

Endonasal treatment of acute invasive fungal rhinosinusitis in immunocompromised pediatric hematology–oncology patients

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ABSTRACT

Objectives: Acute invasive fungal rhinosinusitis (AIFR) is an aggressive fungal infection in immunocompromised patients with high mortality rates. The aim of this study is to present our experiences on endonasal treatment in immunocompromised pediatric hematology–oncology patients with AIFR.

Methods: Thirteen pediatric hematology–oncology patients treated for AIFR between March 2006 and December 2011 were analyzed retrospectively. We reviewed the following data for all patients: age, gender, predisposing disease, initial symptoms, pathological diagnosis, microbiological results, laboratory findings, surgical procedure, number of operations and treatment outcomes.

Results: Nine of 13 patients with lesions confined to sinonasal cavity were operated with endoscopic approach. Open surgery was performed in four patients, three of them had palatal and buccal lesions and one had facial skin involvement. Endoscopic approach was also used for sinonasal lesions of these four patients. A total of 7 patients died: 4 patients with progression of the underlying disease, 2 patients with sepsis and 1 patient due to renal failure. Survival rate in surgically treated patients was found 46% (6/13 patients).

Conclusions: Endonasal endoscopic approach is both feasible and efficient technique, also enables excellent local control with less morbidity compared to open surgery. This approach is suitable for patients who are diagnosed in the early stages of AIFR and also presents a less traumatic option for patients with poor health status. Open surgical procedure should be preferred in patients with disease extending out of the sinonasal cavity.

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1. Introduction

AIFR is a serious disease, mostly seen in immunocompromised pediatric hematology–oncology patients, with high mortality and morbidity rates [1–3]. Infection is characterized by submucosal infiltration of fungal organisms from the nasal cavity or paranasal sinuses to orbital and intracranial structures [4–6]. Hematological–oncological malignancies, aplastic anemia, hemochromatosis, uncontrolled diabetes mellitus, long-term steroid use and acquired immune deficiency syndrome (AIDS) are the most common predisposing diseases for AIFR [7–10]. Chemotherapy agents and immunosuppressants which are used after bone marrow and solid organ transplantations are other risk factors [11–13].

Patients with AIFR are predominantly infected by species from the order Mucorales (including *Absidia*, *Mucor*, *Rhizomucor* and *Rhizopus*) and *Aspergillus* [14]. There are almost 900 species of *Aspergillus* in nature and *Aspergillus fumigatus* is the most common one in humans [5]. These organisms are normally found in dust, soil and also in upper respiratory mucosa of healthy individuals. They may become pathogenic in immunocompromised patients and may proliferate in the sinonasal cavity and cause ischemic tissue necrosis. Agents of mucormycosis primarily invade the nose, lungs and gastrointestinal system, whereas *Aspergillus* species primarily invade the lungs and then spread to other organs later. AIFR is presented as sinusitis, which shows fast clinical and radiological progression, with typical endoscopic appearances such as black crusts, pale mucosa and necrosis. Definitive diagnosis is established by histopathologic evaluation and culture of nasal biopsy materials. Routine endoscopic examination is appropriate for patients who can cooperate; but for younger and non-cooperable patients general anesthesia may be required. Considering the fast progression of AIFR, frozen section evaluation may be required in critical patients.

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Early diagnosis and treatment are essential for a favorable prognosis. Treatment includes surgical debridement, systemic antifungal therapy and prompt treatment of the underlying systemic disease. Radical surgical debridement is definitely an important treatment modality for advanced cases, whereas endoscopic endonasal debridement and treatment of the underlying disease may be adequate to control AIFR in patients with limited lesions. Endoscopic surgery may also detect bleeding and disease-free areas, thereby helping to decide the extent of surgery.

As far as we know, this study is one of the largest pediatric case series reported with AIFR (13 immunocompromised pediatric hematology–oncology patients). We aimed to share our experience of endoscopic treatment of AIFR.

