



# Prognosis of acute invasive fungal rhinosinusitis related to underlying disease

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## SUMMARY

**Background:** Acute invasive fungal rhinosinusitis (AIFRS) is a rare disease with high morbidity and mortality rates. The objective of this study was to correlate the initial clinical features of AIFRS to the prognosis after surgery.

**Methods:** Thirty-two patients with AIFRS were evaluated retrospectively. The correlation of underlying disease, fungus isolated, and extent of the disease to the clinical outcome of AIFRS was also evaluated. **Results:** The most common underlying disease was hematological malignancy and aplasia ( $n = 20$ ). *Aspergillus* ( $n = 13$ ) and *Mucoraceae* ( $n = 11$ ) were the main fungi found in AIFRS. Mucosal biopsy confirmed fungal invasion to the nasal mucosa in all cases. Computed tomography and endoscopic findings showed a predominance of unilateral disease, with various stages of nasal involvement. All patients underwent surgical debridement and systemic antifungal therapy immediately after diagnosis. Sixteen patients died (50%) due to AIFRS. A poor prognosis was related to the extensiveness of AIFRS and to the underlying disease (patients with aplastic anemia and diabetes had the worst outcomes), but not to the fungus isolated.

**Conclusions:** Early medical and surgical treatment is essential to improve the prognosis of AIFRS patients. A poorer prognosis was associated with underlying disease and extensiveness of AIFRS, but not to the fungus isolated.

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## 1. Introduction

Controversy remains regarding the classification of fungal rhinosinusitis, however the most accepted categorization of this entity was proposed by deShazo et al.,<sup>1</sup> who differentiated fungal rhinosinusitis into non-invasive and invasive forms based on histopathological findings. Invasive fungal rhinosinusitis is sub-categorized into three groups: granulomatous invasive, chronic invasive, and acute invasive fungal rhinosinusitis (AIFRS). Granulomatous invasive rhinosinusitis occurs in immunocompetent patients, and there is a geographic predominance of this disease in Asia. Chronic invasive fungal rhinosinusitis usually occurs in mildly immunocompromised patients, mainly in diabetic individuals; nasal symptoms are occasional, but orbital and neurological symptoms, especially those related to orbital apex syndrome, are pathognomonic of this entity. AIFRS is a special entity because it occurs almost exclusively in immunocompromised patients, particularly in the presence of a cellular immunodeficiency. There is rapid spread of the fungi from the nasal mucosa and sinus to the orbit and brain. Necrosis and angioinvasion are characteristic of

this entity, and the diagnosis is confirmed only after biopsy, revealing fungal invasion associated with necrosis in the nasal mucosa and underlying bone. The mortality rate in this setting is reported to be high, ranging from 50% to 80%.<sup>2–4</sup>

The initial symptoms may not be characteristic, and include fever, nasal discharge, obstruction, and nasal crusting. More extensive disease may present with visual complaints, neurological deficits, or palatal erosion. In immunocompromised patients with these symptoms, especially if they are unilateral, nasal endoscopy is essential, and pale or ischemic mucosae are characteristic of this entity.

New approaches to hematological diseases, HIV/AIDS, and diabetes mellitus have improved survival rates, however some of these medical advances have also resulted in an increase in the population at risk of developing AIFRS.<sup>5</sup> Therefore, recognition of the underlying disease that caused the immunodeficiency and its correction, if possible, are pivotal to improve the survival rate in patients with AIFRS. Hence, the goals of treatment in AIFRS are the reestablishment of the immune response associated with systemic antifungal therapy and surgical debridement of necrotic sites.<sup>2,6</sup>

In this study we reviewed a series of AIFRS patients treated at a tertiary hospital and evaluated the prognostic factors. Results obtained were compared to data reported in the literature.

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## 2. Materials and methods

This was a retrospective study of 32 immunocompromised patients with AIFRS, who were evaluated at the Division of Otorhinolaryngology, School of Medicine of Ribeirão Preto, University of São Paulo. When the disease was suspected a diagnostic biopsy was performed, which was sent immediately to the pathology department. Only patients who had their diagnosis confirmed by histopathology were included in this series. The study was approved by the ethics committee of the institution (process number 4889/2009).

The following clinical parameters were evaluated: the underlying cause of the immunodeficiency, the initial clinical presentation, endoscopic findings (evaluating the extent of the diseased mucosa), and computed tomography (CT) scan findings according to Lund and MacKay.<sup>7</sup> During the first outpatient evaluation, a biopsy of the suspected area was obtained with the aid of a nasal endoscopy, and was submitted to histopathology to confirm the fungal invasion and also to establish the classification of the fungus.

