Osteomyelitis of the Base of the Skull Secondary to *Aspergillus*

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Malignant external otitis is a well-characterized entity, known for its insidious and morbid course in immunocompromized patients. Malignant external otitis occurs most commonly in elderly diabetics and is almost uniformly caused by *Pseudomonas aeruginosa*. If not recognized early in the immunocompromized patient, it can lead to extensive skull base osteomyelitis (SBO), with multiple cranial nerve neuropathies and eventual death. In patients presenting with multiple cranial nerve deficits, mortality ranges from 28% to 60%.1

Fungal SBO is rare, and the diagnosis can be delayed because cultures growing fungal pathogens are often interpreted incorrectly as an opportunistic colonization. This may lead to delayed treatment and greater morbidity for the patient.

We present a patient with SBO secondary to *Aspergillus* and review the literature. His presentation was identical to that of pseudomonal necrotizing external otitis and SBO. However, his poor response to antipseudomonal therapy led to an eventual isolation and treatment of invasive aspergillosis.

**CASE REPORT**

A 65-year-old man presented with severe right otalgia and headache associated with a right facial nerve paralysis. He had been treated previously with topical antibiotic/steroid drops and oral ciprofloxacin and reportedly had intermittent improvement of a chronic right-sided otorrhea. However, over a 3-day period, his pain increased, and he awoke the morning before his clinic visit with facial hemiparesis on the right side. The patient denied vertigo but noticed some hearing loss in the right ear.

His past medical history was notable for a history of a cystectomy for bladder cancer and a subsequent chronic reflux pyelonephritis. He had significant renal insufficiency and an arteriovenous shunt in place, but only had to be hemodialyzed once before, during a prior hospitalization. He was unaware of any significant history of diabetes, but had been treated temporarily, in the past, with oral medications for "borderline" high blood sugar.

Physical examination showed a right-sided House-Brackmann grade V facial nerve paresis. No other cranial nerve deficits were present. Otologic examination showed an edematous right external auditory canal filled with copious purulent exudate. The tympanic membrane was completely obscured by edema and a large rest of granulation tissue originating from the anterior portion of the bony-cartilaginous junction of the canal. Results of his audiogram showed bilateral high-frequency sensorineural hearing loss and a right high-frequency air-bone gap.

Culture swabs of the external auditory canal grew multiple organisms, including *P aeruginosa*, which was sensitive to ciprofloxacin, gentamicin, tobramycin, and ticarcillin. Granulation tissue was biopsied and sent for pathology, as well as for fungal, bacterial, and acid-fast studies. The patient's random serum glucose level was 536. He was admitted for intravenous piperacillin and tobramycin as recommended by the Infectious Disease consultant and for serum glucose control. An ophthalmology consultation was obtained and a lateral tarsorrhaphy stitch was placed in the right eye. Fungal stains of the granulation tissue showed occasional septated, bifurcating hyphae, consistent with *Aspergillus*; however, this was felt to be a noninvasive colonization secondary to long-term use of the topical otic preparation. High-resolution computed tomography (HRCT) of the temporal bone showed extensive osseous erosion of the base of the skull, temporal bone, and mandibular condyle consistent with osteomyelitis. The patient's pain decreased dramatically after 1 week of therapy, and the diabetes mellitus was well controlled with insulin administration. However, following 6 weeks of therapy, the patient's improvement seemed to have plateaued, because pain and granulation tissue per-
TABLE 1. Previously Published Reports of Invasive Fungal Skull Base Osteomyelitis

