Bilateral Otitis Media and Hearing Loss in an Adult

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Bilateral otitis media, an uncommon entity in adults, may represent the initial manifestation of a life-threatening systemic disease. Prompt recognition and treatment of the underlying disease is needed to preserve auditory function and prevent involvement of other organ systems. We present the case of a thirty-four-year-old male with bilateral serous otitis media and progressive hearing loss, which was refractory to antimicrobial therapy and middle ear drainage. A mastoid biopsy revealed necrotizing granulomatous inflammation. The differential diagnosis and probable cause of this unusual finding are discussed.

CASE PRESENTATION

DR. STEPHEN COLODNY (Infectious Disease Fellow): The patient is a 34-year-old white male who presented to the Yale–New Haven Hospital with a two-month history of bilateral ear pain, decreased auditory acuity, and tinnitus. The patient was well until approximately eight weeks prior to admission, when he developed bilateral hearing loss and the sensation of "blockage" in the ears. These symptoms progressed and were accompanied by non-purulent otorrhea, severe tinnitus, intermittent nasal congestion, and occipital headache which radiated to the left superior orbital margin. Four weeks prior to admission, the patient first sought medical attention after he noted blood on an ear swab. Phenoxy methyl penicillin, 500 mg by mouth four times a day was prescribed for presumed otitis media. After two days without relief, therapy was changed to amoxicillin, 250 mg by mouth three times a day. Four days later, therapy was again changed to cefaclor, 250 mg by mouth three times a day, which was continued until admission. One week before admission, a pressure equalization (PE) tube was placed through the patient's left tympanic membrane; the right tympanic membrane had perforated spontaneously. Drainage at the time of PE tube insertion was described as serous. The patient's symptoms did not improve following insertion of the PE tube. A culture of the ear drainage grew a few colonies of coagulase-negative staphylococci, and a throat culture showed a scant growth of Hemophilus influenzae. The patient noted cough productive of some whitish sputum for one week prior to admission, and he felt intermittently warm, although his temperature was never taken. He denied rigors, vertigo, nausea, vomiting, dysuria, hematuria, or hemoptysis.

The patient's past medical history was significant for a partial nasal septoplasty performed three years prior to admission for nasal congestion. Post-operatively the
nasal congestion persisted, requiring chronic use of oxymetazoline hydrochloride nasal spray. One year prior to admission, the patient had an episode of posterior cervical adenopathy which resolved with antibiotic treatment. There was no history of allergies or prior ear infections.

The family history was significant in that his twelve-year-old daughter had recently suffered from "swimmer's ear." There was no family history of tuberculosis. The patient denied recent foreign travel, occupational exposure to known toxins, and insect or animal bites. He is employed as an electrician.

On physical examination the patient was a well-developed white male with obvious bilateral hearing loss. He was afebrile, and other vital signs were normal. Both tonsils were slightly enlarged, but no exudate or erythema was present. Fundoscopic exam was normal. The nasal mucosae were slightly erythematous, but no polyps were visible. The external auditory canals were normal. The right tympanic membrane had a central perforation which was draining serosanguinous fluid. The left tympanic membrane had a PE tube in place, which was surrounded by erythema and was draining some straw-colored fluid. There was neither sinus nor mastoid tenderness. His neck was supple, and a few shotty nodes were palpable in the anterior cervical chains. No other adenopathy was present. The chest was clear to percussion and auscultation. The heart was normal, as were the abdomen and extremities. The neurologic exam was normal except for markedly decreased auditory acuity bilaterally. A Weber test lateralized to the left side.

Laboratory data included normal serum electrolytes, blood urea nitrogen, creatinine, bilirubin, transaminase (SGOT), alkaline phosphatase, prothrombin time, and partial thromboplastin time. The white blood cell count was 9,400 cells/µl, and the hemoglobin and hematocrit were 12.5 g/dl and 36.2 percent, respectively. A Westergren erythrocyte sedimentation rate was 32 mm/hour (normal <20 mm/hour). Chest and sinus X-rays were normal. A computerized tomographic (CT) scan showed a decrease in the mastoid air cells bilaterally and opacification of the middle ears bilaterally. There was no evidence of bony destruction. Audiometry revealed marked, bilateral reduction in both air and bone conduction.

Does anyone in the audience have questions or want additional information at this time?

DR. VINCENT ANDRIOLE (Professor of Medicine and Chief, Infectious Disease Section, Yale Department of Medicine): Was a urinalysis obtained?

DR. COLODNY: A urinalysis was not obtained at the time of admission.

DR. ANDRIOLE: During his previous hospitalization for a partial nasal sepnoplasty, was any tissue submitted to pathology?

DR. COLODNY: No.

DR. FRANK BIA (Associate Professor of Medicine, Infectious Disease Section, Yale Department of Medicine): Did this patient have a family history of diabetes or a history of chronic infections as a child?

