

Acute Invasive Fungal Rhinosinusitis: Presentation of 19 Cases, Review of the Literature, and a New Classification System



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Purpose: The aim of this study was to determine the correlation between acute invasive fungal rhinosinusitis (AIFRS) and underlying diseases, micro-organisms, presenting symptoms, extent of disease, radiologic findings, and outcomes and propose a new classification system.

Materials and Methods: The data of 19 AIFRS cases were analyzed retrospectively. Magnetic resonance imaging and computed tomography were performed in all patients preoperatively. All patients underwent at least 1 surgical debridement.

Results: Hematologic diseases were the most common (52%) underlying diseases. Patients with type 2 diabetes and those with multiple etiologies causing immunosuppression had the lowest survival. *Aspergillus* and *Mucoraceae* species were isolated in 9 patients but were not associated with poor prognosis. Headache and nasal discharge or crusting were the most common presenting symptoms. Premaxillary involvement was significantly correlated with poor prognosis ($P = .001$). Unilateral involvement was correlated with poor prognosis, although this finding was not significant ($P = .111$). The overall mortality rate was 61.2%. Patients with neutropenia that was corrected had 80% survival ($P = .014$). Cessation of corticosteroids and regulating blood glucose levels in patients with immunosuppression from corticosteroid use resulted in 75% survival.

Conclusion: There is no single curative treatment for AIFRS. For a favorable prognosis, underlying conditions must be treated in addition to surgical debridement and antifungals.

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Acute invasive fungal rhinosinusitis (AIFRS) is a rare disease characterized by progressive submucosal fungal invasion of the nasal cavity and paranasal sinus mucosa.^{1,2} Other major types of fungal rhinosinusitis include chronic invasive fungal sinusitis (CIFRS), allergic fungal rhinosinusitis (AFS), fungus ball (mycetoma), and saprophytic fungal growth (SFG).

In cases of AIFRS, fungal hyphae rapidly spread into blood vessels and cause vasculitis, followed by tissue infarction and hemorrhage. Some researchers use the term *fulminant* instead of *acute*, which implies a disease duration shorter than 4 weeks, because of the rapidly destructive and fatal nature of the disease.

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AIFRS requires urgent diagnosis and treatment; otherwise, the mortality rate can be as high as 50 to 80%.^{3,4} *Aspergillus* and *Zygomycetes* species (*Absidia*, *Rhizopus*, *Rhizomucor*, and *Mucor*) are the most common pathogens that cause AIFRS and are abundant in the air, dust, and soil.^{1,2,5}

Hematologic diseases or malignancies, poorly controlled type 1 or 2 diabetes mellitus (DM), corticosteroids or other immunosuppressive agents, solid organ or bone marrow transplantation, acquired immunodeficiency syndrome (AIDS), malnutrition, and many other causes of immunosuppression can cause AIFRS.^{2,6-8} This retrospective study aimed to determine the correlation between AIFRS and underlying diseases, etiologic micro-organisms, presenting symptoms, extent of disease, radiologic findings, and outcomes of medical and surgical treatment in 19 patients with AIFRS.

Materials and Methods

The study included 19 patients with histopathologically confirmed AIFRS who were followed at Hacettepe University Hospital (Ankara, Turkey) from January 2006 through December 2014. Approval of the Hacettepe University noninterventional clinical research ethics board had been obtained before the study (2015/354-15). Patient records were retrospectively analyzed for presenting symptoms, underlying diseases, causative micro-organisms, neutrophil count at the time AIFRS was diagnosed and during the course of treatment, medical and surgical treatment, and treatment outcome. Magnetic resonance imaging (MRI) or computed tomography (CT) was performed in all patients.

MANAGEMENT OF AIFRS

All patients were referred from other departments because of suspected AIFRS. A detailed history and a thorough physical examination, including rigid or fiberoptic endoscopic examination, were performed. If suspicion of AIFRS was not high, then daily follow-up was preferred. If pale ischemic mucosa or necrotic black crusts had been observed, then surgery was planned urgently. CT scans of all patients had been ordered and carefully evaluated before surgery. Endoscopic evaluation under general anesthesia, tissue sampling, and debridement of necrotic crusts until bleeding of healthy tissue were performed for all patients. Tissue samples were collected for microbiological and pathologic examinations for diagnosis.

Many patients had been using antifungals at the time of consultation because of fever of unknown origin or systemic fungal infections. If a strong suspicion for AIFRS was present, then intravenous (IV) liposomal amphotericin B therapy was initiated

empirically. Doses were tailored according to the patient's weight, prior health status, and side effects. After the surgery, close follow-up with endoscopic examinations was continued until discharge. If a progression was detected during the course, then debridement surgeries were performed. If the histopathologic diagnosis was *Aspergillus* species, then the antifungal was switched to IV voriconazole. If AIFRS was excluded with histopathologic evaluation, then empirical antifungal was ceased but close follow-up continued until the underlying condition was corrected. Every stage of patient follow-up was managed with a multidisciplinary approach.

