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Fungal sinusitis in immunocompromised pediatric patients with neoplasms. *Annals of Otolaryngology Rhinology and Laryngology*, 100:331-336,1991.

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FUNGAL SINUSITIS IN IMMUNOCOMPROMISED CHILDREN WITH NEOPLASMS

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This paper reviews the treatment and diagnosis of immunocompromised patients with fungal sinusitis at St Jude Children's Research Hospital. Sinusitis of all types was found to be more common in patients with hematopoietic neoplasms than in patients with solid tumors; 42 % of patients with leukemia had abnormal sinus radiographs. Eight cases of pathologically proven fungal sinusitis were identified. All patients were undergoing chemotherapy for either acute myeloblastic leukemia or acute lymphoblastic leukemia and had neutrophil counts less than 100 cells/mm³. The most common findings were fever, facial pain, and abnormal sinus radiographs. Surveillance cultures of the upper aerodigestive system did not reliably predict sinus pathogens. An aggressive treatment approach consisting of early administration of amphotericin B (intravenously and via catheter irrigations of the sinuses) and surgical drainage is advocated. There was an 80 % survival rate in patients in remission who were undergoing maintenance chemotherapy. All patients undergoing chemotherapy for relapse died.

KEY WORDS - children, fungal infections, leukemia, sinusitis.

INTRODUCTION

Opportunistic fungal infections commonly occur in immunosuppressed patients with neoplastic disease. These infections are most often found in patients with lymphoproliferative neoplasms, with the highest incidence in patients with acute leukemia.¹ Mirsky and Cuttner² found severe fungal infections at autopsy in 28 % of patients who had died of acute leukemia. The most common organism was *Aspergillus* species, followed by *Candida* species. Zygomycetes (*Rhizopus* species and *Mucor* species) was found less commonly and only in conjunction with *Aspergillus* species or *Candida* species.² Cho and Choi³ found fungal infections in 22 % of patients who died of leukemia. Candidiasis and aspergillosis occurred with almost equal frequency, with mucormycosis (zygomycoses) occurring less frequently. Degregorio et al⁴ found at least a 27 % incidence of invasive fungal infection and an autopsy rate of 52 % in patients treated for acute leukemia. Most of these patients had candidiasis, and the others, aspergillosis. Fifty-two (25 %) of 199 children dying with leukemia at St Jude Children's Research Hospital had fungal infections at autopsy.⁵

Aspergillus species most commonly infect the lungs,^{1,3,6} with involvement of the brain, heart, gastrointestinal tract, kidney, and liver also reported.¹ Pulmonary aspergillosis can be difficult to diagnose, as many patients die of the disease before treatment is initiated.⁴ *Candida* species most often infects the oropharyngeal and gastrointestinal tract, followed in frequency by pulmonary and disseminated disease.³

Localized fungal sinus involvement in pediatric immunocompromised patients is rare and few cases have been reported.⁶⁻¹⁰ In one of the largest series, Berkow et al reported five patients with aspergillosis of the paranasal sinuses, all of whom had acute lymphoblastic leukemia in relapse or neuroblastoma with bone marrow involvement; all patients died of the infection. To characterize the presentation, diagnosis, and treatment of localized fungal sinusitis, we undertook a retrospective study of patients at St Jude Children's Research Hospital.

METHODOLOGY

All sinus and nasal biopsy reports from 1970 to 1989 at St Jude Children's Research Hospital were reviewed. A total of 101 patients underwent 114 surgical procedures on the sinuses. Seventy-eight procedures (69 patients) were for diagnosis; the remaining 36 procedures (32 patients) were for the treatment of sinusitis (Table 1). A total of 7 patients with eight episodes of biopsy-proven invasive fungal sinusitis were identified. All patients had localized fungal sinusitis, although 1 patient developed

TABLE 1. MALIGNANCY AND TYPE OF SINUSITIS

Diagnosis	Type of Sinusitis		
	Acute	Chronic	Fungal
Acute lymphoblastic leukemia	3	16	4
Acute myeloblastic leukemia	1	1	4*
Rhabdomyosarcoma of nasopharynx			5†
Acute lymphoblastic leukemia with lymphoma of nasopharynx			2*

* One patient with two different episodes.