2. Materials and methods

Patients diagnosed with AIFR who had been treated in our clinic between March 2006 and September 2011 were retrospectively evaluated. Thirty-eight patients were included, and 16 of them were pediatric patients. Three of these pediatric patients had died before the surgical treatment because of the poor health status. Thirteen patients treated for AIFR were reviewed and analyzed in this study. Patients with hematological or lymphoid malignancies who were primarily followed-up by the pediatric hematology–oncology departments were consulted for fever of unknown origin, facial pain, rhinorrhea, nasal obstruction, all of which may be features of AIFR. All patients were endoscopically examined, and biopsies were taken for pathological diagnosis and for cultures of necrotic or

suspicious lesions. Sedation and general anesthesia were required for very young pediatric patients for endoscopic examination and biopsy. Paranasal sinuses of the patients were radiologically evaluated with computed tomography (CT) with axial and coronal sections. Patients with suspicion of orbital and intracranial involvement also evaluated with magnetic resonance imaging (MRI). We reviewed the following data for all patients: age, gender, predisposing factors, initial symptoms, pathological diagnosis, microbiological investigations, imaging tests, laboratory findings, number and types of surgical procedures, and treatment outcomes.

Preoperatively, patients' hematocrit and platelet values were kept above 30% for hematocrit and 40,000/ml for platelets, respectively. Endoscopic surgery under hypotensive anesthesia was performed in all patients, and open surgery was required in 4 patients. Debridement was done until healthy tissues were observed macroscopically. Details of the operations are shown in Table 1. Nasal tamponades with antibiotics were used for bleeding control and they were discharged at postoperative second day. Saline was used for nasal irrigation in the postoperative period. Epithelializing creams and gels were used to reduce crust formation and facilitate healing. The patients were re-examined on alternate days until epithelization of the cavities was completed. Sedation was used at non-cooperative young patients for endoscopic examination in postoperative period. Also general anesthesia was required for examination and debridement for patients with suspicious findings postoperatively. When recurrent or remaining fungal infection was suspected, patients were taken to operation room for re-surgery. Decision for reoperation was

Table 1
Demographic characteristics and clinical outcome of the patients.

No.	Sex/age	UD	Pathologic disease	Affected areas (with endoscopy and CT)	Surgery	Operation count	Follow up (month)	Outcome/cause of death
1	M/9	ALL	Mucormycosis	Right IT and MT, maxillary and ethmoid sinusitis, posterior septum	Right IT and MT resection, MMA, total ethmoidectomy, posterior partial septum resection	4	30	Alive
2	M/18	ALL	Mucormycosis	Anterior septum	Anterior partial septum resection	1	12	Alive
3	M/12	AML	Mucormycosis	Anterior septum, hard palate	Anterior partial septum resection, lesion excision on hard palate	3	9	Alive
4	F/4	ALL	Aspergillosis	Left MT, posterior septum	Left MT resection, posterior partial septum resection	3	36	Alive
5	F/5	ALL	Mucormycosis	Right MT, maxillary and ethmoid sinusitis	Right MT resection, MMA, total ethmoidectomy	1	7	Alive
6	M/6	AML	Aspergillosis	Anterior septum, right buccal region	Partial anterior septum resection, lesion excision on buccal region	1	7	Alive
7	M/16	AML	Aspergillosis	Septum, bilateral MT, hard palate	Septum resection, bilateral MT resection, bilateral MMA, lesion excision on hard palate	2	6	Death/renal failure
8	F/7	ALL	Mucormycosis	Left MT and IT, left maxillary sinusitis	Left MT and IT resection, MMA, total ethmoidectomy	2	2	Death/UD
9	M/6	ALL	Mucormycosis	Right maxillary, ethmoid vs. sphenoid sinusitis, maxillary sinus medial wall, MT	Right medial maxillectomy, total sphenoidectomy, MT resection	2	9	Death/sepsis and resistant diarrhea
10	M/16	NHL	Mucormycosis	Left MT	Left MT resection, anterior ethmoidectomy	1	1	Death/UD
11	M/8	ALL	Aspergillosis	Right MT, right maxillary sinusitis fistulated skin lesion	Right MT resection, medial maxillectomy, skin lesion excision and reconstruction with rotation flap	2	3	Death/UD
12	M/9	Aplastic anemia	Mucormycosis	Inferior face of left MT, left maxillary sinusitis	Left MT resection, MMA	1	7	Death/sepsis
13	F/8	ALL	Aspergillosis	Right MT, maxillary sinusitis	Right MT resection, MMA	2	3	Death/UD

M, male; F, female; UD, underlying disease; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NHL, non Hodgkin lymphoma; MT, middle turbinate; IT, inferior turbinate; MMA, middle meatal anastomosis.

given in according to infection parameters (white blood cell count, C-reactive protein, procalcitonin, peripheral blood smear), endoscopic and radiologic evaluation. For antifungal treatment amphotericin-B was administered for 90 or 120 days postoperatively at 3–5 mg/kg dose. Patients with acute lymphoblastic leukemia (ALL) also received granulocyte colony-stimulating factor (G-CSF) in order to increase the neutrophil count. Other patients did not receive any treatment for fungal infection. Patients with no positive infection parameters or endoscopic and radiologic findings at postoperative 90–120 days were accepted as recovery.

