Prognostic Factors in the Outcome of Invasive Fungal Sinusitis in a Pediatric Population

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Background: Pediatric invasive fungal sinusitis (IFS) is rare, and its prognosticators are poorly understood. The aim of this study was to determine important factors affecting outcome.

Methods: A 10-year retrospective review at a tertiary academic children’s hospital was performed using an International Classification of Diseases, 9th revision, and a procedure-based search after institutional review board approval. All relevant demographic and clinical information was collected.

Results: Fourteen immune-compromised patients (male:female = 7:7, mean age = 10 years, range 2–16 years) were identified who had hematologic malignancies (11), diabetes mellitus (2) and unknown predisposing factors (1). Fungal species included Aspergillus (5), Mucor (5), Alternaria (2), Rhizopus (1) and Scopulariopsis (1). The cohort underwent an average of 6.1 (median = 5) endoscopic sinus surgeries and were treated with aggressive antifungal therapy. Four deaths occurred in the study population: 2 attributable to IFS and 2 attributable to their underlying malignancies. There was a significant difference in the median absolute neutrophil count (ANC) at follow-up after treatment of IFS between the survival and the mortality subgroups, with ANC being 4290.5 and 169, respectively (P < 0.001).

Conclusions: Despite the small sample size, this study represents the largest case series in the medical literature on pediatric IFS. Age, gender, underlying cause for immunodeficiency and mycologic agent were not important prognosticators. ANC appears to be the only factor responsible for survival. The role of endoscopic sinus surgeries in survival is indeterminate.

Key Words: immunocompromise, mucormycosis, aspergillosis, fungal sinusitis, sinus debridement

Invasive fungal sinusitis (IFS) causes morbidity and mortality in the immunocompromised patient population. It is characterized as an aggressive and often fatal angioinvasive infection of the nose, paranasal sinuses and neighboring structures. Although IFS has historically been considered rare, with the evolution and improvement of nasal endoscopy, it has been increasingly diagnosed in immunocompromised patients with hematologic malignancies, immunosuppression and poorly controlled diabetes mellitus.

The causative fungal organisms that typically function as saprophytes in the environment can become pathogenic in humans under certain circumstances. The typical species responsible for sinonasal invasive infections are Aspergillus, as well as Rhizopus, Rhizomucor and Mucor species. Although clinical suspicion for IFS is elevated in immunocompromised patients with rapidly progressive sinusitis, the diagnostic standard is histopathologic evaluation and culture of nasal biopsies. Gillespie et al. showed a diagnostic sensitivity of 75% and specificity of 100% with middle turbinate biopsy. Nasal endoscopy typically demonstrates areas of mucosal ischemia or tissue necrosis, and radiologic studies typically show nonspecific findings of sinus opacification. Histopathologic confirmation of the diagnosis requires the presence of invasive fungal elements within the submucosal tissues.

Medical and surgical treatments have improved, but mortality has remained high. Survival rates in the general population have varied in the literature from 20% to 80%. Previously identified negative prognostic factors include the presence of a hematologic malignancy, advanced age and intracranial involvement. Survival success is determined by early diagnosis and prompt initiation of culture-directed antifungal therapy and surgical debridement.

The paucity of pediatric data is causing pediatric clinicians to extrapolate adult experience for the pediatric population. The aim of this study is to determine important factors affecting outcome in the pediatric population with IFS.

METHODS

Institutional review board approval was obtained before beginning this study. A 10-year retrospective chart review at Children’s Hospital Colorado was performed using both an International Classification of Diseases, 9th revision, and a procedure-based search of the institution’s electronic medical record between January 2001 and December 2011. In addition to searching for “acute invasive fungal sinusitis” (AIFS) and “invasive fungal sinusitis,” a combined search looking for any patients who underwent sinus procedures and had a diagnosis of an immune-compromised condition was examined. Charts were then individually reviewed to confirm the diagnosis and treatment of AIFS. Patients were included in the study if they had a confirmed histologic and microbiologic diagnosis of IFS, as well as adequate follow-up at least 6 months after the resolution of their disease. Patients were excluded if they did not have a histologic and microbiologic confirmation of IFS, if they had a diagnosis of allergic fungal sinusitis or if they were lost to follow-up before the resolution of their treatment.

Demographic, diagnostic and treatment data were collected for each patient. Demographic data collected included gender, ethnicity and age at time of diagnosis and underlying medical condition causing immunosuppression. Diagnostic variables included number of computed tomography (CT), CT findings, organism and sensitivities from culture, white blood cell at the time of diagnosis and at follow-up, and absolute neutrophil count (ANC) at diagnosis and midpoint through the antifungal therapy. Treatment variables examined included number and type of surgical interventions, antibiotics and antifungals administered and length of follow-up. Mortality was defined as death as a result of IFS, and deaths attributable to the inciting cause for the immune-compromised state were not included in the calculation of IFS mortality. Statistical significance was calculated based on a two-tailed t test with unequal variance.
Confirmation of IFS was based on endoscopic, histologic and microbiologic findings. The survival cohort was defined as those patients who cleared their AIFS infection.

