

Acute invasive fungal rhinosinusitis: Survival analysis and the prognostic indicators

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ABSTRACT

Background: Acute invasive fungal rhinosinusitis (AIFR) is a highly mortal, progressive fungal infection of the paranasal sinuses and surrounding structures that is almost always seen in patients who are immunocompromised. Despite the use of newer antifungal treatments and early diagnosis, the prognosis of AIFR does not improve significantly. Due to the higher incidence of patients who are immunocompromised and have more complex disease, AIFR is a growing medical issue in tertiary medical centers.

Objective: The aim of this study was to present the outcomes and analyze the prognostic indicators of patients with AIFR who underwent surgery.

Methods: Between October 2009 and November 2014, 37 patients who underwent surgery for AIFR at a tertiary care university hospital were included in the study. Overall survival and disease-specific mortality and survival rates were calculated to estimate survival function. The impact of age, sex, underlying disease, extent of AIFR, applied medical treatment, and causative species (*mucormycosis*, *aspergillosis*) were also taken into consideration. Also, the effect of a variety of laboratory parameters, such as hemoglobin, leukocyte, neutrophil, lymphocyte, platelet, and C-reactive protein (CRP) levels, to survival were evaluated.

Results: The median follow-up time was 58 days (interquartile range = 304). Overall and disease-specific mortality rates were 64.9 and 51.4%, respectively. Fever was the most common symptom (86.5%), along with nasal obstruction and/or fullness (48.6%) and epistaxis (48.6%). Age and sex did not have a significant impact on survival ($p > 0.05$). Palate involvement was significantly associated with mortality ($p < 0.05$). According to the results of Cox, regression analysis for disease-specific mortality rate, leukocyte and neutrophil counts as well as CRP levels had a significant effect on survival function ($p < 0.05$).

Conclusions: Palatal involvement was associated with a higher mortality in our study. Also, leukocyte counts, neutrophil counts, and CRP values had a significant impact on survival function. The reversal of the underlying disease and immunosuppression is as important as the medical and surgical treatment.

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Acute (fulminant) invasive fungal rhinosinusitis (AIFR) is characterized by invasion of the nasal cavity and paranasal sinuses with fungal organisms, and has a high potential of infiltrating palate, orbital, and intracranial structures.¹ This disease is almost always confined to patients who are immunocompromised and debilitated. Although AIFR is a rare disease, there is a rise in the incidence of AIFR due to the increased number of patients who are immunocompromised. Advances in the field of medicine, such as new chemotherapeutic drugs, and the long-term use of corticosteroid and immunosuppressive agents after organ or bone marrow transplantation have led to an increase in the population susceptible of developing AIFR. Due to the higher incidence of patients with more complex disease and immunocompromised, AIFR is a bigger medical issue in tertiary medical centers.

Prompt diagnosis and early intervention is of great importance in AIFR because the mortality rate can be as high as 50–80%.^{2,3} AIFR tends to spread very aggressively and often progresses over hours. Because patients who are immunosuppressed have attenuated host response to invasive infection, their early diagnosis becomes challenging. Most of the time, the symptoms are nonspecific. One must maintain a high level of suspicion in the presence of fever and/or sinonasal symptoms, such as orbital swelling, facial pain, epistaxis, or nasal congestion, in patients who are immunocompromised. An endoscopic examination and biopsies of any ischemic or necrotic tissues immediately are mandatory whenever there is a suspicion for AIFR. Typical endoscopic examination include purple-black crusting, necrosis, pale mucosal areas, and, sometimes, recognition of hyphae. A definite diagnosis is made by the histopathologic presence of fungal

elements in mucosa, submucosa, blood vessels, or bones of the sinuses, and of cultures of biopsy specimens.⁴ Aggressive surgical debridement to bleeding healthy tissue and intravenous antifungal therapy are the proposed mainstays of the treatment.⁵

Various fungal species have been known to cause AIFR, with the most common pathogens being *Mucoraceae* and *Aspergillus*.⁴ The spores of these fungi are found ubiquitously throughout the environment; therefore, exposure is inevitable in all population groups, although progression to AIFR is avoided with an intact immune system.⁶ The aim of this study was to elucidate the prognostic factors that have an impact on the survival of patients who underwent surgery due to AIFR. The secondary aim was to discuss the controversial points in the management of AIFR.

