Orofacial aspergillosis in acute leukemia


Houston, Texas

The clinicopathologic characteristics of orofacial aspergillosis in thirteen hospitalized patients who developed the infection while receiving chemotherapy for acute leukemia are described. Clinically, the primary sites of infection, in decreasing order of frequency, were the paranasal sinuses, nasal cavity, mouth, and facial skin; the corresponding order for the secondary sites was orbit, nasal cavity, facial skin, and mouth. Pathologically, the fungal lesions in the nasal, oral and sinusoidal cavities were black, ulcerated, and escharotic due as a direct result of tissue destruction by the organism and an indirect result of thrombotic vascular infarction. The orbital lesions were deep red, granulomatous, and productive of proptosis and ectropion. Seven of the thirteen patients had concomitant pulmonary aspergillosis. The orofacial infections were not responsive to antifungal therapy in the absence of remission of the leukemia and restoration of depressed host defenses. In two patients who did achieve remission, the aspergillosis was controlled by the intravenous administration of amphotericin B.


Aspergillosis is at present the second most frequent fungal infection in cancer patients with impaired host defenses, exceeded only by candidiasis. Approximately 60% of the cases of aspergillosis in this population occur in persons with acute leukemia, 20% in persons with lymphoma, and 12% in patients with chronic leukemia. In 1971, 41% of all patients with acute leukemia at Memorial Sloan-Kettering Hospital who came to necropsy had evidence of aspergillosis.

The aspergilli are ubiquitous blue-green molds that grow as saprophytes on organic matter and become parasites by accident. When stained with PAS or Gomori methenamine silver, Aspergillus hyphae measure 2 to 5 microns in width with even diameters that are frequently septate and dichotomously branched at a 45° angle (Fig. 1). Aspergilli produce conidiospores that enter the atmosphere and are inhaled into the nasal and oral cavities, lungs, and paranasal sinuses. Despite almost universal exposure to airborne spores, in and out of hospitals, aspergillosis in man is rare in the absence of predisposing factors, which include immunosuppressive cancer chemotherapy, disease- and treatment-induced leukopenia, and long-term use of antibiotics and/or corticosteroids. Each such factor is highly operative in patients receiving antineoplastic drugs for acute leukemia.

Aspergillus hyphae have the propensity to penetrate mucous membranes and to invade and grow in the walls of small- to medium-sized arteries and veins, producing thrombosis, infarction, and necrosis. Once the infection breaks out of the primary locus, the spread is relentless and unaffected by anatomic barriers. The hyphae produce diffusable toxins that destroy epithelial cells, connective tissue cells, muscle fibers, and bone located in the invasion path.

The vast majority of Aspergillus infections in acute leukemia are localized to the lungs and are not contagious. Aspergillus spores have the proclivity to germinate into proliferative hyphae in a mucous medium. This capacity enables the organism to colonize oronasal portals of entry and to produce infections that invade the contiguous structures. This report focuses on the clinical characteristics of thirteen documented cases of orofacial aspergillosis in adolescents and adults with acute leukemia treated within the Department of Developmental Therapeu-
Fig. 1. *Aspergillus fumigatus* in tissue section showing septate hyphae with dichotomous 45° angle branching. (Hematoxylin and eosin stain. Magnification, X400.)

Fig. 2. Nasal aspergillosis (*Aspergillus flavus*) invading the external nares and philtrum in a patient with acute lymphocytic leukemia.

The thirteen patients ranged in age from 16 to 60 years. There were eight male and five female patients. All were white. Eight patients (six male, two female) had acute lymphocytic leukemia (ALL); two (both female) had acute myelocytic leukemia (AML); two (one male, one female) had acute myelomonocytic leukemia (AMML); one (male) had acute undifferentiated leukemia (AUL). In five the causative organism identified from biopsies, smears of exudates, and/or cultures was *Aspergillus flavus*; in three, *Aspergillus fumigatus*; in one, *Aspergillus glaucus*; in four the *Aspergillus* was not speciated. Seven had concomitant *Aspergillus* pneumonia, and six did not.

Four of the patients had a single focus of orofacial *Aspergillus* infection confined to the palate, nasal cavity, antrum, and skin of the forehead. Seven had two anatomic areas of involvement, and two had three. The overall frequency distribution was nasal cavity, six; orbit, six; maxillary sinus, five; skin, four; ethmoid sinus, two; mouth, two. One palatal lesion and three lesions of the nasal cavity were bilateral; all others were unilateral. The clinical characteristics of the facial and oral *Aspergillus* infections are detailed below.