HISTOPATHOLOGY

All biopsy specimens were sent to the departments of pathology and microbiology and were evaluated by a pathologist and a microbiologist. Specimens were examined on sections stained with hematoxylin and eosin. Special stains with periodic acid-Schiff or Grocott-Gomori methenamine silver stain also were used to highlight the organisms and allow a clearer assessment of the morphology. Morphologic features of the fungal hyphae and septa were examined in addition to tissue necrosis and vascular infarct of the involved tissue.

MRI TECHNIQUE

MRI of the sinuses and nasal cavity was performed using a 1.5-T scanner (Symphony, Siemens, Erlangen, Germany; Achieva, Philips Healthcare, Netherlands; or Signa HDxt 1.5 T, GE Healthcare, Milwaukee, WI) and a standard head coil. The standard sinus and nasal cavity MRI protocol included sagittal T1-weighted (W), axial fat-saturated T2W, axial and coronal T1W, coronal short tau inversion-recovery, and axial diffusion weighted imaging. In addition, postcontrast fat-saturated T1W axial and coronal T1W images were obtained after administration of gadolinium 0.2 mmol/kg.

CT TECHNIQUE

CT was performed using a 4- or 16-channel multi-detector CT scanner (SOMATOM Plus 4 Volume Zoom, Sensation 16, Siemens; or GE Lightspeed 16 Detector Scanner, GE Healthcare) in the axial plane from the top of the frontal sinuses to the tip of the incisors and 2-mm slice thickness. CT and MRI images were retrospectively reviewed by a blinded neuroradiologist experienced in head and neck imaging. Images that could not be obtained for retrospective review were not included in the study. Based on radiologic and clinical findings, the involved regions were classified according to a

proposed classification (Hacettepe University AIFRS Classification):

1. Unilateral involvement of the nasal cavity or paranasal sinuses
2. Bilateral involvement of the nasal cavity or paranasal sinuses
3. Retro-antral region, pterygopalatine fossa, infraorbital fissure, or infratemporal fossa
4. Premaxillary region or skin involvement
5. Orbital involvement
6. Intracranial disease

STATISTICAL ANALYSIS

All data were analyzed using PASW Statistics 18.0 for Windows (SPSS, Inc, Chicago, IL). Categorical data are presented as frequency. Survival analysis was performed using the Kaplan-Meier method, and survival curves were compared between independent groups using the log-rank test. Analyses were evaluated according to a type I error level of 5% and the level of statistical significance was set at a *P* value less than .05.

Results

The study included 19 patients with AIFRS (9 female and 10 male). Mean age of the patients was 36.2 years (range, 2 to 72 yr). Seven patients were younger than 18 years (pediatric patients). The most common presenting symptom was headache and facial pain (*n* = 9 [47.3%]), followed by nasal discharge and crusting (*n* = 5 [26.3%]). Facial swelling, palatal lesion or pain, ocular pain or swelling, and a decrease in visual acuity were noted in 3 patients (15.7%). All presenting symptoms are listed in Table 1.

The most common underlying condition was hematologic disease (*n* = 12 [63.1%]). Other causes of immunodeficiency were corticosteroid-induced DM (*n* = 4 [21%]) and type 2 DM (*n* = 3 [15.7%]). Hematologic pathologies included acute myeloid leukemia (AML; *n* = 5), acute lymphocytic leukemia (ALL; *n* = 3), pure red blood cell aplasia (*n* = 1), aplastic

anemia (*n* = 1), and hemophagocytic syndrome (*n* = 1). Autoimmune conditions, such as Behçet disease, treated with steroids were other common underlying diseases in 4 patients. Of these patients, 3 had multiple etiologies: 2 patients had a hematologic disease and corticosteroid exposure and 1 patient had type 2 DM and corticosteroid exposure. Interestingly, 1 patient who had no previous DM was treated with steroids, and this patient developed increased blood glucose levels and then mucormycosis. Complete blood cell count levels of all presenting patients were reviewed. Ten of 19 patients had severe neutropenia (absolute neutrophil count, <500 cells/ μ L). Subtypes of accompanying diseases and medical conditions are presented in detail in Table 2.

CT was used preoperatively to determine the extent of fungal invasion in all 19 patients. MRI was used in 13 patients primarily because of suspected orbital or cerebral fungal invasion. In total, 9 patients (47.3%) had unilateral involvement of the nasal cavity or paranasal sinuses, 10 (52.6%) had bilateral involvement of the nasal cavity or paranasal sinuses, 17 (89.4%) had involvement beyond the paranasal sinuses, and 12 (63.1%) had orbital or intracranial involvement. Regions involved and survival rates are presented in Table 3.