† Two patients with two different episodes.

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TABLE 2. DIAGNOSIS OF CHILDREN WITH NEOPLASMS AT ST JUDE CHILDREN'S RESEARCH HOSPITAL (1962-1989)

<i>Neoplasm</i>	<i>No. of Patients</i>
Solid tumors (total)	2,945
Hematopoietic tumors (total)	2,812
Acute lymphoblastic leukemia	2,140
Acute myeloblastic leukemia	574
Hodgkin's disease	447
Non-Hodgkin's lymphoma*	433
Other leukemias	84
Head and neck tumors	759
(both solid and hematopoietic)	3
Orbit	32
Neck Thyroid	5
Facial bone	15
Retinoblastoma	144
Nasopharyngeal carcinoma	37
Central nervous system	354
Other	169

* 121 were head and neck tumors.

TABLE 3. YEAR IN WHICH OPERATION WAS PERFORMED

Year	Type of Sinusitis		
	Acute	Chronic	Fungal*
1970-1974		8	
1975-1979		12	
1980-1984	2	1	1
1985-1989	2	3	7

Four patients had two procedures associated with two different episodes of sinusitis.

*All cases were reported after January 1, 1984.

pulmonary involvement 10 to 19 days after the initial sinus infection.

The hospital records of the patients with sinusitis were reviewed. All cases had histologic confirmation of the infection. Histologically these fungi were identified by the following criteria. *Candida* species are characterized by pseudohyphae and yeast forms. *Aspergillus* species are characterized by septate hyphae with dichotomous branching at 45° angles. *Zygomycetes* is characterized by broad, aseptate, irregular hyphae with variable branching.

Presenting symptoms, associated malignancy, and treatment of both the malignancy and sinusitis were recorded.

RESULTS

All patients with sinusitis, regardless of the cause,

TABLE 4. SYMPTOMS AND THERAPY OF FUNGAL SINUSITIS PATIENTS

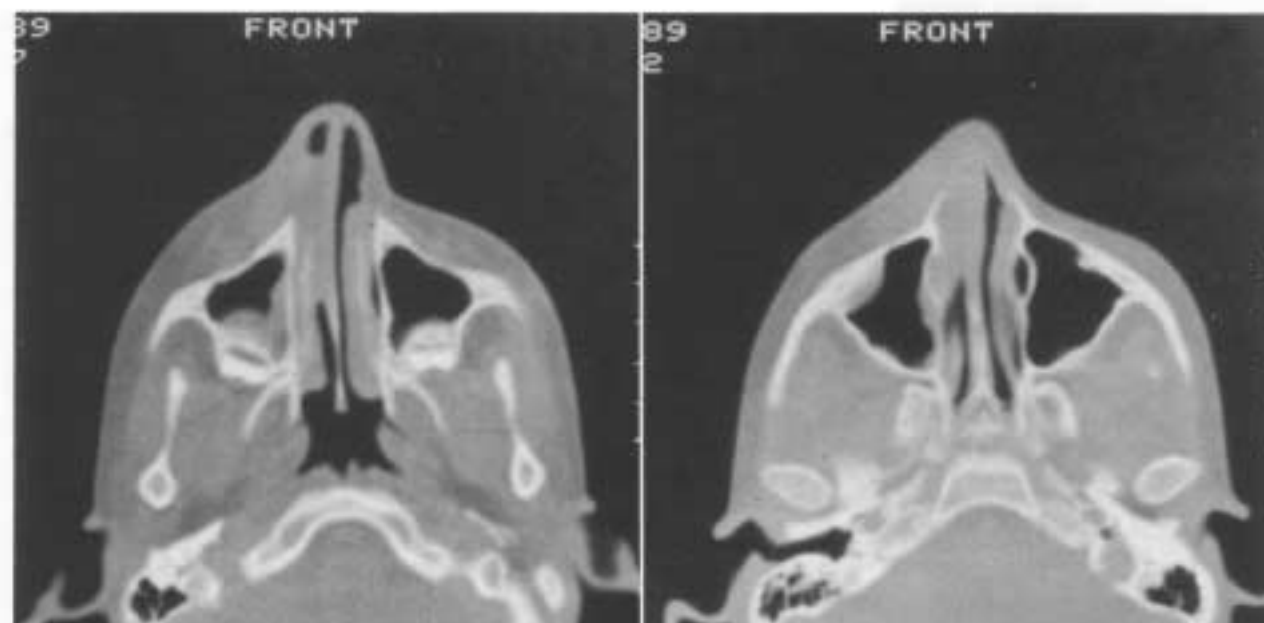
<i>Case No.</i>	<i>Symptoms</i>	<i>Fever (d)</i>	<i>Granulocytopenia < 100</i>	<i>Site of Fungal Infection</i>	<i>Operations</i>
1	Facial pain, day 23	19	Day 10* to day 30	R maxillary	R AM, day 25 L
	Facial pain, day 15	5	Day 3 to day 19	L ethmoid	ethmoidectomy, day 19
2	Headache, day 21	15	Day 20 to day 47 [†]	R maxillary, R ethmoid	R Caldwell-Luc, L AM, BI ethmoidectomy; day 32
3	Facial pain, drainage; day 20	9	Day 6 to day 26	R maxillary, R anterior ethmoid, R nasal turbinate	R AM, R ethmoidectomy; day 23
4	Headache, day 21; edema, day 26	19	Day 15 to day 29	L ethmoid, L sphenoid	L sphenoidectomy; day 32 and day 36
5	Headache, edema; day 11	11	Day 11* to day 18	L maxillary, L anterior ethmoid	BI AM, L catheter; day 16
6	Facial pain, edema; day 21	23	Day 13 to day 81	R maxillary, BI ethmoid	BI Caldwell-Luc, BI ethmoidectomy, R catheter; day 28
7	Facial pain, edema; day 16	14	Day 12* to day 21	R maxillary, R nasal turbinate	L AM, L catheter; day 19

