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Case report

Angioinvasive opportunistic filamentous mycoses in immunocompromised patients

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Abstract

Immunocompromised individuals are at greater risk for disseminated fungal infections. Immunocompromised individuals in the community have increased because of medical advances, thereby increasing the incidence and prevalence of opportunistic mycoses [1]. The following case series illustrates the importance of having a high clinical suspicion for skin manifestations concerning for deep fungal infections.

Keywords: fungal infections, wounds, immunosuppression

Case synopsis

Case 1: A 60-year-old man with a past medical history of intravenous drug use, HIV on HAART therapy (CD4 count of 186), cirrhosis secondary to hepatitis C virus, diabetes mellitus, hypertension, and end stage renal disease was admitted for consideration for liver transplantation. The patient subsequently became hypotensive, requiring vasopressors, and was transferred to the medical intensive care unit. A dermatology consultation was requested regarding an enlarging, painful ulcer on the patient's left wrist at the site of a previous intravenous line placed ten days prior to admission.

On physical examination, the patient had a tender, swollen left wrist with a 5 x 6 cm necrotic ulcer. The remainder of his skin exam was unremarkable.

Histopathology: A punch biopsy with PAS stain was performed at the edge of the ulcer. The biopsy demonstrated an ulcer with necrosis of the epidermis and subcutaneous tissue. There was diffuse infiltration of non-septate hyphal elements compatible with *Rhizopus* species (sp.) throughout the biopsy; the

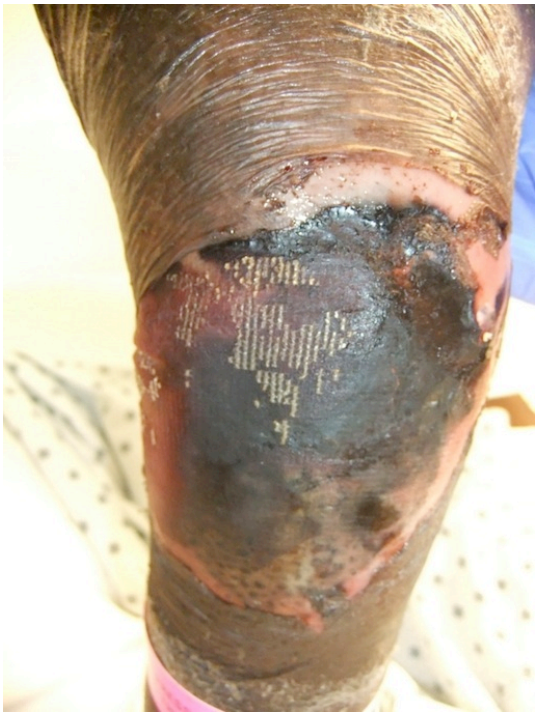
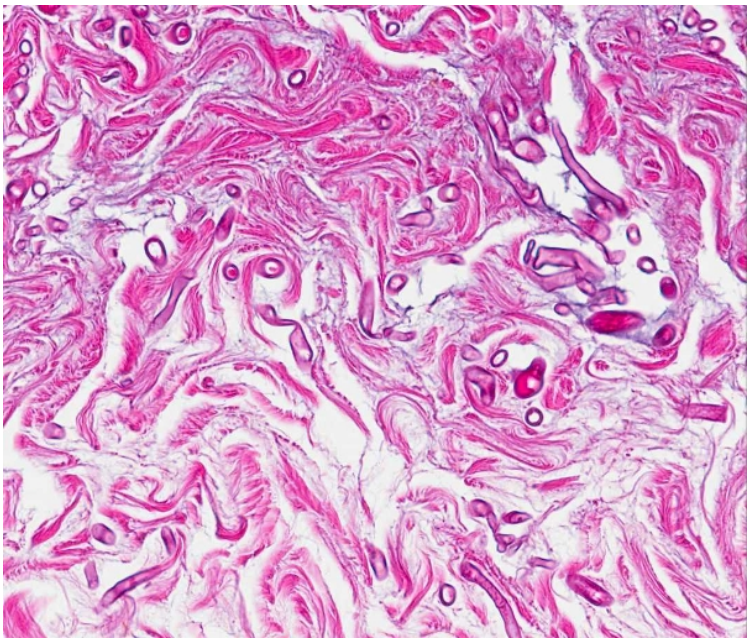


Figure 1. 5 x 6 cm superficial necrotic ulcer on Left wrist

organism also grew on tissue fungal culture. The subcutaneous tissue had fat necrosis with non-polarizing crystal-like clefts within adipocytes. PAS and GMS stains were positive for non-septate fungal hyphae.