Age, gender, underlying disease and fungus subspecies were analyzed statistically for survival and number of operations. Number of operations was also analyzed for survival solely.

2.1. Statistical analyses

Mann–Whitney *U* test and Chi square test or Fisher's exact test were applied for comparisons. Mean or median survival rates were estimated with the use of the Kaplan–Meier method. Results were represented as mean $\pm$ SD, median (min–max) and *n* (%). A *p* value <0.05 considered as significant. Statistical analysis was performed using the statistical package SPSS v 18.0.

3. Results

Thirteen patients (9 males and 4 females) aged between 4 and 18 years were included in this study. All patients had an underlying hematological or oncological disease: acute lymphoblastic leukemia in 8 patients, acute myeloid leukemia in 3 patients, non-Hodgkin's lymphoma in 1 patient and aplastic anemia in 1 patient. Neutrophil counts of patients were less than 500/ μ l at diagnosis. Ten patients had thrombocytopenia ($<50,000$ platelets/ml) and 6 of them had severe thrombocytopenia ($<10,000$ platelets/ml). Patients' age, gender, predisposing factors, isolated fungi (subspecies of fungal infection), infection sites, type of surgery, number of operations, pathologic diagnosis and reasons of death are summarized at Table 1.

The most common symptom at initial presentation was fever (76.9%, *n* = 10), followed by nasal obstruction (69.2%, *n* = 9), rhinorrhea (53.8%, *n* = 7), nasal crusting (46.1%, *n* = 6), facial pain (38.4%, *n* = 5) and facial edema (30.7%, *n* = 3). One patient (7.6%) had orbital cellulitis with facial edema (Fig. 1). Eleven patients (69.2%) had black-gray crusting and 6 patients (46.1%) had ulcerations on nasal mucosa in endoscopic examination.

Clinical and radiologic evaluation, revealed that 11 patients had middle turbinate (Fig. 2), 6 patients had septum and 2 patients had inferior turbinate involvement. Ten patients had multifocal disease and 3 patients had unifocal disease (2 septum and 1 middle turbinate). Three patients had hard palate (Fig. 3a and b), 1 patient had facial skin involvement. On CT imaging, 8 patients had unilateral and 1 patient had bilateral non-specific sinusitis. The most frequently infected sinus was the maxillary sinus (*n* = 4) and 5 patients had multiple infected sinuses (Fig. 4a–d).

Histopathological examinations of biopsies were reported as mucormycosis in 8 patients, aspergillosis in 4 patients and 1 patient had both mucormycosis and aspergillosis. Microbiologic cultures were performed with surgical specimens. Histopathological diagnosis were confirmed with culture in only 5 patients (38%). *Rhizopus* was identified in 3 patients (Nos.: 1, 5, 9) and *Aspergillus fumigatus* was identified in 2 patients (Nos.: 6, 11). *Rhizopus* subgroup identification could not be done.

Endoscopic surgery was performed in all patients. Combined technique was performed in 4 of these patients. Two patients had hard palate involvement. These lesions were limited to mucosa without bone involvement therefore excision of these lesions with a safe margin was enough. One patient had a superficial lesion at



Fig. 1. Preoperative photograph of patient (No.: 7) with bilateral orbital cellulitis.

buccal mucosa which was also excised. Another patient with 1 cm $\times$ 1 cm facial skin lesion at right cheek was operated and local rotation flap was performed for reconstruction additionally. Patients had to be operated several times, due to recurrences. Number of operations were encountered between 1 and 4 (mean was 1.9 ± 1.0). Success at single surgery was achieved at 5 patients whereas 8 patients had to be operated multiple times. No significant difference was found between patients who had multiple or single operation according to risk factors such as age, gender, underlying disease, fungus subspecies (Table 2) (*p* > 0.05).

