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Invasive External Otitis Caused by *Aspergillus*

Peter Phillips, Graham Bryce, John Shepherd, and Don Mintz

Invasive external otitis occurs almost exclusively in patients with longstanding diabetes. Except for occasional cases, the etiologic agent has been *Pseudomonas aeruginosa*. We report a case caused by *Aspergillus* species in a diabetic patient with acute leukemia. Persistent infection was documented by culture and histology after a course of intravenous amphotericin B (total dose, 2 g). Clinical resolution occurred in association with a 3-month course of oral itraconazole. Four previously reported cases of invasive aspergillus otitis are reviewed.

Invasive external otitis begins in the external auditory canal and extends to involve the adjacent subcutaneous tissues and temporal bone. The clinical course consists of a chronic osteomyelitis of the base of the skull that is usually slowly progressive and may be associated with cranial nerve involvement. Prompt diagnosis and prolonged therapy with intravenous antibiotics active against *Pseudomonas* are essential to the reduction of morbidity and mortality. Results of therapy are best in patients without evidence of neurologic involvement at the time of initial diagnosis [1].

Organisms other than *Pseudomonas aeruginosa* that have been recovered from the external auditory canal or surgical specimens in invasive external otitis include *Staphylococcus epidermidis, Staphylococcus aureus, Staphylococcus species, Candida parapsilosis, Candida albicans, the enterococcus, Streptococcus species*, and diphtheroid species [1]. The significance of these organisms in this setting is uncertain. A review of invasive external otitis indicated that *P. aeruginosa* accounted for 99.2% of 262 reported cases [2]. We report a case of invasive external otitis caused by *Aspergillus* and treated successfully with itraconazole. A literature review identified four other cases of invasive aspergillus otitis.

**Case Report**

A 64-year-old woman was admitted to the hospital because of pancytopenia on 28 June 1987, after presenting with a sore throat. She had a 15-year history of non-insulin-dependent diabetes mellitus (NIDDM), mild hypertension, and carcinomas of the larynx, colon, and cervix. Her surgical history included a hysterectomy, laryngectomy, and transverse hemicolecotomy. Her only medications at the time of admission were hydrochlorothiazide (25 mg orally per day) and chlorpropamide (500 mg orally per day).

Physical examination revealed a low-grade fever (38°C orally). There was a hemorrhagic lesion (diameter, 1 cm) on the hard palate and a grade 2/6 systolic murmur heard at the left sternal border. The liver was palpable 3 cm below the right costal margin. The remainder of the examination on admission was normal.

Initial laboratory investigations included a total white blood cell count of 1.2 × 10⁶/L, with a differential count of 0.2 × 10⁶ granulocytes/L, 0.9 × 10⁶ lymphocytes/L, and 0.1 × 10⁶ monocytes/L. The hemoglobin was 66 g/L, the platelet count was 13 × 10⁹/L, and blood glucose was elevated at 296 mg/dL.

Bone marrow examination on the day after admission demonstrated a hypercellular marrow with 29% blasts that stained positive for Sudan black. The proportion of blast cells on marrow biopsy was higher, and the best diagnosis was thought to be acute myelogenous leukemia (FAB M2 classification).

Cytotoxic chemotherapy was started on 4 July and the patient remained neutropenic (<0.5 × 10⁹ granulocytes/L) until 30 July. Febrile neutropenia prompted antimicrobial therapy with vancomycin, pipercillin, and gentamicin beginning on 30 June. Tobramycin was substituted for gentamicin on 4 July. Candidemia was treated with intravenous amphotericin B starting on 10 July; this drug was continued at a dose...
of 30 mg daily. On 23 July the patient developed bilateral earache; examination revealed erythema, tenderness, and swelling of the ear canal, pinna, and soft tissues anterior to the ear; these signs and symptoms were more marked on the left. There was an area of necrotic tissue on the inferior aspect of the left conchal bowl. On 28 July a left facial palsy developed. An examination under anesthesia on that day showed both external ear canals to be filled with white debris, with granulations also present on the left side. The left tympanic membrane appeared thickened, and a myringotomy revealed serous fluid in the middle ear space. Incision into the necrotic area of the left inferior conchal bowl showed necrotic cartilage extending to involve the tragus; the involved areas were resected and a myringotomy was performed. A biopsy of the left ear showed septate fungal hyphae and necrosis of cartilage and soft tissue (figure 1). Gram staining of operative specimens collected during treatment with amphotericin B, vancomycin, and ceftazidime showed no pus or organisms. However, *Aspergillus* species was recovered from cultures. No anaerobes were isolated.