The surgical and clinical approaches in the treatment of AIFRS were retrieved from the medical records, as well as the clinical follow-up of each patient.

The analysis of variance (ANOVA) test was used to correlate the type of fungus isolated, the endoscopic findings at first outpatient evaluation, and the underlying disease, to the clinical outcome. Also, the extent of the disease on CT scan was compared between patients with a good outcome and those with a poor outcome, using the unpaired Student's *t*-test with the Welch correction. Differences were considered to be statistically significant when  $p < 0.05$ .

## 3. Results

Of the 32 study patients, 14 were male and 18 were female; patients ranged in age from 8 to 70 years. The underlying causes of the immunodeficiency were: hematological disease (aplastic anemia ( $n = 5$ ) and leukemia ( $n = 15$ )), diabetes ( $n = 6$ ), AIDS ( $n = 5$ ), and renal failure ( $n = 1$ ).

The most frequent symptoms reported by the patients were fever, nasal obstruction, headache, and purulent rhinorrhea with nasal crusting. In 18 patients, complaints were unilateral, whereas in 14 the symptoms were bilateral. Extra-sinonasal extension was



**Figure 1.** Palate necrosis in a bone marrow transplant child with acute invasive fungal rhinosinusitis.



**Figure 2.** Leukemia patient with acute invasive fungal rhinosinusitis localized to the middle turbinate. Note the severe mucosal edema in unilateral middle turbinate.

observed in three patients, one with palatal ulcers (Figure 1), the second with ulcers in the nasopharynx, and the third with brain extension of the disease.

The most common endoscopic findings were pale or necrotic mucosae, intense necrotic nasal crusting, and hyaline or thick mucus secretion. The middle meatus and middle turbinates were the sites most frequently involved ( $n = 26$ ), followed by the inferior turbinates ( $n = 11$ ) and nasal septum ( $n = 8$ ). During nasal endoscopy, unilateral necrosis was found in 23 cases and bilateral necrosis in six. The remaining three patients had no changes on endoscopy.

CT scans revealed changes in bone density and sinus opacity in all cases. There was a predominance of unilateral involvement (26 of 32 cases). The middle meatus was the most affected site ( $n = 26$ ), either isolated ( $n = 9$ ) (Figure 2) or associated with maxillary and ethmoidal opacity ( $n = 17$ ). Two patients presented more diffuse opacity, from frontal to sphenoid (Figure 3). Three patients had orbital involvement (Figure 4) and one had intracranial extension.

The outpatient biopsies confirmed the fungal invasion to the nasal mucosa in all cases. The fungi isolated were: *Aspergillus* in 13 patients, *Mucoraceae* in 11, and *Fusarium* in two; the fungus classification could not be obtained in six cases (Table 1). There was a significant correlation of fungus classification with associated diseases ( $p < 0.01$ ): for diabetic patients there was a correlation with cultures positive for *Mucoraceae* (five out of six), while for patients with leukemia there was a positive correlation with *Aspergillus* (nine out of 15).

All patients underwent surgical debridement and systemic antifungal therapy. The majority of the patients ( $n = 26$ , 81%) underwent unilateral surgery. The standard surgical procedure

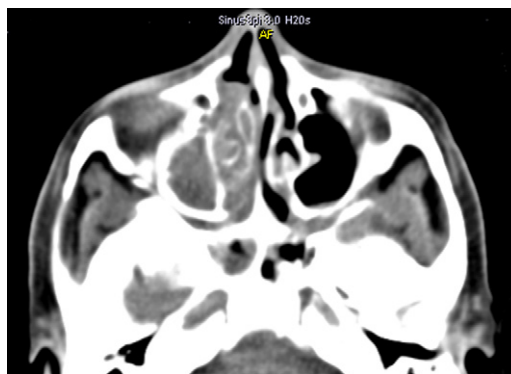


**Figure 3.** Patient with unilateral acute invasive fungal rhinosinusitis, diffuse to all sinuses on the left side. Note the change in density in the bony area, suggesting bone erosion, and the important mucosal edema.

