Advances in Infectious Diseases, **2013, 3, 263-268**
Published Online December 2013 (http://www.scirp.org/journal/aid)
http://dx.doi.org/10.4236/aid.2013.34040

Invasive Fungal Sinusitis in Immunocompromised Patients: A Multicenter, University Hospital Experience in Shiraz

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Received September 28th, 2013; revised October 28th, 2013; accepted November 6th, 2013

ABSTRACT

Objective: It is to determine the causes of invasive fungal sinusitis in patients of Shiraz University hospitals, Iran. **Methods:** This cross-sectional study was conducted during 18 months (from 21 March 2009 till 22 September 2010) in three Shiraz University Hospitals. Thirty-six patients with sings of invasive fungal sinusitis were enrolled, and tissue samples were investigated for histopathology, culture and antifungal susceptibility test. The laboratory results with host factor and sinus computed tomography scan were evaluated for classification of patients as proven, probable and possible invasive fungal sinusitis. **Results:** Thirty-five patients have involved with at least one risk factor (immune compromised disease, diabetes mellitus, or use of immune suppressed drugs). Radiological findings of parasinus invasion or necrosis were present in 20 patients. By histopathology, 21 patients were considered as proven, from these, 17 samples had positive growth. The culture aetiology agents were 4 Candida, 8 Aspergillus, and 5 Mucor. All positive culture samples were matched with histopathology findings. Significant associations were considered for radiologic finding and histopathology and culture ($p < 0.05$). From 8 patients with mucormycosis histopathology, 6 suffered from diabetes mellitus. None of the antifungal agents were effective on these three types of infections. **Conclusion:** DM is the most common predisposing factor for IFS followed by ALL and AML. The most common aetiology of IFS was found to be Aspergillus fumigant followed by Mucormycosis and Candida. None of antifungal agents could successfully cover all the species.

Keywords: Fungal Sinusitis; Mucor Mycosis; Aspergillus; Invasive Fungal

1. Introduction

Opportunistic fungal infections are usually results of immunosuppression and immunodeficiency. Currently several etiologies of immunosuppression lead to increase prevalence of invasive fungal infection (IFI) including leukemia, diabetes mellitus (DM), AIDS, solid organ transplantation, bone marrow transplantation and chemotherapy [1]. All these conditions result in neutropenia which should be treated with wide-spectrum antibiotics. IFI is considered as an important complication of neutropenia which is suspected with persistent fever for 72 - 96 hours after treatment with broad-spectrum antibacterial antibiotic [1-3]. However, since the culture methods are insensitive and radiologic findings are nonspecific, the diagnosis of invasive fungal infection remains a challenge [4]. An international consensus on the diagnosis of opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants was established by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases (MSG-NIAID) [5,6]. Delay in the treatment of invasive fungal infection during neutropenia causes high mortality in patients with transplants and hematological malignancy [4,5,7]. The uncertainty in

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disease diagnosis results in under- or overtreatment of invasive fungal infection. Despite the availability of several new antifungal agents, including triazoles and echinocandins, the effectiveness of antifungal therapy remains uncertain and the effectiveness of neutrophil recovery may not be sufficient if the recovering neutrophils are dysfunctional [8].

Invasive fungal sinusitis (IFS) is a rare disease largely attributable to Aspergillus and Mucor in patients with stem cell transplants and hematological disease [9]. Though the mortality of IFS in immunocompromised patients ranges from 50% to 80% [7,9,10], early physical findings are nonspecific and ambiguous (*i.e.*, nasal obstruction, purulent discharge, and epistaxis). Water's view plain radiographs do not distinguish invasive fungal sinusitis from chronic allergic sinusitis. Bony erosion and tissue destruction are often found only in the advanced stage by computed tomography [11,12]. Recent introduction of serial Aspergillus galactomannan antigen test may provide early evidence of IFS. As data regarding this issue are scarce in our region of southern Iran, we performed this study to determine the epidemiology of IFS and the drug sensitivities of the etiological factors in Shiraz, southern Iran.

