Ototogenic skull base osteomyelitis (SBO) is classically described as an infection of the external auditory canal that invades the base of the skull, often resulting in progressive cranial nerve palsies. This is a disease primarily of elderly persons with diabetes and is associated with substantial morbidity and mortality. The infectious organism in the majority of cases is *Pseudomonas aeruginosa*. We have recently encountered two atypical cases of otogenic SBO that were caused by the fungus *Aspergillus*.

**CASE REPORTS**

**Case 1.** A 46-year-old woman with a longstanding history of chronic middle ear infection underwent induction chemotherapy for acute myelogenous leukemia. Two weeks later, at a time when she was severely leukopenic (WBC = 100), severe otalgia and purulent otorrhea developed. Several days later, a rapid onset complete facial palsy developed. Evaluation, including gallium, technetium, and CT scans, revealed osteomyelitis of the skull base, extending from the mastoid to the lateral wall of the sphenoid sinus. Repeated cultures of the ear drainage failed to yield a bacterial pathogen. *Aspergillus flavus* was noted, but this was thought to be a contaminant. An empirical trial of antipseudomonal therapy was begun. Several weeks later, despite high-dose intravenous tobramycin and ticarcillin, otalgia and otorrhea persisted. Mastoidectomy was undertaken, primarily to secure tissue for diagnostic purposes. Surgical findings included necrosis of the tympanic membrane remnant and both the middle ear and mastoid mucosa. The mastoid bone was softened and avascular.

On histopathologic examination, numerous septated, branching fungal hyphae, consistent with aspergillus, were seen infiltrating both the osseous and soft tissue components of the specimen. A prolonged course of amphotericin B resulted in a dry and pain-free ear. The woman’s complete facial palsy persisted through the time of her death from leukemia 13 months after her initial presentation.

**Case 2.** An 82-year-old man had undergone bilateral radical mastoidectomies in the 1940s after a blast injury. He had experienced intermittent painless otorrhea for many years. During a particularly severe and painful exacerbation of his chronic otitis media, an acute facial palsy developed. CT, gallium, and technetium scans were performed, but revealed no evidence of skull base osteomyelitis. Culture of the ear drainage revealed *Aspergillus fumigatus* and no bacterial pathogens.

After several days of empirical antipseudomonal and gram-positive antibiotic coverage, he was discharged on a regimen of oral antibiotics. Severe otalgia and intermittent otorrhea persisted despite treatment with repeated oral and ototopical antibiotics. Three months after presentation, gallium, technetium, and CT scans were repeated. Once again, no evidence of osteomyelitis was noted. The retrospective diagnosis of Ramsay Hunt syndrome complicated by post-herpetic neuralgia was considered. During frequent follow-up visits, his pain and discharge increased and diminished over the ensuing months. Repeated ear cultures were negative. Three months after his second series of scans, he manifested a 10-day history of voice change. Examination revealed paralysis of the glossopharyngeus, vagus, accessory, and hypoglossal nerves. At this time, both gallium and technetium scans were markedly positive, with uptake involving the entire posterolateral skull base ipsilateral to the cranial palsies (Fig. 1, A and B). CT scan revealed extensive bony destruction in the region of the jugular and hypoglossal foramina (Fig. 2, A and B). Intravenous antipseudomonal antibiotics were re instituted, with partial resolution of otalgia and otorrhea.

Three weeks into this hospitalization, the patient died of a myocardial infarction. Cultures of the otorrhea obtained on admission were initially negative; however, 1 week post mortem, growth of *Aspergillus fumigatus* was evident. Autopsy revealed basilar meningitis and extensive osteomyelitis of the skull base. Histopathologic examination demonstrated the branching, septate fungal hyphae, typical of *aspergillus* species, both in the bone and soft tissue components of the skull base (Fig. 3). Gram stain revealed no other infecting organisms.

**DISCUSSION**

Deep ear pain, purulent otorrhea, and progressive cranial nerve palsies herald the onset of otogenic skull
Fig. 1. Case 2. A, Combined gallium and technetium scan of the head and neck region; lateral view. Arrows denote the area of intense uptake in the temporal bone. B, Combined gallium and technetium scan of the head and neck region; anteroposterior view. Arrows indicate the intense uptake in the temporal bone.

Base osteomyelitis (SBO). The typical clinical setting is "malignant external otitis," in which infection gains access to the skull base via the floor of the external auditory canal. This scenario is most common in elderly persons with diabetes and is almost always caused by Pseudomonas aeruginosa. Unlike most otologic infections, Pseudomonas SBO evolves through anterograde thrombophlebitis and marrow infection rather than involvement of the mucosally lined pneumatic spaces of the temporal bone.
Fig. 2. Case 2. A, Computerized tomography scan of the right temporal bone before the development of skull base osteomyelitis. Note the smooth calcified margins of the jugular foramen (JF) and carotid canal (C). B, Computerized tomography scan in the same patient after the development of skull base osteomyelitis. Note the extensive osseous erosion in the region of the jugular foramen (JF) and carotid canal (C).

Combining our two cases with those in the literature, there are now six cases of *Aspergillus* SBO available for study.\(^5\)\(^6\) There are a number of important differences between fungal SBO and that caused by bacterial pathogens. In four of the six reported cases, the disease originated from the middle ear or mastoid, rather than the ear canal. Longstanding chronic otitis media was present in each of these cases. Immunocompromise associated with leukemia was also prevalent in these patients. Two had acute myelogenous leukemia associated with marked granulocytopenia and a third had chronic lymphocytic leukemia. The remaining three patients had no demonstrable immune impairment, although all were of advanced age. None of the six patients reported to date had diabetes mellitus.