All patients underwent primary or recurrent endoscopic debridement. Six patients underwent recurrent endoscopic surgery, 2 (33.3%) of whom survived and could be cured. The time from initial to repeat surgery

Table 2. CLINICAL FEATURES AND ACCOMPANYING DISEASES OF PATIENTS

Accompanying Medical Condition	n (%)
Hematologic diseases	
AML	5 (26.3)
ALL	2 (10.5)
Hemophagocytic syndrome	1 (5.3)
ALL + hemophagocytosis + MDS	1 (5.3)
Hemophagocytic syndrome + autoimmune hemolytic anemia	1 (5.3)
Aplastic anemia	1 (5.3)
Pure red cell aplasia	1 (5.3)
Autoimmune diseases	
Behçet disease	2 (10.5)
Wegener granulomatosis	1 (5.3)
Temporal arteritis	1 (5.3)
Type 2 DM + microvascular disease	2 (10.5)
Severe neutropenia (absolute neutrophil count, <500 cells/ μ L)	10 (52.6)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; DM, diabetes mellitus; MDS, myelodysplastic syndrome.

Table 1. PRESENTING SYMPTOMS

Presenting Symptoms	n (%)
Headache or facial pain	9 (47.3)
Nasal discharge or crusting	5 (26.3)
Facial swelling	3 (15.7)
Palatal lesion or pain	3 (15.7)
Ocular symptoms	3 (15.7)

Table 3. REGIONS OF INVOLVEMENT AND SURVIVAL RATES

Regions Involved	n (%)	Survived, n	Survival Rate, %
Unilateral involvement of nasal cavity or paranasal sinuses	9 (47.3)	6/9	66.6
Any bilateral involvement	10 (52.6)	1/9 (unknown, 1)	11.1
Involvement beyond paranasal sinuses (inclusive)	17 (89.4)	6/16 (unknown, 1)	37.5
Retro-antral region, pterygopalatine fossa, infraorbital fissure, infratemporal fossa	14 (73.6)	5/14 (unknown, 1)	35.7
Premaxillary region, skin involvement	12 (63.1)	1/11 (unknown, 1)	9
Orbital involvement	11 (57.8)	2/10 (unknown, 1)	20
Intracranial involvement	7 (36.8)	2/6 (unknown, 1)	33.3
Orbital or intracranial involvement	12 (63.1)	3/11 (unknown, 1)	27.2

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ranged from 1 to 76 days. *Mucoraceae* species were isolated in 9 patients (50%) and *Aspergillus* subtypes were isolated in 9 (50%). In all patients, angioinvasive hyphae were observed and AIFRS was confirmed. In 1 patient the causative micro-organism could not be determined, but angioinvasion was diagnostic of AIFRS. In total, 11 patients had been using systemic antifungal treatments for at least 1 week because of resistant fever before the diagnosis of AIFRS. Of all patients, 18 were treated with IV liposomal amphotericin B (3 to 5 mg/kg per day, empirical dose tailored according to the causative micro-organism and renal function); IV liposomal amphotericin treatment continued during hospitalization and was switched to long-term oral voriconazole or itraconazole after discharge. Of the 10 patients who had neutropenia at diagnosis, neutropenia was corrected in 5 during treatment.

The overall survival rate in patients with AIFRS was 38.8%; the survival rate in adult patients (41.6%) was slightly higher than that in pediatric patients (33.3%). The highest survival rate (75%) was noted in patients with steroid-induced DM without another underlying immunodeficiency. Survival was 80% in patients with neutropenia in whom neutropenia was corrected. Patients with type 2 DM and combined

etiologies had the lowest survival rate (0%). Survival rates according to underlying disease are listed in Table 4.

Discussion

Paranasal fungal infections include AIFRS, CIFRS, AFS, mycetoma, and SFG. Clinical behavior, prognosis, and treatment alternatives of different types of paranasal fungal infections show great variation; therefore, accurate differential diagnosis is important.

CIFRS is an invasive fungal rhinosinusitis similar to AIFRS but usually affects immunocompetent patients with a much slower disease progress. *Aspergillus flavus* is a common causative agent but other *Aspergillus* species can be responsible. CIFRS can be granulomatous or nongranulomatous (indolent). Presenting symptoms are similar to those of AIFRS and treatment includes endoscopic debridement and long-term antifungal treatment.⁹⁻¹¹

AFS is a noninvasive fungal sinusitis. Aerosolized fungal antigens cause an allergic reaction and eosinophilic mucin and inflamed mucosa accompany fungal hyphae. Systemic atopy and increased serum or local immunoglobulin E levels are seen. AFS usually presents as unilateral sinusitis that is resistant to medical

Table 4. SURVIVAL RATES ACCORDING TO UNDERLYING DISEASE

Underlying Diseases	n (%)	Patients Survived, n	Survival Rate, %
Hematologic disease	10 (52.6)	4/10	40
Type 2 DM	2 (10.5)	0/1 (+1 unknown)	0
Corticosteroid use (inclusive)	7 (36.8)	3/7	42.8
Steroid-induced DM	4 (21.0)	3/4	75
Type 2 DM + corticosteroids	1 (5.2)	0/1	0
Hematologic disease + corticosteroids	2 (10.4)	0/2	0

Abbreviation: DM, diabetes mellitus.

