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Case Report Open Access

Fusariosis: Five Cases in Immunodepressed Patients

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Abstract

Fusariosis can cause disseminated infection among individuals with severely impaired immunity, representing the second leading cause of invasive fungal infection with poor prognosis and often leading to death in those individuals. The authors describe five cases of immune compromised/ neutropenic patients hospitalized in the Clementino Fraga Filho University hospital hematology ward with this fungal infection. It is of utmost importance for Dermatologists and Oncologists to know about this association.

Keywords: Fusariosis; *Fusarium*; Immunodepression

Introduction

Fungal infections are a major complication in immune compromised individuals and are associated with high mortality. *Fusarium* species are acknowledged causes of localized infections in immunocompetent individuals, but among those with severely compromised immunity, they are often widespread and represent the second major cause of invasive fungal infection, after Aspergillosis, with a rather poor prognosis, especially if it is not possible to progress to immune reconstitution. The most frequent aspect of widespread fusariosis is the development of skin lesions of varying morphology, which areoften the only source of diagnostic material. The recognition of this infection's clinicopathological patterns is therefore important, allowing early diagnosis and intervention.

Materials and Methods

Five cases of immunosuppressed/neutropenic patients hospitalized in the Hematology ward of the Clementino Fraga Filho University Hospital are reported. Those patients evolved with varied dermatologic manifestations of disseminated fusariosis, and in some cases with a fatal outcome. We review the literature on this increasingly frequent condition with extremely reserved prognosis [1].

Case 1

A 65-year-old Black woman was diagnosed with hypoplastic myelodysplasia and hospitalized for epigastric pain to be clarified, fever and general health decay. Laboratory tests revealed anemia and global white cell count of 200 cells, with 20 neutrophils/mm^3.

The patient presented macules, papules and erythematous nodules on the legs (Figure 1), which, over the days, increased in size and became more infiltrated with purplish-brown color, topped by some blisters and central necrotic crust (Figure 2); with a halo of peripheral desquamation in some lesions.

Seven days before the onset of skin lesions, she underwent scraping in the region between the toes, which is a routine examination in the hematology service for neutropenic patients. *Fusarium sp*. grew in culture and prophylactic posaconazole was administered since then.

In the fungal culture made from a skin lesion biopsy there was also growth of *Fusarium sp*. The patient was treated with voriconazole and cefepime without improvement of the skin condition, anemia and leukopenia. She died a little over a month after hospitalization.

Case 2

A 21-year-old White HIV+ man, under treatment for acute

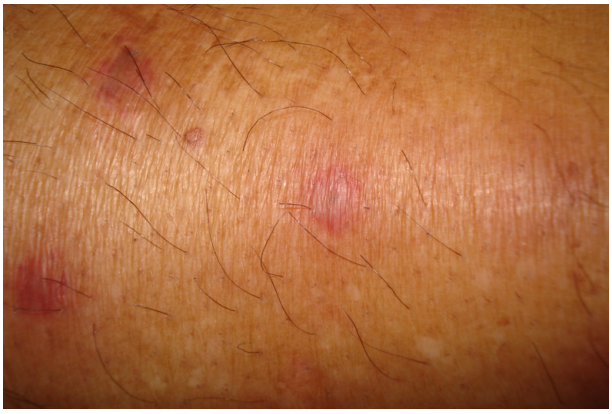

Figure 1: Case 1 – Initial erythematous skin lesions.

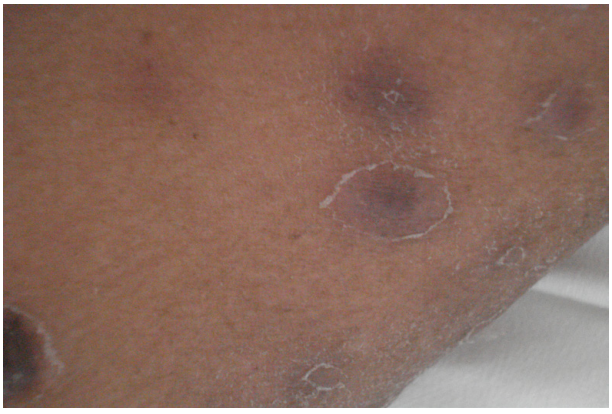

Figure 2: Case 1 – Later skin lesions became violaceous.