RESULTS

Demographics
A total of 14 patients met our study criteria during the study period. There were 7 males and 7 females. Six patients identified as Caucasian (43%), 5 as Hispanic or Latino (36%), 2 as Asian (14%) and 1 as African American (7%). Average age at the time of diagnosis was 11 years old (standard deviation ± 4.8, range 2–16 years old). All patients had an evidence of an underlying immune-compromised state: 11 (79%) had an underlying hematologic malignancy undergoing chemotherapy or having undergone bone marrow transplantation, 2 had uncontrolled diabetes mellitus and 1 had a compromised immune system for unknown reasons. None of demographic factors were associated with mortality.

Outcomes
Within the cohort of 14 patients, there were 4 deaths during the study period, 2 of which were directly related to AIFS and 2 of which were unrelated and occurred after the patients had successfully cleared their fungal infection. Therefore, by study definitions, there were 12 survivors and 2 deaths from AIFS (mortality rate = 14.3%), both immunosuppressed secondary to treatment of an underlying hematologic malignancy. The mortality group consisted of 1 Rhizopus infection and 1 Aspergillus infection, and there was no significant impact on survival attributable to the pathogenic species of infection.

Presenting Symptoms
Fever (93%), facial pain (64%) and nonspecific sinus symptoms (58%) were the most common symptoms at the time of presentation. Less common symptoms at presentation included rhinorrhea (42%), vision changes (29%) and facial or palate numbness (8%). No differences existed between the survival and the mortality groups based on presenting symptoms.

Imaging
All patients received a CT scan at the time of diagnosis. All patients showed evidence of mucoperiosteal thickening on CT scan; only 5 of 14 patients showed evidence of extra-sinus extension. Extra-sinus disease extension was not statistically associated with survival.

Diagnosis and Treatment
All patients were taken to the operating room for initial endoscopic examination and biopsies. Both fungal cultures and pathologic examination of biopsy materials were obtained in all patients, and fungal species identified were Aspergillus (5), Mucor (5), Alternaria (2), Rhizopus (1) and Scopulariopsis (1). Overall, this cohort underwent a mean of 6.1 operations and median of 5, with a range of 3–14 surgeries. There was no statistical difference between the number of surgeries performed and mortality. In conjunction with surgery, all patients received prolonged cultured- or debridement is an integral part of the management of AIFS, but in this study, its role in survival is indeterminate. Given the mortality rate of 14.3%, a larger, prospective study is necessary to provide the power to determine whether other factors, including number and nature of surgeries, might also provide a role in the survival outcomes of this aggressive infection.

Early and aggressive surgical intervention with endoscopy and debridement is an integral part of the management of AIFS, but in this study, its role in survival is indeterminate. Given the mortality rate of 14.3%, a larger, prospective study is necessary to provide the power to determine whether other factors, including number and nature of surgeries, might also provide a role in the survival outcomes of this aggressive infection.

Absolute Neutrophil Count
ANC was evaluated at the time of diagnosis, during active treatment period and at the time of follow-up. There was no significant difference in ANC at the time of diagnosis between the survival and the mortality groups. However, there was a significant difference between the survival and the mortality subgroups in the recovery of ANC at a midtreatment interval, with mean ANC being 4290.5/mm³ and 169/mm³, respectively (P < 0.001). Survival was associated with a recovery of ANC to within normal limits, whereas both patients within the mortality group had no recovery of their ANC at the time of death.

DISCUSSION
This study characterized a case series of IFS in a pediatric population examining multiple potential prognosticators for survival from the underlying fungal infection. None of the demographic or clinical factors played a role in the final survival or demise outcome from IFS. Likelihood of recovery of ANC to normal levels as determined by the midtreatment ANC level was the only positive prognostic indicator for survival.

Within our study, there were 4 deaths, but only 2 of those deaths were attributable to IFS. The other 2 deaths were secondary to the development of a high-grade glioma and recurrence of the patient’s underlying hematologic malignancy. It is important to realize that pediatric patients at risk for invasive fungal infection are, as a cohort, at a significantly higher risk of mortality from both underlying malignancies and other infections. In examining the effects of AIFS on this population, it is important that mortality from fungal infection not be overestimated. In our study, mortality from AIFS was 14.3%, significantly lower than historic data have suggested.

One reason that may account for lower mortality in this population than the adult population is that in patients admitted for treatment of the underlying malignancy or illness, there is a higher index of suspicion and careful observation for clinical changes, and these factors may lead to earlier diagnosis and treatment of AIFS, which has been known to be a positive prognostic factor in treatment.

REFERENCES