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treatments. Physical examination or CT scan might show an expanded sinus secondary to fungal growth, thick secretions, and polypoid mucosa. Treatment includes removal of fungal debris, secretions, and systemic steroids.

Mycetoma is a noninvasive chronic fungal growth confined to a paranasal sinus. The presentation can range from asymptomatic to progressively destructive disease. Systemic atopy is not seen. Treatment of mycetoma is surgical removal of the fungus ball.⁹

SFG is characterized by growth of fungal hyphae on crusts usually within a paranasal sinus. SFG can follow nasal surgery and mechanical removal of the crusts is sufficient as a treatment modality.

AIFRS is a rare disease characterized by progressive submucosal fungal invasion of the nasal cavity and paranasal sinus mucosa.^{1,2} Unlike other chronic fungal rhinosinusitis types, rapid progression of AIFRS requires urgent diagnosis and treatment; otherwise, the mortality rate increases dramatically.

The incidence of AIFRS in immunocompromised patients is approximately 2%¹² and the most common site of infection is the lungs, followed by the sinonasal cavity.⁹ Although initial symptoms in most cases are nonspecific, according to a systematic review, the most common presenting symptom of AIFRS is facial swelling (64.5%), followed by fever (62.9%) and nasal congestion (52.2%). Ocular symptoms occur as the presenting symptom in approximately 50% of patients, headache occurs in slightly fewer than 50%, and palatal necrosis occurs in 20.8%.¹³ The most common presenting symptom in the present study was headache and facial pain (47%), followed by nasal discharge and crusting (26%). Facial swelling—the most commonly reported presenting symptom—was the third most common in the present study ($n = 3$), as were palatal necrosis or pain ($n = 3$) and ocular pain or swelling or a decrease in visual acuity ($n = 3$). Ocular symptoms were far less common in the present study than previously reported.¹³

According to the current literature, hematologic diseases and malignancies are the most common underlying diseases in patients with AIFRS.^{2,5,12-14} In the present study, 52% of patients had an underlying hematologic disease or malignancy, such as ALL and AML. Other conditions underlying AIFRS include immunosuppressive treatment, poorly controlled DM (corticosteroid exposure was the second most common etiology [36.8%] followed by poorly controlled type 2 DM [10.5%]), AIDS, malnutrition, iron accumulation (as in hemochromatosis), and other causes of cellular immunodeficiency.^{1,2,7,8,12,13}

A high level of suspicion of AIFRS is crucial in susceptible immunocompromised patients. Once AIFRS is suspected, careful examination of the nasal cavity, nasopharynx, and oral cavity through a rigid or fiber

optic endoscope, ophthalmologic examination, and neurologic examination should be performed.^{2,8,10,12,13}

Anterior rhinoscopy alone is not sufficient in high-risk patients. Extreme care is necessary to prevent mucosal trauma that could facilitate infiltration of fungal spores.¹ Pale or necrotic mucosa, ulcers or granulation, intensive crusting, and thick nasal secretions are the most common endoscopic findings.^{2,8,12} In patients with such findings, surgery is required with the patient under general anesthesia. Deep biopsy samples from suspected sites can be obtained or debridement can be performed if the level of suspicion of AIFRS is high. Biopsy examination of the middle turbinate has been suggested for diagnosis of AIFRS when mucosal involvement is unclear,¹² because the middle concha is the most common site of involvement. The septum and hard palate also are common sites of involvement.^{3,14}

CT and MRI are essential for the differential diagnosis of fungal infection and for determining extent of AIFRS. Although the sensitivity of high-resolution noncontrast CT is limited during the early phases of AIFRS and might not yield findings that can be differentiated from nonspecific sinusitis,^{9,13} there could be findings indicative of the possibility of AIFRS, including unilateral thickening of nasal cavity mucosa, obliteration of peri-antral fat, osseous erosion, and orbital, cavernous sinus, or brain involvement in immunocompromised patients.^{9,15-17} MRI is more sensitive than CT for detecting early mucosal changes of AIFRS.¹⁵ In patients with predisposing factors and sinus disease, AIFRS should be strongly considered, especially in the presence of focal lack of enhancement of normally enhancing mucosa and restricted diffusion indicative of tissue necrosis.¹⁸ In addition, MRI is more sensitive than CT for detecting intraorbital and intracranial disease involvement, including the cavernous sinus. Similarly, leptomeningeal involvement, which occurs in late-stage AIFRS, can be very subtle and can be confirmed only by contrast-enhanced MRI; however, despite advancements in imaging technology, early detection of AIFRS and its differentiation from other types of sinusitis in the early stages remain challenging. In the present study, retro-antral soft tissue attenuation (Fig 1) at CT and enhancement in the retro-antral fat plane (Fig 2) at MRI were among the earliest and most specific findings of AIFRS.