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myelocytic leukemia, subtype M1, relapsed after chemotherapy. He was hospitalized with high fever, headache and myalgia. On the 17th day of hospitalization, with laboratory tests showing pancytopenia with global white cell count of 90, with 21 neutrophils/mm^3, erythematous papules appeared on the upper right arm, back and left leg (Figure 3). One of the lesions featured a violet center. The direct mycological examination of the biopsy fragment of the skin lesion presented septated hyphae and, on histopathologic examination by HE staining, structures compatible with hyalohyphomycosis (fusariosis or aspergillosis type). There was no growth in culture. During hospitalization, the patient evolved with altered level of consciousness and loss of bilateral visual acuity, probably by retinal vein thrombosis due to fusariosis. He was treated with amphotericin B for three days (suspended by the increase of nitrogenous compounds) and voriconazole for 24 days. Upon his clinical stability, the patient was discharged on the 40th day of hospitalization with oral prescription of voriconazole, with hematology, infectious diseases and ophthalmology outpatient care.

Case 3

A 37-year-old White male with chronic myeloid leukemia, submitted to an allogenic bone marrow transplant 10 years before, was hospitalized for severe pancytopenia compatible with blast crisis, needing a transfusion. About 20 days after admission, a nodular lesion in the anterior region of the left arm appeared, with subsequent emergence of new and painful erythematous subcutaneous nodules on the posterior left forearm, right shoulder and gangrenosum-like ecthyma lesion on the anterior side of the left leg (Figure 4). Concurrent to the skin lesions, the patient presented fever, pulmonary nodules and left sphenoid sinusitis, associated with severe neutropenia. Hypothetical diagnosis of disseminated fusariosis was considered, corroborated by the presence of hyalo-hyphomycetes in the lesion histopathology of the left forearm. Culture for fungus was negative. Regimen of amphotericin B and voriconazole led to the improvement of skin lesions and general condition of the patient, who was discharged after 20 days, with subsequent outpatient care.

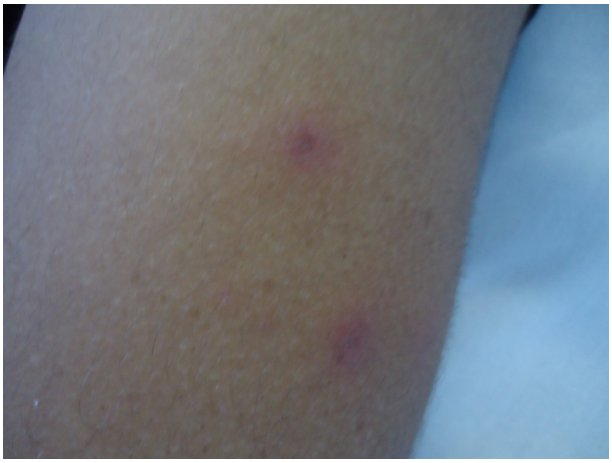

Figure 3: Case 2 – Erythematous skin lesions.

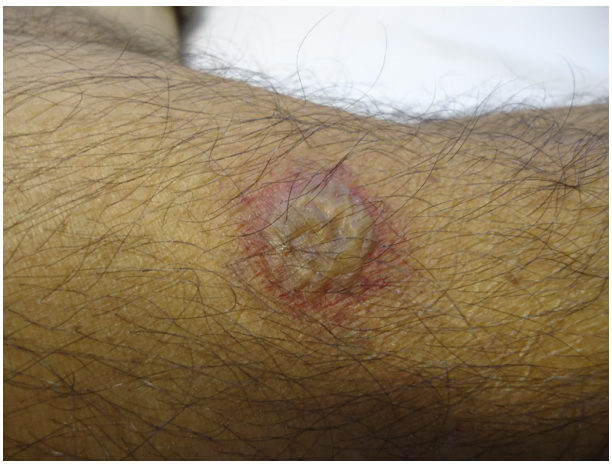

Figure 4: Case 3 – Gangrenosum-like ecthyma lesion.