DR. COLODNY: No.

DR. GEORGE THORNTON (Clinical Professor of Medicine, Chief of Medicine, Waterbury Hospital): Was there any history of tuberculosis exposure?

DR. COLODNY: The patient gave a history of a distant relative who had tuberculosis, but on closer questioning he had little or no exposure to this person.
DR. BIA: It appears this patient has an acquired disease, rather than delayed presentation of a congenital disease. Based on the information presented, the differential diagnosis must include granulomatous diseases such as Wegener’s granulomatosis and tuberculosis. Other possibilities include sarcoidosis, midline granuloma, syphilis, lymphoproliferative malignancies, and vasculitis, specifically lymphomatoid granulomatosis and allergic granulomatosis of Churg and Strauss [1]. I would like to review his chest X-ray, obtain a urinalysis, specifically looking for hematuria, and repeat the liver function tests. I doubt a bacterial etiology, since the only bacteria isolated was a coagulase-negative staphylococcus species. If this was a bacterial otitis media, one would expect to isolate *S. pneumoniae, H. influenzae*, or *B. catarrhalis*, although the latter two organisms are primarily pathogens in children.

DR. COLODNY: The initial urinalysis revealed many red blood cells in the urine sediment. However, no red blood cells were seen in two subsequent urinalyses. The chest X-ray was reviewed by a radiologist and was normal.

DR. THORNTON: I would still be concerned about tuberculosis. Did he have skin tests placed? *Mycobacterium tuberculosis* is one of the few infectious causes of bilateral otitis media. It is well-described, although uncommon. One of the first cases of extrapulmonary tuberculosis I evaluated occurred in a young boy who had undergone many operations for chronic mastoiditis and chronic otitis media. He finally turned out to have tuberculosis.

DR. COLODNY: A PPD skin test was non-reactive, as were control antigens.

DR. ANDRIOLE: In cases in which *Mycobacterium tuberculosis* involves the mastoid, is the chest X-ray abnormal?

DR. THORNTON: That is a variable finding.

DR. ANDRIOLE: Another consideration would be obstruction of the eustachian tubes due to a nasopharyngeal process. Was this ruled out adequately?

DR. COLODNY: The CT scan included cuts through the nasopharynx and eustachian tubes. No eustachian tube obstruction was evident.

DR. BIA: It appears at this time that a tissue biopsy is needed to make the diagnosis.

DR. COLODNY: The patient underwent biopsies of the nasal mucosa, tympanic membrane, and mastoid. Dr. Heinemann will present the histopathology.

DR. SCOTT HEINEMANN (Resident in Pathology): Biopsy material was obtained from the right tympanic membrane, the right mastoid, and the left nasopharynx. Examination of the tympanic membrane revealed inflammatory tissue containing many histiocytes and eosinophils. The nasal mucosa showed mild chronic inflammation. Sections of mastoid mucosa revealed multiple necrotizing granulomas in a background of inflammation and necrosis (Fig. 1). The granulomas were formed by spindle-shaped histiocytes palisading around the periphery of necrotic foci (Fig. 2). Multinucleated giant cells were present at the periphery of the granulomas and scattered throughout the background (Figs. 1 and 2). Many small- and medium-sized blood vessels had foci of fibrinoid necrosis in their walls (Fig. 3), but a primary vasculitic process was not evident. The remaining infiltrate was composed of histiocytes and lymphocytes with neutrophils clustered in areas of necrosis. Eosinophils were present but not frequent. No malignant or atypical cells were seen. Special tissue stains for bacteria, acid-fast bacilli, and fungi were negative. Routine bacterial cultures grew a single colony of *Propionobacterium acnes*; both mycobacterial and fungal cultures were negative. In
summary, the lesion appears to be an extravascular necrotizing granulomatous process with associated fibrinoid degeneration of blood vessel walls. The possibility of a primary vasculitis cannot be excluded.

A necrotizing granulomatous process involving the upper respiratory tract should immediately suggest Wegener's granulomatosis. Patients with Wegener's granulomatosis can present with upper respiratory and otic symptoms long before pulmonary or renal manifestations of the disease develop [2]. Fienberg reviewed upper respiratory mucosal biopsies obtained during the prodromal phase of Wegener's granulomatosis in
12 patients and found that the combination of focal necrosis, fibrinoid degeneration, palisading granulomas, and giant cells was characteristic [3]. Vascular changes, specifically fibrinoid degeneration or granulomatous vasculitis, were present in eight of the 12 patients. Other retrospective evaluations of mucosal lesions in Wegener’s granulomatosis have demonstrated only nonspecific inflammation [4,5]. These disparate findings may reflect sampling from superficial lesions or differences in histopathologic interpretation.