The patient's neutropenia improved by 29 July, when the total granulocyte count was 1.6 \( \times 10^9 \)/L. On 4 August there were 18.0 \( \times 10^9 \) granulocytes/L, and neutropenia did not recur during the hospital stay. A bone marrow biopsy documented hematologic remission on 20 August. Treatment with amphotericin B was continued from 10 July to 17 September (total dose, 2 g) and was associated with nausea and dizziness. After completion of therapy, the left ear was improved but still swollen and erythematous.

The patient was discharged home on 28 September but was readmitted on 6 October because of worsening inflammation and reduced hearing of the left ear. The physical examination was notable for swelling, erythema, and fluctuance of the left pinna (figure 2, left). Purulent discharge from the left ear and persistent left facial palsy were noted. The patient was afebrile. Laboratory results from 9 October included an erythrocyte sedimentation rate of 75 mm/h and a granulocyte count of 6.12 \( \times 10^9 \)/L. A gallium scan showed uptake in the left petrous temporal bone consistent with chronic osteomyelitis. Computed tomography of the head on 9 October showed destruction of the left auricular cartilage, opacification of the left mastoid air cells and middle ear, and cortical irregularity suggesting bone destruction in the middle ear and the left external auditory canal. Incision and drainage of the pinna yielded purulent material and necrotic cartilage. Polymorphonuclear leukocytes, but no organisms, were seen on gram stain. *S. epidermidis, Streptococcus viridans,* and diphtheroids—but no fungi—were isolated from cultures. However, histopathologic studies showed soft tissue invasion with filamentous fungi, and *Aspergillus* species was cultured again from specimens collected at repeat incision and drainage of the pinna.

**Figure 1.** Photomicrograph of left external ear biopsy specimen taken in July 1988. The tissue section was prepared with methenamine silver stain. Hyphal forms consistent with *Aspergillus* species are seen to be invading cartilage and adjacent fibrous tissue (original magnification, \( \times 160 \)).
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on 15 October. Mycobacterial cultures from the same specimens were negative. A repeat bone marrow biopsy on 15 October showed hypocellular marrow but no evidence of leukemic relapse.

Because of adverse effects experienced previously, the patient refused a second course of amphotericin B. After informed signed consent had been obtained, treatment with itraconazole (400 mg orally per day) was started on 24 October. The dose was reduced to 200 mg/d because of possible drug-induced nausea, and therapy was continued until 22 January 1988. The patient experienced gradual resolution of the left ear inflammation, and a follow-up gallium scan was normal on 3 December (1987). She remained afebrile both before and throughout the course of itraconazole. The left facial palsy persisted, but there was no progression of cranial nerve involvement. No evidence of leukemic relapse was seen until the patient developed progressive pancytopenia and blast cells in the peripheral blood on 15 February 1988. She died on 16 April of relapsing acute myelogenous leukemia. An autopsy was not performed. Despite recurrent neutropenia there was no clinical evidence of otitis externa before death (figure 2, right).

Discussion

Invasive external otitis is one of the few infectious clinical syndromes for which only one etiologic agent, \textit{P. aeruginosa}, is almost always responsible [2–6]. The diabetic leukemic patient described in this report had invasive otitis externa due to \textit{Aspergillus}, as documented by histology and culture. That this patient initially may have had a mixed infection that responded to antibacterial therapy is possible but unlikely, since the process evolved during treatment with broad-spectrum antibiotics active against \textit{Pseu-}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{\textit{Left}: Left ear before itraconazole therapy (October 1987), when the pinna was erythematous and swollen. \textit{Right}: Left ear 6 weeks after completion of a 3-month course of itraconazole (March 1988).}
\end{figure}
domonas. The course was complicated by cranial neuropathy involving the facial nerve. Despite resolution of neutropenia, the patient had persistent clinical and microbiologic evidence of disease activity following a course of intravenous amphotericin B (total dose, 2 g). She refused a second course of amphotericin B but received a course of oral itraconazole. Clinical resolution during the latter treatment was not associated with any change in hematologic status.