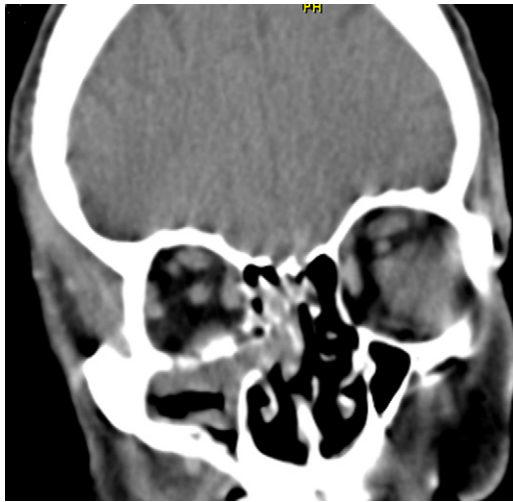


**Figure 4.** Patient with unilateral acute invasive fungal rhinosinusitis and proptosis. The lamina papyracea bone is affected and the inferior orbital muscle is infiltrated.

included endoscopic debridement of all sites involved, including maxillary antrostomy and anterior ethmoidectomy for all surgical cases. In addition to surgical treatment, all patients received systemic antifungal therapy. Amphotericin B was the drug of choice, employed as monotherapy in 21 patients and in association with other antifungal drugs in six patients. In those cases where

*Aspergillus* was promptly identified or when amphotericin could not be used due to adverse effects, voriconazole and fluconazole were the drugs employed.

After surgery, patients were followed-up with periodic endoscopic examinations during antifungal therapy, and further CT scans or biopsies were requested depending on the endoscopic findings. Five patients required revisional surgery. Sixteen patients (50%) died within 30 days of the AIFRS diagnosis due to the extent of fungal invasion, pneumonia, or sepsis. The remaining 16 (50%) patients with AIFRS are long-term survivors.

The fungus identified in the specimens did not correlate with the clinical outcome after surgery; 46% of patients with *Aspergillus* and 60% with *Mucoraceae* died. In contrast, the clinical outcome was associated with the underlying disease, and patients with a poorer prognosis included those with aplastic anemia (all five patients died) and diabetes mellitus (five out of six patients died); those with an intermediate prognosis included patients with hematological diseases (six out of 15 patients died). Patients with AIDS/HIV or renal insufficiency presented a better prognosis (all six patients are currently alive). Statistical analysis between these three sub-groups through ANOVA was significant ( $p < 0.005$ ).

Moreover, the prognosis was related to the extent of the disease observed during surgery: in patients with ischemia limited to the turbinates or lateral wall, the mortality rate was 33%; when the nasal septum was involved, the mortality rate increased to 67%, and ultimately, when dissemination extended beyond the nasal cavities, the mortality rate reached 100% in our series. The ANOVA test was statistically significant for this comparison ( $p < 0.05$ ).

**Table 1**

Underlying diseases, fungal identification, extensiveness of disease, and follow-up of the study patients

