Mycopathologia (2018) 183:941–949
https://doi.org/10.1007/s11046-018-0257-6

SHORT COMMUNICATION

Infections Caused by *Fusarium* Species in Pediatric Cancer Patients and Review of Published Literature

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Received: 1 September 2016 / Accepted: 6 March 2018 / Published online: 21 March 2018

Abstract *Fusarium* species have emerged as responsible for a broad spectrum of infections, including superficial, locally invasive and disseminated ones, especially in the hospital environment. Since there are few reports of invasive and disseminated fusariosis in children, the aim of this study was to report four cases of nosocomial infection caused by this microorganism in children with cancer hospitalized in a public children's hospital located in Brazil. Two of these patients were female and two were male. All patients presented febrile neutropenia, while three patients had acute lymphocytic leukemia and one patient had Wilms' tumor as underlying disease. In two cases, fungi were isolated from blood and identified as *Fusarium oxysporum* species complex after phenotypic and genotypic studies, while in two other cases fungi were isolated from skin biopsies and identified as *Fusarium solani* species complex. One patient died 12 days after the onset of cutaneous lesions. All isolates, after susceptibility testing, presented high levels of minimum inhibitory concentration for itraconazole, voriconazole and amphotericin

Handling Editor: Anne D. van Diepeningen.

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B. Considering the emergence of filamentous fungi as etiologic agents of nosocomial infections, health professionals should be aware of the problems these infections, especially fungal ones, may cause to debilitated patients.

Keywords *Fusarium* spp. · Children · Cancer · Nosocomial infection

Introduction

Invasive fungal infections have caused high mortality and morbidity rates in patients with hematologic malignancies and prolonged neutropenia following chemotherapy. In pediatric patients, these infections seem to have increased during the last decades, especially due to the higher survival rate of children with primary and secondary immunodeficiency [1, 2].

Fusarium species, *Aspergillus* species and fungi of the order Mucorales are among the most clinically important filamentous fungi. Filamentous fungi of the *Fusarium* genus cause a broad spectrum of opportunistic infections in humans, including superficial, locally invasive and disseminated infections. The clinical form of fusariosis largely depends on the host immune status and on the portal of entry for the microorganism [3].

The most common clinical manifestations of fusariosis in immunocompetent hosts are onychomycosis, keratitis and allergy [4–6]. Immunocompromised patients have high risk of developing fusariosis, which is related to deep and prolonged neutropenia and/or severe T cell immunodeficiency [7]. In this population, fusariosis is typically invasive and widespread, leading to high mortality rates [8].

Although more than 100 *Fusarium* species have been identified, opportunistic *Fusarium* species in humans are grouped into seven complexes: *Fusarium solani, F. oxysporum, F. incarnatum-equiseti, F. fujikuroi, F. clamydosporum, F. dimerum and F. sporotrichioides* [9]. *Fusarium solani* species complex (FSSC) is responsible for nearly 60% cases, while *Fusarium oxysporum* species complex (FOSC) causes approximately 20% cases, and their distribution may depend on the studied region [4].

Since fusariosis is still a rare infection, problems related to it lie in difficult diagnosis and treatment. Little is known about the best therapeutic approaches to fusariosis cases, and response to treatment depends on the patient immune status. In patients with hematologic and oncologic diseases, especially those with prolonged neutropenia, fusariosis may be refractory to antifungal therapy [10].

Considering the emergence of filamentous fungi of the *Fusarium* genus as pathogens of nosocomial environment and the scarce reports of invasive and disseminated fusariosis in children, this study aimed to report four cases of nosocomial infection caused by this microorganism in children with cancer admitted to a public children's hospital, which is a tertiary referral center for pediatric oncology among other pediatric subspecialties, located in the city of São Paulo, Brazil.

Presentation of Cases

Case 1

An 11-year-old female patient with ALL was admitted to the oncology center due to febrile neutropenia; clinical evolution was stable but fever and neutropenia remained even after broad-spectrum antimicrobial therapy with vancomycin, meropenem and micafungin during 14 days. In the radiologic evaluation, small nonspecific ground-glass nodules were detected by means of computed tomography (CT) of the chest, and serial measurement of galactomannan was negative. Blood culture was positive for *Fusarium* spp. The treatment was modified to amphotericin B lipid complex (3 mg/kg) associated with oral voriconazole (200 mg/kg every 12 h). The patient remained stable, presented medullary recovery within 1 week after positive blood culture, was afebrile 5 days after the new antifungal therapy and was discharged home after 2 weeks to proceed with the treatment, on an outpatient clinic basis, with oral voriconazole (200 mg/kg every 12 h) during additional 4 weeks. The patient was followed up for 6 months, progressed well and no adverse events of antifungal therapy were observed.

