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Original Article

Acute Fulminant Fungal Sinusitis in Patients with Acute Leukemia

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Abstract

Background: Acute fulminant fungal sinusitis is a rapidly progressive disease with high mortality (50-80%) and occurring with increasing frequency in patients with acute leukemia. The purpose of the present study was early diagnosis of this lethal infection.

Methods: In a cross-sectional study, 142 patients with hematological malignancies were studied immediately by initiation of chemotherapy to determine early clinical and radiological findings of invasive fungal sinusitis. This infection was confirmed by pathological and mycological methods.

Results: Acute fulminant fungal sinusitis was diagnosed in 8 patients with acute leukemia. The most common isolated fungi was *Aspergillus flavus* (n= 5) followed by *Aspergillus fumigatus* (n= 2) and *Rhizopus* sp. (n= 1). Despite prompt surgical and medical therapy, the disease in our patients was very aggressive with a rapid clinical course and high mortality.

Conclusion: The present report shows the poor prognosis of invasive fungal sinusitis in neutropenic patients; the necessity to take intensive preventive measures and the application of new diagnostic methods for early detection of fungal infection in these high risk patients.

Key words: Aspergillus, *Leukemia, Neutropenia, Sinusitis, Iran*

Introduction

Acute fulminant fungal sinusitis has an invasive and destructive nature and mainly occurs in immunocompromised patients. The prognosis is poor and mortality has been reported to be as high as 50-80% (1-6). Fever, headache, nasal obstruction and facial swelling in an immunocompromised patient may be the earliest indication of this disease (1-3, 7). Although computed tomography scanning (CT scan) of invasive fungal sinusitis (IFS) is non specific, but opacification of sinuses, bony destruction and soft tissue edema, indicate severe inflammatory process in sinuses (1, 8-10). Definitive diagnosis is made only by tissue biopsy and culture (1, 6, 11, 12).

Since early diagnosis of acute fulminant fungal sinusitis is essential to start urgent treatment and improvement outcome of patients, better comprehension of presenting clinical features in high- risk individuals leads to early diagnosis and prompt surgical and medical treatment.

This study shows cases of acute fulminant IFS in patients with acute leukemia and identifies early clinical features and evaluates diagnostic methods.

Materials and Methods

This cross-sectional study was done from August 2003 through January 2006 at Namazi Hospital in Shiraz, Iran. One hundred forty two leukemic patients who were undergoing chemotherapy were studied immediately by initiation of treatment for clinical and radiological findings, suggestive of fungal sinusitis. Paranasal sinus X-ray and CT scan were done in patients with fever,

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headache, rhinorrhea, nasal obstruction and facial swelling and they underwent endoscopic sinus surgery if there were mucosal thickening, opacification of sinuses, airfluid level and other lesion compatible with sinusitis on radiological imaging. IFS was diagnosed if hyphae within sinus mucosa, submucosa, blood vessels or bone were seen in sections stained with Hematoxylin and eosin (H & E) and Gomori methenamin silver (GMS). To identify causative agent, all specimens were examined by direct microscopy after treatment of a preparation with potassium hydroxide (KOH), Gram and Giemsa stains. A portion of each tissue biopsy were inoculated on sabouraud, sabouraud with chloramphenicol and brain heart infusion agar media and incubated at 25 and 37^{o} C. Patients with acute fulminant fungal sinusitis underwent aggressive surgical debridment and systemic antifungal therapy with amphotericin B.

Results

In the present study from 142 patients with hematological malignancies who were undergoing chemotherapy, 45 patients presented clinical symptoms presumptive of fungal sinusitis, but CT scan of paranasal sinuses of these patients showed varying degree of mucosal edema and some amounts of opacification of sinuses in 17 cases. Direct microscopic examination of the biopsy materials, from these 17 patients showed only branched septate hyphae in7 patients and aseptate hyphae in one patient. Mycological culture of the samples also yielded pure growth of fungi in above mentioned 8 cases and most commonly isolated fungi was *Aspergillus flavus* (n= 5) followed by *Aspergillus fumigatus* (n= 2) and *Rhizopus* sp. (n= 1). Histopathological examination of the specimens also revealed tissue invasion by fungal elements in those cases and branching septate (Fig. 1, 2) and broad branched aseptate hyphae (Fig. 3) were seen in tissue sections. Therefore, 5.6% of the patients were found to have IFS during the study period.