In conclusion, the histologic findings in this patient are entirely consistent with the early manifestations of Wegener’s granulomatosis. However, in the absence of pulmonary or renal involvement, vasculitis must be present to make a definitive diagnosis of a limited form of Wegener’s granulomatosis. In this patient a primary vasculitis is not definitely present, although the fibrinoid degeneration of blood vessels is very suggestive.

DISCUSSION

The differential diagnosis of granulomatous otitis media includes infectious and non-infectious diseases. Tuberculosis is the most commonly diagnosed infectious granulomatous disease. However, tuberculosis is unlikely in this patient in view of a negative PPD skin test and negative tissue acid-fast stains and mycobacterial cultures. Other mycobacterial and fungal infections are also unlikely for similar reasons. Unusual bacterial infections such as brucellosis and tularemia can elicit a granulomatous response. In addition, a granulomatous response may occur during chronic pyogenic infections. These bacterial etiologies seem improbable since there was no response to several different antibiotics, and tissue gram stains and bacterial cultures were negative. Thus, infectious etiologies are confidently excluded.

The non-infectious granulomatous disease can be divided into neoplastic, vasculitic, connective tissue, foreign body, and idiopathic disorders. Neoplasms of the head and neck, which could produce necrosis and granulomatous inflammation, include malignant midline reticulosis, malignant histiocytosis, lymphoepithelioma, and Hodgkin’s disease. These diseases were excluded by the absence of any malignant or atypical cells in the biopsy specimens. Other granulomatous inflammatory processes which should be considered in addition to Wegener’s granulomatosis include lymphomatoid granulo-
matosis and allergic granulomatosis of Churg and Strauss. Patients with these conditions, however, do not present with symptoms limited to the middle ear. An otic presentation is also atypical for connective tissue diseases such as relapsing polychondritis. Sarcoidosis may have a clinical presentation similar to Wegener's granulomatosis, but the degree of tissue necrosis and the morphology of the giant cells seen in this patient's biopsy are very atypical for sarcoidosis. Similarly, foreign body granulomatous reactions, such as berylliosis, do not cause extensive tissue necrosis and are usually limited to the lung.

In summary, the clinical findings, culture results, and histopathology in this patient are most consistent with Wegener's granulomatosis.

COMMENT

Wegener's granulomatosis is an uncommon disease characterized by necrotizing vasculitis and granulomatous inflammation of the upper and lower respiratory tract and kidneys. Other sites which may be involved include the ears, eyes, skin, joints, and nerves [2]. Otic involvement may be manifest as external otitis, serous or purulent otitis media, cholesteotoma, or mixed sensorineural and conductive hearing loss [1,2,6-10]. Otic disease is not unusual in Wegener's, although it is rarely the only site of involvement. In a recent review of 85 patients with Wegener's granulomatosis, 25 percent had otitis media and 6 percent had hearing loss [2]. Other estimates of the rate of otic disease have ranged from 20–40 percent [4]. Most important, otic disease may be present for weeks to months before pulmonary or renal manifestations appear [4]. In such patients, the significance of the otic findings is often not recognized until life-threatening pulmonary or renal disease develops. Thus, persistent otic disease in an adult warrants a thorough diagnostic evaluation to exclude Wegener's granulomatosis.

The cause of Wegener's granulomatosis is unknown. Recently, DeRemee et al. reported clinical improvement in 11 of 12 patient with Wegener's granulomatosis who were treated with trimethoprim-sulfamethoxazole [10]. This apparent response to antimicrobial therapy led the authors to speculate that the immunologically mediated injury in Wegener's granulomatosis is triggered by an infectious agent. Unfortunately, the criteria used to define clinical improvement in these patients were not clearly specified by the authors. Nevertheless, this intriguing theory and novel therapeutic approach warrant further investigation.

The current treatment of choice for Wegener's granulomatosis is cyclophosphamide in combination with glucocorticoids. Complete disease remission can be induced in over 90 percent of patients with this regimen, and approximately 25 percent of patients can be tapered off therapy without disease relapse [2]. This outcome is a remarkable improvement over the 80–90 percent one-year mortality rate reported before the development of effective therapy [11]. The patient presented in this report was treated initially with prednisone, which produced a rapid improvement in otalgia and auditory acuity. Multiple pulmonary and mediastinal nodules developed, however, necessitating the addition of cyclophosphamide. After the addition of cyclophosphamide, the pulmonary lesions regressed, and no new disease manifestations have appeared.

In summary, Wegener's granulomatosis, an aggressive, idiopathic inflammatory disorder most widely recognized by its renal and pulmonary manifestations, is a well-described cause of otitis media and hearing loss. Otic involvement is found in approximately 25 percent of patients at presentation and develops in up to 40 percent
of patients at some time during the illness. Diagnostic and therapeutic delays may occur when disease manifestations are limited to the upper respiratory tract. This case clearly demonstrates the need for a thorough diagnostic evaluation of persistent otitis media in adults to exclude Wegener's granulomatosis and other progressive systemic diseases.

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