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# Invasive Fungal Rhinosinusitis: 41 cases

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**ABSTRACT**

*Acute invasive fungal rhinosinusitis occurs almost exclusively in patients with immunodeficiency, particularly cellular immunodeficiency. AIFRS rapidly spreads through nasal mucosa and sinus to the orbit and brain. Necrosis and vascular invasion are characteristics of AIFRS. Diagnosis is made by biopsy and obvious fungal invasion associated with necrosis in the nasal mucosa and underlying bone. High mortality rate has been reported in these patients (50-80%). This case study reviewed patients treated for AIFRS in 2012 to 2014. Diagnosis was based on clinical course of acute disease (less than 4 weeks) and fungal invasion confirmed by the pathology. Among 41 patients with AIFRS, fever was the most common initial manifestation (n = 33, 80.5%). Involvement of orbit (100% vs. 18.2%, p<0.001,) skull base (100%, p=0.001) palate and nasal floor (83.3% vs. 15.2%, p=0002) and lateral nasal wall (50.0% vs. 6.1%, p=0.019) was significantly higher in died patients than the improved patients. Recovery was reported in 80% of patients receiving endoscopic and pharmaceutical treatment. Early treatment of patients with sinus mucormycosis using endoscopic surgery improves overall survival. Poor prognosis was associated with extranasal involvement such as orbit and central nervous system (CNS) involvement.*

**Keywords:** Acute invasive fungal rhinosinusitis, survival

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## INTRODUCTION

Fungal rhinosinusitis includes a wide range of pathological and immune responses in the form of allergic granulomatous invasive sinusitis. However, there is no census about its exact classification and labeling [1]. In the most accepted classification, fungal rhinosinusitis is divided pathologically into invasive and non-invasive groups. Invasive fungal sinusitis itself involves three groups including granulomatous, chronic invasive and acute invasive [2]. Acute invasive fungal rhinosinusitis (AIFRS) is a potentially fatal infection which often occurs in patients with immunodeficiency [3]. AIFRS occurs in patients with immunodeficiency in less than 4 weeks course of the disease [4]. Two diagnostic criteria are proposed for AIFRS: 1) sinusitis is confirmed by imaging; 2) histopathological evidence indicates hyphae in sinus mucosa, submucosa, blood vessels or bone. Presence of hyphae in sinus mucosa is specific for tissue invasion. Hyphae is absent in mucosa of patients with chronic bacterial sinusitis or patients with allergic fungal sinusitis and mycetoma [2]. Early diagnosis and treatment, including aggressive surgical debridement, antifungals, and modification of risk factors are essential for improvement of AIFRS [5]. AIFRS occurs almost exclusively in patients with immunodeficiency, particularly cellular immunodeficiency. AIFRS rapidly spreads through nasal mucosa and sinus to the orbit and brain. Necrosis and vascular invasion are characteristics of AIFRS. Diagnosis is made by biopsy and obvious fungal invasion associated with necrosis in the nasal mucosa and underlying bone. High mortality rate has been reported in these patients (50-80%) [6-8]. This

study addressed patients with AIFRS and their prognostic factors. Demographic data, symptoms, underlying diseases, treatment results and prognostic factors of the patients are presented as follows.

## MATERIALS AND METHODS

This case study reviewed patients treated for AIFRS in 2012 to 2014. Medical documents were reviewed in terms of demographic data, clinical symptoms, medical and surgical treatment and clinical outcomes. Diagnosis was based on existing guidelines [9] including acute clinical course (less than 4 weeks) and fungal invasion on sinus mucosa, submucosa, or bone confirmed in pathology. Treatment included anti-fungal regimen and endoscopic and open surgery. Differentiation of mucor and aspergillus was based on pathology. Involvement of orbit and CNS, involved sites and their number were determined by imaging and intraoperative findings. The results provided an overview of AIFRS symptoms, treatment, survival and relevant factors. Data distribution was compared between improved patients, lost patients and all patients as a whole. The collected data was analyzed by SPSS software, version 19. Quantitative data was reported as mean ± SD; qualitative data was reported as numbers (%). T-test was used to measure differences in quantitative variables between the two groups; chi-square test was used to measure differences in qualitative variables between the two groups (p=0.05).