IV administration of amphotericin B is the gold standard for the treatment of AIFRS. Although amphotericin B is an effective antifungal, it is associated with such serious side effects as nephrotoxicity and hepatotoxicity, which can become life-threatening in patients with an already poor health status and determinative for discontinuation of the treatment.¹¹ Liposomal amphotericin B is a derivative of amphotericin B that has the same antifungal activity but with milder side

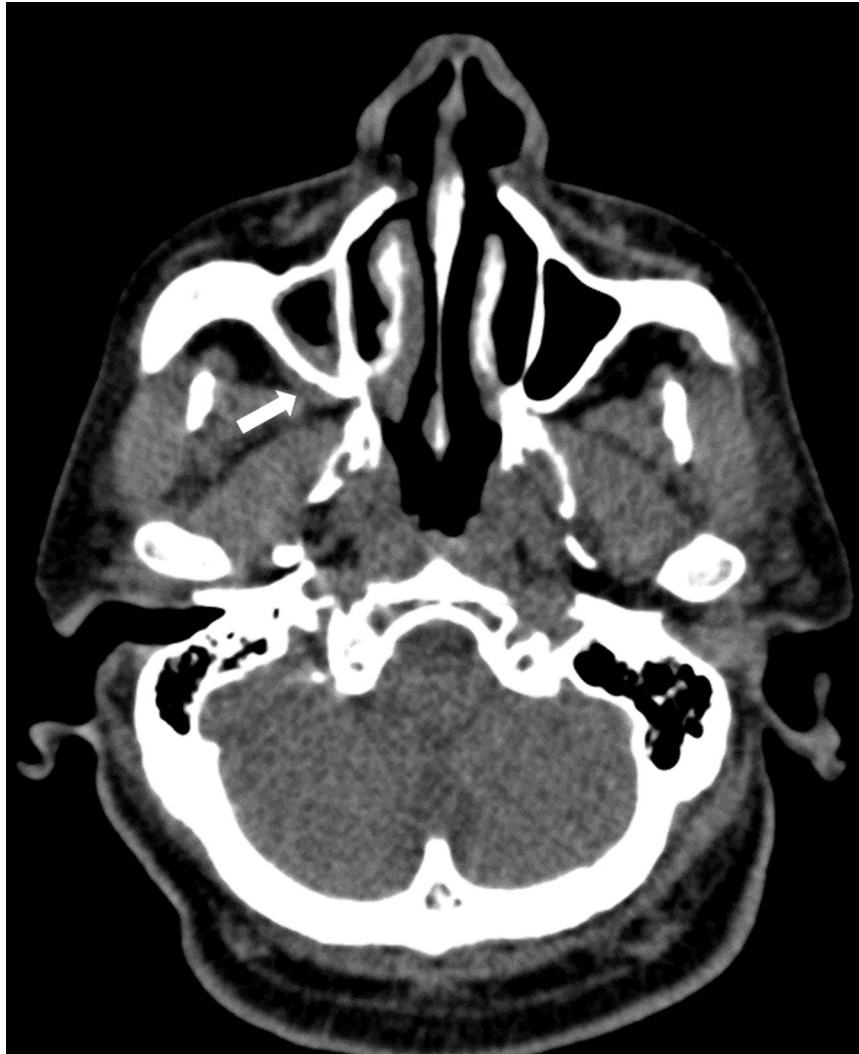


FIGURE 1. Axial computed tomogram of a 56-year-old man with acute myeloid leukemia shows peripheral opacification in the right maxillary sinus and right retro-antral soft tissue attenuation (arrow) from acute invasive fungal rhinosinusitis.

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effects. Voriconazole is a new alternative to amphotericin B that is associated with fewer side effects and is more effective against invasive aspergillosis.¹⁶ Although IV liposomal amphotericin B is expensive, it is the preferred formulation and empirical treatment of choice before precise histopathologic diagnosis at the authors' hospital. If AIFRS is histopathologically proved to be associated with *Aspergillus* species, then the protocol is to switch from IV liposomal amphotericin to IV voriconazole. In the present study, all patients received amphotericin B at some point during their treatment. In addition, 11 of the 19 patients received systemic antifungal treatment for at least 1 week before the diagnosis of AIFRS owing to fever resistant to antibacterial treatment.