METHODS

This study was carried out at a tertiary care university hospital in concordance with international ethical standards and the World Health Organization Helsinki Declaration. It was approved by the institutional review board of Ege University.

Patient Selection

Between October 2009 and November 2014, patients who underwent surgery due to AIFR were included in the study. Thirty-seven patients (24 male and 13 female patients) were included.

Diagnosis of AIFR was achieved by the criteria as follows:

- A duration of the symptoms for <4 weeks
- The presence of at least one of the symptoms, such as fever, nasal obstruction, or AIFR complications (orbital, intracranial, cavernous sinus, skin, palate involvement)
- The presence of hyphae on direct examination of the biopsy specimen
- Involvement of the paranasal sinuses or surrounding structures on computed tomography and/or magnetic resonance imaging
- The presence of necrotic tissue or granulation tissue on direct or

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endoscopic examination of the sinonasal cavity or surrounding structures

Procedure

All of the patients had a complete head and neck examination, and special attention was given to the endoscopic nasal examination. Multiple biopsy specimens and mycologic cultures of the suspicious mucosal lesions and necrotic tissue were made before surgery. Systemic antifungal therapy was administered by the infectious diseases consultant after invasive fungal infection was considered. The patients were treated either with amphotericin B alone or in combination with caspofungin, voriconazole, or posaconazole. All of the patients underwent surgical treatment, along with systemic antifungal treatment. Patients had computed tomographies and magnetic resonance imaging in axial and coronal planes before surgery. Blood samples were obtained just before the surgery, and these samples were taken into consideration when performing the statistical analysis. A thrombocyte count of $>50000/\text{mm}^3$ and a hemoglobin level $>10 \text{ g/dL}$ were maintained before the initiation of surgical debridement. Packed red blood cells and/or platelet concentrates were prepared before the surgery if necessary. Endoscopic or open surgery was performed related to the extent of the disease and necrosis. Necrotic tissues were debrided until macroscopically healthy, bleeding margins were reached. Orbital exenteration was performed if the orbit had been entirely invaded by the disease without any vision or eye movement.

Biopsy specimens were examined under direct light microscopy, and fungal species were determined by their characteristic morphologic appearance. Mucormycosis was identified with its nonparallel 90° branching hyphae, which form irregular patterns without septa, whereas aspergillosis was identified with its characteristic septated, regularly branched hyphae with a branching angle of 45° .⁷

Patient records were retrospectively reviewed, and demographic data, clinical presentation, comorbidities, the causative fungal species, treatment modalities, and outcomes of the patients were evaluated. Survival data were obtained both from patient records and the national death index for the correctness of the information and determination of the cause of death. Mean follow-up time was 243.6 days (range, 3–1800 days).

Outcome Measures

Overall survival and disease-specific survival rates were calculated to estimate survival function. The impact of age, sex, underlying disease, extent of AIFR, applied medical treatment, and causative species were also taken into consideration. Also, the effect of a variety of laboratory parameters, such as hematocrit and hemoglobin level; total leukocyte count; neutrophil, lymphocyte, platelet, and C-reactive protein (CRP) levels, to survival were evaluated. Prognostic factors that were included in the statistical analysis are shown in Table 1.

Statistical Analysis

Statistical analysis was done by using computer software (SPSS version 22.0; SPSS Inc., Chicago, IL). The χ^2 exact test was used for comparison of categorical data, whereas independent and paired samples *t*-tests were used for the analysis of parametric variables; Wilcoxon and Mann-Whitney *U* tests were used for the analysis of nonparametric variables based on the distribution pattern of the data. The distribution pattern was determined by using the Shapiro-Wilk test. Correlation analysis was performed *via* the Spearman or Pearson correlation analysis, depending on the type of the variable. Receiver operating characteristic analysis was applied for scale variables, which might be a factor for selected criteria. Survival analysis was made with the Kaplan-Meier method, and the effects of multiple independent factors were evaluated with Cox regression analysis.

