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Original Article

Invasive Fungal Otitis Media in Diabetic Patients: A Case–Based Review

Yuanjun Liu[1], Lin Han[1], Jie Cao[2]

[1]Department of Otorhinolaryngology, Head and Neck Surgery, Peking University, Peking University People's Hospital, Beijing, China
[2]Department of Otorhinolaryngology, Head and Neck Surgery, Capital Medical University, Beijing Friendship Hospital, Beijing, China

ORCID IDs of the authors: Y.L. 0000-0003-0990-1334, L.H. 0000-0002-8865-8039, J.C. 0000-0001-6650-9713.

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BACKGROUND: Invasive fungal otitis media is clinically rare. The clinical features are often atypical in the early stages of the disease, and delayed treatment results in poor outcomes.

METHODS: In this study, we report 2 patients with invasive fungal otitis media with diabetes. The early diagnosis was confirmed by comprehensive methods such as laboratory tests and imaging examinations, and the condition was significantly improved by antifungal drugs and surgical treatment.

RESULTS: By reviewing the literature, we found that invasive fungal infections confined to the middle ear and mastoid were rarely reported, and the diagnosis and treatment were still controversial.

CONCLUSION: In this article, we summarized and evaluated the different diagnoses and treatment methods so as to better diagnose and improve the cure rate in the early stage of invasive fungal infection of the middle ear.

KEYWORDS: Invasive fungal otitis media, middle ear surgery, diagnosis, treatment

INTRODUCTION

Fungal infections of ears are more common in the external auditory canal than in the middle ear,[1] and invasive fungal infections originating from the mastoid and the middle ear are rarely reported. This article reports 2 patients with invasive fungal otitis media who were admitted to our hospital in 2020, and both were clinically cured after surgery combined with drug treatment.

CASE PRESENTATION

Case 1

A 58-year-old man presented with pain in the left mandibular molar 10 months ago, and the pain did not relieve after tooth extraction. Later, the scope of pain gradually expanded to the left ear and maxillofacial region. A few months later, the pus appeared in the left ear, which failed to be treated with anti-infection and tympanic tube insertion treatments. Since the onset of headache with neck pain, he was diagnosed with meningitis after lumbar puncture in other hospitals. The case history revealed type 2 diabetes mellitus for 20 years and diabetic nephropathy for 10 years. Physical examination revealed a large amount of yellow purulent secretions in the left external auditory canal, and the tympanic tube was in place. The white blood cell (WBC) count, neutrophil count and percentage, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin (PCT) all increased in varying degrees during the illness (Figure 1); the following microbial culture of ear secretion was done: *Aspergillus flavus* (++++), *Klebsiella pneumoniae* (++); positive serum galactomannan antigen test (GM test) result (0.84 > 0.5). Computed tomography (CT) scan showed opacification of his left mastoid air cell system and middle ear, as well as extensive bone erosion and destruction of temporomandibular joint, petrosal apex, occipital condyle, and zygoma (Figure 2). Enhanced magnetic resonance (MR) images showed diffuse soft tissue thickening with necrosis in the nasopharynx, left temporomandibular joint, and around zygomatic arch, temporal occipital scalp, widely involving the surrounding structures, considering a high probability of inflammatory lesions. Positron emission tomography scanning ([^{18}F] FDG-PET) showed that the left zygomatic bone, bilateral temporal bones, some skull base bones, and