Day 0 taken as start of chemotherapy. AM - large antromaxillary window with maxillary sinus biopsy, BI -- bilateral

* First recorded blood count; onset not accurately known.

† Last recorded blood count, at time of discharge to terminal care.

had either leukemia or a head and neck tumor that involved the sinuses (Table 1). During this period of time, there were 2,945 patients admitted for the treatment of solid tumors and 2,812 patients admitted for the treatment of lymphoproliferative malignancies (Table 2). All of the surgical procedures for acute sinusitis occurred from 1980 on, and for fungal sinusitis, from 1984 on (Table 3). All episodes of fungal sinusitis were associated with profound granulocytopenia (neutrophil counts below 100 cells/mm³) (Table 4). Chemotherapy was last given 3 days after to 21 days before (median, 9 days before) the onset of symptoms. The most consistent finding was facial pain, tenderness, and headache associated with fever. Patients in relapse had more intense chemotherapy than those in remission. Sinus radiographs and computed tomography scan findings were always abnormal and displayed various degrees of mucosal thickening to complete opacification of the sinuses (see Figure). In no patient were air fluid levels demonstrated. Unfortunately, the very high incidence of abnormal radiographs in patients with leukemia makes the presence of an abnormality not diagnostic of acute sinusitis. All patients were febrile at the time of symptom onset, although one temperature (case 5) was initially only 37.5°C. All patients received antibiotics. The initial treatment consisted of amikacin, vancomycin, and ticarcillin, which were usually started when the patient became febrile. Surgical intervention and sinus



(Case 7) Computed tomographic scan of maxillary sinus involved with invasive aspergillosis. Only abnormality is mucosal thickening. A) Lower portion of sinus. B) Higher portion of sinus.

biopsy were performed 2 to 11 days after the onset of symptoms (Table 4).

The most common organism found was *Aspergillus* species. *Rhizopus* species and *Candida albicans* were found in one case each. Surveillance cultures were predictive only in one patient (Table 5), who had sinusitis due to *C albicans*. *Candida albicans* was cultured from the throat in two other patients and was not predictive of the cause of the sinusitis. Operative cultures of the sinus identified the cause of the infection in seven of eight cases (Table 5).