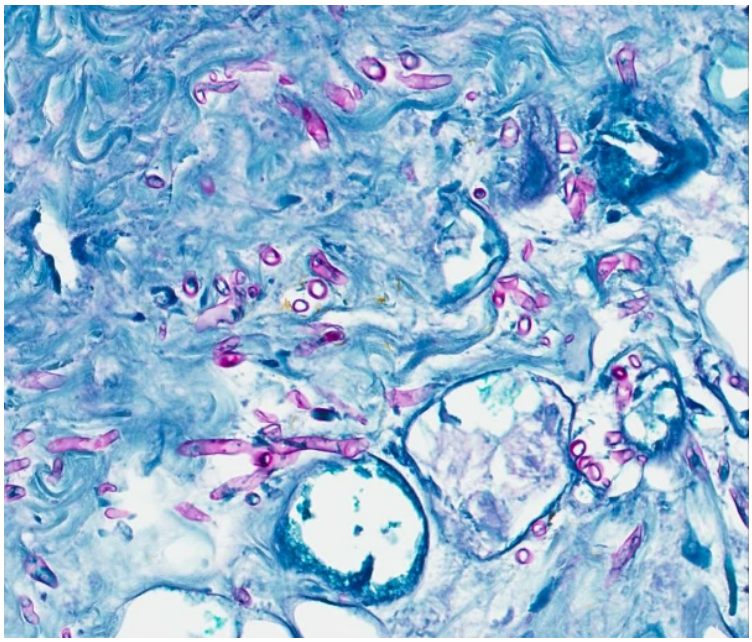


Figure 2. H&E (10x) image of punch biopsy of necrotic ulcer on left wrist. **Figure 3.** PAS stain (10x) highlighting the presence of non-septate fungal hyphal elements

The patient was treated with surgical debridement and intravenous amphotericin B. However, he expired from septic shock three days later.

Case 2: A 61-year-old man with past medical history of chronic lymphocytic leukemia, initially diagnosed in 2005 and in remission until 2011, presented with fatigue, shortness of breath, and easy bruising. The patient was found to have acute myeloid leukemia (AML) and he was admitted for induction chemotherapy. His hospital course was complicated by enterococcus bacteremia and *C. difficile* colitis.

On day 33 of induction chemotherapy, the patient noted an enlarging ulcer on his scalp that had been expanding for 3 weeks and began after he hit his head on a showerhead.

On physical examination, there was a 2 x 1.5 cm shallow ulcer with an erythematous border and hemorrhagic crust. The remainder of his skin exam was unremarkable. His laboratory data was significant for pancytopenia.

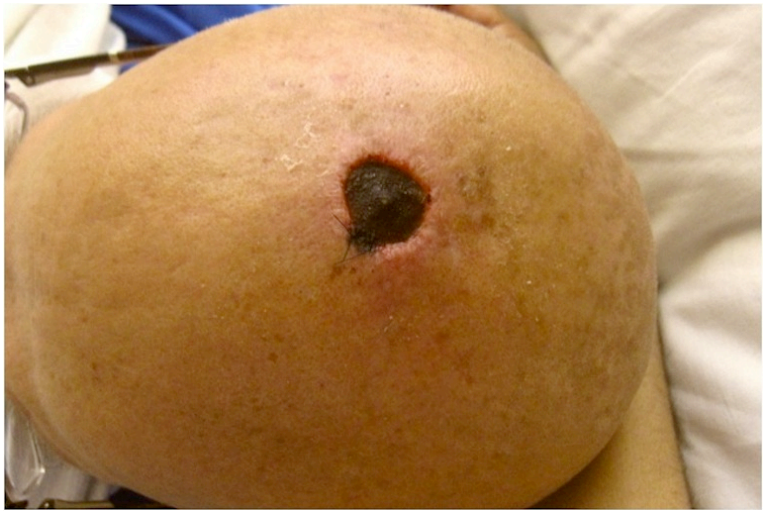


Figure 4. 2 x 1.5 cm ulceration with erythematous border and hemorrhagic crust on scalp