**Nasal aspergillosis**

Nasal aspergillosis in this series arose either locally or by extension of an infection that originated in the maxillary sinus and eroded the bony wall between the antrum and nasal cavity. The infection was manifested by swelling, pain, fever, ulceration, crusting, and necrosis of the inferior turbinates, nasal septum, and lateral nasal walls which rendered the involved surfaces insensitive. Antral origin was reflected by the presence of a greenish gelatinous nasal discharge that contained particulate matter and fungal elements. Subsequent progression was very rapid and destructive. As shown in Figs. 2 and 3, the favored invasion route from the nasal cavity was anteriorly through the external nares to the philtrum and then on to the circumoral skin and labial and
Fig. 3. Nasal aspergillosis (*Aspergillus fumigatus*) invading the external nares, ala nasi, circumoral skin, and mouth in a patient with acute myelocytic leukemia.

buccal mucosa. The track was delineated by blackened necrotic tissue surrounded by little or no inflammatory reaction.

**Sinus aspergillosis**

Aspergillosis is the most common fungal infection of the paranasal sinuses in both healthy and immunocompromised subjects. In the former, the infection is local in nature and resembles chronic nonspecific sinusitis. Aspergillosis should be suspected whenever an uncomplicated unilateral maxillary sinusitis does not respond to antibiotic therapy. In those immunosuppressed by antileukemia chemotherapy, the infection is fulminating, invasive, and bone-destructive, often reaching into the nasal cavity, orbit, and skin. Historically, the maxillary antrum has been the most prevalent site of paranasal sinus aspergillosis, followed in sharply descending order by the sphenoid, ethmoid, and frontal sinuses. In this study aspergillosis was limited to the maxillary and ethmoid sinuses in a ratio of 3:1.

Antral aspergillosis was manifested by unilateral facial swelling and disfigurement, local tenderness or numbness, fever, headache with neuralgic pain about the eye and cheek, sinus fullness, and nasal discharge or nasal obstruction (Fig. 4). Rhinoscopic changes included edematous and polypoid abnormalities of the mucosa and pale cyanotic conchae. In one case the chief complaint was odontalgia-like pain involving the upper anterior teeth. In two patients with antral aspergillosis there was fistulation from the infected sinus through the facial skin at the junction of the ala nasi and the bridge of the nose; in one patient with ethmoid aspergillosis there was a fistulous opening of the skin between the orbit and the nose. Fistulation was evidenced by round or oval cutaneous orifices filled with a black, dense, greasy exudate (Fig. 5). Radiographs showed massive opacification within the affected sinus, destruction of the surrounding bone, and in some instances penetration into the orbit, nasal cavity, or overlying skin.

**Orbital aspergillosis**

Each of the six cases of orbital aspergillosis was unilateral, originating in the maxillary or ethmoid sinus and entering the orbit by eroding through the
Fig. 6. Orbital aspergillosis (Aspergillus fumigatus) with red paraocular granulomatous lesion and ectropion of the lower eyelid in a patient with acute lymphocytic leukemia.

Fig. 7. Orbital and sinonasal aspergillosis (Aspergillus flavus) showing proptosis, ectropion, and blepharitis of right eye in a patient with acute lymphocytic leukemia.

Fig. 8. Palatal aspergillosis (Aspergillus flavus) in a patient with acute myelocytic leukemia.

Fig. 9. Aspergillosis of skin (Aspergillus sp.) at junction of scalp and forehead showing purplish ulcerated plaque in a patient with acute undifferentiated leukemia.

Aspergillus of the eye can lead to iridocyclitis, endophthalmitis, focal retinitis, choroiditis, chemo-
sis, corneal ulcers, and ophthalmoplegia.\textsuperscript{5-8} Chemosis and corneal ulcerations were the most common findings in the patients with ocular aspergillosis in this series. Although orbital aspergillosis may destroy the eyeball, perforate the orbital roof, and enter the frontal lobe of the brain, these sequelae were not encountered because of the comparatively short survival time of the infected patients.

Aspergillus stomatitis

Oropharyngeal aspergillosis in patients with hematologic malignancies is featured by yellow-black, necrotic ulcerations of the soft palate and
Aspergillus fumigatus particularly prominent as a cause of invasive disease and of lesions beginning in the nose and paranasal sinuses in immunosuppressed patients, \(^1\) a finding confirmed by the present study.