Table 1 Multivariate Cox regression analysis of the prognostic factors associated with disease-specific survival

Variable	<i>p</i> Value
Age	0.475
Sex	0.300
Underlying disease	0.289
Extent of disease	0.289
Medical treatment	0.925
Causative fungal species	0.388
Hematocrit level	0.889
Hemoglobin level	0.968
Total leukocyte count	0.044
Neutrophil count	0.038
Lymphocyte count	0.103
Platelet count	0.354
CRP count	0.004

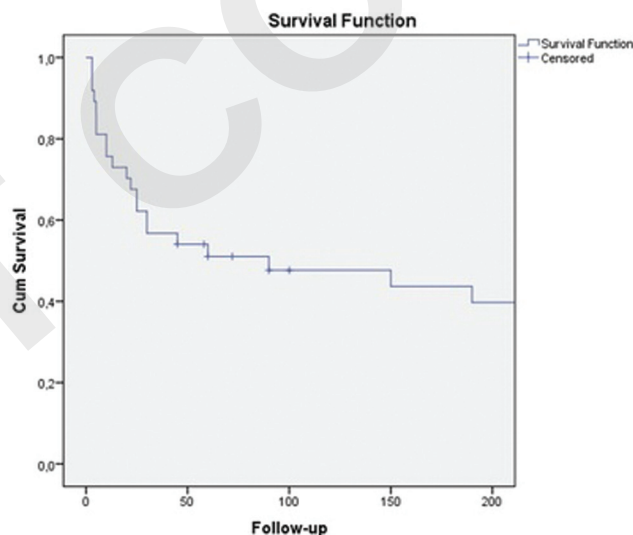


Figure 1. Overall survival rates according to the Kaplan-Meier survival analysis.

Data were expressed as mean (standard deviation), percentage, minimum–maximum, odds ratio, 95% confidence interval, and median (interquartile range [IQR]) when appropriate. A $p < 0.05$ was considered statistically significant.

RESULTS

Thirty-seven patients, with a median age of 55 years (range 12–88 years) who underwent surgery for AIFR were included in the study. Twenty-four of the patients died during follow-up, which made an overall mortality rate of 64.9%. However, 19 of the patients died of fungus-related sepsis, which made a disease-specific mortality rate of 51.4%. Overall and disease-specific survival functions are given in Figs. 1 and 2, respectively.

Age and sex did not have a significant impact on survival ($p > 0.05$). All of the patients had a known risk factor that made them vulnerable to invasive fungal infection. Twenty-five of the patients (67.6%) had hematologic neoplasms or conditions (17 had leukemia; 4 had aplastic anemia, 4 had lymphoma); eight (21.6%) had uncontrolled diabetes; three (8.1%) had hepatocellular carcinoma; and one (2.7%) had immunosuppression related to Crohn's disease, with long-term high-dose systemic steroid use. Underlying disease was not predictive of the mortality rate ($p > 0.05$). Fever was the most common symptom, along with nasal obstruction

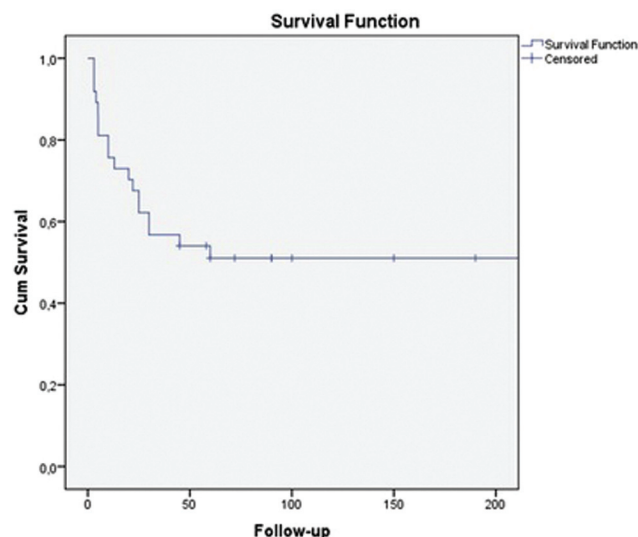


Figure 2. Disease-specific survival rates according to the Kaplan-Meier survival analysis.

and/or fullness, and epistaxis, which yielded a percentage of 86.5, 48.6 and 48.6, respectively. Intranasal crusting, rhinorrhea, facial pain, ulceration and discoloration of the nose, periorbital edema, orbital pain, cranial nerve paralysis, and necrosis of the palate were the other symptoms.

