely virulence factors is the presence of melanin in the cell wall, which is common to all dematiaceous fungi. There are putative mechanisms by which melanin may act as a virulence factor. It may present a protective advantage by scavenging free radicals and hypochlorite that are produced by phagocytic cells in their oxidative burst and that would normally kill most organisms. In addition, melanin may bind to hydrolytic enzymes, thereby preventing their action on the plasma membrane. These multiple functions may help explain the pathogenetic potential of some dematiaceous fungi, even in immunocompetent hosts.[1-3]

Fungal elements observed in phaeohyphomycotic tissue may be branched, thick-walled hyphae or hyphal fragments, subspherical cells/ oval yeast-like cells or short chains of oblong or elliptical cells. The hyphae and fungal cells in the tissue are generally brown but may also be depigmented.[11]

The treatment of subcutaneous phaeohyphomycosis is not standardized. There are no trials comparing different strategies for the treatment of infections caused by dematiaceus fungi. Surgical excision alone of subcutaneous cysts has been successful in a number of cases, but oral systemic therapy with an azole antifungal agent is frequently used in combination with surgery.[7] Itraconazole has been the preferred choice for antifungal systemic therapy as *in vitro* susceptibility of most strains of dematicaeus fungi to this drug are high. In our patient, successful response was received with a-six-month itraconazole treatment.

Although amphotericin B, fluconazole, ketoconazole, and 5-fluorocytosine have been proposed for the treatment of phaeohyphomycosis, these drugs were considered as an alternative therapy for patients with severe disease, poor response, or hepatotoxicity to itraconazole.[7]

In conclusion, subcutaneous phaeohyphomycosis is a rare disease, causing ulceration and draining nodules not only in immunosuppressed patient but also by inoculation due to trauma.

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