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patient Age</th>
<th>Risk Factor</th>
<th>CN Palsies</th>
<th>Organism</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham et al^4</td>
<td>85</td>
<td>none</td>
<td>7</td>
<td>A fumigatus</td>
<td>AA, AB, M</td>
<td>Osteo cured</td>
</tr>
<tr>
<td>Petrak et al^9</td>
<td>68</td>
<td>AML</td>
<td>7</td>
<td>A fumigatus</td>
<td>AA, AB, M</td>
<td>Osteo cured</td>
</tr>
<tr>
<td>Stanley et al^11</td>
<td>70</td>
<td>COM, COM</td>
<td>none</td>
<td>A fumigatus</td>
<td>AB, M</td>
<td>Osteo cured but died of sepsisemia</td>
</tr>
<tr>
<td>Menachof and Jackler^11</td>
<td>46</td>
<td>AML</td>
<td>7</td>
<td>A flavus</td>
<td>AA, AB, M</td>
<td>Osteo cured but died of leukemia</td>
</tr>
<tr>
<td>Menachof and Jackler^11</td>
<td>82</td>
<td>COM</td>
<td>7, 9, 10, 11, 12</td>
<td>A fumigatus</td>
<td>AA</td>
<td>Osteo cured but died of leukemia</td>
</tr>
<tr>
<td>Bickley et al^12</td>
<td>80</td>
<td>Myelodysplasia</td>
<td>7, 9, 10, 12</td>
<td>Aspergillus species</td>
<td>AA, AB, M</td>
<td>Osteo cured</td>
</tr>
<tr>
<td>Phillips et al^13</td>
<td>64</td>
<td>AML</td>
<td>7</td>
<td>Aspergillus species</td>
<td>AA, AB, I</td>
<td>Osteo cured but died of leukemia</td>
</tr>
<tr>
<td>Strauss and Fine^14</td>
<td>27</td>
<td>AIDS</td>
<td>7</td>
<td>A fumigatus</td>
<td>AB, I, M</td>
<td>Osteo persisted</td>
</tr>
<tr>
<td>Hanna et al^15</td>
<td>61</td>
<td>DM</td>
<td>7</td>
<td>A flavus</td>
<td>AA, AR, M</td>
<td>Osteo cured</td>
</tr>
<tr>
<td>Kountakis et al</td>
<td>65</td>
<td>DM</td>
<td>7</td>
<td>A flavus</td>
<td>AA, AB, M</td>
<td>Osteo cured</td>
</tr>
</tbody>
</table>

Abbreviations: AA, antipseudomonal antibiotics; AB, amphotericin B; AIDS, acquired immunodeficiency syndrome; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CN, cranial nerve; COM, chronic otitis media; DM, diabetes mellitus; I, itraconazole; I&D, incision and drainage; M, mastoidectomy; Osteo, osteomyelitis.

sisted. Repeat cultures of the granulation tissue showed no organisms, and biopsy samples indicated chronic inflammation. Because the patient’s condition failed to improve and purulent material within the middle ear and external auditory canal persisted, a repeat HRCT scan of the temporal bone was performed (Fig 1). Progression of bone destruction was evident, and surgical exploration with biopsy was recommended. A mastoidectomy of the right side with drainage of subtemporal abscess and decompression of the facial nerve were performed. Multiple biopsies were sent from the mastoid, retro pharynx, and subtemporal space. In addition, purulence present in the external auditory canal was recultured. The facial nerve appeared to be nonviable, with granulation tissue enveloping it at the stylomastoid foramen and along its vertical segment. Histopathology showed invasive Aspergillus throughout the temporal bone specimens (Fig 2) and otorrhea cultures grow A flavus. The patient was placed on intravenous amphotericin B, with a goal 2,000 g total dose. There was no evidence of malignancy in the biopsy samples that had been obtained. The patient began to improve rapidly on antifungal therapy. His pain decreased, and the granulation tissue receded completely. His follow-up gallium scan, done 4 weeks after the institution of amphotericin-B, showed decreased overall uptake. Ten months later, he is free of pain and has no evidence of otorrhea or granulation tissue. The patient’s facial nerve function never improved.

DISCUSSION

Fortunately, malignant external otitis is less frequently encountered since the evolution of greater awareness and broad spectrum antibiotics. Nonetheless, once the base of the skull is involved, response to treatment can be poor. Management must be aggressive and long-term. Complete resolution of the infection may take several months. Antimicrobials for SBO should be continued at least until the patient is symptom free and a follow-up gallium scan is negative.