According to many excellent reviews, correction of the underlying disease and resolution of neutropenia are the most important prognostic factors for survival

in patients with AIFRS.^{1,5,8,12} In the present study, 10 patients had neutropenia at the time AIFRS was diagnosed; resolution of neutropenia was achieved in 5 of these patients, who had a significantly higher survival rate (80%; $P = .014$)—further evidence of the importance of correcting neutropenia for a good prognosis. Median survival time in patients in whom neutropenia could not be corrected was 15 days (Fig 3). Patients with easily correctable conditions, such as corticosteroid-induced DM, had the highest survival rate (75%) in the present study. Patients in the present study with hematologic diseases had intermediate prognosis (survival rate, 52.6%) in accordance with the literature^{12,13}; their general health status and the success of treatment to increase leukocyte counts were correlated with their survival rate. The survival rate in patients with type 2 DM and in those with multiple underlying diseases was 0%. The authors

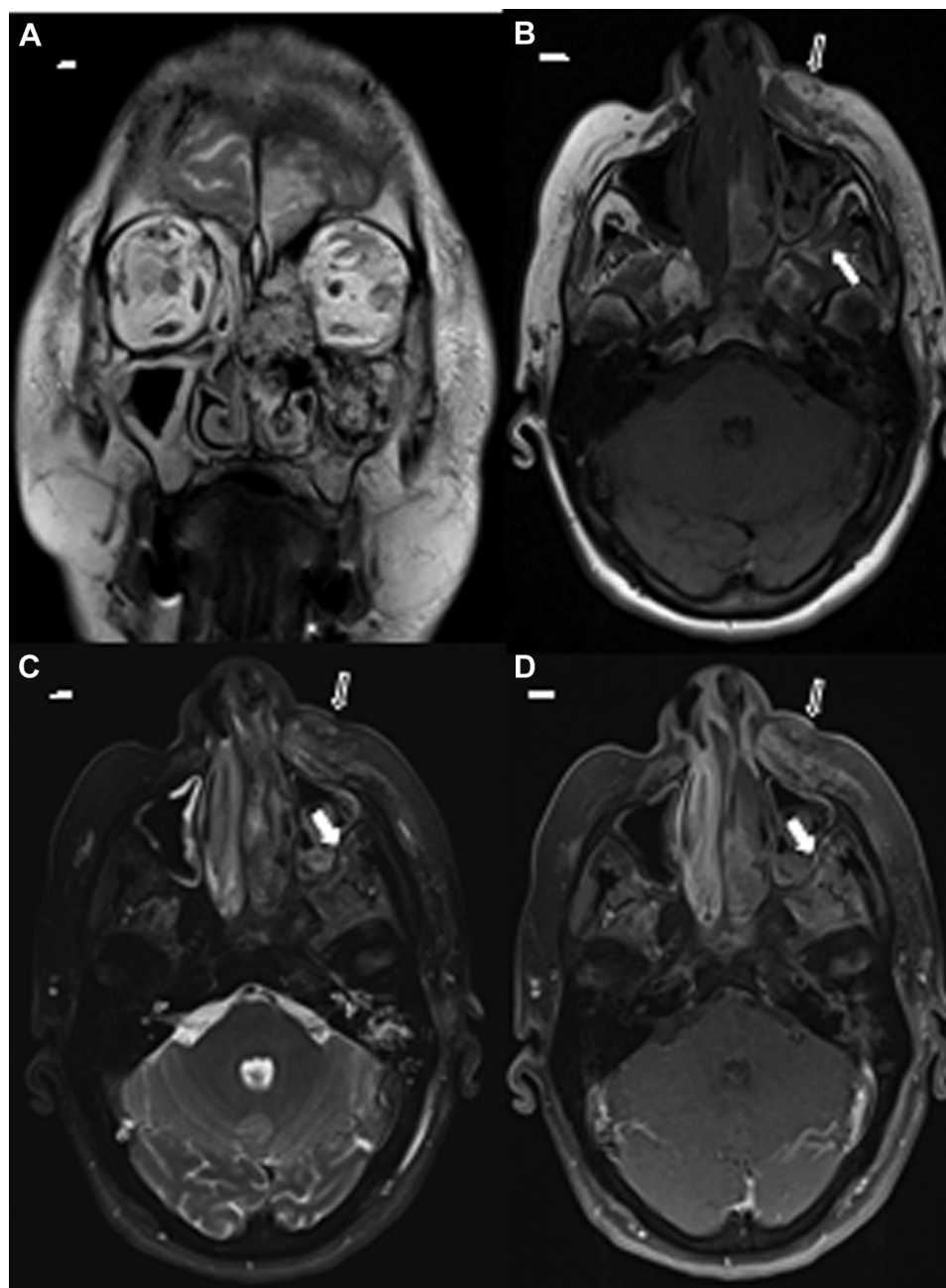


FIGURE 2. A 52-year-old woman with acute invasive fungal rhinosinusitis from steroid-induced diabetes mellitus whose presenting symptoms were headache and left premaxillary facial swelling. A, Sagittal T2-weighted image shows hyperintense heterogeneous signal change filling the left maxillary and anterior ethmoidal cells. B, Axial T1-weighted, C, T2-weighted, and D, postcontrast T1-weighted images show T1 hypointense and T2 hyperintense signal changes and enhancement of retro-antral fat (white arrows), pterygoid muscles, and premaxillary fat (hollow arrows) from invasive fungal infection.

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believe their poor prognosis was due to irreversible degenerative changes caused by long-term type 2 DM, including peripheral micro- and macrovascular diseases and organ failure. DM has been reported to have controversial survival rates with AIFRS. Some researchers have reported better prognosis in patients with DM because of the partial reversibility of their pathology, such as hyperglycemia or acidosis,^{13,15,17}

whereas others have not observed a relevant difference¹⁴ than the overall prognosis or noted less favorable prognosis.^{12,18}