The clinical features of the patients with IFS in this study are summarized in Table 1. All of the patients had acute leukemia (AML and ALL), the mean age of them were 23.8 yr (range 17-48 yr), two were female and six were male. The common clinical findings were fever, headache and facial swelling and the mean duration symptoms were 12.7 d. Only 3 patients survived and they did not have any permanent disability. These patients were followed for 6 months and none of them showed any sign of recurrence. Disease never developed in 9 patients with negative results on biopsy.

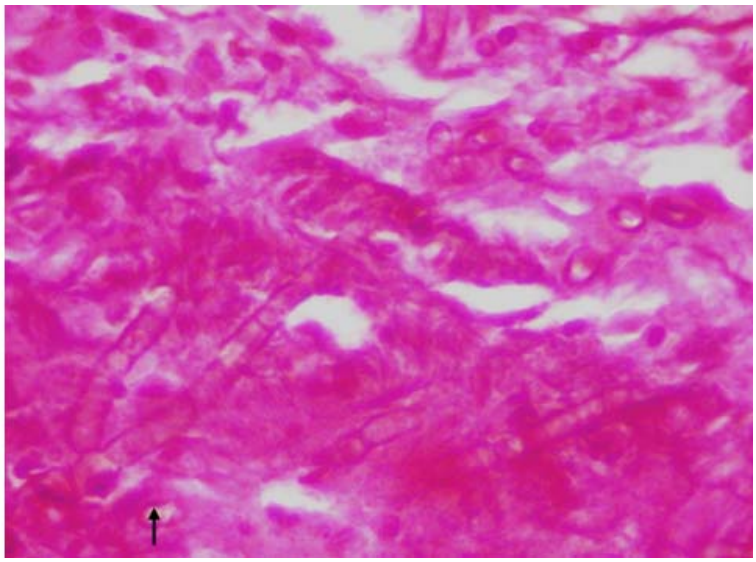

Fig. 1: Aspergillosis of paranasal sinus. Dichotomous hyphae of *Aspergillus flavus*(H &E, x1000)

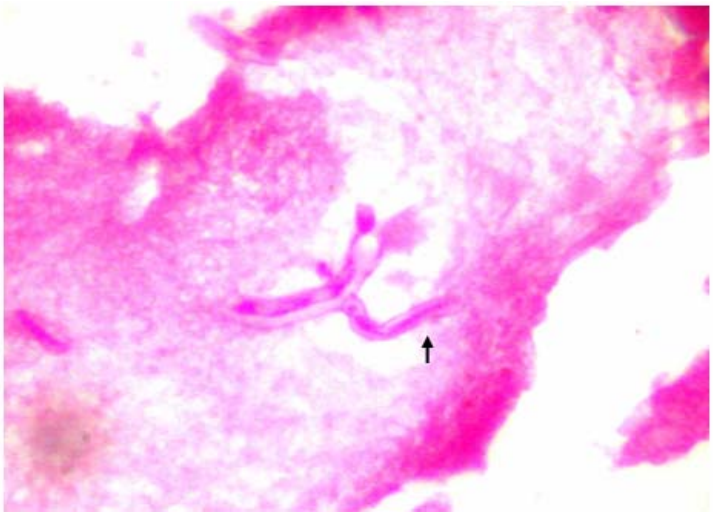

Fig. 2: Aspergillosis of paranasal sinus. Hyphae of *Aspergillus fumigatus*(H&E, x1000)