Recurrent neutropenia had occurred in 4 of 8 reoperated patients and fungal infection was confirmed in these recurrent neutropenic patients histopathologically. On the other hand, this confirmation could not be observed in patients without recurrent neutropenia. These patients had been operated due to endoscopic and radiological suspicions.

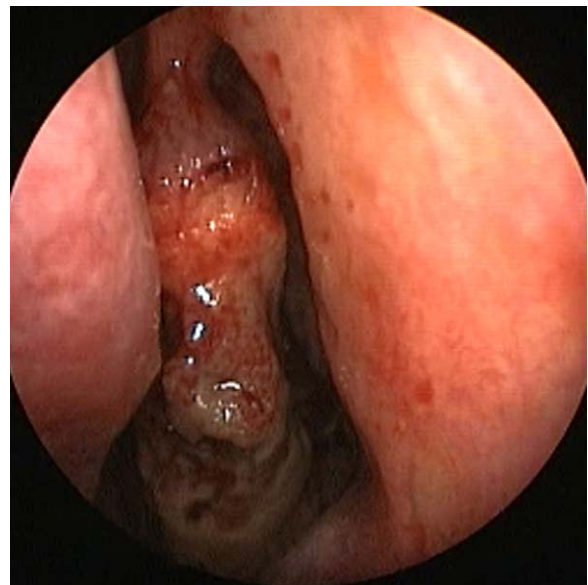


Fig. 2. Endoscopic image of the patient (No.: 10) with left middle turbinate infected with mucormycosis.

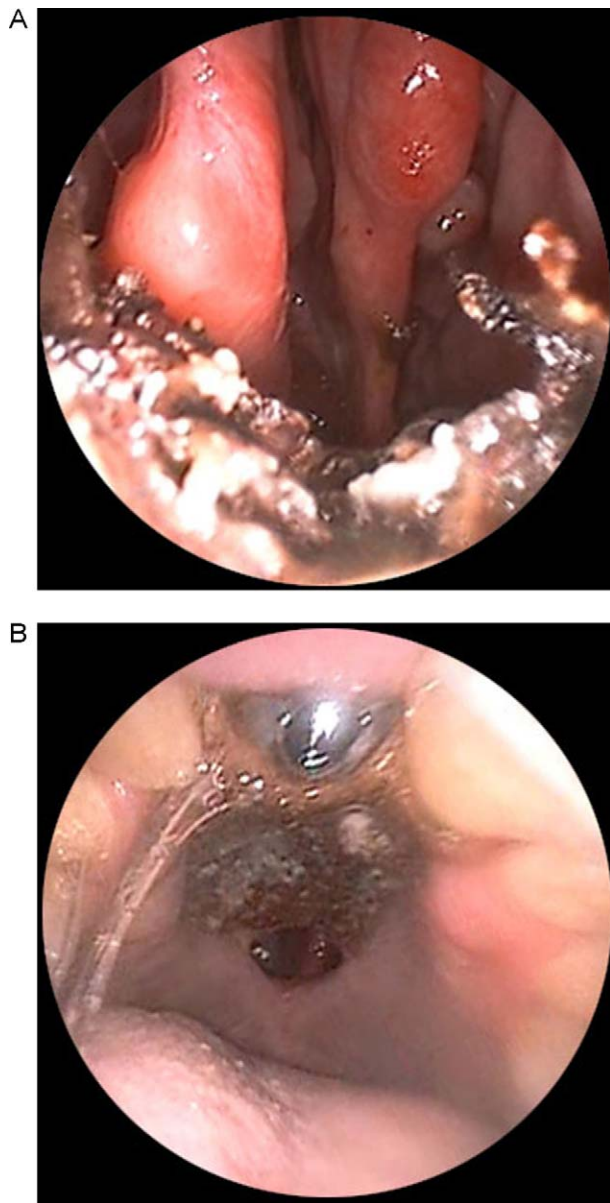


Fig. 3. Endoscopic examination of patient (No.: 5) with septum perforation and black crust formation on the floor of nasal cavity (a) and examination of hard palate of the same patient (b).