Treatment consisted of amphotericin B intravenously (1 mg/kg per day in all patients except patient 6, who received a dosage of 1.5 mg/kg per day), surgical drainage, and in some cases placement of an irrigation catheter. Surgical treatment was similar to that provided for a nonresponding bacterial sinusitis. All nonviable tissue was removed. However, massive operative resection of facial tissue was not needed in any patient. Amphotericin B (50 mg/L of water) irrigations (20 mL four times a day) were performed in a few patients via a red rubber catheter left in the maxillary sinus and secured to the inferior turbinate or floor of the nasal vestibule. Seven patients were thrombocytopenic (platelets less than 40,000/mm³), with three pa-

tients having platelets less than 10,000/mm³. All seven patients required perioperative platelet transfusions. Operative and postoperative platelet counts were kept above 45,000/mm³ to 50,000/mm³ for at least 7 days. Operative blood loss varied from 100 mL to 500 mL.

Early surgical and medical therapy in these patients led to a surprisingly good response (Table 6). Of the five patients in remission, only one died. This patient had the latest institution of therapy and the most malignant location of the infection (sphenoid sinus) (case 4, Table 4). Of the three patients in relapse, two were discharged home for terminal care. Their sinus infections were quiescent at the time of discharge. One patient died after 60 days with an acellular bone marrow and pulmonary aspergillosis. The sinusitis, although still active, did not spread intracranially or progress beyond the tissues adjacent to the sinus.

DISCUSSION

Although the incidence of fungal sinusitis cannot be obtained from our study, it is apparent that fungal sinusitis in immunosuppressed patients is rare and when it occurs is usually associated with leukemia¹¹ or a head and neck primary malignancy. Our

TABLE 5. EFFECTIVENESS OF SURVEILLANCE CULTURES

	Nose	Nasopharynx	Throat	Blood
Total No. of cultures	12 (4)	7 (2)	38 (8)	60 (8)
No. of positive fungal cultures predictive of fungal invasion on biopsy	---	---	2(1)*	---
No. of positive fungal cultures not predictive of fungal invasion on biopsy	1 (1)*	---	2 (1)*	3 (1)*

Numbers in parentheses are numbers of patients, as opposed to numbers of cultures.

*All cultures positive for *Candida albicans*. One patient had candidiasis by culture but invasive aspergillosis on sinus biopsy.

TABLE 6. INFECTING ORGANISMS AND PATIENT OUTCOME IN FUNGAL SINUSITIS

Case No.	Diagnosis	Organism	Outcome†
1	AML in remission	<i>Aspergillus fumigates</i>	Recovery 11 days after onset of symptoms
	AML relapse	<i>Aspergillus flavus</i>	Sinusitis quiescent, but blasts reappeared; patient discharged to terminal care 13 days after onset of symptoms; died 25 days later
2	ALL relapse	<i>Candida albicans</i>	Sinusitis quiescent; patient discharged to terminal care 25 days after onset of symptoms; died 11 days later
3	AML in remission	<i>Aspergillus fumigators</i>	Recovery 10 days after onset of symptoms
4	AML in remission	<i>Aspergillus</i> species	Granulocytes recovered; combination of delayed treatment and surgical diagnosis, along with sphenoid location, led to fungal invasion and thrombosis of internal carotid artery
5	ALL in remission	<i>Aspergillus fumigates</i>	Recovery 16 days after onset of symptoms
6	ALL relapse	<i>Rhizopus</i> species	Facial infection did not spread while patient received amphotericin B and catheter irrigations; developed diffuse bilateral pulmonary infiltrates on day 10 and <i>Rhizopus</i> species left lower lobe pneumonia on day 19; died on day 60 with nonrecovering bone marrow
7	ALL in remission	<i>Aspergillus flavus</i>	Recovery 13 days after onset of symptoms

ALL - acute lymphoblastic leukemia, AML - acute myeloblastic leukemia.

* All patients had localized sinus infection at time of initial diagnosis and all cases had pathologic confirmation.