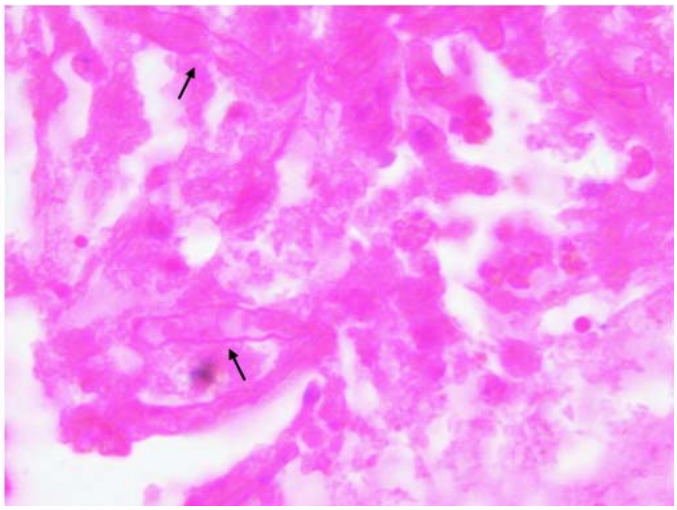

Fig. 3: Zygomycosis of paranasal sinus. Broad aseptate hyphae of *Rhizopus* sp. (H&Ex1000)

Table 1: Isolated fungi and clinical data of patients with fulminant fungal sinusitis

Case No.	Age (yr) & Sex	Clinical presentation	Duration of symptoms(d)	Underlying condition	Isolated fungi	Outcome of patients
1	48-Male	Fever, rhinorrhea, nasal obstruction	7	AML-M1	*A. flavus*	Alive
2	18-Male	Fever, headache	34	AML-M2	*A. flavus*	Died
3	18-Male	Fever, facial swelling	15	ALL-L2	*A. flavus*	Died
4	20-Female	Fever, headache, facial swelling	5	AML-M2	*A. flavus*	Died
5	17-Male	Headache, rhinorrhea	7	AML-M2	*A. funigatus*	Alive
6	36-Female	Fever, facial swelling	16	AML-M4	*Rhizopus* sp.	Died
7	17-Male	Fever, headache, facial swelling	10	ALL-L2	*A. flavus*	Died
8	17-Male	Fever, headache	8	ALL-L2	*A. funigatus*	Alive

ALL= Acute lymphoblastic leukemia
AML= Acute mylogenous leukemia
Fever= Fever persisting more than 48 hours

Discussion

Acute fulminant fungal sinusitis is an invasive and destructive infection with high mortality and occurring with increasing frequency in patients with acute leukemia (2, 3, 6, 13). Since the diagnosis of this infection is confirmed often too late, a high degree of awareness and effort is essential for an early diagnosis to improve the outcome of patients. It is suggested that IFS begins in the nasal cavity following inhalation of environmental spores and mucosal disruption by immunodeficiency to allow proliferation of fungi and initiation of infection. Angiocentric invasion leads to tissue ischemia and necrosis, gives a typical white or black discoloration of nasal mucosa suggesting the earliest manifestation of such infections. Therefore, a careful look at the middle and inferior turbinate, the septum and the floor of the nose is warranted (2, 3, 7, 14). Although varying degree of macroscopic changes in the appearance of the nasal mucosa were seen in our patients but unlike other reports these signs appeared late, when clinical symptoms had occurred. The common initial symptoms in these patients were persistent fever, followed by headache and facial swelling. These findings were similar with other reports (2, 15, 16), but the disease was very aggressive in our patients, they showed a rapid clinical course and despite early diagnosis and aggressive therapy, all but three died within a median time of two weeks from onset of clinical symptoms. These findings may be due to severe neutropenia secondary to use of intensive newer and stronger chemotherapy regimens that resulted in greater immunodeficiency and more fulminant course of fungal infection. In addition, this patient group had a decreased inflammatory response with subtle initial symptoms in the early stages of the disease. However within a short period of time infection rapidly spread from its primary site in the nasal cavity to involve surrounding structures (15-17). For early diagnosis of IFS in high risk patients, before the fungi can cause extensive destruction and intracranial spread, a nasal biopsy could be done even if the nasal mucosa appears normal because survival improves if the disease is limited to nasal or sinus cavities (18-20).