Corresponding author: Lin Han, e-mail: hanlinpku@163.com

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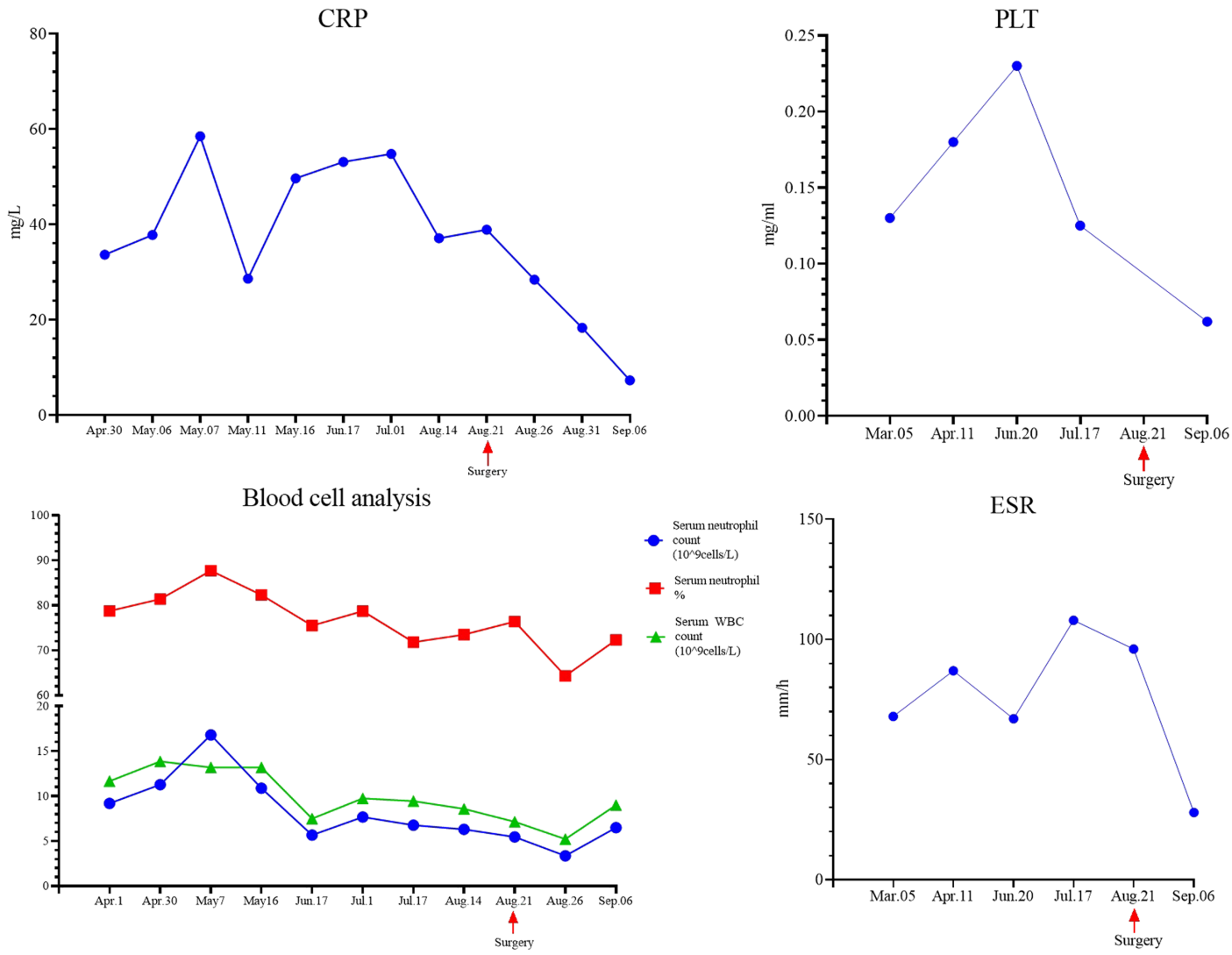

Figure 1. Changes in white blood cell (WBC) count, neutrophil count and percentage, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) at different time points.

cervical vertebrae C2 and C3 presented dot-like foci with increased [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F] FDG) uptake (Figure 3a-c). According to the medical history and examination, the patient was diagnosed with invasive fungal otitis media, with the skull base and cervical spine invaded. Voriconazole (200 mg.q.12 h.po) and amoxicillin potassium clavulanate (1.2 g.q.8 h.iv.) were given as antifungal and antibacterial therapy, and left ear open mastoidectomy and type II tympanoplasty were performed under general anesthesia. During the operation, massive granulation and necrotic bone were seen in the mastoid and tympanic cavity. All suspected necrotic bone was removed until exposure to the fresh incisal edge. The specimens of mastoid and tympanic tissue were taken for examination during the operation. The pathology showed chronic inflammation of mucosa, hyperplasia of fibrous tissue, and a small number of fungal hyphae in some tissues. After the operation, the headache symptoms of the patient were significantly relieved and the neck pain was gradually

