Aspergillus Sinusitis in Cancer Patients

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Paranasal sinusitis occurred in 52 immunosuppressed cancer patients treated over 5 years at the University of Maryland Cancer Center. Twenty-one patients had aspergillus sinusitis; Aspergillus sp, including flavus and niger were directly recovered from sinus in 19 of the 21 infections. Two other patients with sinus involvement and positive nose cultures for Aspergillus flavus or fumigatus and microbiologically documented pulmonary aspergillosis were considered clinically, although not microbiologically, documented. Predisposing factors for aspergillus sinusitis during the 60 days prior to infection diagnosis were granulocyte count less than 500 μl (mean duration, 42 days versus 14 days for sinusitis of other etiology; $P < 0.001$), prolonged hospitalization (mean duration, 22 days versus 14 days for patients with nonfungal sinusitis; $P < 0.001$), and prolonged antibiotic therapy (mean duration, 22 days versus 9 days; $P < 0.001$). Treatment with amphotericin B was initially successful for 18 of 21 patients; however, 11 of 18 patients had infection recurrence that always developed at time of tumor exacerbation and reinstitution or intensification of chemotherapy. These findings suggest that aspergillus sinusitis in cancer patients is seen in association with prolonged neutropenia and antibiotic therapy, is amenable to therapy, but tends to recur with relapse of malignancy.


The prevalence of pulmonary aspergillosis and the importance of its early diagnosis have been recognized and stressed in recent years; however, non-pulmonary involvement, including that of the sinus, has not been frequently reported. At the University of Maryland Cancer Center (UMCC), an increasing number of cases of aspergillus sinusitis has been diagnosed in recent years. This insidious infection, which can easily be missed in its early stage, may confer a poor prognosis because of its tendency for serious local tissue damage and invasion of contiguous structures.

This report describes risk factors, occurrence, and outcome of therapy for aspergillus sinusitis over 5 years in patients with profound, persistent chemotherapy-induced myelosuppression. Prompt recognition and treatment of this infection may improve the clinical course of the patient.

Materials and Methods

Patient Population

Patients with cancer (leukemia, lymphoma, or advanced metastatic solid tumors) admitted to the UMCC over a recent 5-year period were studied. All patients received inpatient and outpatient care in a single hospital location from a non-rotating group of physicians, nurses and paramedical personnel.

Laboratory Data

Granulocyte counts, antibiotic usage, and nasal surveillance culture results were reviewed for the 60 days prior to documented onset of sinusitis. Results of anterior rhinoscopy (examination, biopsy, and culture results), sinus aspirate, or biopsy culture/histology were also analyzed.

Infection Documentation

Each case was defined antemortem as: (1) microbiologically documented sinusitis based upon specimens obtained directly from sinus (MDS) or by positive culture biopsy from a nasal turbinate lesion (MDNT); or (2) clinically documented sinusitis (CDS), in which case no direct culture from sinus or nasal turbinate could be obtained.

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<table>
<thead>
<tr>
<th>Number of patients observed</th>
<th>Total number</th>
<th>ANLL</th>
<th>ALL</th>
<th>CML</th>
<th>Other tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with aspergillus sinusitis</td>
<td>1331</td>
<td>205</td>
<td>41</td>
<td>21</td>
<td>1064</td>
</tr>
</tbody>
</table>

* Fisher's exact test.
ANLL: Acute nonlymphocytic leukemia; ALL: Acute lymphocytic leukemia; CML: Chronic myelogenous leukemia-blast crisis.

Nasal surveillance cultures positive for *Aspergillus sp* plus microbiological documentation of pulmonary aspergillosis were reported for this latter category. These definitions have been described previously: the diagnosis of invasive aspergillosis was made when the above criteria were met in association with maxillary sinus roentgenographic infiltrate plus the demonstration of characteristic septated branching hyphae from smears obtained from sinus aspirate. Cultures were considered diagnostic only if there was subsequent histologic identification of typical hyphae.

Each infected or potentially infected patient was examined regularly by a member of the UMCC Section of Infectious Diseases. Decisions on infection occurrence and classification were made prospectively and entered into prospectively maintained separate records.

Statistical significance for the difference in proportions was accomplished using Fisher's exact test, while significance for the difference in means was accomplished using Student's *t* test. In all cases, two-tailed *P* values are reported.