2. Materials and Methods

2.1. Study Population

This was a cross-sectional study being performed in Iran during a 1.5-year period from 21 March 2009 till 22 September 2010 including 36 immunosuppressed patients who were further diagnosed to have IFS. Patients with solid organ transplant, hematopoietic stem cell transplants, hematological disease (including severe aplastic anemia, pure red cell aplasia, and hematological malignancy), AIDS and sinusitis diagnosed during their hospital stay were enrolled in this study. Demographic features, history of bone marrow transplant, history of neutropenia (ANC < 500/mL), hematological disease status, underlying medical diseases, prolonged corticosteroid therapy (>3 weeks), receiving nucleoside analogue and T-cell suppressor during the previous 3 months and congenital immunodeficiencies were recorded in a questionnaire. The study protocol was approved by the institutional review board of Shiraz University of Medical Sciences and all required patients provided their informed written consents.

2.2. Sinusitis Diagnosis

During the study period, those immunosuppressed patients who developed sinusitis were routinely underwent sinus X-ray evaluation and afterwards, otolaryngologist was consulted for focal evaluation and tissue culture. CT and MRI sinus study, surgical biopsy and debridement were performed according to clinicians' decision.

IFS was diagnosed according to EORTC/MSG-NIAID consensus criteria in 2008 [5,6]. The host factors included prolonged neutropenia (<500 neutrophils/mm^3 for >10 days) temporally related to the onset of fungal disease, receipt of an allogeneic stem cell transplant, prolonged use of corticosteroids, immunosuppressive agents, or nucleoside analogues during the past 90 days. The clinical criteria included imaging showing sinusitis plus at least one of the following three signs: acute localized pain, nasal ulcer with black eschar, extension from the paranasal sinus across the bony barrier. The microbiological criteria included culture or isolation of fungus from surgical material or sinus aspirate samples, and detection of Aspergillus galactomannan antigens in serum. All the samples were cultured in Sabouraud Dextrose Agar media and sensitivity to amphotericin B 1, capsofungin acetate, voriconazole, itraconazole, ketokonazol were further examined.

2.3. Proven, Probable, and Possible Invasive Fungal Sinusitis

Proven, probable, and possible IFS were defined mainly according to the EORTC/MSG-NIAID criteria [5,6]. Proven IFS was defined by the presence of fungi associated tissue damage on histopathologic examination of a biopsy specimen; or positive culture result, consistent with infection, from a sample obtained aseptically from a clinically or radiologically abnormal site. Probable IFS was defined by the presence of at least one host factor criterion, one microbiological criterion, and one clinical criterion. Possible IFS was defined by the presence of at least one host factor criterion and one clinical criterion.

2.4. Statistical Analysis

Statistical analyses were performed using the SPSS software, version 16.0 (SPSS Inc., Chicago, Ill., USA). The chi-square test was used to compare the proportions between groups. The results are expressed as mean ± SD and proportions as appropriated. A two-tailed p-value less than 0.05 was considered statistically significant.

3. Results

Overall we included 36 patients among whom there were 15 (41.6%) man and 21 (58.4%) women. The mean age of the patients was 40 years with maximum age of 70 years. Sixteen (44%) of the patients were diagnosed to have DM. Thirty patients had at least one co-morbidities or sinus destruction. The most common predisposing condition was ALL in 5 and AML in 5 followed by sinus surgery in 3, CML in 3, CLL in 1, major β-thalassemia in 2, aplastic anemia in 1, Hodgkin's lymphoma in 1, non-Hodgkin's lymphoma in 2 and other diseases (congenital

immmunodeficiencies, polycythemia vera) in 7. Bone marrow transplantation was performed in 19.4% of patients. Overall, 47.2% received immunosuppressant and 41.7% received cytotoxic agents. Twenty-three patients were on anti-fungal treatment at time of inclusion in the study. Regarding clinical signs, 31 (86.1%) had nasal congestion while 30 (83.3%) had facial pain and 18 (50%) had epistaxis. Ocular involvement was reported in 9 patients and 11 patients had neurological involvement. Unilateral involvement of VII nerve and bilateral involvement of III were the most common neurological complications. Radiological signs of sinus invasion were reported in 20 (55.6%) patients out of which 18 (50%) had clinical signs of nasal, orbital or palate involvement. Severe neutropenia was reported in 11 (30.6%) of patients (**Table 1**).