The disease was confined to the nasal cavity and paranasal sinuses in 67.6% of the patients ($n = 25$). There was hard palate involvement in five patients (13.5%), orbital involvement in three patients (8.1%), skin involvement in two patients (5.4%), cavernous sinus involvement in one patient (2.7%), and frontal lobe involvement in one patient (2.7%). Extent and localization of the disease was significantly related to mortality ($p < 0.05$).

The causative pathogen belonged to the Mucoraceae family in 19 patients (51.4%) and to the *Aspergillus* species in 18 patients (48.6%). Mucormycosis (in 13 of 19) associated mortality was significantly higher than that of aspergillosis infection (in 5 of 18) ($p < 0.05$). Although *Aspergillus* was more commonly seen in patients with hematologic conditions (56%), Mucoraceae was the predominant pathogen in patients with diabetes (57.1%).

The median hemoglobin and hematocrit levels were 9.2 g/dL (IQR = 2 g/dL) and 26.7% (IQR = 6.2%), respectively. Median leukocyte, neutrophil, lymphocyte, and platelet counts were 1830/mm³ (IQR = 8610/mm³), 819/mm³ (IQR = 5440/mm³), 440/mm³ (IQR = 880/mm³) and 71,000/mm³ (IQR = 150,000/mm³), respectively. The median CRP value was 8.70 mg/dL (IQR = 10.48 mg/dL). Of the laboratory parameters, only CRP levels had a statistically significant impact on disease-specific mortality rate ($p < 0.05$).

Besides surgery, all of the patients received an amphotericin B regimen as a part of their antifungal treatment. In addition, nine patients received either voriconazole or posaconazole to the amphotericin B treatment. However, the addition of voriconazole or posaconazole did not have a statistically significant effect on prognosis ($p > 0.05$).

According to the results of Cox regression analysis for the disease-specific mortality rate, leukocyte and neutrophil counts as well as CRP levels had a significant prognostic effects on survival function ($p < 0.05$). The type of the fungi had a significant impact on disease-specific mortality on the χ^2 test; however, it could not reach a statistically significant level on multivariate analysis ($p = 0.07$). Regarding the extent of the disease, only hard palate involvement was a significant poor prognostic factor in multivariate analysis. Receiver operating characteristic analysis of CRP values re-

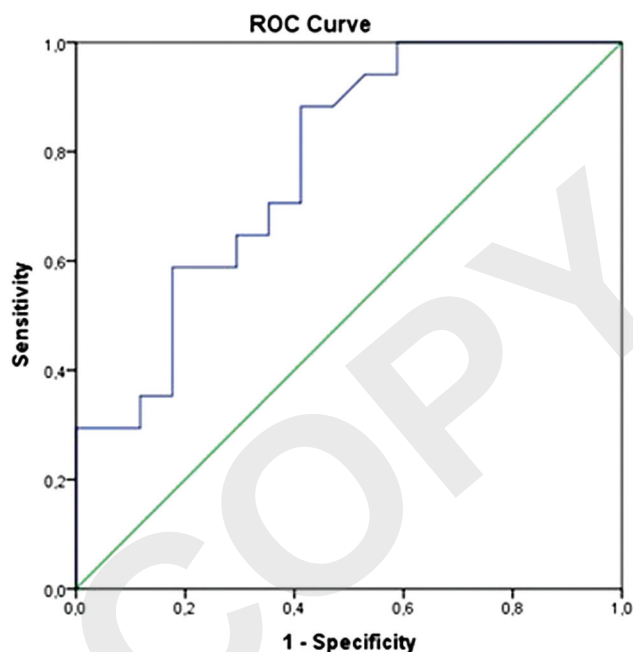


Figure 3. Receiver operating characteristic curve of CRP as a prognostic factor in patients with AIFR.

vealed that the area under the curve was 0.77 ($p < 0.05$). A cutoff CRP level of 4 mg/dL yielded a sensitivity of 94.1% and a specificity of 47.1% (Fig. 3).

