Mycopathologia (2016) 181:457–463
DOI 10.1007/s11046-016-9987-5

Fusariosis in a Patient with Acute Myeloid Leukemia: A Case Report and Review of the Literature

Mario Delia · Rosa Monno · Giorgia Giannelli · Amato Antonio Stabile Ianora · Lidia Dalfino · Domenico Pastore · Carmen Capolongo · Carla Calia · Annamaria Tortorano · Giorgina Specchia

Received: 17 April 2015 / Accepted: 1 February 2016 / Published online: 23 March 2016

Abstract *Fusarium* spp. causes infections mostly in patients with prolonged neutropenia. We describe the case of a disseminated *Fusarium solani* infection in a patient with acute myeloid leukemia which never reached complete remission during its clinical course. The patient had profound neutropenia and developed skin nodules and pneumonia in spite of posaconazole prophylaxis. *F. solani* was isolated from blood and skin biopsy, being identified from its morphology and by molecular methods. By broth dilution method, the strain was resistant to azoles, including voriconazole and posaconazole, and to echinocandins. MIC to amphotericin B was 4 mg/L. The patient initially seemed to benefit from therapy with voriconazole and amphotericin B, but, neutropenia perduring, his clinical condition deteriorated with fatal outcome. All efforts should be made to determine the correct diagnosis as soon as possible in a neutropenic patient and to treat this infection in a timely way, assuming pathogen susceptibility while tests of antimicrobial susceptibility are pending. A review of the most recent literature on invasive fungal infections is reported.

Keywords *Fusarium* · Fungal infection · Leukemia · Fusariosis

M. Delia · L. Dalfino · D. Pastore · G. Specchia
Department of DETO, University of Bari, Bari, Italy

R. Monno (✉) · C. Capolongo · C. Calia
Department SMBNOS, University of Bari, Bari, Italy
e-mail: rosa.monno@uniba.it

G. Giannelli · A. A. S. Ianora
Department DIM, University of Bari, Bari, Italy

A. Tortorano
Department of Biomedical Science for Health, University of Milan, Milan, Italy

Introduction

It is well known that invasive mold infections (IMI) may occur in patients affected by hematological malignancies and by other medical conditions associated with immunosuppression. In particular, *Aspergillus* spp. are the commonest pathogens causing IMI, but new diagnostic techniques have contributed to the detection of other fungal pathogens such as *Trichosporon*, *Fusarium*, *Scedosporium*, *Alternaria* [1, 2]. Although primary antifungal prophylaxis (PAP) is routinely administrated in immunocompromised patients and in those with acute myeloid leukemia (AML) during remission induction chemotherapy, the occurrence of rare IMI is still described and is associated with treatment failure and high mortality rate. *Fusarium* spp. are second only to *Aspergillus* as a cause of IMI in hematological malignancies, and its cure remains a challenge for both clinicians and microbiologists [3–8]. We report the case of a disseminated *F. solani* infection in a primary refractory AML patient who initially benefited from voriconazole plus L-amphotericin therapy, while

worsening perduring neutropenia. Duration of neutropenia, rather than the microbiological features themselves, appears to be crucial for the outcome in this kind of IMI.