Case 2

A 6-year-old male patient with relapsed acute lymphocytic leukemia (ALL) was hospitalized to the oncology center on the first day of febrile neutropenia and nonspecific cutaneous vesicular lesions. The

patient received empiric therapy with vancomycin, meropenem, micafungin and acyclovir; at admission, blood culture was positive for *Fusarium* spp. The antifungal treatment with amphotericin complex lipid (3 mg/kg) associated with oral voriconazole (8 mg/Kd every 12 h) was started after 48 h of admission. Clinical evolution was good with medullary recovery in 10 days and resolution of symptoms after 16 days (patient remained afebrile and cutaneous lesions resolved). Biopsy of the cutaneous lesions was not performed. After 10 days, the patient was discharged home and was prescribed oral voriconazole (200 mg/kg every 12 h) during additional 4 weeks. Serum levels of voriconazole were not evaluated since this test was not available at the institution. The patient was followed up for 8 months, progressed well and no adverse events of antifungal therapy were observed.

Case 3

A 9-year-old male patient was hospitalized for recurrence of ALL, receiving chemotherapy, presenting prolonged neutropenia (10 days) and fever. The patient received empiric treatment with piperacillin–tazobactam and after 4 days became afebrile. After 1 week, the patient maintained neutropenia and evolved with the appearance of necrotic skin lesions on the upper and lower limbs, and biopsy was compatible with fungal infection. The culture was identified as *Fusarium* spp. These results led to the introduction of oral voriconazole treatment (200 mg every 12 h), and the patient had good clinical evolution, with medullary recovery in 1 week after the onset of symptoms and complete resolution of cutaneous lesions in 3 weeks. Total treatment lasted approximately 8 weeks. The patient was followed up for 12 months, progressed well and no adverse events of antifungal therapy were observed.

Case 4

A 7-year-old female patient with recurrent Wilms' tumor in the lungs was admitted to the oncology center due to febrile neutropenia, which evolved to typhlitis, demanding surgical approach, followed by septic shock due to vancomycin-resistant *E. faecium*. Although receiving empiric broad-spectrum antimicrobial therapy and care in the intensive care unit, the patient showed no sign of improvement but deep neutropenia for more than 10 days and initial necrotic cutaneous lesions. The patient then received antifungal treatment with amphotericin B lipid complex (4 mg/kg) associated with voriconazole (8 mg/kg every 12 h). The case evolved to refractory shock, multiple organ and system dysfunction and death 12 days after the onset of cutaneous lesions. Biopsy of the lesions was compatible with fungal infection, and the culture was identified as *Fusarium* spp.

Materials and Methods

All four reported fusariosis cases occurred during the year of 2015, and the pediatric patients were admitted to the Oncology wards of the Infantil Darcy Vargas Hospital located in the city of São Paulo, SP, Brazil. Fungal strains were isolated from blood (two cases) and skin biopsy (two cases) from these patients. Positive blood cultures were detected based on automated BACTEC® system (Becton–Dickinson, USA). To prove the infection, a minimum of two blood cultures were performed at different times. Fungi were isolated from the skin lesions by performing at least two cultures on Sabouraud dextrose agar and Mycosel agar.

After culture isolation, the four strains were identified based on their macroscopic and microscopic characteristics (giant colony and slide culture) and molecularly studied for species confirmation through amplification and sequencing of ITS region with primers ITS1 and ITS4 [11] and TEF gene region with primers EF1 and EF2 [12]. The nucleotide sequences obtained in this study have been submitted to GenBank. Sequence similarity was compared with the database available in *Fusarium* MLST database. For the phylogenetic analysis of the four samples studied, with the final EF-sequence, multiple sequence alignment was carried out using ClustalW, while phylogenetic trees were built by adopting the maximum likelihood method and Mega 7 software [13].

Antifungal susceptibility test of fungal isolates was done by following the M38-A2 guidelines of Clinical and Laboratory Standards Institute (CLSI) [14] for moulds. Quality control isolates (*Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258) were included. The following antifungal drugs were tested: amphotericin B, itraconazole and voriconazole.