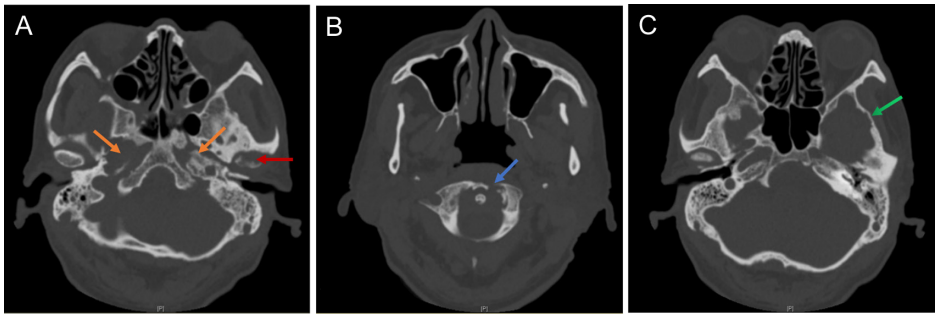

Figure 2. Computer tomography of the temporal bone in case 1, extensive bony destruction of the temporomandibular joint (A, red arrow), petrosal apex (a, orange arrow), occipital condyle (b, blue arrow), and zygoma (c, green arrow).

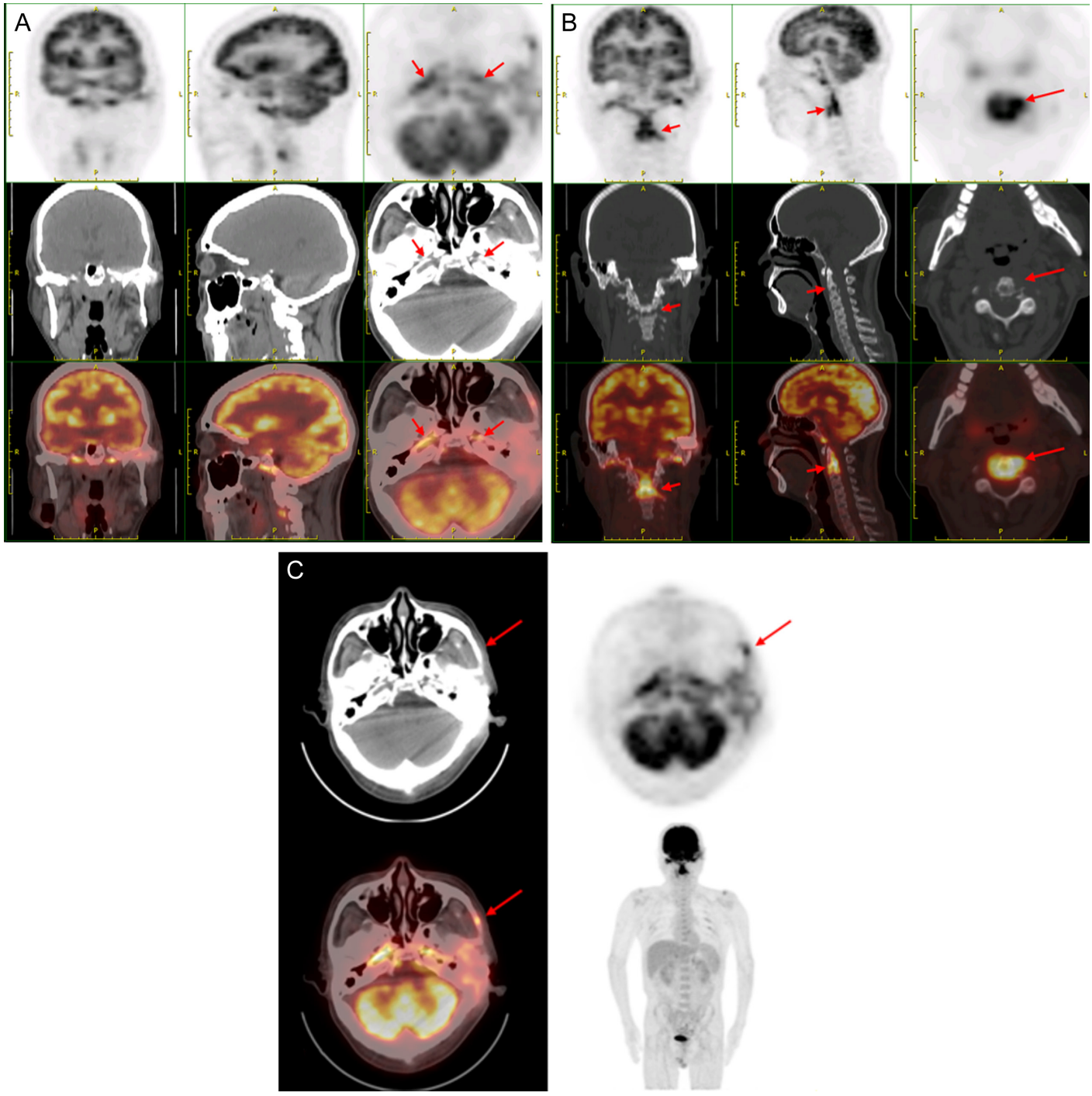

Figure 3. A-C. Positron emission tomography-computed tomography of the patient in case 1. The left zygomatic bone, bilateral temporal bones, part of the skull base, C2, and C3 showed dot-like foci with increased fluoro-2-deoxy-D-glucose uptake (SUVmax: 8.1), and the bilateral distribution was basically symmetrical. The corresponding parts of the computed tomography showed local cortical defects and soft tissue swelling.

relieved. Erythrocyte sedimentation rate and C-reactive protein levels were significantly decreased (Figure 1). The inflammatory indicators gradually decreased to normal levels. Two months after the operation, the left ear was dry.

Case 2

A 58-year-old man presented with a 5-year history of severe hearing loss, chronic otorrhea, otalgia, and ear fullness from both ears. The symptoms could be relieved after antibiotic treatment but recurred periodically. Then, persistent right ear fullness with the pain in the right maxillofacial region appeared, which worsened 1 month ago. He had a 15-year history of T2 diabetes with poor glycemic control. Physical examination revealed swollen right maxillofacial area and bulged posterior wall of the right external auditory canal and the tympanic membrane. The tympanic membrane signs disappeared. Microbial culture of ear secretion resulted in normal flora and positive serum GM test (1.90 > 0.5). B-Mode ultrasonography showed scattered point-like strong echoes on the right maxillofacial region