Studies have shown that the incidence of filamentous fungal infection is increasing in immunocompromised patients and almost all cases of IFS caused by moulds. Among filamentous fungi, *A. fumigatus* and *A. flavus* are the two most frequent etiologies of IFS (21-25). But unlike other studies implying to *A. fumigatus* as the commonest etiologic agent of IFS (15, 24), in our study, *A. flavus* was the commonest isolated fungi. This finding is compatible with other studies in Sudan, Southern Arabia and some other reports (2-4). Approximately 8-12% of fungal infections in patients with hematologic diseases have been found to be caused by the mucorals and rhinocerebral mucormycosis being usually a rapidly progressive disease with high mortality (16, 21, 25, 26). In this study a 36 yr old woman with AML had fulminant invasive fungal infection of the sinonasal tract which was caused by *Rhizopus* sp. and extended rapidly to the orbit and brain. This patient died about two weeks from onset of clinical symptoms, in spite of aggressive surgical and medical therapy. This finding shows the fulminate course of mucormycosis and the importance of early diagnosis of the infection before appearance of clinical manifestation.

In conclusion, IFS in leukemic patients who are undergoing chemotherapy has a rapid and fulminant course with high mortality. Survival of patients from this life threatening problem is depended on the early diagnosis and aggressive surgical and medical therapy and correction of the immunological deficits. But clinical symptoms can be subtle and CT scans of sinuses usually are not specific and do not correlate well with pathological findings. Nasal endoscopy with biopsies contributes to confirmation of diagnosis. A nasal biopsy also may be considered for early diagnosis of this infection even if the nasal mucosa appears normal.

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The authors declare that they have no conflict of interests.

