Invasive Fusariosis in Patients with Hematologic Diseases

Subjects: Allergy

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Invasive fusariosis is a serious fungal disease affecting high-risk hematologic patients, especially AML patients receiving induction remission chemotherapy and allogeneic HCT recipients. The most frequent clinical presentation is disseminated disease, with fever, metastatic skin lesions, pneumonia, and positive blood cultures. The outcome is largely dependent on recovery of host defenses, with virtually a 100% death rate in persistently neutropenic patients, despite monotherapy or combination antifungal therapy.

Keywords: fusariosis ; fungal infection ; fungemia ; immunocompromised ; neutropenic

1. Introduction

Invasive fungal disease (IFD) is a serious complication in patients with hematologic malignancies, with the highest incidence occurring in patients with acute leukemia and in hematopoietic cell transplant (HCT) recipients [1][2]. Until the 1980s, yeasts, particularly Candida species, were the most frequent agents of IFD. However, with the introduction of fluconazole prophylaxis, IFD caused by molds became more prevalent [3]. While Aspergillus species account for the majority of cases of IFD in hematologic patients, infection caused by other molds, such as Fusarium species, may occur, with a relatively high incidence in some areas of the globe [4].

2. Fungus

Fusarium species are ubiquitous filamentous fungi, commonly found in the soil, plants, and water [4]. They are important agents of disease in plants [5] and are part of water biofilms in hospital water systems worldwide [6][7][8][9]. In non-immunocompromised individuals, the most frequent infections caused by Fusarium species are onychomycosis and keratitis [10][11]. Immunosuppressed patients with hematologic diseases may develop invasive fusariosis, with disseminated skin lesions, positive blood cultures, and a poor outcome [12].

The genus Fusarium comprises more than 300 phylogenetically distinct species, grouped in more than 20 species complexes [13][14]. However, Fusarium species causing disease in humans are grouped into seven species complexes (**Table 1**): Fusarium solani species complex (FSSC) , Fusarium oxysporum species complex (FOSC), Fusarium fujikuroi species complex (FFSC), Fusarium incarnatum-equiseti species complex (FIESC), Fusarium chlamidosporum species complex (FCSC), Fusarium dimerum species complex (FDSC), and Fusarium sporotrichoides species complex (FSAMSC) [15]. Approximately 70% of cases of invasive disease occurring in hematologic patients are caused by FSSC and FOSC [4], but there are geographic differences in species distribution [16][17][18].

Table 1. Most frequent species complexes of the genus *Fusarium* involved in human infections and their respective species within each complex.

Species Complex	Species Complex
***Fusarium solani* species complex**	***Fusarium fujikuroi* species complex**
Fusarium falciforme	***Fusarium acutatum***
Fusarium keratoplasticum	***Fusarium anthophilum***
Fusarium lichenicola	***Fusarium andiyazi***
Fusarium petroliphilum	***Fusarium fujikuroi***
Fusarium pseudensiforme	***Fusarium nygamai***

Species Complex	Species Complex
	Fusarium proliferatum
	Fusarium verticillioides
***Fusarium oxysporum* species complex**	***Fusarium incarnatum-equiseti* species complex**
Fusarium oxysporum	***Fusarium incarnatum***
Unnamed	***Fusarium equiseti***
	Unnamed
***Fusarium sporotrichoides* species complex**	***Fusarium dimerum* species complex**
Fusarium aermeniacum	***Fusarium dimerum***
Fusarium brachygibbosum	***Fusarium delphinoides***
Fusarium langsethiae	***Fusarium penzigii***
Fusarium sporotrichioides	
***Fusarium chlamidosporum* species complex**	
Fusarium chlamidosporum	

The detection of the growth of Fusarium in clinical specimens is not difficult in a routine mycology laboratory. Fusarium species grow rapidly on many media without cycloheximide. The colonies in potato dextrose agar are pink, red, gray, or yellow, with velvety to cottony surfaces. The genus is easily identified by the typical banana-shaped macroconidia. However, species identification requires molecular methods [19] or mass spectrometry using matrix-assisted laser desorption–ionization flight time (MALDI-TOF). The latter has been evaluated in both pure colonies and blood culture bottles, and is the easiest method for species identification [19][20]. Adventitious sporulation is characteristic of Fusarium , and the yeast-like structures, called aleuroconidia, are responsible for the frequent occurrence of positive blood cultures and metastatic skin lesions [12]. In tissue, the hyphae of Fusarium are hyaline, septate with acute-angle branching, with an appearance similar to Aspergillus. Sometimes aleuroconidia are found in tissue together with hyphae, which is suggestive of Fusarium . However, since the appearance of these hyaline hyphae in tissue is quite similar among different fungi, the term hyalohyphomycosis is more appropriate when the genus is not identified. This underscores the importance of culture of tissue biopsy, together with histopathology. If culture is not available or does not grow the fungus, in-situ hybridization in paraffin-embedded tissue may help to define the genus [21].