DISCUSSION

AIFR is an opportunistic infection that requires special attention, particularly in individuals who are immunocompromised and patients with uncontrolled diabetes mellitus because of its highly morbid and fatal course. In the patients who are immunocompromised, the most common site of infection is the lung, followed by the nasal cavity and paranasal sinuses.⁸ AIFR is described as a fungal sinusitis in patients who are immunocompromised and with histopathologically prominent vascular invasion having a duration of <4 weeks. Due to the invasive nature of the disease, the disease can involve the nasal cavity, paranasal sinuses, nose, skin, palate, orbit, and intracranial structures.

The diagnosis of AIFR entails a high risk of suspicion in patients who are immunocompromised and who have symptoms such as fever unresponsive to antibiotherapy, facial pain, nasal congestion, rhinorrhea, epistaxis, orbital swelling, or cross-sectional imaging findings. These patients require immediate careful otolaryngologic examination, with special care given to nasal endoscopy. Cultures and specimens for histopathologic examination must be obtained from suspicious lesions (black crusted, necrotic, pale, or ulcerative lesions). The diagnosis is established with the demonstration of tissue and vessel invasion in biopsy specimens and/or microbiologic diagnosis. Although final pathology section remains the criterion standard for the diagnosis of AIFR, frozen-section biopsy specimen analysis for AIFR was shown as a highly predictive tool for a rapid and effective diagnosis in patients with suspected AIFR.⁹ The highly rapid progressive nature of the disease generally warrants rapid intervention. The fast progression of one patient's lesion is shown in Fig. 4a and b, which includes two images taken only with a 4-hour interval. Therefore, detection of the hyphae on direct microscopy, with emerging clinical signs, are, most of the time, sufficient for an immediate surgical treatment. The most common isolated fungal agents are *Aspergillus* and Mucoraceae.^{1,5,10,11} Mucor was isolated in 19 patients



Figure 4. (a–d) A 12-year-old patient with aplastic anemia and with mucormycosis of the external nose and nasal cavity. (a, b) The fulminant course and disease progression in only 4 hours. (c) Visible hyphae in the nasal cavity on postoperative day 1. (d) The response to topical amphotericin B treatment.



Figure 5. (a–c) A 66-year-old patient with non-Hodgkin lymphoma and with invasive aspergillosis with orbital involvement. (a) Necrosis of the left infraorbital skin with severe chemosis. (b) The operated cavity after surgical resection. (c) Six months after surgery and reconstruction.

(51.4%), and *Aspergillus* was isolated in 18 patients (48.6%) in our group of 37 patients.

AIFR often presents with nonspecific symptoms. The most common symptom is fever unresponsive to broad-spectrum antibiotics.¹¹ Early symptoms mimic rhinosinusitis. As the disease progresses and complications occur, it is possible to encounter symptoms such as facial swelling, ophthalmoplegia, loss of visual acuity, proptosis, and change in mental status. Fever was the most common symptom (86.5%) in our patients, followed equally with nasal obstruction and/or fullness and epistaxis (48.6%). Intranasal crusting, rhinorrhea, facial pain, ulceration, and discoloration of the nose, periorbital edema, orbital pain, cranial nerve paralysis, and necrosis of the palate were the other symptoms.

Twenty-five patients (67.6%) underwent solely endoscopic surgery for AIFR. Twelve patients (32.4%) required different amounts of open surgical debridement for palate invasion and for orbital or skin involvement. Because of the rapid progression of the disease, it is of utmost importance to establish an early diagnosis. Endoscopic surgery is feasible when the disease is confined to the