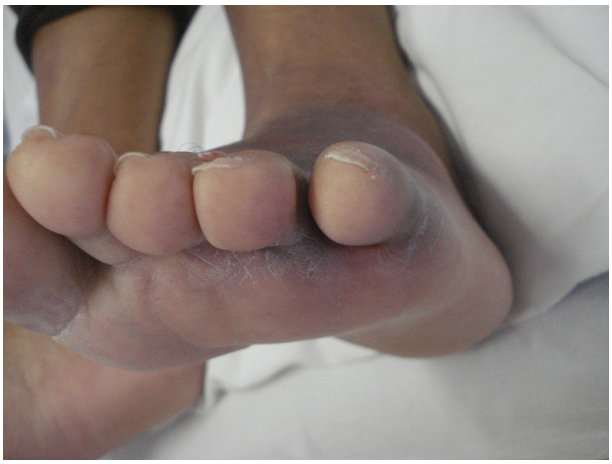

Figure 5: Case 4 – Nodular, erythematous lesions with a necrotic center.

Case 4

A 66 year-old White male, with acute myeloid leukemia subtype M4, underwent chemotherapy. The patient developed bone marrow aplasia after the 4th day of induction and febrile neutropenia on the 9th day. Samples were collected and treatment with cefepime started. On the same day, the patient developed intertrigo in the region between the 4th and 5th left toes (Figure 5). The mycological direct examination of the skin scraping of the affected area showed irregular septated hyaline hyphae. No fungus grew in culture; there were reports of inadvertent use of topical miconazole by the patient. We decided to start prophylactic voriconazole. The patient evolved without fever, but there was subsequent fever recurrence after the seventh day of cefepime use, when nodular, erythematous lesions with a necrotic core appeared in the right hypochondrium, left tibial region, right forearm, dorsum, and left temporal cervical region. New samples from the skin lesions were collected, with adjustment of voriconazole dose to the therapeutic regimen. By the Grocott and PAS methods, the biopsies of skin lesions evidenced numerous tubular septated fungal structures, at an acute angle within the interstitium vessels and the area of loss of the epithelial lining. The patient evolved to a stable cutaneous picture with no new lesions and no enlargement of old lesions and was discharged after 19 days.

Case 5

A 54 year-old White man was admitted for investigation of exuberant bleeding after tooth extraction, gingival bleeding and fever. The diagnosis was acute myeloid leukemia of the M3 subtype. A few days after admission, the patient presented febrile neutropenia with negative blood cultures; cefepime was prescribed. Approximately two months after admission, he presented eroded lesions, with greenish

crusts in the scrotum. With the suspicion of herpes simplex infection, treatment was initiated with systemic acyclovir without improvement. The patient then underwent skin lesion biopsy, which showed in histopathology epidermis and dermis, including vascular structures, diffusely populated by numerous septated hyphae, consistent with cutaneous fusariosis. He was treated with posaconazole, without improvement, and died in less than three months after hospitalization.

Discussion

Fusariosis is a non-contagious form of hyalohyphomycosis by opportunistic filamentous fungus of the *Fusarium* species, whose habitat is the soil, plants and water. Hyalohyphomycosis is a term that describes infections caused by hyaline hyphae [2].The wide distribution of the fungus is due to its ability to grow in various forms of substrates and its effective dispersion mechanism [3]. Anaissie et al. demonstrated the presence of the fungus in hospital air and water systems [4]. Thirteen pathogenic species for humans were recognized. The most commonly isolated are *F. solani, F. oxysporum, F. verticillioides* and *F. proliferatum*, with skin and blood being the most affected tissues [5].

The fungal portal of entry is uncertain, skin being a potential source of invasion. Lesions in the hallux are suggested by many authors. *Fusarium* has also been isolated from upper and lower airways, which may indicate the entry point [5].

Disseminated disease may be associated with various comorbidities, such as neutropenia, lymphopenia, extensive burns, diabetes mellitus, neoplasia, AIDS, bone marrow and solid organ transplants and immunosuppression of various etiologies. Pancytopenia and bone marrow aplasia greatly increase the risk of infection, whilst the role of steroids as a risk factor is controversial [3-6].

The importance of immunity in the fusariosis pathogenesis has been proven *in vitro* and *in vivo*. There is a unique susceptibility of severely immunocompromised individuals to disseminated fusariosis and a strong relationship between immune reconstitution and prognosis. Innate immunity plays an important role in the protection against infection. Macrophages and neutrophils damage the fusarial hyphae by means of G-CSF, GM-CSF and IL-15 [3]. Legrand et al., on an animal scale, compared the response to inoculation with *F. solani conidia* in neutropenic and non-neutropenic mice. The infection in animals with normal neutrophils count is characterized by necrotizing abscesses with hyphae, bleeding and infiltration of neutrophils and macrophages, whilst neutropenic animals did not present exuberant cellular inflammatory response even with a much greater fungal load [7]. The importance of the response mediated by T-cells was also demonstrated [3]. Fusariosis has several virulence factors, including the ability to produce mycotoxins, including tricotecenes, which suppress humoral and cellular immunity and can cause tissue invasion [3].