Case Description

A 44-year-old male was referred to the Hematological Unit of Policlinico, Bari, Italy, in April 2014 with fatigue and weight loss. At admission, results of a physical examination were normal, but laboratory tests showed severe anemia (hemoglobin 6.7 g/dL, platelet count $43 \times 10^3/\mu L$, leukocyte count $4.5 \times 10^3/\mu L$ and neutrophil count $1.8 \times 10^3/\mu L$). Both liver enzyme activities and renal function were normal with levels of C-reactive protein at 4 mg/L. Patient diagnosis was of AML with poor prognosis (AML with complex karyotype, NPMI1Awt, FLT3 ITD unmutated; MO or AML without maturation; according to French–American–British classification and WHO 2008, respectively) [9], and he promptly underwent remission induction chemotherapy with "3 + 7" protocol (cytarabine 100 mg/mq for 7 days and doxorubicin 50 mg/mq for 3 days) while on prophylaxis with posaconazole (600 mg daily), without obtaining complete remission (CR). The re-induction chemotherapy protocol (FLAG-Ida) (fludarabine 30 mg/mq/daily for 5 days, cytarabine 2 g/mq/daily for 5 days, idarubicin 10 mg/mq/daily for three days) also failed to achieve CR. At, respectively, +40 and +12 days from the start of the remission induction and re-induction chemotherapy protocol, and with profound neutropenia (<500 granulocytes/μL), he developed high fever (up to 40 °C) without chills. Three sets of blood were drawn for fungal and bacterial culture (BD BACTEC™, Italy) and sent to the Laboratory of Microbiology and Virology of Policlinico, Bari, Italy. The subculture of the broth blood culture on Sabouraud dextrose agar (bioMérieux, Italy) yielded a fast-growing fungal colony after 3 days of incubation. The obverse and reverse color was white, and a cottony texture was observed. A cotton blue-lactophenol stain was performed. At microscopic observation, typical hyaline septated hyphae branching at 45 °C and hyaline multicelled macroconidia with two to five septa, banana in shape, were present. The mold was identified on its morphological characteristics as *Fusarium* spp. and identified as *Fusarium solani* by molecular methods, sequencing the translation elongation factor 1α (TEF gene) according to the method previously reported at the Laboratory of Mycology at the University of Milan, Italy [2]. Antibodies (IgG and IgM) against *Candida* and *Aspergillus* were negative as was the QuantiFERON test for diagnosis of latent tuberculosis. Serum [1–3] β-D-glucan was not assessed. Serum *Candida* mannan antigen and *Aspergillus* galactomannan antigen (Bio-Rad—Milan, Italy) were also negative. The patient developed skin lesions with central darkening due to ischemia and necrosis. The skin lesions were randomly scattered over the body and in particular over his face, trunk and upper limbs (Fig. 1). Microscopic examination of a skin biopsy showed the presence of hyphal elements, and a mold with the same morphological characteristics of that grown from the blood culture was isolated and identified as *F. solani*. There was also lung involvement, the patient having a nonproductive cough. Abnormal thoracic computerized tomography findings were of bilateral lung nodules (Fig. 2a). Minimum inhibitory concentrations (MICs) were determined by both the broth microdilution method (BMD) following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [10] and by Etest. MICs determined by BMD methods were: posaconazole > 32 mg/L, voriconazole = 16 mg/L, itraconazole > 16 mg/L and amphotericin B = 4 mg/L. MICs detected by Etest were: posaconazole > 32 mg/L, voriconazole > 32 mg/L, fluconazole > 256 mg/L, caspofungin > 32 mg/L, anidulafungin > 32 mg/L, micafungin > 32 mg/L, flucytosine > 32 mg/L. Amphotericin