At the time this paper was written, 6 patients (46%) were still alive without the signs of AIFR. Mean and median survival times calculated with Kaplan–Meier method were found to be 18 and 9 months, respectively. Seven patients died, due to various reasons: progression of the underlying disease in 4 patients, sepsis in 2 patients and renal failure in 1 patient. According to risk factors such as age, gender, underlying disease, number of operations; no significant difference was found between dead and alive patients (Table 2) ($p > 0.05$). Surgery could not be performed in 3 patients, 2 had pulmonary invasive fungal infection and 1 patient with severe thrombocytopenia and poor health status due to the underlying disease. These patients died in 3–5 days and excluded from this study. One of the patients with multifocal disease (paranasal sinuses and pulmonary) had orbital involvement and orbital exenteration had been planned combined with endoscopic approach. This patient died before the operation because of the progression of underlying disease, and persistent neutropenia. There were no other patients with orbital lesion.

4. Discussion

AIFR is an opportunistic infection that occurs almost exclusively in immunocompromised patients [2,3,14]. Diseases such as hematological malignancies, aplastic anemia, hemochromatosis, uncontrolled diabetes and AIDS, which cause neutrophil dysfunction are among risk factors [7–9,15,16]. The most common predisposing factor in pediatric group is hematological malignancies, similar to adult patients [10,16]. The cases we present in the present study are entirely hematologic and oncologic patients. Similar to other reports in the literature, most common subgroups were acute myeloid leukemia and acute lymphoblastic leukemia [2,3,13]. In previous studies the most frequent agent in uncontrolled diabetic patients was reported as mucormycosis and in hematologic and oncologic patients as invasive aspergillosis [9,12]. Mucormycosis is the most common agent in the present study.

The first symptoms of AIFR are generally nonspecific. The most common initial symptoms are fever, facial pain, rhinorrhea and nasal congestion. Resistant fever, rhinitis, sinusitis, facial fullness, symptoms related to orbital involvement or cavernous sinus diseases, mucosal or skin findings like ulcerated necrotic tissues in hard palate or gingiva, suspicious lesions in nasal cavity and abnormal CT findings should raise suspicion of AIFR [2,3,11]. Ophthalmoplegia, proptosis, orbital cellulitis, vision failures and changes in mental situation are the signs of intracranial and orbital involvement. In previous studies, 20–60% of patients had different local symptoms. The most common symptoms in our patients were fever, nasal obstruction, rhinorrhea, nasal crusting, facial pain and facial edema (in order of frequency) [11]. As reported by others, our cases also had non-specific early symptoms.

The physical findings and symptoms can be subtle during the earlier stages of AIFR but alteration in the appearance of the nasal mucosa is the most consistent sign. Nasal examination with fiberoptic or rigid endoscopes should be performed in immunocompromised patients with fever of unknown origin or localizing symptoms. Mucosal abnormalities such as discoloration, ulceration and granulation can be seen in endoscopic examination. White discoloration of the mucosa indicates tissue ischemia and black discoloration is a late finding of tissue necrosis [11]. Decreased vascularity and sensation of nasal mucosa indicate fungal invasion [13]. Gillespie et al. [11] reported that, the most common locations of mucosal abnormalities were in middle turbinate, septum, hard palate and inferior turbinate in order of frequency. Middle turbinate and septum were the most commonly infected areas in our patients, similar to other reports [11,13]. Endoscopic examination must be performed for every patient and tissue specimens should be taken from suspicious lesions. The fiberoptic endoscopes allow detailed visualization of the nasal cavity and detection of early mucosal changes in invasive fungal disease [12]. Sometimes this procedure can only be performed with general anesthesia in pediatric patients. This approach also permits more aggressive removal of debris and crust.

Extra-sinonasal involvement is a poor prognostic factor for morbidity and mortality. Besides endoscopic nasal examination, a complete, careful head and neck examination should also be performed in all patients. Visual acuity, facial sensation and the cranial nerves should be checked. Soft, cold and non-tender periorbital edema can be a sign of rhinocerebral mucormycosis [17,18]. Oral cavity should also be checked carefully for palatal and buccal involvement. Unilateral gangrene and perforation of the hard and soft palates may occur due to involvement of the palatine arteries.