(clinical swelling area). Mastoid CT showed multiple soft tissue density shadows in bilateral mastoids and tympanic cavity, surrounding auditory ossicles and bone destruction at temporomandibular joint. The left ear open mastoidectomy and type II tympanoplasty were performed in both ears (interval 2 months). The patient was treated with voriconazole (200 mg, q.12 h., iv.) and ceftriaxone sodium (2 g, q.d, iv.). Histopathology revealed fungal hypha in both tympanic tissues. His facial swelling and pain were relieved after the operation, and the ears were dry 3 months after the operation.

DISCUSSION

In recent years, the incidence of invasive aspergillosis (IA) has gradually increased. Invasive aspergillosis occurring in the middle ear is relatively rare, and the entry point of fungal infection is mostly acute or chronic infection of the external ear or middle ear. Long-term local administration of anti-inflammatory drugs and steroids, combined with diabetes or immunodeficiency are the main risk factors for IA in middle ear. We searched the reports of invasive mycotic otitis media with or without complications published in PubMed and EMBASE database using the following keywords: "invasive," "otitis media" or "mastoiditis," and "*Aspergillus.*" The reports exclude some cases that are not mainly caused by middle ear lesions, such as "invasive otitis externa" and "skull base osteomyelitis." A total of 7 cases were included,[2-8] and their demographics, underlying conditions, treatment, and outcome data are listed in Table 1. We found that most cases were administrated with different antibiotics repeatedly until treatment failed before the diagnosis of invasive mycotic otitis media. Diabetes is the most common risk factor for invasive fungal otitis media. Two patients reported repeatedly using various antibiotics for a long time, but the final effect was not good. Besides, 2 diabetic patients had poor long-term glycemic control. When we encountered such patients, the possibility of fungal infection should be considered. By reviewing the literature, it is suggested that early surgical intervention and antifungal treatment are the key points to slow down the progress of the disease and improve the cure rate. The symptoms of the 2 patients we reported were also significantly relieved after the lesions were completely removed by surgery.