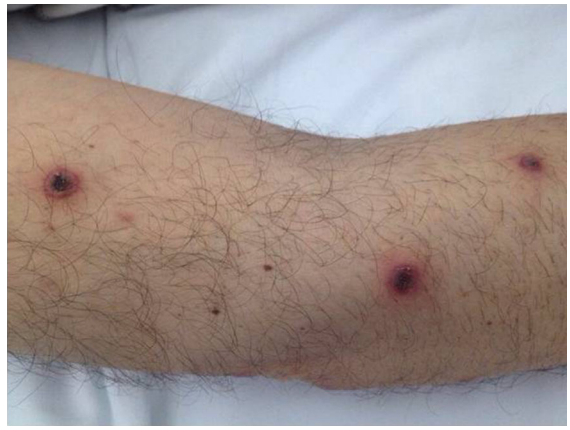

Fig. 1 Cutaneous lesions on upper limbs caused by *F. solani*

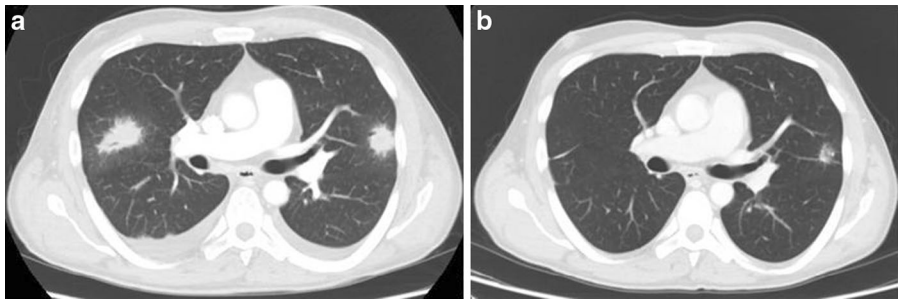

Fig. 2 **a** CT scan of thorax: right and left upper lobe nodules with ground-glass opacity associated. **b** Reduction of right and left lesions after liposomal amphotericin B plus voriconazole

was not tested. Unfortunately, the data from the susceptibility testing were available only after 20 days. Meanwhile, he was empirically treated with a combination antifungal therapy: liposomal amphotericin B (L-AmB) (5 mg/kg/day) and voriconazole (4 mg/kg/day; 6 mg/kg/first day loading dose). After 28 days of treatment, improvement was documented by the disappearance of cutaneous manifestations and a CT thoracic scan showed a reduction of lesions (Fig. 2b). The patient was discharged with oral voriconazole (400 mg daily) and an improved clinical condition (resolution of skin lesions and negativity of blood culture) in spite of refractory AML (granulocyte count $< 1 \times 10^3/\mu L$, platelet count $5 \times 10^3/\mu L$, hemoglobin level 8.5 g/dL, bone marrow blasts 60 % of the re-induction treatment). After 28 days of combination therapy and 23 days of oral voriconazole, the patient underwent chemotherapy with clofarabine (22.5 mg/mq for 5 days) and cytarabine (1.5 g/mq for 5 days) while maintaining oral voriconazole. After 13 days, febrile neutropenia appeared together with cutaneous manifestations. L-AmB was again started, and voriconazole switched to parenteral administration. After 9 days, his clinical condition rapidly worsened with severe lung involvement (Fig. 3) and his hemoparameters (pO2: 60 mmHg; pCO2: 55 mmHg) required noninvasive ventilation. The patient was transferred to the intensive care unit for severe respiratory failure. He progressed to death after 1 day.

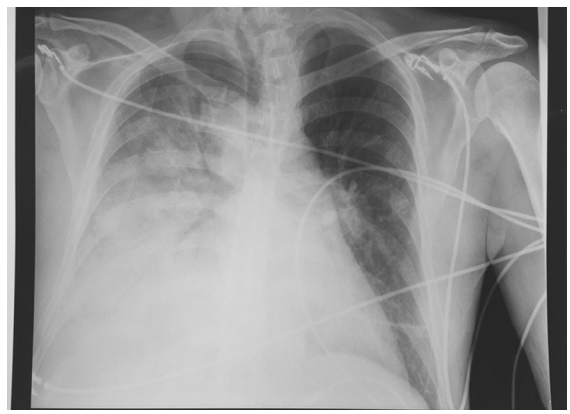

Fig. 3 Chest radiograph: consolidative lesions with central lucency involving basal and medial lobes of the right lung

Discussion

The incidence of disseminated invasive fungal infection, often with a fatal outcome, has risen dramatically in patients with prolonged neutropenia due to leukemia therapy. Therefore, *Fusarium* spp. are becoming more commonly recognized as opportunistic pathogens in neutropenic patients. Recently, other *Fusarium* spp. other than *F. solani,* such as *F. oxysporum*, *F. verticilloides*, *F. petroliphilum, F. napiforme F. andiyazi* and *F. proliferatum* have emerged as a cause of invasive fusariosis in patients with hematological malignancies or after organ transplantation [11–15]. Disseminated fusariosis is reported in patients with lymphoblastic leukemia [16–18]. *Fusarium* spp. lung infection is reported also in bone marrow transplant recipients and liver transplantation [19, 20]. This infection has occasionally been described in immunocompetent patients. Reconstruction work has been implicated in *F. verticilloides* bloodstream infections in seven immunocompetent patients. The exposure to a high concentration of spores during construction activities in the healthcare