Although noninvasive infection of the external ear canal (otomycosis) by *Aspergillus niger* is not uncommon [7], we could find only four other reports of invasive external otitis caused by *Aspergillus*. Three diagnoses were considered definite [2, 8, 9] and one was considered probable [11]. The diagnosis was established by culture and histology in three cases. No mention was made of histopathologic confirmation for the probable case outlined by Fisher et al. [10].

Reports of the definite cases are summarized in table 1. None of the previously reported cases were in diabetic patients. All but one patient had hematologic malignancy, including preleukemia and acute leukemia. Cranial neuropathy involving the facial nerve was common to all confirmed cases, with one instance of multiple cranial nerve involvement. Three patients were treated with a combination of systemic antifungal therapy and surgical debridement. The total dose of amphotericin B ranged from 1,500 to 2,500 mg. However, relapses were noted after courses of 1,500 and 2,000 mg of amphotericin B in cases no. 2 and 4, respectively; both of these patients had also been treated surgically. Favorable outcomes were associated with additional courses of antifungal therapy as outlined in table 1. Surgical therapy consisted of mastoidectomy, temporal bone debridement, or debridement of the pinna. None of the patients with definite cases died as a result of invasive otitis.

The case we considered to be probable was included in a review of invasive aspergillosis primarily involving patients with hematologic malignancy or solid tumors [10]. Culture of the exudate from the external ear yielded *Aspergillus* species and *Serratia marcescens*. Treatment was initiated with amphotericin B; the patient died 12 days later, after receiving a total dose of 531 mg. Autopsy revealed invasive pulmonary aspergillosis; however, the histopathologic findings for the ears and adjacent tissues were not described.

Itraconazole is a triazole antifungal agent. Its spectrum of activity, including *Aspergillus fumigatus*, and its lack of documented hepatic or endocrinologic toxicity distinguish it from ketoconazole [11, 12]. Itraconazole is available only as an oral formulation, and its absorption has been poor in some patients, particularly those with leukemia who are undergoing cytotoxic chemotherapy [13]. Uncertainty regarding oral absorption and fungistatic (rather than fungicidal) activity has made some in-

<table>
<thead>
<tr>
<th>Case [reference]</th>
<th>Age (y)/sex</th>
<th>Underlying disease</th>
<th>Granulocyte count ((\times 10^9/L))</th>
<th>Diagnostic method</th>
<th>Cranial neuropathy</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [8] 80/M Myelodysplasia</td>
<td>2.6</td>
<td>C, H</td>
<td>7, 8, 9, 10, 12</td>
<td>AMB (1,500 mg)</td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 [2] 85/M None</td>
<td>20.1</td>
<td>C, H</td>
<td>7</td>
<td>(1) Surgery, AMB (1,500 mg) (2) AMB (1,000 mg) plus rifampin†</td>
<td>Relapsed, improved, survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 [9] 68/M AML</td>
<td>&quot;Neutropenia&quot;</td>
<td>C, H</td>
<td>7</td>
<td>Surgery, AMB (2,000 mg)</td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 [PR] 64/F AML, NIDDM</td>
<td>0.2</td>
<td>C, H</td>
<td>7</td>
<td>(1) AMB (2,000 mg), surgery§ (2) Surgery, itraconazole¶</td>
<td>Relapsed, resolved, survived</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. AMB = amphotericin B; C = culture; H = histology; AML = acute myelogenous leukemia; NIDDM = non-insulin-dependent diabetes mellitus.

* Radical mastoidectomy.
† 600 mg twice daily for 1 week, then 600 mg once daily for 2 weeks.
‡ Mastoidectomy, partial temporal bone debridement.
§ Debridement of pinna.
¶ Incision and drainage of pinna.
* 200 mg/d for 3 months.
vestigators reluctant to study ketoconazole and itraconazole in the management of deep fungal infections in severely immunocompromised patients. Although it is difficult to draw conclusions from the limited published experience with itraconazole for invasive aspergillosis infections [14-17], preliminary observations have been encouraging.

In our patient, who was intolerant of amphotericin B, it was hoped that itraconazole would suppress the infection. There were no signs of persistent otic infection in the 3-month period following itraconazole therapy and prior to the patient's death, which was caused by leukemic relapse. A distinction between suppression and cure of infection could not be made.

This case illustrates two points. First, organisms other than _P. aeruginosa_ may be responsible for invasive otitis externa in the immunocompromised host; this point underscores the importance of obtaining an etiologic diagnosis. Second, our experience provides further support for the use of itraconazole as an alternative to amphotericin B in the management of invasive aspergillosis.

### References