Histopathology: Punch biopsy from the scalp was performed. PAS staining showed branching septate hyphae invading the walls of dermal vessels. Tissue fungal culture grew *Aspergillus fumigatus*. The patient was treated with voriconazole 200 mg twice a day,and his ulcer stabilized.

Case 3: A 71-year-old man with a past medical history significant for Crohn disease and refractory AML currently undergoing chemotherapy, presented to his oncologist with an “ulcer” on his left thigh that he noticed after pulling weeds from his yard. On initial presentation, the ulcer was 8 x 7cm with central necrosis, hemorrhagic crust, and a violaceous border. Aside from a low-grade fever, the patient was otherwise stable with no other complaints. Because the ulcer continued to enlarge, the patient was admitted for further management and a dermatology consultation.

On physical examination, a 10 x 10 cm violaceous subcutaneous nodule with a 1.5 x 1.5 cm area of central eschar and yellow-brown borders was present lateral to the patient's left knee. Punch biopsy was performed to rule out a deep fungal infection. The patient was started on amphotericin B, vancomycin, and piperacillin-tazobactam.

Histopathology: Punch biopsy revealed numerous septate branching hyphae consistent with angioinvasive hyalohyphomycosis. The patient's fungal culture of his left lower extremity grew *Fusarium* sp. resistant to oral antifungal azole therapy. It was likely that he was directly inoculated while gardening. He was continued on amphotericin B for a total of 7 weeks of therapy with improvement of the left lower extremity nodule.

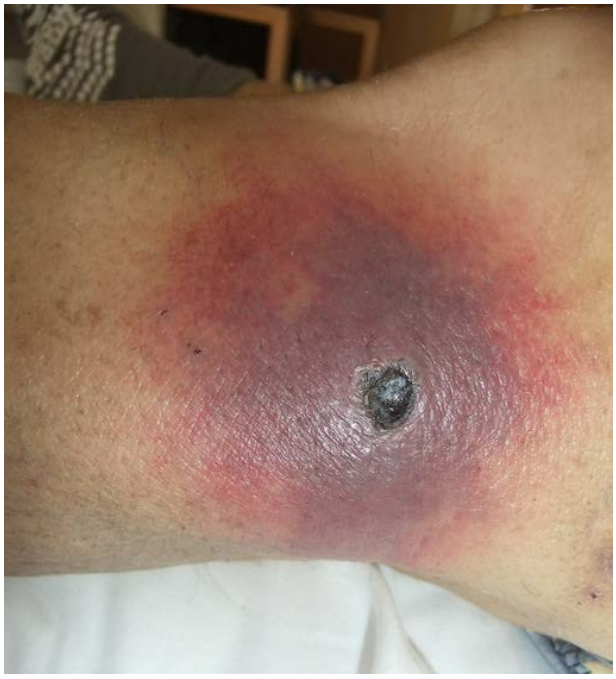


Figure 5. 10 x 10 cm violaceous subcutaneous nodule with a 1.5 x 1.5 cm area of central eschar and yellow-brown borders on left lower extremity

Discussion

Invasive opportunistic mycotic pathogens may cause life-threatening infections in immunocompromised hosts and can present with cutaneous manifestations. Clinicians should have a low threshold to biopsy non-healing wounds in immunocompromised patients; investigations for H&E and tissue culture should both be done.

The three cases presented here: cutaneous mucormycosis from *Rhizopus* sp. occurring at an old intravenous site, *Aspergillus fumigatus* from a showerhead, and *Fusarium* sp. via direct inoculation after gardening, are examples of cutaneous fungal infections in immunosuppressed patients. Skin findings are often the initial presentation or site of entry for systemic fungal infections and can be classified into several groups including superficial dermatophyte infections with little potential for dissemination; superficial candidiasis; opportunistic fungal skin infections with distinct potential for dissemination; fungal sinusitis with cutaneous extension; and cutaneous manifestations of disseminated fungal infections [2].