## RESULTS

In 2011-2014, 41 patients were diagnosed with AIFRS (mean age 15.1 ± 34.8). Prevalence of the disease was slightly higher in males than females (n= 25, 61% vs. n = 16, 39%). Immunodeficiency resulted from hematologic malignancies (n=36, 87%), diabetes (n=3, 7.3%) and cirrhosis in HCV (n=2, 4.9%), respectively. Pathology found mucor organism in 80.5% (n = 33), aspergillus in 17% (n = 7) and both in one patient. Initial manifestation of the improved patients compared to the lost patients included fever (n = 30, 90.9% vs. n = 2, 33.3%), visual symptoms (n = 3, 9.1% vs. n = 2, 33.3%) and central nervous system (n = 0, 0.0% vs. n = 2, 33.3%). All patients (n = 41, 100%) were treated with amphotericin and 24% (n = 10) received GCSF at the same time.

**Table 1: statistical result**

| Variable | | Total patients | Improved patients | Lost patients | P value |
|---|---|---|---|---|---|
| **Age** | | 34.87±15.12 | 33.57±14.93 | 41.83±17.81 | 0.324 |
| **Gender** | Male | 25 (61%) | 19(57.6%) | 5(83.3%) | 0.376 |
| | Female | 16(39%) | 14(42.4%) | 1(16.7%) | |
| **Cause of immunodeficiency** | Blood | 36(87%) | 33(100%) | 2(33.3%) | <0.001 |
| | Diabetes | 3(7.3%) | 0.00 | 2(33.3%) | |
| | Clinical | 2(4.9%) | 0.00 | 2(33.3%) | |
| **Initial manifestation** | Sight | 6(14.6%) | 3(9.1%) | 2(33.3%) | .003 |
| | CNS | 2(4.9%) | 0(0.0%) | 2(33.3%) | |
| | Fever | 33(80.5%) | 30(90.9%) | 2(33.3%) | |
| **Organism** | Mucor | 33(80.5%) | 26(78.8%) | 6(100.0%) | .244 |
| | Aspergillus | 7(17.1%) | 6(18.2%) | 0(0.0%) | |
| | Both | 1(2.4%) | 1(3.0%) | 0(0.0%) | |
| **Anti-fungal drug** | Amphotericin | 41(100%) | 33(100.0%) | 6(100.0%) | |
| | GCSF | 10(24.4%) | 9(27.3%) | 0(0.0%) | .305 |
| | Etc. | 12(29.3%) | 7(21.2%) | 4(66.7%) | .042 |
| **Bilateral involvement** | | 32(78%) | 26(78.8%) | 5(83.3%) | 1.000 |
| **Ocular involvement** | | 14(34.1%) | 6(18.2%) | 6(100.0%) | <0.001 |
| **Nervous system involvement** | | 4(9.8%) | 0(0.0%) | 4(100.0%) | <0.001 |
| **Only endoscopic surgery** | | 34(82.9%) | 33(100.0%) | 1(16.7%) | <0.001 |
| **Time from symptom to diagnosis to date** | | 4±1.78 | 4.33±1.79 | 2.50±1.04 | 0.005 |
| **Number of involved sites** | | 4.34±1.68 | 3.48±1.52 | 6.83±1.16 | <0.001 |
| **Number of surgeries** | | 1.25± .44 | 1.21±0.41 | 1.50±0.54 | 0.266 |
| **Involved site** | Maxillary | 31(75.6%) | 24(72.7%) | 6(100.0%) | .305 |
| | Ethmoid | 36(87%) | 29(87.9%) | 6(100%) | 1.000 |
| | Sphenoid | 28(68.3%) | 22(66.7%) | 5(83.3%) | .645 |
| | Frontal | 24(58%) | 17(51.5%) | 6(100%) | .064 |
| | Lateral nasal wall | 5(12.2%) | 2(6.1%) | 3(50.0%) | .019 |
| | Septum | 25(61%) | 18(54.5%) | 6(100.0%) | .065 |
| | Palate and nasal floor | 11(26.8%) | 5(15.2%) | 5(83.3%) | .002 |
| | Skull base | 4(9.8%) | 0(0.0%) | 4(100%) | <0.001 |

Two patients died before surgery. Endoscopic debridement was performed completely in 87% (n = 34) of the patients. Out of 4 (9.8%) patients who needed CSF leak repair due to the skull base involvement, two patients received endoscopic repair; however, both patients developed central nervous system involvement in the course of the disease and eventually died. During the studied period, 8 patients (19%) died, among whom 2 patients died before the surgery, 2 patients died because of CNS involvement and one patient died in post-operational endoscopy due to the rupture of internal carotid artery. All the mortality cases occurred in less than one month of diagnosis. Sinus involvement occurred at most (n = 36, 87%) in ethmoid and at least (n = 24, 58%) in frontal sinus. bilateral involvement occurred in 78% (n = 32) of patients. Lateral nasal wall involvement occurred in 12% (n = 5). Septum involvement occurred in 61% (n = 25). Involvement of palate and nasal floor was observed in 26% (n = 11) of patients. Skull base involvement was observed in 9% (n = 4), among whom CNS symptoms were initially manifested in 2 patients and developed in clinical course of the disease in two other patients. Orbit involvement occurred in 34% (n = 14), among whom it was initial manifestation in 42% (n = 6) all the result show in Table 1.