3. Diagnosis of Invasive Fusariosis

The confirmation of the diagnosis of invasive fusariosis depends on the growth of the organism in culture of biologic materials and/or the demonstration of tissue invasion by hyphae. As mentioned above, the sole demonstration of septate, acute-branching, and hyaline hypha in tissue is not enough to establish the diagnosis of invasive fusariosis as other hyaline molds have the same histopathologic picture. In such circumstances, the most appropriate diagnosis is hyalohyphomycosis.

The most frequent sources of diagnosis are the blood and skin biopsy. Among 84 hematologic patients with invasive fusariosis, the diagnosis was made by culture in 65 patients (77.4%): blood culture (26 cases), culture of a fragment of skin biopsy (18 cases), culture of blood and skin biopsy (12 cases), culture of sinus tract (eight cases), and culture of a bronchoalveolar lavage (BAL) fluid (one case). In the remaining 19 cases, the diagnosis was made by culture and histopathology (blood and skin in 18, and sinus in one) [22]. In another series with 233 cases of invasive fusariosis, detailed information about the diagnosis was available in 224 cases: culture alone in 138 (61.6%), culture and histopathology in 83 (37.0%), and histopathology alone in three. The skin was the main source of diagnosis in 100 cases, followed by blood (85 cases) [23].

Although considered specific for aspergillosis, serum galactomannan, as detected by the Platelia Aspergillus enzyme immunoassay (BioRad), may be positive in infection caused by other fungi, including Fusarium species [24]. We evaluated the performance of serum galactomannan in hematologic patients with invasive fusariosis diagnosed in three centers in Brazil. Among 18 patients, 15 (83%) had at least one positive serum galactomannan test (median of 4 positive tests). Serum galactomannan was positive before the first clinical manifestation of invasive fusariosis in 8 patients, and in 11 before the diagnosis of fusariosis [25]. In other study, we compared the characteristics of 36 patients with invasive

aspergillosis with 26 patients with invasive fusariosis. Serum galactomannan was positive in 88.6% and 73.3% of patients with aspergillosis and fusariosis, respectively, with no differences in the median number of positive tests and galactomannan values [26]. Therefore, in regions where invasive fusariosis is more frequent, patients with lung nodules and positive serum galactomannan may have either aspergillosis or fusariosis.

Another fungal biomarker that has potential in the diagnosis of invasive fusariosis is serum 1,3-β-D-glucan. We evaluated the performance of 1,3-β-D-glucan in 13 patients with invasive fusariosis. Twelve of the thirteen patients (92.3%) had at least one positive 1,3-β-D-glucan serum level (median of four). The test was positive before the diagnosis of invasive fusariosis in 11 of the 12 patients, at a median of 10 days. Comparing this group with a control group of hematologic patients with similar underlying diseases and treatments, the sensitivity, specificity, and positive and negative predictive values of two consecutive positive beta-glucan tests were 85%, 69%, 7%, and 99%, respectively. We concluded that, while the test is positive in the majority of patients with invasive fusariosis, the low positive predictive value strongly limits its usefulness in the diagnosis [24].

4. Management of Invasive Fusariosis

In contrast with the lack of correlation between antifungal susceptibility tests and the outcome, there is a close relationship between immunity and survival. Analyzing prognostic factors in 84 hematologic patients with invasive fusariosis, the 90-day probability of survival was 0% if patients had persistent neutropenia and were receiving corticosteroids, 4% in those with persistent neutropenia only, 30% in patients receiving corticosteroids but not neutropenic, and 67% in patients without any of these two factors [22]. In our analysis of the outcome of 233 cases of invasive fusariosis (215 with hematologic diseases), variables associated with poor outcome (90-day mortality) were again receipt of corticosteroids (HR 2.11), neutropenia at the end of treatment (HR 2.70), and primary treatment with deoxycholate amphotericin B (HR 1.83) [23].

Primary anti-mold prophylaxis is usually indicated in hematologic patients at high risk to develop invasive fusariosis, including AML in induction remission [27] and allogeneic HCT [28]. In patients receiving anti-mold prophylaxis, breakthrough infection may occur, including fusariosis [29][30][31].

Patients with a prior history of invasive mold disease and who will subsequently be exposed to a period of immunosuppression may theoretically be at risk to present with recurrence of the fungal infection. The use of secondary prophylaxis in such circumstances has been well established in invasive aspergillosis [32][33][34], but there is limited data in other mold infections. We evaluated the usefulness of secondary prophylaxis for invasive fusariosis in a multicenter retrospective study of 40 patients who were successfully treated for invasive fusariosis and were exposed to subsequent periods of immunosuppression (neutropenia in 35 and graft versus host disease in 5). Relapse of invasive fusariosis occurred in 2 of 8 patients (25%) who were not on prophylaxis and in 3 of 32 (9.4%) who received secondary prophylaxis (mostly voriconazole). Considering only patients who had prior disseminated fusariosis, relapse occurred in 2 of 2 (100%) not on secondary prophylaxis and in 3 of 26 (11.5%) who received secondary prophylaxis ($p = 0.03$) [35]. In light of these data, we believe that secondary prophylaxis (voriconazole or a lipid preparation of amphotericin B) should be strongly considered in patients with prior invasive fusariosis who will be exposed to subsequent periods of immunosuppression, especially if the disease was disseminated.

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