Several conditions predispose to fungal infections. These include hematological malignancy, neutropenia, diabetes mellitus, diabetic ketoacidosis, iron overload, trauma, prolonged corticosteroid use, intravenous drug use, and prolonged use of antifungal agents [3]. Additional risk factors include vascular and urinary catheters, chemotherapy, broad-spectrum antibiotics, and corticosteroid therapy, such as for graft-versus-host-disease [2]. The rate of these opportunistic infections in immunocompromised patients has been increasing. A retrospective cohort study on the epidemiology of mold infections in 5,589 patients who had hematopoietic stem cell transplantation at the Fred Hutchinson Cancer Research Center in Seattle, WA from 1985 through 1999 determined an increasing incidence of invasive infection caused by *Aspergillus* spp. and other molds after 1992. Overall 1-year survival rate for patients with *Aspergillus* spp., *Zygomycetes*, *Fusarium* spp., and *Scedosporium* sp. infections was approximately 20% [4].

Although two opportunistic yeast infections do exist as normal human flora, *candida albicans* and *malassezia furfur*, the majority of opportunistic mycoses are exogenous fungi occurring in nature as free-living saprophytes or plant parasites [1]. The opportunistic filamentous mycoses occur frequently in tropical and humid environments [5]. Hyalohyphomycosis describes infections caused by exogenous fungi composed of hyaline (non-dematiaceous) septate, branched hyphae without pigment that have light colored cell walls [4]. These fungi include include spp. of *Penicillium, Paecilomyces, Acremonium, Beauveria, Fusarium, Scopulariopsis, Scedosporium, Pseudoallescheria*, and many others [1]. Invasive infections from hyalohyphomycetes have been previously reported [6-8]. *Penicillium marneffei*, a dimorphic fungus, has become an important opportunistic pathogen in HIV-positive patients [9].

Of patients with *Fusarium* fungemia, 70% or more manifest with skin lesions [10-11] and lesions were significantly more common in immunocompromised compared to immunocompetent patients (72% vs. 52%; P = .03) [11]. Skin lesions vary and can occur as red or gray macules with central ulceration or necrosis, papules, pustules, subcutaneous nodules, vesicles, or bullae [10]. A retrospective study identified 44 cases of invasive fusariosis in patients with hematological malignancies at MD Anderson Cancer Center in Houston, TX and reported all-cause mortality at 12 weeks to be 66% [12]. Local debridement and antifungal agents with coverage against *Fusarium* (amphotericin B, itraconazole, voriconazole, and posaconazole) should be promptly initiated [11].

Infections of the *Aspergillus* genus are found ubiquitously in nature and can also cause infections in immunocompromised hosts. Common species known to infect humans are A. *fumigatus*, A. *flavus*, A. *niger*, A. t*erreus*, and A. *nidulans* [13]. Primary cutaneous aspergillosis only involves the skin and occurs at trauma and wound sites [14]. Primary cutaneous aspergillosis has been documented in patients with underlying hematologic or lymphoreticular malignancy and use of intravenous catheters, arm boards, or tape [13]. Secondary cutaneous aspergillosis is more common, occurs after inhalation of conidia fungal spores, and causes a lung infection that can disseminate to the skin. *Aspergillus* spp. infections been increasingly reported in HIV-infected individuals [15]. *Aspergillus* and *Fusarium* spp. infections in the skin can also invade blood vessels, resulting in thrombosis and tissue necrosis [16]. These pathogens may spread hematogenously and cause deep infections such as osteomyelitis [10]. Treatment of *Aspergillus* spp. infections involves immediate surgery and/or itraconazole or voriconazole [17].

Phaeohyphomycosis is a term for a heterogeneous group of exogenous mycotic organisms with dark colored cell walls that contain dematiaceous melanin pigmented yeastlike cells, pseudohyphae-like elements, hyphae, or any combination of these forms in tissue [18]. Over 100 species are reported, and common causes include *Exophiala jeanselmei* and *Wangiella dermatidis* [19]. In tissue these infections appear as short, irregular, pigmented hyphae [17]. Treatment involves surgical excision, although reports exist of treatment with antifungal agents such as itraconazole [20].

