Invasive aspergillosis of paranasal tissues in children with malignancies

Paranasal aspergillosis was encountered in five children with relapsed malignancies. All had received broad-spectrum antibiotics within two weeks of development of aspergillosis, and all had absolute granulocyte counts <200/mm³ for at least three weeks. None had received prior antifungal therapy. There was an average delay of eight days before the correct diagnosis was established by either biopsy or culture. These data emphasize the need to obtain surveillance cultures of the upper respiratory tract passages in severely neutropenic patients receiving prolonged antibiotic therapy, and raise a question concerning prophylactic use of antifungal therapy in this group. (J PEDIATR 103:49, 1983)

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ASPERGILLUS INFECTION has been reported with increasing frequency in the immune-compromised host[1-4] and is the second most common fungal infection in patients with malignancy.[5-7] *Aspergillus* species is the most commonly encountered fungal genus in the environment.[8] Inhalation of spores present in dust and soil is thought to be the primary route of entry.[8] Environmental exposure to *Aspergillus* has been shown to lead to invasive disease in the immune-compromised host.[9, 10]

Invasive *Aspergillus* species infections in the immune-compromised host involves the respiratory tract in more that 90% of cases, the lung being the primary organ of involvement.[1-4] Despite the fact that aspergillosis is the most common fungal infection of the nose and paranasal sinuses,[8, 10, 11] this site is rarely reported to be infected in patients with neoplastic disease. Only three of 98 patients with documented aspergillosis had nose and paranasal sinus infection.[1] Of patients with invasive disease in the nose and paranasal region, only nine were younger than 18 years of age.[1, 9, 12, 13] In 1979, Singer[14] reported invasive aspergillosis of the nose seen in one patient at our institution. We report four additional cases, summarize the existing literature on previously reported cases in children, and make suggestions for early diagnosis and treatment.

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CASE REPORT

In March 1980, acute lymphocytic leukemia was diagnosed in a 6-year-old white boy. Remission was induced with vincristine, L-asparaginase, and prednisone according to Children's Cancer Study Group protocol 161. The patient was noted to have low IgG and IgM values at the time of diagnosis, and received plasma transfusions from his mother every three weeks. He received central nervous system prophylaxis, and maintenance therapy consisted of 6-mercaptopurine and methotrexate. He remained in continuous complete remission, and was seen August 17, 1981, for neutropenia (granulocyte count 121/mm³). A small nasal ulceration was noted and was treated topically with neosporin ointment. He returned on August 20 with fever and persistent neutropenia, and was given nafcillin and gentamicin after blood and urine cultures were obtained. A bone marrow aspiration at that time revealed replacement with 85% lymphoblasts. Reinduction chemotherapy, including vincristine, prednisone, and L-asparaginase, was begun. All cultures remained negative, the antibiotic therapy was discontinued, and the patient was discharged on August 25, afebrile but with continued neutropenia. He returned on August 30 with fever, neutropenia, and pain in the right nostril. Again he was given nafcillin and gentamicin after cultures of blood, urine, and right nasal discharge were obtained. A chest radiograph was considered to be clear of infiltrates. On September 3, the culture of the nasal discharge grew *Aspergillus*

Table. Paranasal aspergillosis in children

Patient	*Initial age (yr)*	*Symptoms, signs, or diagnosis*	*Underlying disease*	*Neutropenia < 200/mm³*			*Sepsis*	*Antifungal treatment*	*Leukocyte transfusion*
				At presentation	*Duration >3 wk*	*Recovery to >500/mm³*			
1	15	Facial swelling	ALL relapse	+	+	−	−	+ (Rifampin, 5-FC)	−
2	14	Epistaxis and nasal ulcer	Neuroblastoma with bone marrow involvement	+	+	−	Pseudomonas	+	−
3	6	Facial swelling, nasal pain	ALL relapse	+	+	−	−	+	+
4	10	Facial swelling	ALL relapse	+	+	−	−	+	−
5	13	Facial swelling	ALL relapse	+	+	−	β-Streptococcus	+	−
6	Child	Sinusitis, periorbital cellulitis	ALL relapse	+	?	?	β-Streptococcus	−	?
7	Child	Sinusitis	All relapse	+	?	?	Pseudomonas	+	?
8	Child	Sinusitus, periobital cellulitis	ALL relapse	+	?	?	Enterocolitis	+	?
9	13	Nasal ulceration	Aplastic anemia	+	?	−	−	+	+
10	12	Swelling of nasolabial fold	ALL induction	+	?	+	−	+	−
11	15	Nasal crusting	AML relapse	+	?	Temporary	*E. coli*	+	?
12	18	Maxillary pain	ALL	+	?	?	?	+	−
13	4	Pansinusitis	ALL	?	?	?	?	?	?
14	16	Nasal swelling	AML	+	?	+	?	+	?