The fungus can trigger various infectious conditions of varying severity, including: keratitis (more common in contact lens wearers), peritonitis (reported in patients undergoing peritoneal dialysis), sinusitis, pneumonia, thrombophlebitis, fungemia, endophthalmitis, septic arthritis, osteomyelitis and skin infections. In immunocompetent patients the most commonly described pictures are keratitis and onychomycosis [3].

Skin clinical manifestations

The clinical signs of mycosis can be divided into three patterns [5].

Superficial form: It is found in healthy and immunocompetent patients, with no previous history of skin damage. It can be manifested as intertrigo between the toes, pain, erosion and maceration, more common in patients with hyperhidrosis and who walk barefooted; and paronychia, revealing pustules, erythema and desquamation, in which the labor activity that involves handling water proves to be a risk factor. Onychomycosis may be present in both forms and in such manifestation, the most commonly isolated species is *Fusarium oxysporum* [3].

Histological examination shows hyperkeratosis, parakeratosis, mild spongiosis and acanthosis. Some eosinophils are eventually seen and, in the stratum corneum, many hyphae and spores are found.

Exogenous unilocular – traumatic origin: In this form, patients are often in a good general condition. The mycosis develops a few weeks after trauma or foreign body penetration in the skin. A hardened erythematous halo of approximately 4 cm in diameter develops around the wound. There may be abscess formation and straw-colored exudate. Histopathologic examination shows fibrosis with granulomatous inflammatory response; elongated and septated hyphae can be seen.

Endogenous multilocular form – metastatic invasion of disseminated fusariosis: More common in individuals with the previously mentioned comorbidities, it is related to neutropenia and defective T cell immunity. The lesions are polymorphic, in general, macules, papules and nodules that evolve with peripheral erythematous halo and central necrosis. Gangrenosum-like ecthyma and target shapes are common; blisters can arise. On histopathologic examination, hyphae predominate in capillaries and small vessels, infiltrating the surrounding tissues, causing edema, focal necrosis and epidermolysis; sometimes hyphae are found without inflammatory response [3-6].

Diagnosis

The diagnosis is confirmed by the clinical epidemiology, direct mycological examination and tissue culture, and sometimes blood culture. In some cases the histopathological examination is of great value. *Fusarium sp*. are usually fast growing on various culture media, provided it has no cycloheximide [8]. A cottony aerial mycelium may be present or not and color varies depending on the species (Figure 6). *Fusarium* typically produces both macro- and microconidia (Figure 7). Macroconidia are hyaline, number of cells (form 2 to several) and format (fusiform to sickle shaped) are varied. Microconidia are 1- to 2-celled, hyaline, fusiform, pyriform to ovoid, curved or straight. Chlamydoconidia may be present or not.

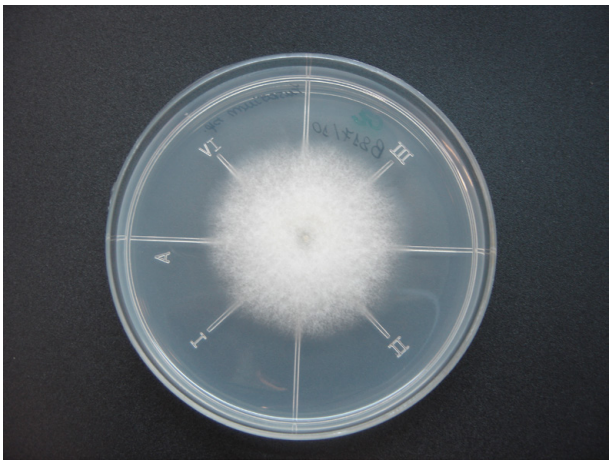

Figure 6: Culture – 7 days in Agar Czapek.