Results

Phenotypic study of strains isolated from blood and skin lesions revealed microscopic and macroscopic characteristics (hyaline, multicellular and fusiform macroconidia) typical of the *Fusarium* genus. Using molecular identification and phylogenetic analyses, the samples were characterized as *F. oxysporum* and *F. solani* species complex. The two samples identified as FOSC were most closely related to *F. oxysporum* species complex 132 (FOSC 132—*Fusarium* sp—100%). In isolates identified as FSSC one was most closely related to *F. solani* species complex 2-i (FSSC 2-i—*F. keratoplasticum*—100%) and the other isolate was most closely related to an as yet unnamed lineage within the *F. solani* species complex (FSSC 35-a—*Fusarium* sp—99.73%) (Table 1 and Fig. 1).

Susceptibility test in vitro was performed for all samples and high values of minimum inhibitory concentration (MIC) were obtained for all studied antifungals. MIC values were not interpreted since there are still no clinical breakpoints formally proposed for fungi of the *Fusarium* genus (Table 1).

A review of reported disseminated fusariosis in immunocompromised pediatric patients is presented in Table 2, demonstrating the importance of the infection in this population.

Discussion

During the last 25 years, the frequency and the diversity of invasive fungal infections have changed [26]. The genus *Fusarium* includes fungi that are environmentally disseminated in the soil, air and water, common to tropical and temperate areas [7]. The principal portal of entry for *Fusarium* spp. is the airways, followed by the skin at the tissue breakdown site and possibly the mucosal membranes. Reservoirs of infectious *Fusarium* species in hospital environments, especially in the plumbing and water systems, have been reported [21, 27, 28]. Fusariosis transmission dynamics was not investigated in this study.

In immunocompromised patients, mainly children, fusariosis occurs as a serious and disseminated disease [29], which is the most frequent and challenging clinical form of this infection, accounting for approximately 70% all cases [3].

Besides acute leukemia and T cell immunodeficiency, prolonged and deep neutropenia is one of the major risk factors for invasive fusariosis [8]. Granulocytes and macrophages play an important role in defending the immune system against *Fusarium*. Granulocytes inhibit the growth of hyphae, while macrophages inhibit the germination of conidia and the growth of hyphae [3, 30]. In our study, the underlying disease was acute lymphocytic leukemia in

Table 1 Molecular identification and susceptibility testing of the four *Fusarium* samples isolates from pediatric cancer patients

Cases	Molecular identification			In vitro sensitivity (antifungal/MIC μg/mL)
	Isolate	Identified species	Accession number GenBank	
Case 1	F-01	*Fusarium* sp (FOSC 132)	MF625657[a]	Itraconazole - > 8
			MG601227[b]	Voriconazole - 2
				Amphotericin B - 1
Case 2	F-02	*Fusarium* sp (FOSC 132)	MF625658[a]	Itraconazole - > 8
			MG601229[b]	Voriconazole - 4
				Amphotericin B - 1
Case 3	F-03	*F. keratoplasticum* (FSSC 2-i)	MF625660[a]	Itraconazole - > 8
			MG601228[b]	Voriconazole - > 8
				Amphotericin B - 2
Case 4	F-04	*Fusarium* sp (FSSC 35-a)	MF625659[a]	Itraconazole - > 8
			MG601226[b]	Voriconazole - 2
				Amphotericin B - 1