Patients 6 through 8, reference 9; patients 9 through 12, reference 13; patient 13, reference 1; patient 14, reference 12.
+, Present; −, absent; ?, not stated; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; H, histologic confirmation; M, microbiologic confirmation; NA, not available.

flavus, and a biopsy of the right naris revealed invasive aspergillosis. The patient underwent several surgical procedures for debridement, and was administered amphotericin B plus 5-flucytosine, as well as white blood cell transfusions. However, the lesions progressed, leading to airway obstruction requiring tracheal intubation. Despite continued induction chemotherapy, remission was never obtained. The patient developed kidney failure, liver dysfunction, and intracranial bleeding. He died October 5, 1981.

RESULTS

Five patients with aspergillosis involving the paranasal region were seen in our institution between 1977 and 1981 (Table, patients 1 to 5). All patients had replacement of normal bone marrow elements by malignant cells and all had absolute granulocyte counts <200/mm³ at presentation. In no patient did granulocyte counts recover to levels >500/mm³. All were given broad-spectrum antibiotics (an aminoglycoside and antistaphylococcal penicillin) for periods ranging from two to four weeks prior to onset of invasive aspergillosis. Four of the five patients were given daily infusions of amphotericin-B, with total doses ranging from 135 to 750 mg. However, all five patients died with active fungal disease between 12 and 90 days after onset of fungal disease. One patient was given corticosteroids during the active fungal infection. The presenting signs and symptoms included facial swelling and pain in the nasal area in four of the five patients. Nasal mucosal ulceration was observed in two. There was an average delay of eight days from the onset of presenting symptoms to biopsy, diagnosis, and therapy of invasive aspergillosis.

Outcome	*Diagnosis/species*	*Start of therapy at onset of symptoms*
Died	H, M/*A. flavus*	8
Died	H/NA	6
Died	H, M/*A. flavus*	14
Died	H, M/*A. flavus*	4
Died	H, M/*A. flavus*	6
Died	H/?	?
Died	H/?	?
Died	H, M/?	?
Died	H/?	?
Alive	H/?	?
Died	H/?	?
Alive	H/?	?
Died	M/*A. fumigatus*	?
Alive	H/?	?

Antemortem diagnosis was made in all cases. Two patients had radiographic evidence of pulmonary involvement, which developed in the terminal days of their illness. Pulmonary involvement, as determined radiographically, was not the initial event in any patient.

DISCUSSION

Aspergillosis of the paranasal tissue complicating malignancy has been reported previously in nine pediatric patients.[1, 9, 12, 13] (Table, patients 6 to 14). As noted, eight of nine were neutropenic (absolute granulocyte count <500/mm^3) at the time invasive fungal disease became apparent. Fifty percent had documented sepsis either before or concurrent with fungal involvement, and all had been given broad-spectrum antibiotics prior to development of fungal invasion. Four patients were treated with corticosteroids, and two were noted to have pulmonary involvement subsequent to paranasal involvement. The disease was fatal in all patients in whom there was no recovery of the granulocyte count to normal levels, or remission of the malignancy. Presenting signs of fungal invasion in these nine patients included paranasal swelling and pain in 55%, pain in area of the sinuses in 25%, and nasal crusting or ulceration in 25%. Aggressive surgical intervention was described in 50% of reports. No clear indication of time lapse between development of symptoms and diagnosis of invasive aspergillosis was provided in past case reports.

The outcome of invasive aspergillosis of the nose and paranasal tissue was usually fatal. When our five cases are combined with those already reported, the mortality is 79%. Aisner et al.[15] emphasize the need to screen patients receiving broad-spectrum antibiotics by obtaining nasal cultures for *Aspergillus* species. However, they do not emphasize the relevance of positive cultures with regard to the possibility that local invasive disease may ensue. Rather, they relate the positive fugal cultures to future development of invasive pulmonary disease. Before recommendation of routine screening cultures of the nose as a means of predicting local invasion, knowledge of local colonization patterns and a larger prospective evaluation of children undergoing chemotherapy would be necessary.