References

1. Sohail MA, Al Khabori M, Hyder J, Verma A (2001). Acute fulminant fungal sinusitis: Clinical presentation, radiological findings and treatment. *Acta Trop*, 80(2):177-85.
2. Chakrabarti A, Sharma SC (2000). Paranasal sinus mycoses: *The Indian J Chest Dis and Allied Sci*, 42(4):293-304.
3. Al-Bhlal LA (1996). Fungal infection of the nasal cavity and paranasal sinuses: review of 26 cases. *Annals of Saudi Medicine*, 16(6): 615-621.
4. Dunn JJ, Wolfe MJ, Trachtenberg J, Kriesel JD, Orlandi RR, Carroll C (2003). Invasive fungal sinusitis caused by *Scytalidium dimidiatum* in a lung transplant recipient. *J Clin Microbiol*, 41(12): 5817-19.
5. Samadi DS, Goldberg AN, Orlandi RR (2001). Granulocyte transfusion in the management of fulminant invasive fungal rhinosinusitis. *Am J Rhinol*, 15(4) 263-65.
6. Malhotra PS, Danahey D, Sidman J (2001). Bilateral lateral rhinotomy incisions for medial maxillectomies in the management of pediatric invasive fungal sinusitis. *Laryngoscope*, 111(11pt1): 1960-63.
7. Richardson MD, Warnok DW (2003). *Fungal infection: diagnosis and management* 3 rd ed. Blackwell, Massachusetts, pp.:162, 233.
8. DelGaudio JM, Swain RE Jr, Kingdom TT, Muller S, Hudgins PA (2003). Computed tomographic findings in patients with invasive fungal sinusitis. *Arch Otolaryngol Head Neck Surg*, 129(2): 236-40.
9. Howells RC, Ramandan HH (2001). Usefulness of computed tomography and magnetic resonance in fulminant invasive fungal rhinosinusitis. *Am J Rhinol*, 15(4):255-61.
10. Liu M, Zhou B, Liu HC, Zhang SZ, Wang YX, Huang Q (2003). Acute fulminant invasive fungal sinusitis. *Zhonghua Er Bi Yan Hou Ke Za Zhi*, 38(4): 251-54.
11. Erkilic S, Aydin A, Bayazit YA, Güldüre E, Deniz H, Bayazit N, et al. (2003). Histopathologic assessment of fungal involvement of the paranasal sinuses in Turkey. *Acta Otolaryngol*, 123(3): 413-16.
12. deShazo RD, O'Brien M, Chapin K, Soto-Aguilar M, Gardner L, Swain R (1997). A new classification and diagnostic criteria for invasive fungal sinusitis. *Arch Otolaryngol Head Neck Surg*, 123(11): 1181-88.
13. Walsh TJ, DE Pauw B, Anaissie E, Martino P (1994). Recent in the epidemiology, prevention and treatment of invasive fungal infections in neutropenic patients. *J Med and Vet Mycol*, 32(supplement 1): 33-51.
14. Milroy CM, Blanshard JD, Lucas S, Michaels L (1989). Aspergillosis of the nose and paranasal sinuses. *J Clin Pathol*, 42:123-27.
15. Hunt SM, Miyamoto RC, Cornelius RS, Tami TA (2000). Invasive fungal sinusitis in the acquired immunodeficiency syndrome. *Otolaryngol Clin North Am*, 33(2):335-47.
16. Lerchenmuller C, Goner M, Buchner T, Berdel WE (2001). Rhinocerebral zygomycosis in a patient with acute lymphoblastic leukemia. *Ann Oncol*, 12(3): 415-19.
17. Hope WW, Walsh TJ, Denning DW (2005). The invasive and saprophytic syndrome due to *Aspergillus* spp. *Med Mycol*, 43 (supplement 1): 5207-38.
18. Gillespie MB, Huchton DM, O'Malley BW (2000). Role of middle turbinate biopsy in the diagnosis of fulminant invasive fungal rhinosinusitis. *Laryngoscope*, 110(11): 1832-36.

19. Gillespie MB, O' Malley BWJr, Francis HW (1998). An approach to fulminant invasive fungal rhinosinusitis in immunocompromised host. *Arch Otolaryngol Head Neck Surg*, 124(5): 520-26.
20. Otto KJ, Delgaudio JM (2006). Invasive fungal rhinosinusitis: what is the appropriate follow up? *Am J Rhinol*, 20(6): 582-85.
21. Wehl G, Hoegler W, Kropshofer G, Meister B, Fink FM, Heitger A (2002). Rhinocerebral Mucormycosis in a boy with recurrent acute lymphoblastic leukemia: long term survival with systemic antifungal treatment. *J Pediatr Hematol Oncol*, 24(6): 492-94.
22. Pasqualotto AC (2008). Differences in pathological and clinical syndromes due to Aspergillus fumigatus and Aspergillus flavus. *Med Mycol*, 25: 1-10.
23. Antoine GA, Gates RH, Park AO (1998). Invasive aspergillosis in a patient with aplastic anemia receiving amphotericin B. *Head Neck Surg*, 10(3):199-203.
24. Horré R, Schumacher G, Marklein G, Krömer B, Wardelmann E, Gilges S, et al. (2002). Case report. Maxillary sinus infection due to *Emericella nidulans. Mycoses*, 45: 402-5
25. Wali YA, Al Lamki Z, Al Kindi H, Taqi AM, Shah W, Soliman H(2001). Case report, successful outcome of invasive nasal sinus zygomycosis in a child with relapsed acute lymphoblastic leukemia due to liposomal amphotericin B. *Mycoses*, 44(5):195-99.
26. Parikh SL, Venkatraman G, Delgaudio JM (2004). Invasive fungal sinusitis: A 15 year review from a single institution. *Am J Rhinol*, 18(2): 75-81.