CT should be performed in patients with AIFR suspicion. At the early stage of disease, CT has high sensitivity and low specificity for mucormycosis. Severe soft tissue inflammation of unilateral nasal cavity is the most consistent early CT finding [19]. DelGaudio et al. [19] reported that bone erosion, facial cellulitis, orbital involvement

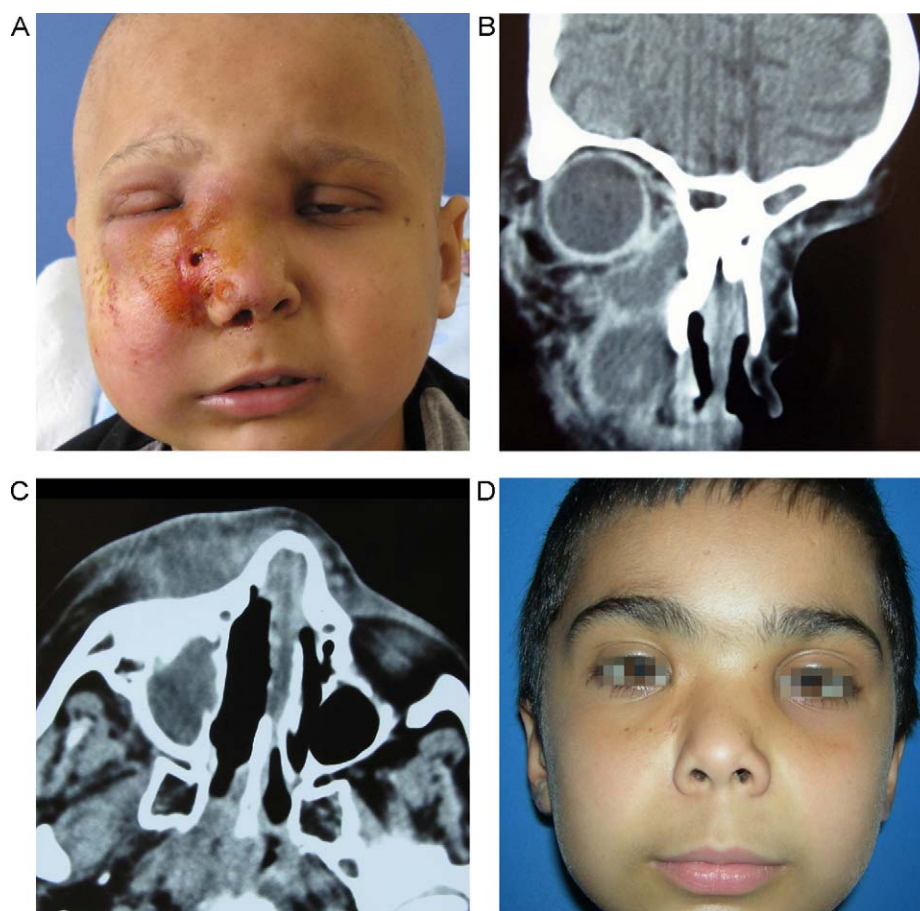


Fig. 4. Preoperative photograph of the patient (No.: 1) with edema, hyperemia and fistulization on right side of facial skin (a), subcutaneous collection image on coronal CT visualization (b), collection in maxillary sinus and subcutaneous tissue image on axial CT visualization (c), and postoperative photograph after 6 months (d). The patient was operated on 3 times already because of AIFR recurrence.

are the findings of the advanced stage disease and highly suggestive for invasive fungal sinusitis. MRI should be performed to evaluate intracranial and orbital extension of disease. Change in mental status, orbital apex syndrome, seizure and stroke can be the signs of intracranial involvement. In a study of Howells and Ramadan [20] MRI was proposed to be the initial radiologic procedure in AIFR patients because of the low specificity and underestimation of the disease on CT scan.

Diagnosis of AIFR requires culture and histological examination of the biopsy material, besides clinical suspicion. The microscopic findings are tissue necrosis with minimal host inflammatory cell

infiltration, hyphal forms within submucosa and angiocentric invasion [21]. Each fungus has specific types of hyphae. Mucormycosis shows broad, ribbon like irregular and non-septate hyphae, whereas *Aspergillus* sp. demonstrate septate and narrow hyphae that branch at 45° angles [22]. In our study, 8 patients had mucormycosis, 4 patients had aspergillosis and 1 patient had them both. It is known that, mucormycosis may also be combined with other fungal infections such as aspergillosis [17]. Biopsies taken from granulations, discolored and ulcerated tissues during nasal endoscopy can provide histological diagnosis. Patients suspected for AIFR without typical endoscopic findings, biopsies can be taken

Table 2

Factors related to clinical outcome.