setting may explain these hospital-acquired infections [21]. There are few reports of invasive fusariosis in children. Over a 15-year period, five cases of IFI were described in immunocompromised children [22], and often as an outbreak in a children's cancer hospital, *F. oxysporum* and *F. solani* being the species isolated [23]. *Fusarium* species possess several virulence factors such as the production of mycotoxins able to suppress humoral and cellular immunity, to cause tissue breakdown and also to produce proteases and collagenases [4]. *Fusarium* clinical manifestations include invasive sinus infection, cutaneous and soft tissue infection, fungemia, pulmonary infection and dissemination to multiple organs with arthritis and osteomyelitis [3, 4]. *Fusarium* spp. lung infections are reported also in transplant patients especially in lung transplant patients seeing as the principle portal of entry of this mold is the airway [24, 25]. Disseminated infections are reported also in bone marrow transplant recipients and liver transplantation [19, 20]. Ocular infections such as keratitis, endophthalmitis both in immunocompetent and in immunosuppressed patients are also reported. Recently, two outbreaks of *Fusarium* keratitis occurring in contact lens wearers who used a specific contact lens solution contaminated with *Fusarium* were reported [26]. The neutropenic patient with disseminated fusariosis (DF) typically has fever, myalgias and, in 75 % of patients, skin lesions which are difficult to distinguish from those caused by other pathogens [1]. The presence of skin lesions at admission to hospital of high-risk hematological patients was significantly associated with the development of fatal invasive fusariosis suggesting the use of antimold prophylaxis in these patients [27]. In addition, the mold has the tendency to invade blood vessels causing tissue necrosis, thrombosis and infarction [28]. In invasive fusariosis, pneumonia occurs in almost 50 % of cases and, as in our patient, alveolar infiltrates, ground glass infiltrates, and pleural effusions are present [29]. A risk factor for IFI in hematological patients is active smoking, while receipt of antithymocyte globulin or hyperglycemia was associated with IFI in hematopoietic cell transplant recipients [30]. A concomitant rhino-orbital mucormycosis and a disseminated fusariosis in a neutropenic patient have been reported, suggesting that PCR methods in tissue section may increase the diagnosis of dual mold infections [31]. Suggesting a cross-reaction indicative of a possible cross reactionbetween antigens of *F. solani* and antigens of *Aspergillus* [6].

The prognosis of fusariosis is directly linked with the immune status of the patient, with high mortality rates in patients with a persistent status of immunodeficiency. A fatal outcome of this infection is often reported with probability of survival of 66.7 and 53.3 % at 6 and 22 weeks after diagnosis [6, 23, 32, 33]. Long-lasting profound neutropenia in our patient may explain the initial benefit from antifungal therapy and the ultimate lack of benefit. It has been documented that, in a hematological population, survival rates slow from 50 to 21 % at 30 and 90 days after diagnosis, respectively. Posaconazole prophylaxis should have protected from IFI [5], but the *F. solani* isolated in our patient was resistant both to posaconazole and to voriconazole. This might be a peculiarity of our case which may explain the reason why, in contrast with documented evidence [6], fusariosis was so disseminated (skin involvement, pneumonia, fungemia) in spite of the use of voriconazole [34, 35]. The European Medicines Agency (EMA) has approved posaconazole both for the treatment and prophylaxis of invasive fungal infections in hematological patients and stem cell transplant recipients [6, 36]. Although there is evidence of posaconazole salvage therapy for proven or probable fusariosis with an overall response rate of 20 % in case of neutropenia [37], our strain of *F. solani* was resistant to all azoles. *Fusarium* spp. have variable in vitro susceptibility to fungal agents, and high MICs to antifungal agents are reported. Therefore, antifungal treatment that should be guided by susceptibility testing may be very difficult. In particular, among *Fusarium* spp., *F. solani* tends to be the species most resistant to several antifungal agents so limiting the antifungal armamentarium [2].