[a]ITS region

[b]TEF gene region

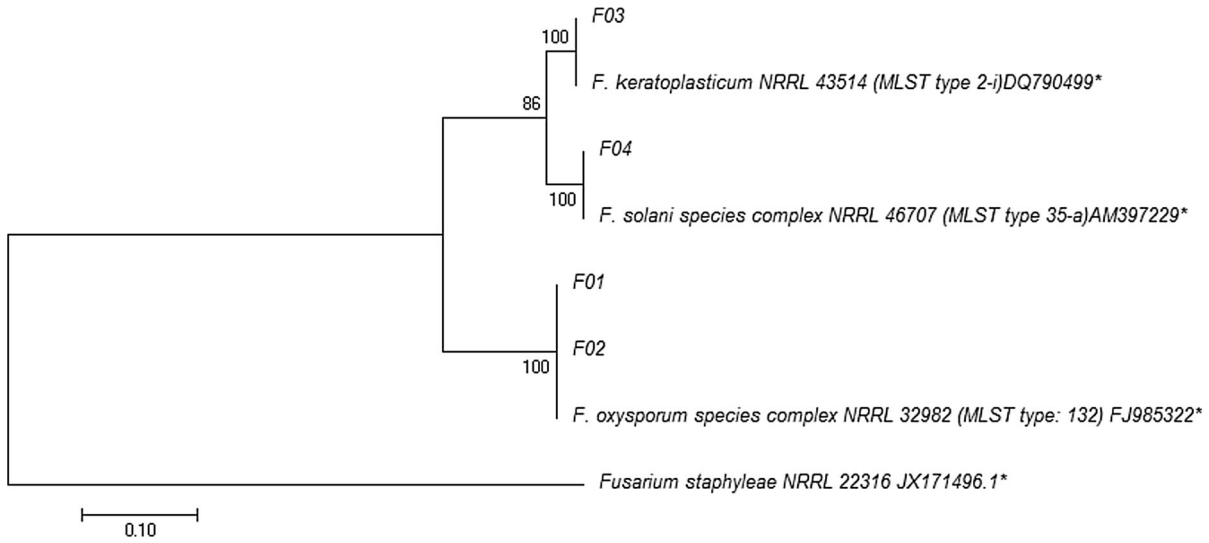

Fig. 1 Molecular phylogenetic analysis by maximum likelihood method based on the locus dataset comprising partial EF-1α gene sequences from four *Fusarium* isolates from this study. (Asterisks) References strains

three cases and Wilms' tumor in one case, and all patients presented febrile neutropenia.

Considering neutropenic patients, both children and adults, the most frequent pattern of disseminated fusariosis is the combination between cutaneous lesions and positive blood culture [21, 22, 25, 29]. In this study, two patients had positive blood culture; of these, only one had vesicular cutaneous lesions. These lesions are characteristic and widespread all over the skin and represent a metastatic infection of the disseminated disease [8].

Involvement of the skin may also represent a primary infection site [5]. Two patients in this study presented skin fusariosis with disseminated necrotic cutaneous lesions, which was detected based on the positive culture of material collected from the lesions. Blood culture, in these patients, was negative for fungi. Taking into account that skin lesions may suggest disseminated infection and that fusariosis, in general, leads to a fatal outcome when left untreated or treated late, such lesions in immunocompromised patients must be thoroughly investigated [31].

In this study, FSSC and FOSC were identified as the agents of fusariosis in the studied cases. Recent research in pediatric patient populations has shown that species belonging to these complexes constitute the third and the fourth most common causes, respectively, of fungal invasive infections [2, 32]. The molecular and phylogenetic studies characterized the isolates as *F. keratoplasticum* (FSSC 2-i), FSSC 35-a and FOSC 132. *Fusarium keratoplasticum* is among the most commonly species of the FSSC found in human infections. This species is often associated with severe opportunistic infections in healthy or immunocompromised human hosts [9, 33, 34]. The last two are not yet named lineages within the complexes.

Mortality rates among patients with disseminated fusariosis (75%) are two times higher than those among patients with localized infection [3], especially for patients with persistent neutropenia. In addition, this disease may be refractory in hematologic and oncologic patients, especially in those with persistent neutropenia [21]. In this study, one patient died and *Fusarium* was only isolated from her skin lesions. Nevertheless, the cause of death was not only attributed to the fungal infection but also to a sum of factors, including cancer relapse with pulmonary metastasis and sepsis due to *Enterococcus*.

A major problem of infections caused by *Fusarium* spp. is their relative resistance to most of the available antifungal compounds [35, 36]. Furthermore, the ideal treatment for fusariosis has not been established for patients with severe immunosuppression due to the rare and complex clinical scenario, while information about resistance mechanisms, MICs values and clinical response to therapy is very limited [37]. Despite the absence of clinical breakpoints for *Fusarium*, MIC

Table 2 Literature review of documented *Fusarium* infections in immunocompromised children