According to Chandler’s classic description in 1968,^2^ P aeruginosa is virtually always the causative organism in SBO. Initial therapy should be directed accordingly; however, it is critical that cultures and biopsies be obtained to confirm the causative organism, as well as rule out an underlying malignancy. As an
elderly diabetic, our patient represented the population most at risk for developing necrotizing external otitis. *P. aeruginosa* appeared on the initial swab of the external canal, as did *Aspergillus*. Both of these opportunistic organisms are known to colonize an excessively moist or traumatized external canal even in the absence of invasive infection.3,4 Despite multiple subsequent biopsies of granulation tissue, we failed to identify either of these two organisms on histopathology, until deeper biopsies were obtained during surgery. It is well-documented that culturing *Pseudomonas*, even in patients with active malignant external otitis, can be difficult.5 It is for this reason that one's hand is often forced to initiate empirical therapy against the most likely offending organism. Because therapy is typically necessary for several weeks to several months to eradicate infection, one may not be alarmed by a very slow improvement on empirical therapy.

Medical treatment is the mainstay of recommended management.5-7 Limited surgery is only advocated in cases that worsen or fail to improve after long-term antibiotics.8 We pursued surgical exploration after 4 weeks of antibiotics provided only limited improvement in our patient’s clinical status. The procedure was performed primarily to obtain further diagnostic information. Once the diagnosis of *Aspergillus* skull base osteomyelitis was made, aggressive medical therapy was instituted.

Our review of the current literature found only nine previous reports of *Aspergillus* causing osteomyelitis of the base of the skull (Table 1).g-15 Eight of 10 patients (including the present case) had risk factors associated with immunosuppression and the most common organism was *A. fumigatus*. Although diabetes mellitus is a common risk factor associated with bacterial malignant otitis externa, it was present in only two patients with fungal SBO. In addition, three patients had chronic otitis media present in the involved ear before developing fungal SBO. Facial nerve palsy was seen in nine of 10 patients, with two patients suffering from multiple cranial nerve palsies. Only one of the cranial nerve palsies improved with treatment even when the skull base osteomyelitis resolved.15

Nine patients were initially treated with antipseudomonal antibiotics unsuccessfully, and one patient was initially treated with amphotericin B. Because of no improvement, nine of 10 patients underwent surgery, which included mastoidectomy in eight patients and incision and drainage in one patient. During the surgical procedures, biopsies and cultures were obtained that indicated the presence of invasive aspergillosis. Once the diagnosis of invasive aspergillosis was made, amphotericin B was added to the treatment regimen. This resulted in improvement of symptoms and osteomyelitis in eight of nine patients. The single patient who was not treated with amphotericin B died of myocardial infarction.
with evidence of persistent osteomyelitis on postmortem histopathologic examination. One patient who was initially treated with amphotericin B had acquired immunodeficiency syndrome (AIDS) and died of central nervous system complications of fungal SBO. Because the pathogen most commonly isolated from patients with SBO is P aeruginosa, otorrhea cultures growing Aspergillus are often dismissed as opportunistic colonization. This occurred in 7 of the 10 reported cases (including the present case) and resulted in delayed institution of antifungal therapy. Although A niger does not appear to cause invasive otitis externa, the presence of A fumigatus or A flavus should alert the physician to pursue further investigation, especially in immunocompromized patients.

Because of the small number of reports of fungal SBO, one can try to extrapolate from the experience with invasive aspergillosis in sinonasal disease to determine optimal therapy for invasive otologic disease. Although hyperbaric oxygen therapy was administered to our patient, compelling evidence exists of its enhancing effects in treating necrotizing otitis externa. From our experience with this case and review of the literature, we are reminded of the importance of obtaining confirmatory cultures, particularly in a patient who fails to respond reasonably to adequate therapy for malignant external otitis. Surgery may be necessary to obtain adequate biopsies and rule out a possible underlying malignant process. Therapy should be continued until serial gallium scans show no nidus of infection.

**CONCLUSION**

1. Immunocompromized and diabetic patients are susceptible to fungal SBO.
2. The most common organisms responsible for fungal SBO are A fumigatus and A flavus.
3. Otorrhea cultures growing A fumigatus and A flavus should not be regarded as opportunistic colonization in patients with SBO without further investigation.
4. Cranial nerve palsies are common in patients with fungal SBO.
5. Biopsies may be necessary to rule out an underlying malignant process or invasive aspergillosis in patients with SBO not responding to antipseudomonal therapy.
6. Treatment consists of amphotericin B for prolonged period of time.

**REFERENCES**