In vitro susceptibilities of *Fusarium* spp. to echinocandins vary between species [38–40]. Recently the three echinocandins (caspofungin, micafungin and anidulafungin) were inactive against 10 *Fusarium* spp. tested with MICs > 8 mg/L [41]. This was confirmed by other authors on clinical isolates of *Fusarium* [42, 43]. *F. solani*, in particular, is intrinsically resistant to echinocandins. Also in our experience the echinocandins were inactive, in vitro, against the *F. solani* isolate.

Amphotericin B is considered the treatment of choice for invasive fusariosis, but, although MICs from 1 to 4 mg/L are reported, interpretative breakpoints have not been established and MICs > 4 mg/L are

usually considered suggestive of resistance [44]. Actually, the lowest MICs have been found for amphotericin B, although the MICs values varied between species, *F. solani* being the specie showing the lowest MICs [2, 42], and resistance in *F. solani* causing disseminated infections in acute leukemia has been reported [45]. A recent epidemiological survey on invasive infections due to *Fusarium* spp. in Europe has demonstrated that azoles (posaconazole, voriconazole and itraconazole) exhibited lower MICs against *Fusarium verticillioides* strains, while 14 isolates of *F. solani* were resistant to all the three azoles tested [2]. Taken together, although the azoles exhibited variable activity against *Fusarium* spp. several authors report successful outcome of treated patients [6, 46]. Of note, the azoles were the most active drugs against the new emerging species *F. napiforme* [15]. Posaconazole and voriconazole were the most frequently employed therapies in invasive *Fusarium* infection and have been linked to the improved survival rates observed in a study of Horn et al. [6] even if in vitro susceptibility testing was not performed. In particular, voriconazole possesses a broad spectrum of activity covering *Fusarium* spp. resistant to fluconazole [47, 48] and may be indicated for treatment of fusariosis with a response rate of 45 % [49], whereas other azoles (itraconazole, ravuconazole) had no effect [42]. On the contrary, posaconazole failed to be effective in 80 % of patients with leukemia and persistent neutropenia [50] as occurred in our patient. A recent study on 21 patients who received posaconazole salvage therapy for proven or probable invasive fusariosis and who had disease refractory or intolerant to standard therapy reported an overall response rate to therapy of, respectively, 48 % and 20 % for patients with persistent neutropenia [37]. Combination therapy with different classes of antifungal drugs is also reported including amphotericin B and voriconazole [44, 51, 52]. Considering the clinical condition of patients affected by disseminated fusariosis (DF) and the difficulty in predicting fungal susceptibility, combination treatment of voriconazole and lipid-based amphotericin B might be considered as first option therapy, while susceptibility results are pending as in our patient whose DF was characterized by subsequent episodes of neutropenia, as already reported [44, 53].

In vitro studies in a murine model of disseminated infection by *Fusarium* spp. showed that the combination of amphotericin B with posaconazole showed the best results prolonging the survival of mice [54].

Fungal susceptibility appears to be crucial in this patient setting, known to be of poor prognosis, while there are conflicting results regarding testing. In fact, there is evidence of susceptibility to voriconazole and amphotericin B [19], although susceptibility testing of mold performed by broth microdilution testing according to CLSI or EUCAST guidelines is laborious, time-consuming and requires skilled personal, and is therefore available in only specialized mycology laboratories. The Etest has been used in some studies with various degrees of agreement for amphotericin B. Of note, because of the fact that the portal of entry is most frequently the sinopulmonary tract, though it can be through periungual and soft tissue infection, thorough environmental cleansing procedures must be implemented to reduce the possibility of mold infection in immunocompromised patients, and in particular in those with a severe neutropenia. The presence of a positive culture for *Fusarium* spp. in alteration of the skin and/or nails of the feet and/or hands (onychomycosis, intertrigo) was significantly associated with the subsequent development of invasive fusariosis, suggesting the use of antimold prophylaxis in this setting [27]. A future promising approach is the role of granulocyte transfusions in profound neutropenia, an important cause of death [55]. In conclusion, all efforts should be made to determine the diagnosis of IFI as soon as possible in a neutropenic patient and to treat the infection in a timely way, assuming pathogen susceptibility while antimicrobial susceptibility testing is pending. In the light of the reported resistance to azoles in *F. solani,* laboratories must be able to perform susceptibility testing and to report antifungal resistance by Etest. Essential agreement between the Etest and the EUCAST method has been demonstrated to be 100 % for itraconazole and voriconazole and 96 % for amphotericin B and posaconazole. The Etest may represent a simple method to determine the antifungal in vitro susceptibility patterns [2].