References	Number of cases	Diagnosis	Infection	Site(s) infection	*Fusarium* species	Skin lesions	Evolution (dead)	Antifungal therapy
Okada et al. [15]	1	Leukemia	Disseminated	Blood	*F. moniliforme*	NR	No	AMB
Chi and Wang [16]	1	ALL	Disseminated	Skin	*F. moniliforme*	Painful erythematous papular nodules	No	AMB
Marcoux et al. [17]	1	Hematologic disorder	Deep cutaneous infection/ disseminated	Skin	*Fusarium* spp.	Necrotic cutaneous lesions	No	AMB, ITR, POS, FL, KET, CASPO
Gurusidappa and Mamatha [18]	1	ALL	Skin lesion	Excised wound	*F. oxysporum*	There is no description of the aspect	No	AMB, KET
Morris et al. [19]	1	AA	Disseminated	Skin, blood	*F. oxysporum*	Not described	Yes	AMB, VOR, CASPO
Morel et al. [20]	1	ALL	Disseminated	Skin	*Fusarium* spp.	Erythematous lesions with necrotic area	Yes	AMB,CASPO, VOR
Litvinov et al. [21]	10	ALL/AML	Disseminated	Urine, skin, blood, bone marrow	*Fusarium* spp.	NR	Yes (7)	AMB, CASPO, VOR
Schwartz et al. [22]	5	ALL (2), AML, JMML, AA	Disseminated	Skin, sputum, bronchoalveolar lavage, blood, cerebral spinal fluid	*Fusarium* spp.	Lesions with necrotic área (2)	Yes (4)	AMB, VOR
Bhattacharya et al. [23]	1	ALL	Disseminated	Skin	*F. solani*	Blackish necrotic lesions	No	AMB, VOR
Rosanova et al. [24]	15	Burn	Wounds infection, boné, disseminated	Burn wound, blood, bone	*Fusarium* spp.	No skin lesions	Yes (1)	AMB, VOR
Hassler et al. [25]	10	Leukemia, Shwachman–Diamond syndrome	Disseminated	Skin, blood, lung	*Fusarium* spp.	NR	Yes (5)	AMB, VOR, echinocandin

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *AA* aplastic anemia, *LAD* type1—leukocyte adhesion deficiency type 1, *NR* not reported or data not found, *HSCT* hematopoietic stem cell transplant, *JMML* juvenile myelomonocytic leukemia, *HLH* hemophagocytic lymphohistiocytosis

values were high for all antifungals employed in this study; thus, all isolates can be considered resistant to itraconazole and most of them can be more sensitive to voriconazole and amphotericin B.

In general, amphotericin B lipid complex, voriconazole and posaconazole have been recommended or employed for the treatment and prophylaxis of fusariosis in adults, although clinical response to them may be considered only modest [3, 37]. This poor activity shown by monotherapies against invasive fusariosis has induced the use of different combination regimens [38–42]. However, no firm recommendation can be provided as there are no statistical studies comparing combination therapy and monotherapy for effectiveness.

There are scarce data on fusariosis treatment in children and minimal data to address evidence-based strategies. Thus, pediatric-specific recommendations on the treatment of invasive fusariosis are mainly based on experiences with adults [6, 43]. Three patients in this study were treated with a combination between amphotericin B lipid complex and voriconazole, and one patient was treated with voriconazole, resulting in resolution of the infection. The only death, as mentioned above, was not specifically related to fusariosis. Although amphotericin B is one of the main agents of choice, voriconazole has been related to successful treatments of disseminated fusariosis in patients with hemato-oncologic malignancies of refractory fungal infections [5, 25, 44]. Nucci et al. [45] reported that the survival rate of patients with invasive fusariosis has increased during the last decade, which was associated with a more frequent use of voriconazole or combination therapies. Posaconazole, recommended for salvage treatment of fusariosis, has been scarcely reported for the pediatric population [46], since the dosage of this compound is still unclear for patients younger than 12 years [6].

Detailed studies on antifungal susceptibility profiles have supported that there are regional differences in the distribution of *Fusarium* species, as well as species-specific differences in antifungal susceptibility patterns, emphasizing the need of species-level identification for best adapted treatment strategies [47].

Diagnosis of *Fusarium* infections usually requires isolation and identification of the infecting pathogen. Currently, the diagnostic tools employed in the hospital laboratory have changed from classic morphological determination of the etiological agent, which sometimes involves prolonged culturing to obtain all structures necessary for species identification, to more rapid DNA- or peptide-based diagnostic tools. Recent studies have shown that morphology alone is not always enough to determine and characterize complex species [48, 49]. Identification of a *Fusarium* isolate based on its phenotype or only to section level might be erroneous in approximately 50% cases [50]. Molecular identification has been currently seen as the best option for species-level identification after culturing *Fusarium* from a patient [6].

Diagnostic and therapeutic challenges related to fusariosis demand further studies. This infection represents a serious problem for children with compromised immunity, highlighting the need for health professionals to be aware of the problems that invasive nosocomial fungal infections may cause to these patients, especially those admitted to high-risk units such as hematology and oncology units. Thus, the present study supports the importance of constant microbiologic investigation among children with suspected invasive fungal infections in order to obtain early etiologic diagnosis and, therefore, adequate antifungal therapy, especially for deep and disseminated infections.

Acknowledgements We would like to thank "Fundação de Amparo à Pesquisa do Estado de São Paulo" (Fapesp - 2014/16507-0) for financial support and Letícia Campos for English review.

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