Invasive aspergillus infections have been increasingly recognized as important clinicopathologic entities, especially in immunocompromised patients.\(^9\) There are nearly 30 aspergillus species known to cause invasive infection in man. The most common type is *Aspergillus fumigatus*, as was seen in four of the six otogenic SBO patients. There are several factors that predispose a patient to invasive aspergillosis: (1) immunodeficiency caused by systemic illness, cytotoxic drug therapy, or...
advanced age; (2) a local point of entry for the fungus; and (3) disruption of normal bacterial flora by antimicrobial therapy. Four of the six patients with SBO appear to have been colonized with aspergillus in the middle ear and mastoid resulting from chronic otitis media. When immune deterioration occurred, the opportunistic fungus gained access to the adjacent bone marrow and intravascular spaces. Preceding the onset of SBO, each of the six patients had undergone antibiotic therapy that presumably fostered fungal overgrowth.

The body has two levels of defense against aspergillus invasion. Polymorphonuclear leukocytes (PMN) appear to play a key role in protection against the mycelial form of aspergillus. Macrophages are instrumental in preventing invasion by the conidial morphology. Macrophages appear to constitute the primary barrier to penetration, with PMNs a secondary mechanism. Both of these lines of defense must be breached for invasion to occur. Corticosteroids may suppress the immune response to both the mycelial and conidial forms. At least four of the six patients with fungal SBO had undergone corticosteroid therapy before the diagnosis of invasive aspergillosis. The mechanism of neural paralysis with typical pseudomonas SBO appears to be a bacterial elaboration of a neurotoxin. Aspergillus is also known to produce endotoxins, one of which appears to act upon neural tissue.

The diagnosis of SBO in a patient with a compatible history and physical findings includes nuclear medicine scans as well as computed tomography (CT). Gallium 67 citrate is actively taken up by white blood cells and is localized to areas of inflammation. Technetium 99m methylene diphosphonate is concentrated in osteoblasts and will demonstrate the effects of bony infection and repair. Infections of the ear canal, middle ear, and mastoid that are complicated by osteomyelitis will show significant uptake of both gallium and technetium, whereas infections limited to soft tissue structures will predominantly accumulate gallium. CT scan provides the fine osseous detail needed to map the anatomic extent of SBO. Although technetium is a more sensitive detector of early osteomyelitis, it does not provide much anatomic detail. Once positive, both technetium and CT scans remain so for prolonged periods of time. Gallium scans, by contrast, revert to normal when acute inflammation has resolved. This makes sequential gallium scans useful in determining the endpoint of antibiotic therapy. Magnetic resonance imaging may be useful in delineating involvement of the soft tissues in the infratemporal fossa and nasopharynx.

Identification of the etiologic agent in otogenic SBO may be difficult when the patient is using antibiotic eardrops. If the infecting organism has not previously been identified, all topical and systemic antibiotics are stopped for 2 days and deep ear culture is obtained. In most of the cases, this will permit identification of the offending gram-negative bacillus. The mere presence of an aspergillus species on culture does not necessarily indicate a fungal SBO, because these organisms are ubiquitous in the ear. Suspicion should be heightened when either Aspergillus fumigatus or flavus is identified, as these have proved capable of causing fungal SBO. Aspergillus niger, which is the most common species isolated from the external auditory canal, has not been reported to cause SBO. The definitive diagnosis of in-
vasive aspergillosis requires biopsy to demonstrate the organism within the soft tissues or bone of the skull base. The treatment of SBO requires prolonged antimicrobial therapy, often lasting for months. The selection of an arbitrary duration of therapy, lasting (for example) 6 weeks, is discouraged. Sequential gallium scans should be obtained and therapy halted when substantial reduction or complete elimination of activity has taken place. Scans are usually obtained at monthly intervals. Early cessation of therapy is associated with a high recurrence rate and greater morbidity and mortality. The role of surgery in SBO is both diagnostic and, perhaps, therapeutic. In the patient with nondiagnostic cultures, mastoidectomy may provide material for culture and histologic analysis essential for accurate diagnosis and selection between antibiotic and antifungal therapy. Surgery may also be indicated when disease plateaus or progresses on appropriate antimicrobial therapy.

The drug of choice for invasive aspergillosis is amphotericin B. Use of this drug in high doses early in the course of invasive aspergillosis may be curative, even in some immunosuppressed patients. The usual dosage for amphotericin B or invasive aspergillosis infections is three grams, administered as a daily dose over many weeks. The optimal total dosage and duration of therapy necessary for complete resolution of aspergillus SBO is not known. Azotemia is a serious and potentially fatal side effect of amphotericin B therapy. A rising creatinine level in one of our patients required reduction to 60 mg three times per week. It was not until this patient received a total of 4.6 grams of amphotericin B that her gallium scan "cooled off" and her therapy was terminated. Of the six patients treated for fungal SBO, three have sustained prolonged remission after amphotericin therapy. The improvement in immunologic function that occurs with cessation of chemotherapy may well play a role in these recoveries.

CONCLUSIONS

1. Aspergillus infection of the ear may cause invasive osteomyelitis of the skull base, accompanied by progressive cranial nerve palsies.
2. These infections tend to arise in immunocompromised and/or elderly patients. Unlike pseudomonas infections, there is no strong association with diabetes mellitus.
3. While most otogenic skull base osteomyelitis arises from infection of the external auditory canal, aspergillus tends to invade via the middle ear or mastoid, usually in the setting of longstanding chronic otitis media.
4. Because aspergillus is ubiquitous in the ear, biopsy of infected tissues is necessary to establish the diagnosis of invasive fungal infection.
5. Biopsy of skull base tissues to identify the presence of an invasive fungus is indicated when bacterial cultures of ear drainage are negative or when disease progresses on systemic antipseudomonal therapy.

REFERENCES