## DISCUSSION

In this study, the most common cause of immunodeficiency was hematologic malignancy followed by diabetes and cirrhosis. The most common initial manifestation was fever (n = 33, 80.5%); most patients showed evidence of fungal sinusitis in diagnostic endoscopy without specific symptoms of sinusitis and merely with treatment-resistant fever. Orbit symptoms were initially manifested in n = 6 (14.6%); however, about one-third of patients (n = 14, 34.1%) developed orbit symptoms in their course of disease. CNS involvement was initially manifested in 2 patients in the form of loss of consciousness which finally led to death of both patients. All diagnosed patients were treated with amphotericin. One fourth of patients (n = 10, 24.4%) received both amphotericin and GCSF. Two patients with underlying disease died before surgery and 39 patients underwent endoscopic surgery. Finally, two patients needed craniotomy and enucleation after endoscopic surgery due to the progressed disease; however, they died before surgery. Another patient needed oral debridement after endoscopic surgery; however, the patient died due to the underlying disease. In follow-up, 8 patients died less than one month after diagnosis. Two of them died before surgery due to the underlying disease. Involvement of orbit (100% vs. 18.2%, p <0.001), skull base (100%, p=0.001), palate and nasal floor (83.3% vs. 15.2%, p = 0002) and lateral nasal wall (50.0% vs. 6.1%, p = 0.019) was significantly higher in lost patients than improved patients. This can be attributed to the difficulty in treatment of these regions or their proximity to eyes and anterior cranial fossa. Like other studies, the most common involved sinus was ethmoid (n = 16, 87%) and maxillary (n = 31, 75.6%). Septum was involved in almost one fourth of patients. In other studies, ethmoid involvement was associated with the increased risk of mortality [10]. However, this study found no significant relationship, which can be due to the increased clinical suspicion and early diagnosis. Nevertheless, like previous studies, involvement of orbit and anterior cranial fossa still accounts for a large percentage of mortality. Like other studies [11], endoscopic surgery was successful in controlling the disease. Two patients underwent CSF leak repair due to skull base involvement and one patient received endoscopic treatment in infratemporal fossa. Endoscopic surgery was not associated with serious complications. In one case, internal carotid artery ruptured in post-operational endoscopy, which led to death. However, its risk factors included evidence of disease invasion to the carotid artery in sphenoid sinus found by pre-operational imaging and destructive nature of the disease. Endoscopic surgery is increasingly becoming popular considering the underlying disorders of these patients and advantages of endoscopic surgery in reducing cost, time and mortality rate. The mean time from manifestation of symptoms to diagnosis was higher in improved patients (6.8 ± 1.1 vs. 4.3 ± 1.7, P = 0.005). Moreover, the number of involved sites was lower in improved patients (6.8 ± 1.1 vs. 3.4 ± 1.5, P = 0.001), indicating late diagnosis in early stages of the disease with lower involvement and milder symptoms due to lower clinical suspicion. This reflects the need for reducing diagnostic threshold in patients with lower specific findings.

Survival was higher in these patients compared to previous studies [8]. Although one-fifth of patients needed further surgery, about 80% of patients improved at a 6-month follow-up. One advantage of this study is the larger number of cases examined compared to previous studies. Another advantage is that the samples were collected over 2 years, which is less than similar studies. However, this study had some limitations. One limitation is the type of the study examining the number of cases. Considering the sample size, complete analytic results cannot be achieved. It was better to conduct a cohort study with a larger sample size. Another limitation is the 6-month follow-up. Longer follow-up may affect the results. In this regard, further cohort studies with larger sample sizes and longer follow-ups are suggested for risk factors of mortality. This may help better judgements about risk factors of mortality before surgery. Early treatment of patients with sinus mucormycosis by endoscopic surgery leads to higher survival rate. However, poor prognosis is associated with extranasal involvement such as orbit and CNS involvement.

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