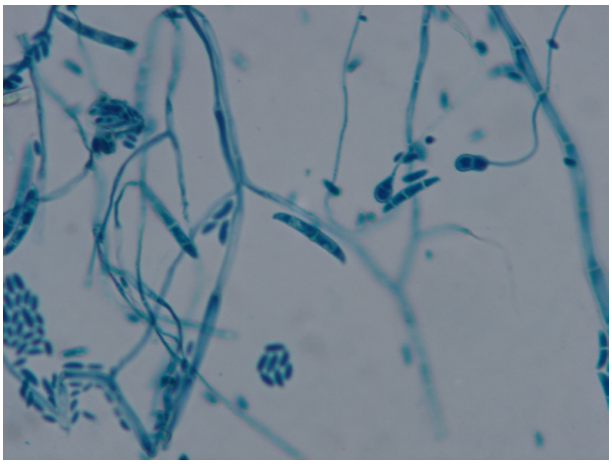

Figure 7: Microculture – 7 days in agar potato-dextrose (cotton blue, 400X).

Treatment of Disseminated Forms

Fusarium sp. has an innate resistance to multiple antifungals, which makes their treatment extremely challenging, especially in patients with myelosuppression. The localized forms benefit from surgical debridement associated with oral antifungal [9]. In the disseminated forms, it has a poor prognosis and mortality can reach 70% of cases, despite treatment [10].

Mortality is higher in patients with severe immunosuppression and prolonged neutropenia, the latter being the most important prognostic factor [11].

Despite conflicting studies on *in vitro* susceptibility and failure in practice, amphotericin B remains the preferred treatment in disseminated fusariosis, but there is no established standard therapy [9].

Other drugs have proven effective, such as voriconazole and posaconazole. Reported cases demonstrate the effectiveness of voriconazole with responses that vary from 45 to 63%, while the mortality rate with other antifungal agents is 70% [9]. Voriconazole has the advantage of being less nephrotoxic than amphotericin B [12]. Although it is a well-tolerated drug both orally as intravenously, about 50% of users experience some side effects. Posaconazole has also been effective, but there are no comparative studies with voriconazole [10]. Among patients with hematologic malignancies and history of bone marrow transplantation, the healing rate of 32% was reached with amphotericin B deoxycholate, 46% with amphotericin B lipid complex, 45.5 to 47% with voriconazole, and 50% with posaconazole [13-17].

Liu et al. [18] advocate the combined use of medications for the treatment of infections associated with immunosuppression, based on case report and literature review. They demonstrate that 70% of treatments with two drugs were successful and 29% of all cases responded to therapy with or without neutrophilic recovery. The most used treatment regimens in these cases were liposomal amphotericin B with voriconazole, followed with amphotericin B deoxycholate with voriconazole and liposomal amphotericin B with terbinafine.

For neutropenic patients, neutrophils colonies growth factor or neutrophils transfusion must be prescribed. Patients with normal neutrophils count benefit from the administration of neutrophils colonies growth factor and interferon gamma. The removal of central venous catheter is mandatory in case of isolated fungemia [3].

Conclusion

Fusarium sp is the second most common pathogenic filamentous fungus in cases of disseminated infections, especially in patients with hematologic malignancies [8]. Based on the observation of our cases and on literature review, we conclude that skin lesions are common and early manifestations of fusariosis, in contrast to opportunistic infections by other fungi, such as *Candida sp.* and *Aspergillus sp.*, playing a sentinel role in the early diagnosis and reinforcing the need to recognize the most frequent lesions in the disease (in target, gangrenosum-like ecthyma shape). The skin is the primary site of the mycosis' severe and disseminated infection, and also is the most susceptible material and sometimes the only one that allows the pathogen's isolation. The clinical manifestations are diverse and may also vary according to the host's immunity. The mortality from the infection is high, regardless of the condition being localized or disseminated, depending mostly on the neutrophils count for prognosis [1]. Nucci et al., in an analysis of 84 patients with hematologic malignancies and fusariosis, revealed a 50% and 21% mortality rate, 30 and 90 days after the diagnosis, respectively [13]. The prognosis of the disease in immunocompromised patients is directly related to the immunology recovery. Almost 100% of patients die if neutropenia persists.

Prophylactic measures to avoid contact with patients at risk can and should be taken. These individuals can be accommodated in rooms with HEPA filter and positive pressure and should be kept away from sinks and showers of shared use. The time and intensity of immunosuppression and neutropenia should be reduced as much as possible and skin lesions (in particular onychomycosis, paronychia and intertrigo) that act as the gateway for systemic involvement should be diagnosed and treated prior to the beginning of the antineoplastic therapy [3].