	Prognosis		Operation		Total
	Death	Alive	Multiple	Single	
Sex					
M/F	5 (55.6%)/2 (50.0%)	4/2	5 (55.6%)/3 (75.0)	4/1	9/4
UD					
ALL/other	4 (50.0%)/3 (60.0%)	4/2	6 (75.0)/2 (40.0)	2/3	8/5
Pathologic disease					
Aspergillosis/mucormycosis	3 (60.0%)/4 (50.0%)	2/4	4 (80.0)/4 (50.0)	1/4	5/8
Age (year)					
Mean $\pm$ SD	10.0 $\pm$ 4.2	9.0 $\pm$ 5.3	8.7 $\pm$ 3.7	10.8 $\pm$ 5.8	9.5 $\pm$ 4.6
Median (min–max)	8.0 (6–16)	7.5 (4–18)	8 (4–16)	9 (5–18)	8 (4–18)
Number of operation					
Mean $\pm$ SD	1.7 $\pm$ 0.5	2.2 $\pm$ 1.3	–	–	1.9 $\pm$ 1.0
Median (min–max)	2 (1–2)	2 (1–4)			2 (1–4)

M, male; F, female; UD, underlying disease; ALL, acute lymphoblastic leukemia.

from the most frequent sites such as septum, inferior and middle turbinate. Gillespie et al. [23] recommended superficial middle turbinate biopsy at patients with fever of unknown origin and persistent symptoms after 48 h of intravenous antibiotic treatment. They also notified that superficial middle turbinate biopsy had 75% sensitivity and 100% specificity [23]. Süslü et al. [13] suggested submucosal and cartilage samples can also be helpful.

Late diagnosis of AIFR may lead to serious and fatal consequences. Considering this, frozen section biopsy can also be performed. Ghadiali et al. [14] emphasized the importance of frozen section biopsy in patients with AIFR suspicion. Intraoperative use of this technique can also avoid radical surgeries and prevent further iatrogenic morbidities [14]. The fungal agent cannot be identified with certainty with this technique but non-specific anti-fungal agents can be used. Fungal cultures are the gold standard for the diagnosis and identify the subspecies of the invasive fungus. Microbiologic cultures of affected tissue may demonstrate growth of fungal colonies. Culture also gives the chance to perform antibiogram to determine the proper anti-fungal agent but the slow growth of fungal colonies limits the use of culture as a diagnostic tool. Sensitivity of fungal cultures is reportedly between 30% and 54% in the literature, which is 38.4% ($n = 5$) in the present study [11,24].

Surgery is the main treatment modality of AIFR, either endoscopically or with open technique. Patients benefit from surgery in various ways: (a) progression of disease is decelerated and this allows the bone marrow recovery, (b) fungal load is reduced, which in turn, reduces the burden on recovering neutrophils, and may improve the immunologic status, (c) easy growth of fungus in devitalized tissues is prevented, (d) the ability of antifungal drugs to reach infected areas is enhanced, (e) nasal irrigation and postoperative monitoring for recurrent disease is facilitated, and (f) specimens for culture is provided and detailed histopathological examination is performed [13,17,22].

At the early stages of disease, endoscopic procedures are usually adequate for debridement but in advanced situations; facial resection, maxillectomy or orbital exenteration might be necessary. Debridement of necrotic tissues should be continued until bleeding bone and soft tissue surfaces are reached. Endoscopic resection of turbinates and septum can be performed at patients with local disease. Minor debridement can be performed without histopathological diagnosis but it is essential for radical procedures like facial resection or maxillectomy [13].

There are studies in the literature which indicate successful results with endoscopic and open procedures. Park et al. [2] reported 9 pediatric immunocompromised patients treated only with the endoscopic approach, 7 of which are still alive. Eliashar et al. [12] performed endoscopic treatment on 14 patients with invasive aspergillosis who had bone marrow transplantation, and 8 of them survived. In the study of Wiatrak et al. [25] endoscopic sinus surgery was performed in 6 immunocompromised pediatric patients and open surgery (Caldwell-Luc, external ethmoidectomy, medial maxillectomy) was required during the follow-up, due to progression of the disease. All the patients survived. Kasapoglu et al. [3] compared open and endoscopic approach with adults in their study and reported survival rates as 57.1% and 47.3%, respectively. In another study in which both endoscopic and open procedures were applied, this rate was 46% [13]. In our study, which is one of the largest pediatric case series reported, survival and local control rates were 46% and 100%, respectively, with endoscopic approach to all patients and additional open approach in 4 patients. There are studies that show successful results with endoscopic approach in late stages of AIFR with orbital and cerebral involvement. Jiang and Hsu [26] used endoscopic approach for the treatment of nine patients with rhinocerebral mucormycosis. They performed only endoscopic approach to 6