Overall 21 samples tested positive for KOH including 1 Yeast and Boding Yeast, 3 Pseudo Hyphae, 9 Septated Hyphae and 8 Nonseptated Hyphae. However 16 samples had positive cultures including 4 Candida (2 Candida albicans, 1 Candida glabrata and 1 Candida krusei), 6 Aspergillus flavus, 1 Aspergillus fumigates and 5 Mucormycosis. The culture results had 100% concordance with KOH results (**Table 2**). Posaconazole and Fluconazole were found to have intermediate sensitivity (SDD). This means that the resistance can be overcome by increase in dose. Mucormycosis infection was significantly associated with DM ($p < 0.05$). Fifteen out of 18 patients with signs of local invasion were further found to be proven infection ($p < 0.05$). The most common aetiology of IFS was found to be Aspergillus fumigates followed by Mucormycosis and Candida. None of antifungal could successfully cover all the species. Voriconazole was found to be appropriate for treatment of Aspergillus and Candida while Amphotericin B was found to be appropriate for treatment of Mucormycosis. Posaconazole was found to be effective on both Aspergillus and Mucormycosis.

4. Discussion

In most developing countries, increased prevalence of resistant fungal infections and lack of appropriate diagnostic facilities is an important health issue. In addition, the number of patients suffering from immunodeficiencies is increasing dramatically in these countries. In this study we found that DM is the most common predisposing factor for IFS followed by ALL and AML. The most common aetiology of IFS was found to be Aspergillus fumigates followed by Mucormycosis and Candida. Chen and colleagues [13] demonstrated that IFS occurred in 1.77% of hospitalized patients with hematological disorders. IFS caused significantly higher mortality in AML patients with prolonged neutropenia (>10 days). IFS developed more frequently in patients with AML, myelodysplastic syndrome, and aplastic anemia, but not at all in patients with lymphoma/myeloma. In the literature review, most patients with lymphoma who developed IFS are recipients of myeloablative allogeneic stem cell transplants [14-18]. Compared with other subtypes of hematological malignancy, patients with AML have significantly higher risk of IFS. The risk of developing IFS in AML relates to neutropenia and less to the intensity of chemotherapy regimens.

Prolonged neutropenia in patients with myeloid malignancies may contribute to underlying disease, intensity and dosage of chemotherapy, colony-stimulating factor, and concurrent medication. Invasive mold infection often occurs when a large burden of spores from an environmental source is deposited on mucosal membranes lacking an effective phagocytic host defense [19]. Using cytokine growth factors to decrease the period of chemotherapy-associated neutropenia and using laminar air flow rooms for protection against IFS [20] may reduce the risk of IFS after allogeneic stem cell transplantation [21].

The clinical mycological spectrum of IFS is limited in patients with stem cell transplants and hematological disease [14-18]. Aspergillus and Mucor are the main mold found in biopsy, however, the prevalence is highly variable in different geographic regions [14-18,22,23]. Chen and colleagues [13] founded that Aspergillus flavus (44%) was the most common isolate which is in concordance with our study. Aspergillus flavus, with its unique ability to survive at higher temperatures, is the predominant pathogen in countries, including most of the Middle East,

Table 1. Clinical and host factors of local invasion in 36 patients suffering from invasive fungal sinusitis (IFS).