Oral aspergillosis may be primary or secondary in origin, the latter representing extension from other facial areas. Primary aspergillosis of the palate in a patient with AML caused by *Aspergillus fumigatus* is shown in Fig. 8. The yellow fungal colonization in the palatal midline was seated on a painful ulcer and was surrounded by a ring of blackened necrotic tissue. An example of secondary aspergillosis of the mouth in a patient with AML due to *Aspergillus fumigatus* that began in the nasal cavity is shown in Fig. 3. The fulminating, mutilating, nosemalike infection consumed the wing of the nose, philtrum, lips, and cheeks in sequential fashion.

**Aspergillus dermatitis**

The majority of facial skin lesions caused by *Aspergillus* spp. in patients treated for acute leukemia result from spread of infections arising in the nasal cavity, paranasal sinuses, and orbit that often follow the line of least resistance and fistulate through the overlying skin. Hematogenously disseminated subcutaneous aspergillosis of the face is extremely rare. Primary isolated cutaneous lesions may develop at minor sites of trauma, as in the case shown in Fig. 9. The infection occurred while this patient with AUL was in a “life island” unit. It began as an erythematous and edematous indurated plaque at the junction of the forehead and scalp that became violaceous and progressed to a punched-out necrotic ulcer surfaced by a black eschar that was sharply demarcated from the surrounding skin.

**DISCUSSION**

Aspergilli have a comparatively low order of infectivity in man. Of the more than 160 species and variants thereof listed in the 1982 catalogue of the American Type Culture Collection, \(^1\) only about ten are pathogenic at the human level. *Aspergillus fumigatus* is the most common precipitant of pulmonary aspergillosis, whereas *Aspergillus flavus* is particularly prominent as a cause of invasive disease and of lesions beginning in the nose and paranasal sinuses in immunosuppressed patients, \(^1\) a finding confirmed by the present study.

The pathologic hallmark of fulminant orofacial aspergillosis in patients with acute leukemia is invasion of the regional blood vessels producing tissue infarction, tissue necrosis, and tissue blackening. This sequence is mimicked pathologically and clinically by infections caused by *Mucor* and by *Pseudomonas* spp., each of which must always be considered in the differential diagnosis of suspected orofacial aspergillosis.

Mucormycosis of the rhinocerebral type usually starts on the palate or in the nasal cavity and spreads through the adjacent sinuses, first to the orbit and then to the brain. \(^1\) Earliest symptoms are fever, headache, lethargy, and loss of vision. The earliest sign is a black eschar on the palatal or nasal mucosa. Palatal mucormycosis has a tendency to destroy the palatal bone and to penetrate into the maxillary antrum. Microscopically, *Mucor* hyphae show considerable variation in size and shape and compared to *Aspergillus* hyphae are much larger, much wider, more irregular, and nonseptate, and they have right-angled branching.

The orofacial lesions of *Pseudomonas* infections are typified by a central purple to black area of necrosis encircled by an erythematous halo. They result from direct tissue invasion by the opportunistic aerobic gram-negative rods that invade the regional arteries and veins, creating a vasculitis. *Pseudomonas* organisms produce both leukocyte-repellent and necrotizing factors. The lesions are dry and gangrenous in appearance. In time the necrotic lesion becomes sharply demarcated from the surrounding skin or mucosa and sloughs en masse, leaving a glistening raw-red base of granulation tissue. *Pseudomonas*-induced lesions of the facial skin may take the form of erythema gangrenosum, a round, raised, relatively painless lesion with a gray-black to black center from which the organism can be cultured.

The prognosis for invasive aspergillosis of the orofacial structures in the presence of acute leukemia is extremely poor. Although all thirteen patients in this group were given vigorous antifungal therapy with amphotericin B administered intravenously in doses of 0.6 to 1 mg/Kg/day, with the duration determined by response to treatment, only two survived the infection. Each responder had achieved a chemotherapy-induced complete remission of leukemia and had more than 1,000/mm\(^3\) functioning neutrophils in the circulating blood. McGill, Simpson, and Healy \(^1\) have recently proposed that fulminating aspergillosis of the nose and paranasal sinuses in immunocompromised patients be treated on an individualized basis with intravenous antifungal agents, surgical debridement, granulocyte transfu-
sions, and/or bone marrow transplantation, depending on time and circumstances.

REFERENCES

Reprint requests to:
Dr. Samuel Dreizen
Department of Oral Oncology
University of Texas Dental Branch
Houston, TX 77225