In the past, the term chromoblastomycosis, also called chromomycosis, was occasionally included with pheohyphomycosis. However, these infections are from dematiaceous fungi that develop in tissue as small clusters of cells known as muriform cells [17]. Common sources of infection are *Cladosporium carrionii,* and *Fonsecaea pedrosoi* [1]. Clinically these infections appear as papules, nodules, and verrucous plaques. Treatment options are surgical removal, cryotherapy, or medication therapy with agents such as terbinafine, itraconazole, 5-fluorocytosine, and amphotericin B [21-22].

Zygomycosis or aseptate molds, another group of opportunistic mycotic infections of the subphylum *Mucormycotina* (previously *Zygomycota*) of the *Glomeromycota* phylum of the kingdom Fungi, includes infections of the *Mucorales* order [23]. The majority of the invasive diseases are caused by the *Mucoraceae* family and the resulting disease is called mucormycosis. Organisms include spp. of the *Rhizopus, Lichtheimia* (formerly *Absidia*), *Mucor,* and *Rhizomucor* genera [3, 23]. These fungi are found in the environment in dust, soil, spoiled food, and decaying matter. Infection occurs through direct inoculation, ingestion, or inhalation of spores. Risk factors include diabetes mellitus, hematological malignancies, and solid organ transplantation [24]. Mucormycosis is rare in patients with HIV/AIDS and often occurs in conjunction with intravenous drug use [25], as seen in case 1. A population based surveillance study in the San Francisco Bay area from 1992 to 1993 determined that the annual incidence of mucormycosis was 1.7 cases per 1 million individuals, with an estimated 500 new cases per year [26]. Roden et al. studied 929 cases of mucormycosis from 1885 to 2004 and observed an increasing proportion of immunocompromised patients with mucormycosis [27].

Mucormycosis is classified into rhinocerebral, pulmonary, disseminated, gastrointestinal, and cutaneous forms [24]. Invasive zygomycosis have been previously reported in patients with leukemia or who are allogeneic bone marrow transplant recipients [28-30]. Cutaneous mucormycosis is the third most common clinical form of the disease, after pulmonary and rhinocerebral types [31]. Cutaneous mucormycosis presents as necrosis and black eschar related to angioinvasion with surrounding cellulitis [3]. Primary cutaneous zygomycosis is characterized by necrotic lesions inoculated by trauma, whereas secondary cutaneous zygomycosis occurs as a complication of rhinocerebral or disseminated infection [32]. In the study by Roden et al. [27] cutaneous involvement was the presenting pattern in 176 (19%) of 929 patients, with deep extension to bone, tendon, or muscle in 42 (24%) of 176 cases. Hematogenous dissemination from skin to other organs occurred in 35 (20%) of 176 cases and hematogenous dissemination from other organs to skin occurred in 6 (3%) of 176 cases. Cutaneous zygomycosis from adhesive tape use in four patients with hematological malignancies has been previously reported [33], as well as cutaneous mucormycosis with visceral dissemination in an immunocompromised patient [34]. Treatment of cutaneous zygomycosis involves surgical debridement and antifungal agents such as liposomal amphotericin B. Posaconazole may be used as salvage treatment, as continuation of treatment after initial administration of amphotericin B, or as combination therapy [24].

The diagnosis of opportunistic fungal skin infections is based on clinical suspicion, accompanied by blood cultures, tissue fungal cultures, and skin biopsy results. Treatment consists of surgical debridement and immediate initiation of a broad-spectrum antifungal agent such as liposomal amphotericin B. Other antifungal agents are options, but the efficacy of these agents must be considered. For instance, voriconazole has minimal activity against Zygomycetes [29]. Underlying neutropenia may also be corrected with granulocyte colony stimulating factor [30].