† Recovery was judged as discharge date from hospital.

data also suggest that sinusitis in general (acute and chronic) is much more common in patients with leukemia or head and neck tumors than those with other solid tumors. An unpublished prospective study conducted at St Jude Children's Research Hospital from June 1970 to January 1972 found 41% of 91 patients with acute lymphoblastic leukemia had abnormal sinus radiographs at the time of induction chemotherapy. Thirty-five percent of the abnormalities consisted of minor changes but were still indicative of sinus disease. There are several possible reasons for the high incidence of sinusitis in this patient population. Although both groups of patients receive immunosuppressive chemotherapy, the patients with leukemia tend to develop a profound mucositis. Irradiation is also a factor in head and neck tumors involving the sinuses (ie, nasopharyngeal carcinoma). In five of our patients with leukemia, portions of the sinuses (frontal, sphenoid, and superior ethmoid) received approximately 24 Gy. The fact that two of our patients did not receive any cranial irradiation argues strongly against central nervous system radiotherapy as a major causative factor. Finally, it is possible that even though the leukemia is in remission, there is still a primary immunologic defect in these patients that predisposes them to the development of sinusitis. The finding that many patients with leukemia have radiographic sinus abnormalities at the time of diagnosis suggests either an immunologic defect resulting in chronic sinusitis or a structural change caused by a leukemic infiltrate.

Of the eight cases of fungal sinusitis, four occurred in patients with acute lymphoblastic leukemia and four in patients with acute myeloblastic leukemia. Since the incidence of lymphoblastic leukemia is five times greater than that of myeloblastic leukemia (Table 2), it can be concluded that fungal sinusitis is more common in acute myeloblastic leukemia (χ^2 test, $p < .05$). Other researchers have also

observed the relatively high incidence of aspergillosis in patients with acute nonlymphocytic leukemia¹¹ and in acute myeloblastic leukemia.²

The occurrence of all of the cases of fungal sinusitis after 1984 is probably due to a change in the chemotherapy protocol for acute myeloblastic leukemia and acute lymphoblastic leukemia patients to one that produces more profound marrow suppression. Prolonged granulocytopenia is probably the single most important causative factor for invasive aspergillosis.¹² Other factors have included prolonged hospitalization and the administration of broad-spectrum antibiotics.¹³ The clustering of three cases in the summer of 1989 (along with an associated increase in fungal infections in other sites) is possibly related to major hospital construction. Several researchers have noted that construction is associated with an increase in fungal infections in immunocompromised patients.^{14,15}

A means to prevent fungal sinusitis is not known. Chronic sinusitis is common in patients with leukemia. However, the exact incidence of sinusitis warrants further investigation. At least two of our patients with fungal sinusitis had previous sinus surgery. One patient (case 1) even had two episodes of fungal sinusitis, each caused by a different species of *Aspergillus*, that presented on opposite sides and occurred 16 months apart. This patient had bilateral transantral ethmoidectomies 2 months after the first episode.

Sickles et al¹⁶ reported that the most consistent clinical presentation of infection in profoundly granulocytopenic patients was fever, local tenderness, and erythema. The most consistent symptoms and findings in our patients with fungal sinusitis were pain (facial or headache), fever, and abnormal sinus radiographs. The abnormality on the sinus radiographs may only be mucosal thickening and may not be readily apparent on plain radio

graphs (see Figure). A computed tomographic examination should be considered in all patients suspected of having sinusitis. All patients were febrile at the time of symptom onset, although the temperature of one patient (case 5) was initially only 37.5°C. Facial swelling developed in 50% of the patients. These symptoms were similar to those reported by Berkow et al,⁶ who reported facial pain and swelling in 55% , sinus pain in 25% , and nasal crusting or ulceration in 25% of patients.