References

1. Richardson SE, Bannatyne RM, Summerbell RC, Milliken J, Gold R, Weitzam SS. Disseminated fusarial infection in the immunocompromised host. Rev Infect Dis. 1988;10: 1171–81.
2. Tortorano AM, Prigitano A, Esposto MC, et al. European Confederation of Medical Mycology (ECMM)

epidemiological survey on invasive infections due to *Fusarium* species in Europe. Eur J Clin Microbiol Infect Dis. 2014;33:1623–30.
3. Dignani MC, Anaissie E. Human fusariosis. Clin Microbiol Infect. 2004;10:67–75.
4. Nucci M, Anaissie E. *Fusarium* infections in immunocompromised patients. Clin Microbiol Rev. 2007;20: 695–704.
5. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356:348–59.
6. Horn DL, Freifeld AG, Schuster MG, Azie NE, Franks B, Kauffman CA. Treatment and outcomes of invasive fusariosis: review of 65 cases from the PATH Alliance(®) registry. Mycoses. 2014;57:652–8.
7. Muhammed M, Coleman JJ, Carneiro HA, Mylonakis E. The challenge of managing fusariosis. Virulence. 2011;2: 91–6.
8. Nucci M, Anaissie E. Emerging fungi. Infect Dis Clin North Am. 2006;20:563–79.
9. Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. N England J Med. 1999;341:1051–62.
10. Rodriguez-Tudela JL, Arendrup MC, Barchiesi F, et al. EUCAST Definitive Document EDef 7.1: method for the determination of broth dilution MICs of antifungal agents for fermentative yeasts. Clin Microbiol Infect. 2008;14: 398–405.
11. Ersal T, Al-Hatmi AS, Cilo BD, et al. Fatal disseminated infection with *Fusarium petroliphilum*. Mycopathologia. 2015;179:119–24.
12. Ricna D, Lengerova M, Palackova M, et al. Disseminated fusariosis by *Fusarium proliferatum* in a patient with aplastic anaemia receiving primary posaconazole prophylaxis - case report and review of the literature. Mycoses. 2016;59:48–55.
13. Kebabcı N, van Diepeningen AD, Ener B, et al. Fatal breakthrough infection with *Fusarium andiyazi*: new multiresistant aetiological agent cross-reacting with *Aspergillus* galactomannan enzyme immunoassay. Mycoses. 2014;57: 249–55.
14. Dananché C, Cassier P, Sautour M, et al. Fungaemia caused by *Fusarium proliferatum* in a patient without definite immunodeficiency. Mycopathologia. 2015;179:135–40.
15. De Souza M, Matsuzawa T, Lyra L, et al. *Fusarium napiforme* systemic infection: case report with molecular characterization and antifungal susceptibility tests. Springerplus. 2014;3:492.
16. Labois A, Gray C, Lepretre S. Successful treatment of disseminated fusariosis with voriconazole in an acute lymphoblastic leukaemia patient. Mycoses. 2011;54:8–11.
17. Tan R, Ng KP, Gan GG, Na SL. *Fusarium* sp. infection in a patient with Acute Lymphoblastic Leukaemia. Med J Malaysia. 2013;68:479–80.
18. Jossi M, Ambrosioni J, Macedo-Vinas M, Garbino J. Invasive fusariosis with prolonged fungemia in a patient with acute lymphoblastic leukemia: case report and review of the literature. Int J Infect Dis. 2010;14:354–6.
19. Avelino-Silva VI, Ramos JF, Leal FE, Testagrossa L, Novis YS. Disseminated *Fusarium* infection in autologous stem cell transplant recipient. Braz J Infect Dis. 2015; 19:90–3.