Conclusion

This case series depicts the urgency and importance of having a high clinical suspicion for deep fungal mycoses in immunocompromised patients presenting with skin findings. Prompt diagnosis and expedited treatment prevents adverse outcomes such as multi-organ failure and fatality.

References

1. Ajello L. Hyalohyphomycosis and Phaeohyphomycosis: two global disease entities of public health importance. Eur J Epidemiol. 1986 Dec;2(4):243-51. [PMID: 3542552].
2. Mays SR, Bogle MA, Bodey GP. Cutaneous fungal infections in the oncology patient: recognition and management. Am J Clin Dermatol 2006;7(1):31-43. [PMID: 16489841].
3. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of Mucormycosis. Clin Infect Dis. 2012 Feb;54 Suppl 1:S23-34. [PMID: 22247442].
4. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and Outcome of Mould Infections in Hematopoietic Stem Cell Transplant Recipients. Clin Infect Dis. 2002;34(7):909-917. [PMID: 11880955].
5. Perusquía-Ortiz AM, Vázquez-González D, Bonifaz A. Opportunistic filamentous mycoses: aspergillosis, mucormycosis, phaeohyphomycosis and hyalohyphomycosis. J Dtsch Dermatol Ges. 2012 Sep;10(9):611-21. [PMID: 22925358].
6. Itin PH, Frei R, Lautenschlager S, Buechner SA, Surber C, Gratwohl A, Widmer AF. Cutaneous manifestations of Paecilomyces lilacinus infection induced by a contaminated skin lotion in patients who are severely immunosuppressed. J Am Acad Dermatol. 1998 Sep;39(3):401-9. [PMID: 9738773].
7. Rimawi RH, Carter Y, Ware T, Christie J, Siraj D. Use of voriconazole for the treatment of Paecilomyces lilacinus cutaneous infections: case presentation and review of published literature. Mycopathologia. 2013 Apr;175(3-4):345-9. [PMID: 23334554].
8. Erbagci Z1, Tuncel AA, Erkilic S, Zer Y. Successful treatment of antifungal- and cryotherapy-resistant subcutaneous hyalohyphomycosis in an immunocompetent case with topical 5% imiquimod cream. Mycopathologia. 2005 Jun;159(4):521-6. [PMID: 15983738].
9. Ramos-e-Silva M, Lima CM, Schechtman RC, Trope BM, Carneiro S. Systemic mycoses in immunodepressed patients (AIDS). Clin Dermatol. 2012 Nov-Dec;30(6):616-27. [PMID: 23068149].
10. Bodey GP, Boktour M, Mays S, Duvic M, Kontoylannis D, Hachem R, Raad I. Skin lesions associated with Fusarium infection. J Am Acad Dermatol. 2002 Nov;47(5):659-66. [PMID: 12399756].
11. Nucci M, Anaissie E. Cutaneous infection by Fusarium species in healthy and immunocompromised hosts: implications for diagnosis and management. Clin Infect Dis. 2002 Oct 15;35(8):909-20. [PMID: 12355377].
12. Campo M, Lewis RE, Kontoyiannis DP. Invasive fusariosis in patients with hematologic malignancies at a cancer center: 1998-2009. Journal of Infection. 2010 May. 60(5): 331-337. [PMID: 20138081].
13. Isaac M. Cutaneous Aspergillosus. Dermatol Clin. 1996 Jan;14(1):137-40. [PMID: 8821166].
14. Khardori N, Hayat S, Rolston K, Bodey GP. Cutaneous Rhizopus and Aspergillus infections in five patients with cancer. Arch Dermatol. 1989 Jul;125(7):952-6. [PMID: 2662911].
15. Venkatesan P, Perfect JR, Myers SA. Evaluation and management of fungal infections in immunocompromised patients. Dermatol Ther. 2005 Jan-Feb;18(1):44-57. [PMID: 15842612].
16. Fan Y, Willems L, Leboeuf C, Li W, Lacroix C, Robin M, Socie G, Ribaud P, Verneuil L, Janin A. Skin microvascular thrombosis in Fusarium infection in two early biopsied cases. Case Rep Dermatol. 2010 May 7;2(2):76-81. [PMID: 21113281].
17. Hay RJ. Fungal Infections. Clinics in Dermatology. 2006; 24, 201-212. [PMID: 16714201].
18. McGinnis MR. Chromoblastomycosis and phaeo- hyphomycosis: new concepts, diagnosis, and mycology. J Am Acad Dermatol. 1983;8:1-16. [PMID: 6826791].
19. Matsumoto T, Ajello L, Matsuda T, Szaniszlo PJ, Walsh TJ. Developments in hyalohyphomycosis and phaeohyphomycosis. J Med Vet Mycol 32(suppl 1):329, 1994. [PMID: 7722796].
20. Chuan MT, Wu MC. Subcutaneous phaeohyphomycosis caused by Exophiala jeanselmei successful treatment with itraconazole. Int J Dermatol. 1995;34: 563-566. [PMID: 7591439].
21. Rivitti EA, Aoki V. Deep fungal infections in tropical countries. Clinics in dermatology. 1999;17:171-190. [PMID: 10330600].
22. Lupi O, Tyring SK, McGinnis MR. Tropical dermatology: fungal tropical diseases. J Am Acad Dermatol. 2005;53:931-51. [PMID: 16310053].
23. Morace G, Borghi E. Invasive mold infections: virulence and pathogenesis of Mucorales. International Journal of Microbiology. 2012;2012:349278. Epub 2011 Nov 1. [PMID: 22121366].
24. Skiada A1, Rigopoulos D, Larios G, Petrikkos G, Katsambas A. Global epidemiology of cutaneous zygomycosis. Clin Dermatol. 2012 Nov-Dec;30(6):628-32. [PMID: 23068150].
25. Sanchez MR, Ponge-Wilson I, Moy JA, Rosenthal S. Zygomycosis and HIV infection. J Am Acad Dermatol. 1994 May;30(5 Pt 2):904-8. [PMID: 8169272].