The diagnosis of invasive fungal otitis media is often difficult. The traditional diagnostic method is fungal culture of ear secretion, which has the disadvantages of long culture time and low positive rate: We counted 132 patients with chronic suppurative otitis media who were suspected of having fungal infection in our hospital from January 2020 to January 2022. The ear secretions were collected for fungal culture, and 41 cases were positive, with a positive rate of only 31.1%, including 36 cases of Aspergillus (35/41). Usually, histopathological examination is the golden standard for diagnosing IA, but some patients did not undergo surgical intervention in the early stage of the disease, which made it difficult to obtain specimens resulting in misdiagnosis and missing the best opportunity for treatment. An approach using non-invasive markers of fungal infection has been developed for aiding diagnosis: GM is the polysaccharide of *Aspergillus* cell wall. In the process of fungal hyphae invading tissues, the polysaccharide component GM of fungal cell wall is released and is detected in body fluid.[9] European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group have adopted the positive GM enzyme immunoassay as an important standard for

Table 1. Clinical Features of 7 Patients with Invasive Fungal Otitis Media

Case Author (year)	Ag (Year)/ Gender	Disease	Underlying Disease	Species Isolated	Diagnostic Test	Treatment	Results of Treatment
Ajay et al. (2021)	53/M	*Aspergillus* causing chronic suppurative otitis media	Diabetes mellitus	*A.niger*	Lactophenol cotton blue (LPCB)	Clotrimazole+lidocaine (ear drop, 4 weeks)	Recovery
Masahiro et al. (2015)	63/M	Invasive *Aspergillus* mastoiditis	Diabetes mellitus	Unspecified	Serum b-D-glucan + *Aspergillus* antigen test	Mastoidectomy+ventilation tube insertion; voriconazole (300 mg/day, p.o., 12 months)	Recovery
Mona et al. (2014)	67/M	Invasive *Aspergillus* mastoiditis	None	Unspecified	*Aspergillus* galactomannan	Translabyrinthine approach surgical excision; itraconazole (200 mg/day, p.o., 3 months)	Recovery
Renuka et al. (2012)	65/M	Invasive *Aspergillosis* of temporal bone	Diabetes mellitus	*A.flavus*	Biopsy tissue Gomori-Methanamine Silver (GMS) staining	Exploration+ facial nerve decompression; traconazole (200 mg/day)	Recovery
Chao et al. (2011)	35/F	Invasive otomycosis	None	*A.niger*	Unknown	Voriconazole (400 mg/day, i.v., 5day+400 mg/day, p.o., 5days); tympanoplasty	Recovery
KURUVILLA et al. (2006)	59/M	Invasive fungal mastoiditis	Diabetes mellitus	Unspecified	Histopathological examination	Mastoid exploration +mastoidectomy; itraconazole (p.o.)	Improvement
Kwamena et al. (2005)	19/F	Invasive temporal bone mycoses	Systemic lupus erythematosus	*A.fumigatus*	Histological examination+bacteriologic al culture	Ventilation tube insertion+mastoidectomy; Voriconazole (800 mg/day, i.v., 7days+400 mg/day, p.o., 6 weeks)	Recovery