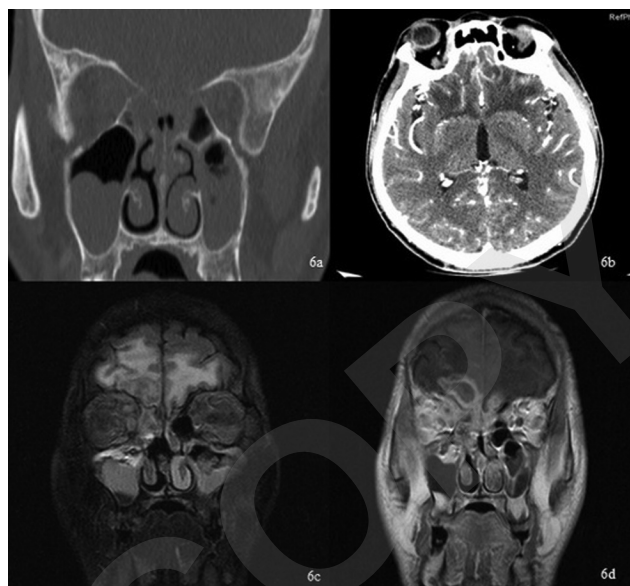


Figure 6. (a–d) Ethmoid sinus and frontal lobe invasion was demonstrated in coronal plane computed tomographies, axial plane computed tomographies, and coronal plane magnetic resonance images.

sinonasal cavity. Our high rates of endoscopic surgery are compatible with high rates of early diagnosis. Various studies report successful outcomes with endoscopic surgery in patients with AIFR.^{1,12–14} Furthermore, Tarkan *et al.*¹⁵ and Park *et al.*¹⁶ reported endoscopic surgery as a feasible and efficient technique in pediatric patients with AIFR.

It is crucial to identify which patients are at risk for developing AIFR to make an early diagnosis. Individuals susceptible to AIFR have an underlying condition known to cause immunosuppression. Hematologic malignancies, aplastic anemia, long-term steroid use, acquired immunodeficiency syndrome, uncontrolled diabetes mellitus, and diseases of iron metabolism and immunosuppressive therapy for organ transplantation are the most commonly encountered underlying conditions. Parikh *et al.*¹⁷ reported that patients with neutropenia patients were more likely to have invasive aspergillosis than mucor. Patients with neutropenia also had more invasive aspergillosis (53.3%) than mucor in our study. In our series of patients, hematologic neoplasms and hematological disease were the most common (67.6%) underlying condition. Eight patients (21.6%) had uncontrolled diabetes mellitus as the predisposing factor, followed by immunosuppression due to chemotherapy for hepatocellular carcinoma in three patients (8.1%) and in a patient with long-term high-dose systemic steroid due to Crohn's disease. Even though Parikh *et al.*¹⁷ reported a higher mortality rate in patients with diabetes, we found that an underlying medical condition was not predictive of mortality ($p > 0.05$).

AIFR has a reported high mortality rate, which ranges between 33 and 80%.^{1,5,9,11,18,19} The median follow-up time was 58 days (IQR = 304 days) in our study. The overall mortality rate was 64.9%. All of the AIFR-related deaths (19) occurred in the 90-day period after the surgical debridement. The disease-specific mortality rate was found to be 51.4%. The Kaplan-Meier survival analysis revealed an overall survival rate of 43.7% and a disease-specific survival rate of 51.1% at the sixth month (Figs. 1 and 2). Our survival outcomes are similar to previous reports.

In a study conducted by Cho *et al.*,¹¹ CRP levels and neutropenia were associated with the prognosis of AIFR. Among the laboratory parameters, lower neutrophil and lymphocyte counts were associated with a worse prognosis ($p < 0.05$). In addition, the prognosis of AIFR was significantly influenced by CRP levels ($p < 0.05$). Although Cho

*et al.*¹¹ obtained a cutoff CRP value of 5.50 mg/dL that best predicted outcomes (area under the curve, 0.882; $p = 0.002$), in our study, a cutoff CRP level of 4 mg/dL (area under the curve, 0.77; $p < 0.05$) yielded a sensitivity of 94.1% and a specificity of 47.1%.