### Results

A total of 1331 patients with cancer were reviewed; of these patients, 52 developed sinusitis. Aspergillus sinusitis was clinically or microbiologically documented in 21 patients, whereas 31 had sinusitis of nonfungal (primarily bacterial) origin.

Most (11/21; 52%) patients with aspergillus sinusitis in this study had acute nonlymphocytic leukemia (ANLL; Table 1). This represents only 5% of all patients with ANLL in our center during the study period; comparatively, more patients (8/41; 20%; Fisher's exact test, *P* < 0.01) admitted to the UMCC with acute lymphocytic leukemia (ALL) developed aspergillus sinusitis as did 2 of 21 (10%) patients with chronic myelogenous leukemia in blast crisis (CML/BC). The mean age of patients with aspergillus sinusitis was 36 years versus a mean age of 52 years for patients with other causes of sinusitis (Table 2). The mean absolute granulocyte count at diagnosis for patients with aspergillus sinusitis was 120/μl (0-550) compared to a mean granulocyte count of 600/μl (0-900) for patients with non-aspergillus sinusitis.

Of the 21 cases of aspergillus sinusitis, 19 were microbiologically documented. The distribution of infection is

![FIG. 1. Orbital phlegmona due to aspergillus sinusitis.](image)
shown in Table 3; 14 of 21 cases were associated with *Aspergillus flavus*. In this study, a patient with maxillary aspergillus sinusitis developed orbital involvement with a very painful orbital phlegmon (Figure 1). Paranasal sinuses were also invaded by *Aspergillus sp* (Figs. 2 and 3). In another patient, aspergillus sinusitis extended to the central nervous system, resulting in an encephalitis (Fig. 4).

Fifteen of the 21 patients (71%) with aspergillus sinusitis previously had a microbiologically documented bacterial infection (Table 4). The frequency of prior infections (35%) among patients having sinusitis of other origin was substantially less (Fisher's exact test, *P* < 0.02). Similarly, bacteremias in the previous 60 days were more common in the fungal group (57%) than in the nonfungal group (13%; Fisher's exact test, *P* < 0.002).

The patients with aspergillus sinusitis were hospitalized for a longer time (*t* (50) = 4.48, *P* < 0.001; Table 5) and received broad spectrum antibiotics longer than the group with sinusitis of other origin (*t* (50) = 9.00, *P* < 0.001). All patients with aspergillus sinusitis had a prolonged period of granulocytopenia at less than 500/μl, with a mean duration of 42 days versus 14 days for patients with non-aspergillus sinusitis (*t* (50) = 14.21, *P* < 0.001). Comparatively, patients with aspergillus sinusitis had prolonged granulocyte levels less than 100/μl, with a mean duration of 12 days versus 4 days for patients with non-aspergillus sinusitis (*t* (50) = 7.76, *P* < 0.001).
Anterior nares cultures were performed as a routine surveillance procedure among patients with acute leukemia at admission and twice weekly thereafter. Of the patients with positive *Aspergillus* nose cultures, 58% had aspergillus sinusitis (Table 6). However, *Aspergillus* also grew in the nose culture in 42% of the patients with sinusitis of other origin. Sinus cultures in these patients were not positive for *Aspergillus*, suggesting that a positive nose culture is not identical with having aspergillus sinusitis. Conversely, of the patients who did not demonstrate *Aspergillus* in their nose cultures, only 10% (compared with the 58% of patients with aspergillus sinusitis; Fisher's exact test, *P* < 0.002) had aspergillus sinusitis; this finding suggests that negative nose cultures equate with lesser probability of having aspergillus sinusitis.

The dosage of amphotericin B administered for therapy of the sinusitis ranged between 1.5 to 1.75 grams and often (18 of 21) resulted in infection resolution (Table 7). However, the infection relapse rate among the 18 successfully treated patients was high; 11 patients had relapses and at autopsy had generalized aspergillosis, whereas only 7 patients had a lasting remission of aspergillus sinusitis. Relapse of aspergillus sinusitis usually coincided with relapse of leukemia and concomitant use of chemotherapy and resultant granulocytopenia. The relative frequency of generalized aspergillosis in patients who initially responded to amphotericin B ranged from 28% to 100%. The total amount of amphotericin B administered did not affect the relapse rate.
TABLE 5. Predisposing Factors of Aspergillus Sinusitis During the 60 Days Prior to the Diagnosis of Sinusitis