	Number	Admission in previous 3 months	DM	Radiological signs of local invasion	Tissue necrosis signs
Proven	21	12	12	18	15
Probable	4	1	2	1	2
Possible	7	2	1	0	0
No IFS	4	2	1	1	1
ALL	36	17	16	20	18

Table 2. Culture and antibiogram results of 36 patients suffering from invasive fungal sinusitis (IFS).

Organism	Antifungal	Resistant	Sensitive	Range	MIC 50%	MIC 90%
Aspergillus (*n* = 7)	Amphotericin B	5	3	0.5 - 16	0.75	16
	Ketoconazole	0	8	0.5 - 3	1	3
	Itraconazole	2	6	0.047 - 32	0.125	32
	Posaconazole	0	8	0.047 - 0.19	0.19	0.19
	Caspofungin	0	8	0.32 - 0.5	0.094	0.75
	Voriconazole	0	8	0.94 - 0.5	0.19	0.5
Mucormycosis (*n* = 5)	Amphotericin B	0	5	0.063 - 0.75	0.125	0.75
	Ketoconazole	1	4	0.25 - 4	0.25	4
	Itraconazole	4	1	0.29 - 64	0.29	64
	Posaconazole	0	5	0.75 - 2	0.75	2
	Caspofungin	4	1	0.14 - 32	4	32
	Voriconazole	3	2	1.15 - 16	1.25	16
Candida (*n* = 4)	Amphotericin B	0	4	0.5 - 1	0.75	1
	Ketoconazole	1	3	0.125 - 32	1	32
	Itraconazole	3	1	0.032 - 32	2.5	32
	Posaconazole	2	2	0.094 - 32	0.25	32
	Caspofungin	0	4	0.125 - 0.29	0.125	0.29
	Voriconazole	0	4	0.032 - 0.75	0.25	0.75
	Nystatin	0	4	4.6 - 9.25	4.6	9.25
	Fluconagole	1	3	0.25 - 64	24	64
Total (*n* = 16)	Amphotericin B	5	12	0.063 - 61	0.5	4
	Ketoconazole	2	15	0.125 - 32	1	2
	Itraconazole	9	8	0.032 - 64	0.29	32
	Posaconazole	2	15	0.047 - 32	0.19	2
	Caspofungin	4	13	0.125 - 32	0.125	4
	Voriconazole	3	14	0.032 - 16	0.25	2

Africa, and Southeast Asia [24,25]. Rare IFS in Asia and Africa were reported, the clinical response varies differently with fungal subtypes, and further epidemiology study should be investigated. Mucormycosis is an emerging cause of IFS with a rapid fatal course in patients with hematological disorders [26,27]. Effective treatment for Mucormycosis should be investigated.

The symptoms and signs of paranasal sinusitis (such as nasal discharge, stuffiness, epistaxis, periorbital swelling, and maxillary tenderness) are nonspecific for IFS [28]. Symptoms and signs such as nose ulceration, eschar of the nasal mucosa, black necrotic lesions, and perforation of the hard palate are more specific, but these findings are present only at an advanced stage [29]. The use of CT and MRI in the diagnosis of invasive fungal sinusitis has been reported [12]. Diagnostic radiological evidence of invasive fungal sinusitis includes erosion of sinus walls, extension of infection to neighboring structures, and extensive skull base destruction. However, most patients do not have classic findings in the early phase of invasive fungal sinusitis. Earlier diagnosis by using serial Aspergillus galactomannan antigen test in the modern medical era to detect IFS, may lead to early introduce anti-fungal agent and surgical debridement, and potentially decreas-

ed morbidity and mortality in high risk patients.

5. Conclusion

In conclusion, DM is the most common predisposing factor for IFS followed by ALL and AML. The most common aetiology of IFS was found to be Aspergillus fumigant followed by Mucormycosis and Candida. None of antifungal agents could successfully cover all the species.

6. Acknowledgments

This research project was financially supported by Health Policy Research Center affiliated with Shiraz University of Medical Sciences. Also, there is no conflict of interest to be declared regarding this manuscript.

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