20. Sganga G, Bianco G, Frongillo F, Lirosi MC, Nure E, Agnes S. Fungal infections after liver transplantation: incidence and outcome. Transplant Proc. 2014;46:2314–8.
21. Georgiadou SP, Velegraki A, Arabatzis M, et al. Cluster of *Fusarium verticillioides* bloodstream infections among immunocompetent patients in an internal medicine department after reconstruction works in Larissa. Central Greece. J Hosp Infect. 2014;86:267–71.
22. Schwartz KL, Sheffield H, Richardson SE, Sung L, Morris SK. Invasive fusariosis: a single pediatric center 15-year experience. J Pediatric Infect Dis Soc. 2015;4:163–70.
23. Litvinov N, da Silva MT, van der Heijden IM, et al. An outbreak of invasive fusariosis in a children's cancer hospital. Clin Microbiol Infect. 2015;21:268.e1–7.
24. Carneiro HA, Coleman JJ, Restrepo A, Mylonakis E. *Fusarium* infection in lung transplant patients: report of 6 cases and review of the literature. Medicine (Baltimore). 2011;90:69–80.
25. Kandeel A, Abu-Elmagd K, Spinner M, et al. Atypical clinical presentation of a newer generation anti-fungal drug-resistant *Fusarium* infection after a modified multi-visceral transplant. Ann Transplant. 2015;20:512–8.
26. Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. JAMA. 2006;296:953–63.
27. Varon AG, Nouer SA, Barreiros G, et al. Superficial skin lesions positive for Fusarium are associated with subsequent development of invasive fusariosis. J Infect. 2014;68:85–9.
28. Anaissie E, Kantarjian H, Jones P, et al. *Fusarium*. A newly recognized fungal pathogen in immunosuppressed patients. Cancer. 1986;57:2141–5.
29. Nucci F, Nouér SA, Capone D, Anaissie E, Nucci M. Fusariosis. Semin Respir Crit Care Med. 2015;36:706–14.
30. Garnica M, da Cunha MO, Portugal R, Maiolino A, Colombo AL, Nucci M. Risk factors for invasive fusariosis in patients with acute myeloid leukemia and in hematopoietic cell transplant recipients. Clin Infect Dis. 2015;60:875–80.
31. de Almeida Júnior JN, Ibrahim KY, Del Negro GM, et al. *Rhizopus arrhizus* and *Fusarium solani* concomitant infection in an immunocompromised host. Mycopathologia. 2016;181:125–9.
32. Dabas Y, Bakhshi S, Xess I. Fatal Cases of Bloodstream Infection by *Fusarium solani* and Review of Published Literature. Mycopathologia. 2015; Nov 5. (Epub ahead of print).
33. Stempel JM, Hammond SP, Sutton DA, Weiser LM, Marty FM. Invasive Fusariosis in the Voriconazole Era: Single-Center 13-Year Experience. Open Forum Infect Dis. 2015; 2(3):ofv099 eCollection 2015.
34. Nucci M, Marr KA, Vehreschild MJ, et al. Improvement in the outcome of invasive fusariosis in the last decade. Clin Microbiol Infect. 2014;20:580–5.
35. Lortholary O, Obenga G, Biswas P, et al. International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. Antimicrob Agents Chemother. 2010; 54:4446–50.
36. Clark NM, Grim SA, Lynch JP 3rd. Posaconazole: Use in the Prophylaxis and Treatment of Fungal Infections. Semin Respir Crit Care Med. 2015;36:767–85.