Localized forms of infection benefit from surgical debridement and topical treatment, while disseminated forms require systemic therapy and immunotherapy, when possible. Systemic treatment can be carried out with high doses of amphotericin B to *F. solani* and *F. verticillioides*, and high doses of amphotericin B or voriconazole for other *Fusarium* species. Sensitivity tests should be performed when possible. There are anecdotal reports of combined treatments with caspofungin and amphotericin B, amphotericin B and voriconazole, amphotericin B and terbinafine, voriconazole and terbinafine.

In our case studies, we can see an improvement of opportunistic infection through the administration of amphotericin B or voriconazole, associated with increased numbers of neutrophils. Regarding the lesions'appearance, except for the last case (greenish crusts on an exulcerated base), we find similarities with the descriptions in the literature, manifesting as nodules and erythematous papules with central necrosis and, in some cases, blistering. The lesions were always surrounded by an erythematous halo. In its evolution, the typical erythema gave rise to erythematous-violet coloration. We also spot a gangrenosum-like ecthyma lesion.

References

1. Nucci M, Anaissie E (2002) Cutaneous infection by Fusarium species in healthy and immunocompromised hosts: implications for diagnosis and management. Clin Infect Dis 35: 909-920.
2. Ajello L (1986) Hyalohyphomycosis and phaeohyphomycosis: two global disease entities of public health importance. Eur J Epidemiol 2: 243-251.
3. Nucci M, Anaissie E (2007) Fusarium infections in immunocompromised patients. Clin Microbiol Rev 20: 695-704.
4. Anaissie EJ, Kuchar RT, Rex JH, Francesconi A, Kasai M, et al. (2001) Fusariosis associated with pathogenic fusarium species colonization of a

hospital water system: a new paradigm for the epidemiology of opportunistic mold infections. Clin Infect Dis 33: 1871-1878.

5. Vennewald I, Wollina U (2005) Cutaneous infections due to opportunistic molds: uncommon presentations. Clin Dermatol 23: 565-571.
6. De Pinho DB, Fernandes LL, Carvalho Barreiros Mda G, Quintella LP, Sodré CT, et al. (2012) Disseminated fusariosis in a bone marrow transplant patient. J Clin Aesthet Dermatol 5: 40- 42.
7. Legrand C, Anaissie E, Hashem R, Nelson P, Bodey GP, et al. (1991) Experimental fusarial hyalohyphomycosis in a murine model. J Infect Dis 164: 944-948.
8. Dignani MC, Anaissie E (2004) Human fusariosis. Clin Microbiol Infect 10 Suppl 1: 67-75.
9. Stanzani M, Tumietto F, Vianelli N, Baccarani M (2007) Update on the treatment of disseminated fusariosis: Focus on voriconazole. Ther Clin Risk Manag 3: 1165-1173.
10. Banerji JS, Singh J C (2011) Cutaneous Fusarium infection in a renal transplant recipient: a case report. J Med Case Rep 5: 205.
11. Nucci M, Marr KA, Queiroz-Telles F, Martins CA, Trabasso P, et al. (2004) Fusarium infection in hematopoietic stem cell transplant recipients. Clin Infect Dis 38: 1237-1242.
12. Bigley VH, Duarte RF, Gosling RD, Kibbler CC, Seaton S, et al. (2004) Fusarium dimerum infection in a stem cell transplant recipient treated successfully with voriconazole. Bone Marrow Transplant 34: 815-817.
13. Nucci M, Anaissie EJ, Queiroz-Telles F, Martins CA, Trabasso P, et al. (2003) Outcome predictors of 84 patients with hematologic malignancies and Fusarium infection. Cancer 98: 315-319.
14. Perfect JR (2005) Treatment of non-Aspergillus moulds in immunocompromised patients, with amphotericin B lipid complex. Clin Infect Dis 40 Suppl 6: S401-408.
15. Lortholary O, Obenga G, Biswas P, Caillot D, Chachaty E, et al. (2010) International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. Antimicrob Agents Chemother 54: 4446-4450.
16. Perfect JR, Marr KA, Walsh TJ, Greenberg RN, DuPont B, et al. (2003) Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 36: 1122-1131.
17. Raad II, Hachem RY, Herbrecht R, Graybill JR, Hare R, et al. (2006) Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. Clin Infect Dis 42: 1398-1403.
18. Liu JY, Chen WT, Ko BS, Yao M, Hsueh PR, et al. (2011) Combination antifungal therapy for disseminated fusariosis in immunocompromised patients: a case report and literature review. Med Mycol 49: 872-878.