Intracranial involvement and cranial neuropathy were significantly associated with shortened survival in a report by Monroe *et al.*²⁰ Intracranial or orbital involvement was not associated with a worse prognosis; however, involvement of the hard palate was significantly associated with a worse prognosis ($p < 0.05$). A patient with extended orbital involvement due to AIFR is shown in Fig. 5. Furthermore, the patient with intracranial involvement, whose radiologic workup is given in Fig. 6, was still alive when the study was completed. The involvement of the hard palate was significantly related with poor prognosis. This is a new finding of this study. All five patients who had hard palate invasion died. The dismal prognosis of the patients with palate involvement might be attributed to the potential reasons listed: (1) it is a finding of late diagnosis, (2) it is a finding of extensive disease, or (3) extensive surgery applied.

Treatment of AIFR requires the control of the underlying predisposing condition, surgical debridement of necrotic tissues, and antifungal chemotherapy.²¹ Surgical treatment facilitates treatment in various ways: (1) decelerates the progression of the disease and allows time for bone marrow recovery; (2) reduces the fungal load, which reduces the burden on recovering neutrophils; (3) prevents easy growth of fungal elements in devitalized tissues; (4) enhances the ability of antifungal drugs to reach infected areas; (5) facilitates nasal irrigation and postoperative monitoring for recurrent disease; and (6) provides specimens for culture and histopathologic examination.^{22,23} Although amphotericin B is the primary antifungal drug used in the treatment of AIFR, new drugs, such as caspofungin, voriconazole, and ravuconazole, have been successfully used in treating invasive fungal infections.^{24–26} However, the combination with caspofungin, voriconazole, or posaconazole did not have an impact on survival ($p > 0.05$) in our study. The effect of topical irrigation with antifungal drugs is controversial.^{12,27} We used topical amphotericin B irrigations for visible fungal elements, and the visible hyphae disappeared in 24 hours, although this did not alter the outcome (Fig. 4c, d).

We applied early aggressive surgical debridement, and it should be performed for all patients with AIFR. Piromchai and Thanaviratnanich²⁸ reported that the time taken to treat the patients was the most statistically significant predictor for mortality. Endoscopic surgery is feasible in the early stages of the disease when the disease is confined to the nasal cavity and paranasal sinuses. As the disease progresses, resection of the skin, palate, nose, orbita, or maxilla may be required. If the hard palate is resected, then we apply a palatal obturator at the time of surgery. Thus, when the disease requires resection of the palate, we consult the department of prosthodontics. The operation site can be easily monitored for recurrence and healing with a palatal obturator. However, in resections that require complex reconstruction, we prefer to delay the reconstruction to a second stage after the operated cavity has healed and the patient had received treatment for his or her underlying medical condition.

Intranasal structures, including the septum and the middle and inferior turbinate, can be resected without causing significant morbidity. Also, these structures can be removed even without a histopathologic diagnosis if there is a high degree of suspicion. However, surgical resection of the palate, nose, facial skin, orbita, or other vital organs requires in-depth evaluation and a definite histopathologic diagnosis for AIFR.

Traditional teaching encourages aggressive surgical resection until viable, bleeding tissue is reached, which often leads to orbital exenteration, skull base resection, and cerebral debridement.^{29–31} Mutchnick *et al.*³² reported a pediatric AIFR case with orbital and intracranial involvement, which was successfully managed without orbital exenteration or cerebral debridement. We also successfully managed an AIFR case with cavernous sinus, frontal lobe, and orbital involvement only with endoscopic resection (Fig. 6a–d). Despite the aggres-

sive surgical recommendations in the previous reports, we think orbital exenteration should be delayed or not performed when the vision is intact.

CONCLUSION

AIFR requires immediate attention for early medical and surgical treatment. For an early diagnosis, one must maintain a high level of suspicion if early symptoms of AIFR develop in patients with predisposing host factors. Palatal involvement was associated with a higher mortality in our study. Also, leukocyte and neutrophil counts and CRP values had a significant impact on survival function. Reversal of the underlying disease and immunosuppression is as important as the medical and surgical treatment. The resection of vital organs should be reconsidered for benefits and morbidities, and performed only in patients with a definitive diagnosis. Orbital exenteration should be performed if the orbit has lost all its functions, including vision. Unfortunately, mortality is still high, even with appropriate antifungal and surgical treatment.

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