<table>
<thead>
<tr>
<th></th>
<th>Aspergillus sinusitis</th>
<th>Other sinusitis</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad spectrum antibiotics</td>
<td>22 (8-34)*</td>
<td>9 (1-17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>22 (8-36)</td>
<td>14 (2-26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Granulocytopenia &lt; 500/(\mu)l</td>
<td>42 (26-53)</td>
<td>14 (3-26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Granulocytopenia &lt; 100/(\mu)l</td>
<td>12 (6-34)</td>
<td>4 (1-9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Mean duration of days (range).
† \(p\) values derived from Student’s \(t\) test for paired observations with 50 degrees of freedom.

Discussion

Aspergillus sinusitis, an infection associated with death or considerable morbidity in myelosuppressed patients, was found in 2% of UMCC patients over a 5 year period. In an endemic environment, aspergillus sinusitis must be considered when “banal” sinusitis is encountered clinically. Patients who are granulocytopenic or undergoing antimicrobial chemotherapy are clearly predisposed to Aspergillus infection. The most often identified species in fungal sinusitis in this study was \(A.\) flavus, often found in respiratory tract infections. This fact may be partly related to the neutropenic state and or to broad spectrum antibiotic treatment that most neutropenic patients receive if suspicion of bacterial infection arises.

Establishing the diagnosis during early infection may be difficult. Our data suggest that a nose culture negative for \(A.\) sp in a patient with sinusitis usually, but not always, indicates sinusitis of non-\(A.\) origin; however, nose cultures positive for \(A.\) sp may or may not indicate aspergillus sinusitis. Since the predictive value of nasal cultures may be variable, prompt use of diagnostic techniques such as sinus aspiration is necessary to make a proper diagnosis and to direct appropriate antifungal therapy. However, a bleeding diathesis such as thrombocytopenia uncorrectable by platelet transfusion will prevent adequate sinus inspection and biopsy; therefore, other methods which might identify potentially infected patients need to be established, including anterior rhinoscopy or serologic evaluation for antigenemia. A minor invasive procedure such as anterior rhinoscopy with biopsy of necrotic-appearing lesions of the nasal turbinate may be valuable and presents little risk to the patient.

Such diligence in establishing diagnosis is important since the infection can spread rapidly. For example, neither surgery nor antifungal treatment will prevent fatal outcome once orbital phlegmona or encephalitis has occurred. Therefore, early recognition, prompt institution of therapy, and resolution of bone marrow function are of greatest importance to the ultimate outcome of this infection; in the current study, patients who developed aspergillus sinusitis were more compromised in regard to selected risk factors than the patients with non-aspergillus sinusitis.

Rapid institution of antymycotic treatment is necessary for aspergillus sinusitis as is the case for pulmonary infection. We would recommend initiating empiric treatment if a number of the risk factors favoring a diagnosis of aspergillosis are present, even in the absence of microbiological proof. Risk factors include endemic environment, prolonged broad spectrum antibiotic treatment (over 10 days), and long duration (greater than 14 days) of granulocytopenia (less than 500 granulocytes/\(\mu\)l). Antifungal therapy can be discontinued if \(A.\) sp cannot be recovered after several days or if the biopsy is negative.

Patients who obtain leukemia remission seem more likely to have remission of their sinusitis, which, in turn, tends to remain in remission as long as the leukemia is in remission. With relapse of the leukemia in our study, aspergillus sinusitis tended to relapse and then to spread, usually to the orbit (\(n = 7\)) and/or to the central nervous system (\(n = 3\)). In spite of this tendency for dissemination, \(A.\) sp was only once isolated from blood cultures despite frequent sampling.

TABLE 6. Significance of Findings in Nose Culture

<table>
<thead>
<tr>
<th>Nose culture</th>
<th>Number of patients</th>
<th>Patients with aspergillus sinusitis</th>
<th>Patients with other sinusitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for (A.)</td>
<td>33</td>
<td>19 (58%)</td>
<td>14 (42%)</td>
</tr>
<tr>
<td>Negative for (A.)</td>
<td>19</td>
<td>2 (10%)</td>
<td>17 (90%)</td>
</tr>
</tbody>
</table>

* Fisher’s exact test.
REFERENCES