37. Raad II, Graybill JR, Bustamante AB, et al. Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. Clin Infect Dis. 2006;42: 1726–34.
38. Arikan S, Lozano-Chiu M, Paetznick V, Rex JH. In vitro susceptibility testing methods for caspofungin against *Aspergillus* and *Fusarium* isolates. Antimicrob Agents Chemother. 2001;45:327–30.
39. Aperis G, Alivanis P. Posaconazole: a new antifungal weapon. Rev Recent Clin Trials. 2011;6:204–19.
40. Chen SC, Slavin MA, Sorrell TC. Echinocandin antifungal drusi fungal infections: a comparison. Drug. 2011;71: 11–41.
41. Martos AI, Romero A, González MT, et al. Evaluation of the E-test method for susceptibility testing of *Aspergillus* spp. and *Fusarium* spp. to three echinocandins. Med Mycol. 2010;48:858–61.
42. Drogari-Apiranthitou M, Mantopoulou FD, Skiada A, et al. In vitro antifungal susceptibility of filamentous fungi causing rare infections: synergy testing of amphotericin B, posaconazole and anidulafungin in pairs. J Antimicrob Chemother. 2012;67:1937–40.
43. Iqbal NJ, Boey A, Park BJ, Brandt ME. Determination of in vitro susceptibility of ocular *Fusarium* spp. isolates from keratitis cases and comparison of Clinical and Laboratory Standards Institute M38-A2 and E test methods. Diagn Microbiol Infect Dis. 2008;62:348–50.
44. Walsh TJ, Gamaletsou MN. Treatment of fungal disease in the setting of neutropenia. Hematology Am Soc Hematol Educ Program. 2013;2013:423–7.
45. Pereira GH, de Angelis DA, Brasil RA, et al. Disseminated amphotericin-resistant fusariosis in acute leukemia patients: report of two cases. Mycopathologia. 2013;175:107–14.
46. Muhammed M, Anagnostou T, Desalermos A, et al. *Fusarium* infection: report of 26 cases and review of 97 cases from the literature. Medicine. 2013;92:305–16.
47. Bhaskaran A, Hosseini-Moghaddam SM, Rotstein C, Husain S. Mold infections in lung transplant recipients. Semin Respir Crit Care Med. 2013;34:371–9.
48. Paramythiotou E, Frantzeskaki F, Flevari A, Armaganidis A, Dimopoulos G. Invasive fungal infections in the ICU: how to approach, how to treat. Molecules. 2014;19: 1085–119.
49. Perfect JR. Management of invasive mycoses in hematology patients: current approaches. Oncology. 2004;18:5–14.
50. Nucci M, Anaissie EJ, Queiroz-Telles F, et al. Outcome predictors of 84 patients with hematologic malignancies and *Fusarium* infection. Cancer. 2003;98:315–9.
51. Durand-Joly I, Alfandari S, Benchikh Z, et al. Successful outcome of disseminated *Fusarium* infection with skin localization treated with voriconazole and amphotericin B-lipid complex in a patient with acute leukemia. J Clin Microbiol. 2003;41:4898–900.
52. Candoni A, Caira M, Cesaro S, et al. Multicentre surveillance study on feasibility, safety and efficacy of antifungal combination therapy for proven or probable invasive fungal diseases in haematological patients: the SEIFEM real-life combo study. Mycoses. 2014;57:342–50.
53. Koehler P, Tacke D, Cornely OA. Bone and joint infections by *Mucorales, Scedosporium, Fusarium* and even rarer fungi. Crit Rev Microbiol. 2014;9:1–14.
54. Ruíz-Cendoya M, Mariné M, Rodríguez MM, Guarro J. Interactions between triazoles and amphotericin B in treatment of disseminated murine infection by *Fusarium oxysporum*. Antimicrob Agents Chemother. 2009;53:1705–8.
55. Kadri SS, Remy KE, Strich JR, Gea-Banacloche J, Leitman SF. Role of granulocyte transfusions in invasive fusariosis: systematic review and single-center experience. Transfusion. 2015;55:2076–85.