| Patient | Underlying disease                                   | Isolated fungus              | Extent of the disease                                                                         | Follow-up |
|---------|------------------------------------------------------|------------------------------|-----------------------------------------------------------------------------------------------|-----------|
| 1       | Aplastic anemia/hepatitis B                          | <i>Aspergillus flavus</i>    | Bilateral inferior turbinates                                                                 | Died      |
| 2       | Aplastic anemia/hepatitis B                          | <i>Mucoraceae</i>            | Bilateral inferior and middle turbinates, ethmoid and maxillary accomplishment                | Died      |
| 3       | Aplastic anemia/ <i>Aspergillus</i> pneumonia        | <i>Mucoraceae</i>            | Diffuse sinus accomplishment                                                                  | Died      |
| 4       | Aplastic anemia                                      | <i>Aspergillus</i>           | Left middle turbinate and left side of nasal septum                                           | Died      |
| 5       | Aplastic anemia                                      | <i>Fusarium</i>              | Left middle and inferior turbinates, lateral nasal wall, nasal septum; intracranial extension | Died      |
| 6       | Acute myeloid leukemia                               | Inconclusive                 | Left middle turbinate and maxillary sinus                                                     | 8 months  |
| 7       | Acute myeloid leukemia/ <i>Aspergillus</i> pneumonia | <i>Aspergillus flavus</i>    | Bilateral middle turbinates                                                                   | 4 months  |
| 8       | Acute myeloid leukemia                               | <i>Aspergillus flavus</i>    | Right middle and inferior turbinates                                                          | 3 months  |
| 9       | Acute myeloid leukemia                               | <i>Mucoraceae</i>            | Left middle turbinate                                                                         | 80 months |
| 10      | Acute myeloid leukemia                               | <i>Aspergillus</i>           | Left inferior and middle turbinates, anterior and posterior ethmoid                           | 7 months  |
| 11      | Acute myeloid leukemia                               | Inconclusive                 | Left middle and inferior turbinates                                                           | 12 months |
| 12      | Acute myeloid leukemia/histoplasmosis                | <i>Mucoraceae</i>            | Right middle turbinate                                                                        | 3 months  |
| 13      | Chronic lymphoid leukemia                            | <i>Aspergillus</i>           | Left middle turbinate                                                                         | 4 months  |
| 14      | Acute myeloid leukemia                               | <i>Aspergillus</i>           | Bilateral middle turbinates, nasal septum                                                     | 24 months |
| 15      | Acute myeloid leukemia                               | <i>Aspergillus flavus</i>    | Right middle turbinate and maxillary sinus                                                    | Died      |
| 16      | Acute myeloid leukemia                               | <i>Aspergillus fumigatus</i> | Left middle and inferior turbinates, lateral nasal wall, orbital infiltration                 | Died      |
| 17      | Acute myeloid leukemia                               | <i>Aspergillus fumigatus</i> | Bilateral middle turbinates and left middle meatus                                            | Died      |
| 18      | Acute lymphoid leukemia                              | <i>Aspergillus flavus</i>    | Left inferior turbinate, right side of nasal septum, nasopharynx, oral lesions                | Died      |
| 19      | Acute lymphoid leukemia                              | <i>Mucoraceae</i>            | Left lateral nasal wall and nasal septum, hard palate, orbital infiltration                   | Died      |
| 20      | Acute myeloid leukemia                               | <i>Fusarium</i>              | Right middle and inferior turbinates, lateral nasal wall                                      | Died      |
| 21      | Diabetes mellitus                                    | <i>Mucoraceae</i>            | Right maxillary sinus mucosal edema                                                           | Died      |
| 22      | Diabetes mellitus                                    | <i>Mucoraceae</i>            | Left middle turbinate                                                                         | 8 months  |
| 23      | Diabetes mellitus                                    | <i>Mucoraceae</i>            | Right middle turbinate, ethmoid opacity, orbital infiltration                                 | Died      |
| 24      | Diabetes mellitus                                    | Inconclusive                 | Left middle turbinates, frontal to sphenoid sinus accomplishment                              | Died      |
| 25      | Diabetes mellitus                                    | <i>Mucoraceae</i>            | Bilateral middle and inferior turbinates, bilateral nasal lateral wall, nasal septum          | Died      |
| 26      | Diabetes mellitus                                    | <i>Mucoraceae</i>            | Right middle and inferior turbinates, lateral nasal wall                                      | Died      |
| 27      | AIDS                                                 | <i>Aspergillus flavus</i>    | Right middle meatus, nasal septum                                                             | 13 months |
| 28      | AIDS                                                 | Inconclusive                 | Right middle and inferior turbinates, lateral nasal wall, nasal septum                        | 4 months  |
| 29      | AIDS                                                 | <i>Mucoraceae</i>            | Right middle meatus, ethmoid opacity                                                          | 5 months  |
| 30      | AIDS/non-Hodgkin lymphoma                            | Inconclusive                 | Left middle meatus, maxillary sinus and middle turbinates                                     | 7 months  |
| 31      | AIDS                                                 | Inconclusive                 | Left sphenoid                                                                                 | 4 months  |
| 32      | Chronic renal failure                                | <i>Aspergillus fumigatus</i> | Left middle meatus                                                                            | 3 months  |

#### 4. Discussion

The main purpose of this study was to determine the clinical features that are associated with the prognosis in patients with AIFRS.

The incidence of AIFRS reported in the literature in immunocompromised patients is around 2%, and patients with hematological diseases are the most susceptible group.<sup>3</sup> In the present study, neutropenia, either due to aplastic anemia or secondary to chemotherapy for hematological malignancies, was the main cause of AIFRS (62%), a finding similar to that reported in other studies in the literature.<sup>8,9</sup>

*Aspergillus* and *Mucoraceae* account for the majority of cases of AIFRS.<sup>3,9</sup> Both fungi are saprophytes, found worldwide in dust and soil.<sup>5</sup> In immunocompromised patients, these fungi can be angioinvasive, resulting in thrombosis and ischemia of the nasal mucosa. This ultimately leads to tissue infarction and bone destruction. We found a high rate of *Aspergillus* (41%), especially among patients with hematological diseases (55%); among patients with diabetes mellitus, 83% had a positive biopsy for *Mucoraceae*. This is in contrast to the findings of Kasapoglu et al.<sup>10</sup> who reported a predominance of *Mucoraceae* involvement. Ingley et al.<sup>5</sup> also observed a higher predisposition to *Aspergillus* among patients with hematological malignancies and to *Mucoraceae* among patients with diabetes mellitus. We did not observe a higher morbidity–mortality rate in patients infected with *Mucoraceae* when compared to those with *Aspergillus*, which is in accordance with the findings of Kasapoglu et al.,<sup>10</sup> but in disagreement with Ingley et al.<sup>5</sup>