26. Rees JR, Pinner RW, Hajjeh RA, Brandt ME, Reingold AL. The epidemiological features of invasive mycotic infections in the San Francisco Bay area, 1992–1993: results of population-based laboratory active surveillance. Clin Infect Dis 1998;27:1138-47. [PMID: 9827260].
27. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005; 41: 634–53. [PMID: 16080086].
28. Nenoff P, Kellermann S, Schober R, Nenning H, Kubel M, Winkier J, Haustein UF. Rhinocerebral zygomycosis following bone marrow transplantation in chronic myelogenous leukaemia. Report of a case and review of the literature. Mycoses. 1998 Nov;41(9-10):365-72. [PMID: 9916458].
29. Kontoyiannis DP, Lionakis MS, Lewis RE, Chamilos G, Healy M, Perego C, Safdar A, Kantarjian H, Champlin R, Walsh TJ, Raad II. Zygomycosis in a tertiary-care cancer center in the era of aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis. 2005; 191: 1350–60. [PMID: 15776383].
30. Shofield C, Stern A, Jevtic A. Disseminated zygomycosis due to Mycocladus corymbifera with cutaneous and cerebral involvement. Australas J Dermatol. 2013 Feb;54(1):e8-11. [PMID: 23373895].
31. Skiada A, Petrikkos G. Cutaneous mucormycosis. Skinmed. 2013 May-Jun;11(3):155-9. [PMID: 23930354].
32. Bonifaz A, Vázquez-González D, Tirado-Sánchez A, Ponce-Olivera RM. Cutaneous zygomycosis. Clin Dermatol. 2012 Jul-Aug;30(4):413-9. [PMID: 22682190].
33. Lalayanni C, Baliakas P, Xochelli A, Apostolou C, Arabatzis M, Velegraki A, Anagnostopoulos A. Outbreak of cutaneous zygomycosis associated with the use of adhesive tape in haematology patients. J Hosp Infect. 2012 Jul;81(3):213-5. [PMID: 22633275].
34. Wirth F, Perry R, Eskenazi A, Schwalbe R, Kao G. Cutaneous mucormycosis with subsequent visceral dissemination in a child with neutropenia: a case report and review of the pediatric literature. J Am Acad Dermatol. 1997 Feb;36(2 Pt 2):336-41. [PMID: 9039214].