patients, and combined with transantral approach on 3 patients. One patient died due to internal carotid artery occlusion and eight patients survived the disease. Avet et al. [27] reported on the use of endoscopic approach in the management of three patients diagnosed with rhinoorbital and rhinoorbitocerebral mucormycosis. All patients had aggressive control of underlying risk factors (diabetes mellitus, immunosuppression) and prolonged intravenous amphotericin-B therapy. Orbital exenteration was not performed on 3 patients and they are reported to be alive. Ketenci et al. [18] reported success at 5 patients with endoscopic approach and death at 9 patients who had facial skin, palatal, orbital involvement and operated with radical procedures like maxillectomy and orbital exenteration. In our study, 5 of 9 patients (55%) operated with endoscopic approach and 2 of 4 patients (50%) operated with combined technique died. These results suggest that high mortality of the disease is not correlated with surgical technique. Technological improvements with increased accessory instruments augments the importance of the endoscopic approach. Batra and Lanza [28] described a series of three cases that underwent endoscopic power-assisted orbital exenteration. One of the patients had invasive fungal sinusitis and this new approach was successfully performed on those three patients. Early detection of AIFR has critical significance and endoscopic approach with low morbidity could be enough for surgical approach.

Low mortality rates in more recent studies and improved survival rates are attributed to early diagnosis, aggressive debridement and combined antimicrobial therapy with antifungal agents. The cause of mortality is progression of the underlying disease and complications despite local control of fungal infection. In our study, other than 6 living patients (47%), one patient with kidney failure, 3 patients with sepsis and 3 patients with progression of the disease died. The survival rate of our group is similar to those reported in former studies [3,13]. These data support an algorithmic approach like controlling the underlying disease, and especially attach a priority for bone marrow functions.

For neutropenic patients, recovering the neutrophil count is the most critical factor for survival. Recurrence of neutropenia in patients who have recovered from IFS can result in recurrence of the IFS in the same location, likely indicating suppression but not eradication of the fungus with recover of the neutrophil count [9]. Kennedy et al. [29] confirmed that neutrophil recovery was required to clear the infection of IFS; however, it alone did not prevent mortality from the infection. In many reports, bone marrow recovery is highlighted as the most important indicator of recovery [11,22,29]. G-CSF has been shown to be effective in promoting bone marrow recovery at neutropenic patients [13]. Neutropenic patients that responded well to G-CSF were considered as potential survivors by Gillespie et al. [11].

The patients with AIFR should be closely followed with endoscopic examination after surgery. The guidelines suggest that the patients must be examined weekly until the neutrophil count is normalized. Monthly controls are also suggested for 6 months after the immune system recovers. We applied a similar protocol in our institution, but Otto and Delgaudio [30] suggests that this protocol may be inadequate in long-term follow-up of invasive fungal sinusitis. It is reported that complications may occur independently from primary disease despite improved immunological functions. The complications include bone invasion causing exposed bone and granulation, or mucosal resection leading to scarring and sinus obstruction. These conditions may lead to bacterial superinfection within the sinonasal cavity and may result in chronic rhinosinusitis. In order to prevent and resolve these complications and sequelae, patients with AIFR should be followed up for a long time until remucosalization of the sinuses, resolution of crusting and cessation of bony sequestration occur.

5. Conclusion

AIIR requires prompt medical and surgical therapy with early diagnosis. Non-specific early symptoms, radiological signs and highly suspicious lesions should be evaluated with endoscopic examination and should be confirmed histopathologically. Complete endonasal surgical debridement is the choice of treatment for lesions limited to the nasal cavity and patients diagnosed in the early stages of disease. Endonasal endoscopic approach is feasible and efficient, enabling excellent local control and less morbidity than open surgery. More radical excision is preferred in the presence of intraorbital extension, palatal or intracerebral involvement. Despite the fact that aggressive surgical therapy and IV antimicrobial therapy are two basic elements of treatment, the determinant of the outcome is the treatment of the underlying cause.

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