Once AIFRS is suspected, a nasal endoscopy is essential to evaluate the signs of fungal involvement. Pale mucosae, ulcers, and granulation are present in up to 75% of patients examined by endoscopy.<sup>2</sup> Other signs such as tissue ischemia or tissue necrosis can easily be seen in more severe cases of AIFRS. Biopsy of the middle turbinate has been proposed as a means of diagnosis before the disease is clearly established.<sup>4</sup> This suggestion was based on the observation that the middle turbinate is the most common intranasal site of fungal invasion in patients with AIFRS.<sup>2,11,12</sup> In our study, we also observed that the middle meatus and the middle turbinates were the most frequently involved sites (81% of cases).

The sensitivity of CT scans in the early stages of AIFRS is limited. Bone erosion is a clear sign that the disease is established, but in general this manifestation is only seen in the later stages.<sup>4,12</sup> Other suggestive signs of AIFRS found on CT scans are unilateral disease, infiltration of the periantral fat planes, and severe mucosal edema. In our study we observed a predominance of unilateral disease with bone erosion, but orbital involvement was unusual (9% of cases). Therefore, biopsy of the middle turbinate, nasal endoscopy, and CT scans, taken together, are essential for an early diagnosis of these patients and may allow a more favorable prognosis.

Once AIFRS is diagnosed, clinical and surgical treatment must be initiated promptly. In our study, the antifungal drug most commonly used was amphotericin B. Voriconazole has been considered the treatment of choice for AIFRS related to *Aspergillus*,<sup>1</sup> and was introduced whenever *Aspergillus* was diagnosed histopathologically.

Debridement of necrotic tissues is important in AIFRS patients since the removal of devitalized tissue increases the ability of antifungal drugs to reach infected areas, reducing the fungal burden and slowing the progression of the disease. Also, this action is not only local, since it reduces the stress on the development of neutrophils, facilitating bone marrow recovery.<sup>12</sup>

In our study, the extent of the disease was inversely related to the prognosis. Patients with AIFRS only in the lateral wall presented a mortality rate of 33%; when AIFRS reached the nasal

septum, the mortality rate increased to 67%. All patients with AIFRS beyond the nasal cavities died as a result of this disease. These findings are in agreement with those of Lin et al.,<sup>13</sup> who demonstrated a mortality rate of 26.7% when invasive aspergillosis was restricted to the nasal cavity and sinuses compared to 88% when the infection was highly disseminated. Gleissner et al.<sup>14</sup> reported a mortality rate of 40% in patients with AIFRS involving *Mucoraceae*, and it reached 89% in patients with disseminated disease. Thus, early diagnosis and treatment are key to a successful outcome in these high-risk patients, as also stated by Kasapoglu et al.<sup>10</sup>

Besides the extent of the disease, the underlying medical condition is another important factor in the disease prognosis.<sup>2</sup> In the present study, the mortality rate in patients with aplastic anemia and diabetes mellitus was high (near 100% when considering both groups together), while those with AIDS/HIV all had a good outcome. Patients with hematological malignancies showed an intermediate prognosis; a third of these patients died due to AIFRS.

The overall mortality rate in our study was 50%. This rate is in accordance with the literature reviewed.<sup>8,9</sup> deShazo et al.<sup>1</sup> stated that the best outcome reported is near 50% survival. To improve this mortality rate, rapid diagnosis and treatment are essential. Survival also depends on controlling the predisposing factors of the immunosuppression, such as improving bone marrow function in patients with hematological diseases or chemotherapy.<sup>9</sup>

In conclusion, this clinical series clearly shows that the diagnosis of AIFRS is difficult and requires multidisciplinary assessment of the patient. Nasal endoscopy, biopsy of the middle turbinate, and CT scans are essential to establish a rapid diagnosis of AIFRS. The extent of AIFRS and the underlying medical disease are the main factors related to the prognosis, but not the classification of the fungus isolated.

*Conflict of interest:* No conflict of interest to declare.

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