Early and extensive debridement is another important prognostic factor in patients with AIFRS.^{1,4,7,8,12,13} Early debridement of necrotic tissue is important in patients with AIFRS, because removal of devitalized tissue increases the ability of antifungal

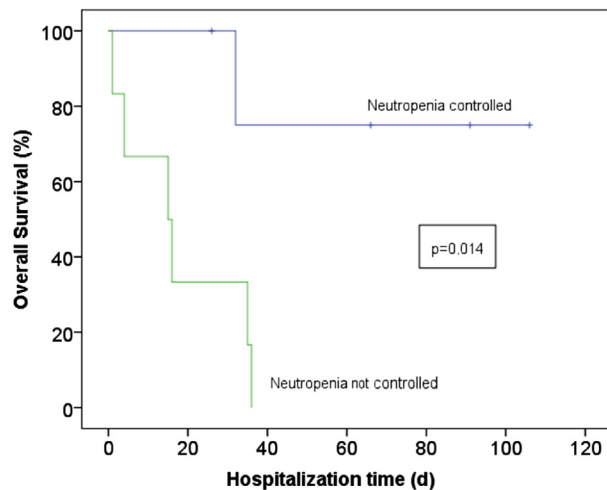


FIGURE 3. Survival rates in patients with neutropenia in whom neutropenia was controlled and not controlled.

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drugs to reach infected areas, thereby decreasing the fungal burden and slowing disease progression.^{1,5,12} Debridement should be continued until vital tissues are reached. The endoscopic approach can be used to accomplish total removal of the disease in most cases, with minimal morbidity.^{1,2,5,8} Furthermore, continued evaluation of the surgical field under magnification during endoscopic surgery facilitates accurate localization of the spread of disease and orientation for postoperative endoscopic follow-up. All necrotic tissue should be removed.¹⁴ All patients in the present study underwent endoscopic debridements. Furthermore, 6 patients underwent at least 1 endoscopic surgery, 2 (33.3%) of whom survived.

The proposed classification method of AIFRS in this study (Hacettepe AIFRS Classification System) summarizes clinical stage and disease morbidity in a simple format. Because cartilage is an avascular tissue, it restricts easy endovascular spread of AIFRS; therefore, while designing the Hacettepe AIFRS Classification System, septal cartilage was considered an important anatomic barrier limiting the bilateral spread of AIFRS. The spread of AIFRS beyond the paranasal sinuses is a clear sign of disease progression and therefore was included in the classification. Premaxillary skin, orbital, and cerebral involvements are associated with major morbidity and later-stage disease and were included in the Hacettepe AIFRS Classification System. The authors intend to evaluate the clinical usefulness of this classification through additional prospective research.

Owing to the rarity of AIFRS, the limited number of relevant studies, and heterogeneous findings of previous studies, it is difficult to determine how spread of disease to particular anatomic sites results in poor outcomes, although dissemination of the disease is clearly