Our experience found surveillance cultures to be unreliable, with only one of eight cases having a true positive culture. There were also two patients with a false-positive culture for *Candida* species with sinus cultures and/or pathologic study revealing aspergillosis. This is in contrast to the findings of Aisner et al¹⁷ who found surveillance cultures positive in 10 of 18 patients having invasive aspergillosis. However, the conclusion based upon either our data or those of Aisner et al is the same: surveillance cultures cannot rule out invasive aspergillosis. Aisner et al did find invasive aspergillosis in 10 of 11 patients with a positive culture. However, Viollier et al¹³ reported positive nasal cultures for *Aspergillus* species in 19 of 21 patients with *Aspergillus* sinusitis, but also in 14 of 31 patients with non-*Aspergillus* sinusitis. (It should be noted that in Viollier's study, *Aspergillus* sinusitis was diagnosed in a subgroup of patients by the combination of positive sinus radiographs, positive anterior nasal culture, and pulmonary aspergillosis.) The relative incidence of acute fungal sinusitis to that of other causes is shown in Table 2. It is possible that the number of acute bacterial sinusitis patients is underestimated, because a few may have been empirically treated with antibiotics, improved, and did not undergo a drainage procedure. However, the vast majority of cases came to biopsy in order to rule out fungal involvement. Our results, like those of other researchers, showed that the vast majority of immunocompromised patients with fungal infection had *Aspergillus* species as the causative organism.¹¹ This finding may be due to the early administration of amphotericin B, since *Candida* species are much more responsive to this drug than are *Aspergillus* species.

On the basis of our experience the following treatment recommendations can be made for the profoundly immunocompromised patient.

1. In a patient with abnormal sinus radiographs, neutropenia, and facial pain, antibacterial and antifungal antibiotics should be started immediately, regardless of whether fever is present or not. Surgical biopsy and drainage should be performed as soon as the patient's hematologic status permits. (The preoperative administration of antibiotics did not preclude the culture of fungus in seven of the eight cases, and it may be unwise to operate on an infected sinus in an immunocompromised patient

without preoperative administration of antibiotics.)

2. In the immunosuppressed patient with fever and abnormal sinus radiographs, antibacterial coverage is certainly indicated. The high incidence of preexisting sinus radiographic abnormalities precludes the assumption that acute sinusitis is the cause of fever in these patients. The role of empiric administration of antifungal agents is currently under study. However, the finding that 22% to 28% of patients with leukemia have fungal infections at autopsy argues strongly toward its use.

3. In the immunosuppressed patient with a fever that has not responded to 7 days of empiric antibiotics, the addition of empiric amphotericin B should be strongly considered. Stein et al¹⁸ and Pizzo et al¹⁹ reported a decreased incidence of fungal infections in febrile neutropenic patients who received empiric amphotericin B therapy.

4. In the immunosuppressed patient without fever or other symptoms, antibacterial and antifungal agents should not be given.

The survival rate of our patients is higher than that stated by Berkow et al⁶ in a report of their own experience and review of the literature. The survival statistics of Berkow et al of only 21% were skewed by the large number of patients in relapse with nonrecovery of their bone marrow. Eighty percent (four of five) of our patients that were in remission survived. Only two of our eight patients died of fungal sinusitis. One had an aplastic bone marrow after 60 days of diagnosis and died of secondary pulmonary involvement. The other patient (case 4) had disease that was diagnosed late (positive biopsy obtained 15 days after onset of symptoms) and had a sphenoid sinusitis. A total of 13 patients could be found, including those in the literature and in our study, who developed fungal sinusitis while undergoing chemotherapy during a relapse.⁶⁻⁸ None of these patients survived.

Our treatment follows the guidelines reported by Berlinger.²⁰ An aggressive approach needs to be taken in the treatment of these patients, with antifungal and antibacterial agents given at the time of onset of symptoms, early surgical drainage, and catheter irrigations of amphotericin B. Granulocyte transfusions, although useful in gram-negative sepsis, have not been extensively studied in fungal infections,²¹ and their use in conjunction with amphotericin B has also been associated with lethal pulmonary reactions.²² Our results are similar to those of Aisner et al¹¹ who reported that all of six patients with pulmonary or sinus aspergillosis in whom the diagnosis was determined and treatment was started early had either a partial or complete response to amphotericin B therapy. The single most important factor affecting outcome is the status (remission versus relapse) of the underlying disease.^{10,11}

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