In the presence of granulocytopenia, the usual signs of inflammation are likely not to be evident.[16] Aspergillosis is usually accompanied by an intense inflammatory reaction,[8] but this may not be obvious when granulocytes are lacking. Corticosteroids may also suppress a local inflammatory reaction. In the majority of our patients and in those reported, an early symptom of paranasal aspergillosis was facial swelling or simply pain in the paranasal region.

Early diagnosis requires a high index of suspicion. Three means of diagnosis involve culture of suspicious lesions or secretions from those lesions on appropriate fungal culture media[8]; histologic analysis by biopsy of suspect lesions, with appropriate staining and microscopic observation for the characteristic septate hyphae[1, 2, 4, 6, 8, 13, 14]; and serologic techniques for precipitating antibodies to aspergillus antigens.[3, 8] We believe that prompt biopsy, whenever the signs and symptoms noted in the table are present, provides the best means of rapid diagnosis and early initiation of treatment. A surgical procedure can remove necrotic tissue with the development of clean surgical margins, allowing better penetration of antifungal therapy into the infected areas.[4, 13] Seroconversion of antibody titers to the aspergillus antigens may also allow early diagnosis.[3] Immunocompromised patients, however, may not form these precipitins.[8] Seroconversion has been suggested as a means to predict prognosis. Fisher et al.[3] showed a survival rate of 64% in those patients who had seroconversion and were given appropriate treatment. Culture as a means of diag-

nosis is important in confirming histologic material, providing species identification and organisms for sensitivity tests. Results, however, may require up to one week,[8] and thus early treatment is not possible if culture is the only means of diagnosis.

Treatment of paranasal aspergillosis at our institution has included several modalities. First is institution of amphotericin-B at an initial dose of 0.3 mg/kg/day, with daily increases to 1 mg/kg/day. This dosage is continued, while observing for changes in renal function tests, for approximately six weeks, depending on clinical response. In certain circumstances (poor initial response) 5-flucytosine has been added on an empiric basis. The second arm of therapy (after intial biopsy) involves debridement of all necrotic tissue in the belief that the antifungal therapy will not penetrate well into tissue devitalized by fungal thrombosis.[8, 13, 14] This has required multiple procedures in all of our patients in whom this approach was utilized. Treatment of the underlying malignancy remains crucial, as only in patients with resolution of granulocytopenia has successful outcome been noted.[13] The use of granulocyte transfusions in the supportive care of granulocytopenic patients with gram-negative bacterial sepsis is well documented.[17, 18] Their use in similar patients with documented fungal sepsis has received little emphasis.[19] Granulocyte transfusions were utilized during the treatment of fungal disease in one of our patients who was receiving amphotericin-B and in one other patient from the literature.[9] Both patients died. The decision to initiate granulocyte tranfusions in our patient was based on the experience of Cohen et al,[19] who reported that patients with chronic granulomatous disease of childhood and fungal infections may benefit from leukocyte transfusions. Amphotericin-B in combination with leukocyte transfusion can lead to respiratory distress, presumably from aggregates of granulocytes that become lodged in the pulmonary microvasculature.[20] Our laboratory has observed that only granulocytes obtained from nylon filters are further induced to aggregate by amphotericin-B.[21] Our patient received granulocytes harvested by centrifugation rather than by filtration leukophoresis, and experienced no respiratory distress. Similarly, patients reported by Cohen et al.[19] experienced no pulmonary compromise; however, the clinician must be aware of this potential complication.

Our patients had received oxygen by mask, and an extensive search was made for evidence of fungal contamination of the oxygen delivery system, but none was found. No other environmental source could be identified.[9, 10]

It has been suggested that prophylactic antifungal therapy be initiated in patients with prolonged granulocytopenia and persistent fever after seven days of continuous broad-spectrum antibiotic therapy.[12, 22, 23] This approach was not used in any of our patients, but deserves further study to evaluate the risk of toxicity from the treatment compared with its therapeutic benefit.

Aspergillosis of the paranasal area in patients with malignancy is a fulminant process requiring early biopsy for diagnosis, institution of antifungal therapy, and aggressive debridement of necrotic tissue. These efforts may be fruitless without recovery of the granulocyte count. Areas for further study include the importance of surveillance cultures for fungi, the values of leukocyte transfusions, and the potential for prevention with prophylactic antifungal therapy.

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