associated with higher morbidity and poor prognosis. It has been reported that unilateral involvement of AIFRS restricted to the nasal cavity and paranasal sinuses has a lower mortality rate (33%) than midline involvement or bilateral involvement (67%).¹² Several studies have reported dramatic increases in the mortality rate (from 26.7 to 40% to 88 to 89%) once the disease is highly disseminated.¹⁹ In the present study, bilateral involvement was associated with a markedly lower survival rate (11.1%), whereas unilateral paranasal or nasal cavity involvement was associated with a higher survival rate (66.6%) than with overall survival rate (38.8%). Although the difference in survival rate was not significant ($P = .111$), relevant findings might have been observed if the present study had included more patients (Fig 4). In the present study, the survival rate was 20% in patients with orbital involvement and 33% in those with intracranial involvement; although the difference was significant ($P = .414$), these rates were lower than the overall survival rate (38.8%) and support previous findings associating orbital and cerebral involvement with poor prognosis.^{6,12,13} Orbital involvement also is an important outcome, because necessary orbital exenteration inevitably causes serious morbidity. The decision is even more difficult in patients with adequate vision. Moreover, orbital exenteration surgery does not appear to affect overall survival.¹³ It might be best to debride only nonfunctional orbital tissue and attempt to preserve sight in patients with adequate vision. Orbital and cerebral involvement can occur through different pathways, usually along the routes of various invaded vessels. Although involvement with the lamina papyracea or cribriform plate is possible, the most probable pathway is

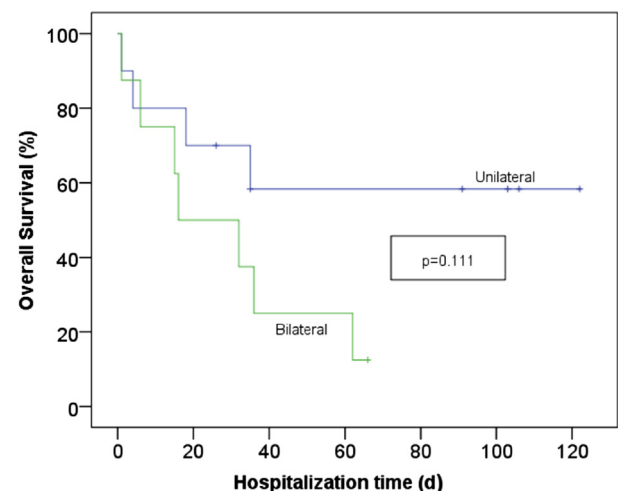


FIGURE 4. Overall survival in patients with unilateral and bilateral acute invasive fungal rhinosinusitis.

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through the pterygopalatine fossa, followed by the inferior orbital fissure, and then retrobulbar and cavernous sinus involvement.²⁰ Hosseini and Borghei²⁰ reported involvement of the pterygopalatine fossa in 100% of patients with rhinocerebral AIFRS and concluded that debridement of the pterygopalatine fossa (the major reservoir) might improve prognosis. In the present study, pterygopalatine fossa involvement was noted in 100% of patients with cerebral involvement and in 81.8% with orbital involvement, which is in agreement with the findings of Hosseini and Borghei.²⁰ Premaxillary involvement or skin involvement in the present study was associated with a significantly higher mortality rate (91%) than overall mortality rate (61.2%; $P = .001$). The authors believe that the high mortality rate in patients with premaxillary or skin involvement in the present study was due to it being a late finding that usually follows bony destruction of the anterior maxillary wall.

For the 11 mortalities, all but 2 patients were in an intensive care unit and were intubated as a result of their slowly progressing clinical status. Two other patients had abundant hemorrhage from thrombocytopenia because of their underlying conditions (aplastic anemia and chemotherapy for leukemia). Neutropenic fever and nephrotoxicity related to amphotericin B were major causes of death and seen in 5 patients (45.4%). Four patients had culture-proved bacterial infection during their last week. Two patients (18.1%) had bacterial infection and nephrotoxicity, which complicated their already severe underlying diseases. One patient (9%) had cerebral fungal invasion as the cause of coma and death.

The mortality rate does not change according to the fungal agent that is causing AIFRS.⁵ In the present study, 9 patients had *Aspergillus* subtypes and 9 had *Mucoraceae* subtypes, whereas in 1 patient the specimen could not be specified, but angioinvasion confirmed AIFRS. The mortality rates associated with *Aspergillus* and *Mucoraceae* species were 55 and 62%, respectively, whereas overall survival was 38.8%; these mortality rates are in accordance with the 20 to 50% survival rates previously reported.^{3,4} Moreover, the survival rate in the pediatric patients was 33% versus 41.6% in adult patients.

To successfully treat AIFRS, which has a highly unfavorable prognosis, underlying immunocompromising conditions must be corrected first.^{1,5,12,13} A high level of suspicion for the development of AIFRS in at-risk patients, early diagnosis, debridement of necrotic tissues, proper antibiotic therapy, and correction of neutropenia using an effective multidisciplinary approach are necessary for successful treatment. The Hacettepe AIFRS Classification System, which categorizes clinical stages and morbidity based on a simple format, requires additional studies to more clearly

determine its clinical value. In addition, patients and their families should be thoroughly informed about AIFRS and its prognosis as early as possible.

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