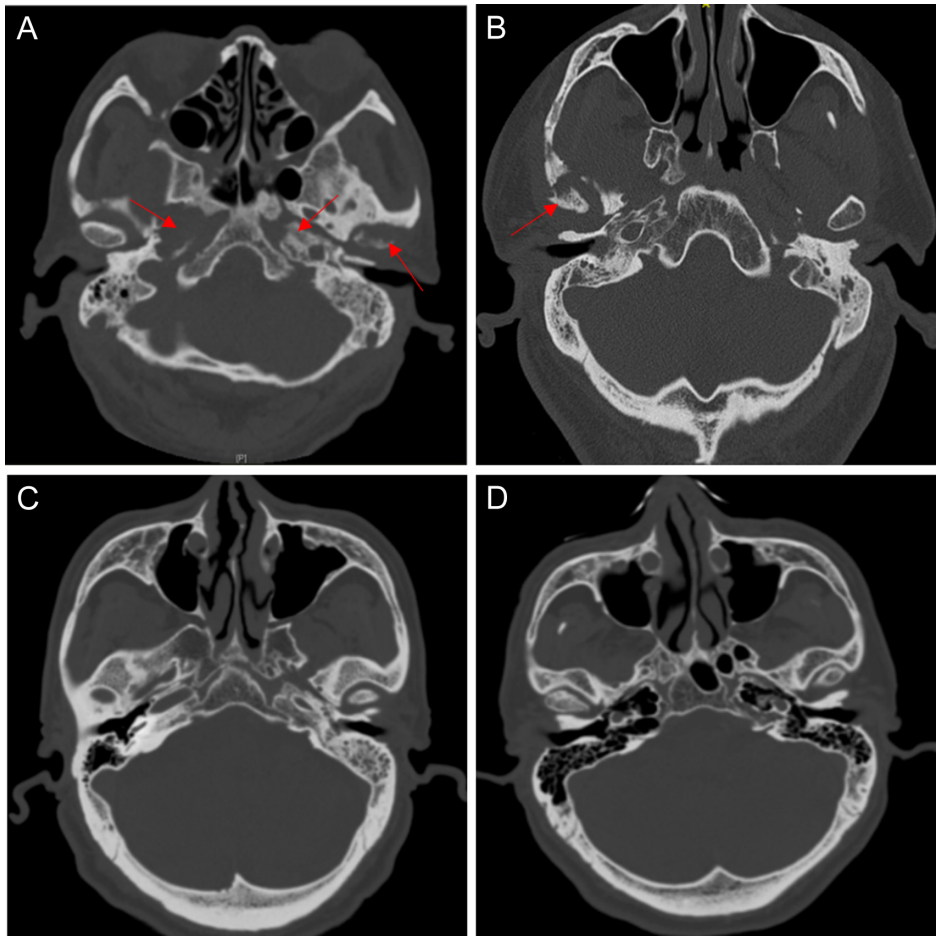

Figure 4. A-D. Computed tomography images of case 1 (A), case 2 (B), chronic suppurative otitis media (C), and normal structures of the temporal bone (D), respectively. Arrows in A and B show obvious bone destruction.

the diagnosis of invasive aspergillosis.[10] A meta-analysis[11] suggested that the GM test was less sensitive in patients with non-neutropenia and those on immune-impacting drugs. However, our 2 cases were retested with a positive GM test, thus confirming the diagnosis. Other study[12] confirmed that (1-3)-β-D-glucan (BDG) levels have a higher diagnostic value for invasive *Aspergillus* or invasive *Candida* infections. We found no relevant studies on the diagnostic sensitivity and specificity of the GM test and the G test for invasive fungal otitis media. Some case reports suggest that the above 2 non-invasive detection methods still have limitations, so the diagnosis of invasive fungal otitis media still needs to be combined with the imaging. Computed tomography is generally considered as the preferred imaging examination to evaluate the degree of bone destruction. We compared the differences in CT images of the temporal bone in patients with normal structures, chronic suppurative otitis media, and invasive fungal otitis media, as shown in Figure 4. Compared to chronic suppurative otitis media, invasive fungal otitis media showed obvious bone erosion and destruction. Magnetic resonance has advantages in identifying soft tissue abnormalities and identifying intracranial extension. In our 2 cases, CT accompanied by varying degrees of bone destruction, and B-ultrasound and MRI indicated soft tissue swelling. Besides, PET-CT used in case 1 can clarify the invasion of bone and soft tissue, which can be regarded as a necessary auxiliary examination method when it is difficult to diagnose invasive fungal infection. In recent years, some prospective studies[13] pointed out that [^{18}F] FDG-PET can monitor the disease evolution of invasive fungal infection and be used for preliminary diagnosis and staging of the disease. Therefore, we recommend that for otitis media with poor long-term infection control, microbial

Table 2. Classification of Fungal Infections of the Ear and Temporal Bone by Chen et al.[14]

Type	Extension of the disease	Characteristics	Treatment
I	Limited otitis externa	Localized infection; no tissue invasion	Cleaning; topical anti-fungal agents
II	Otitis externa with extension into mastoid cavity/ mastoiditis	Bone invasion, granulomatous response, Fibrosis	Topical and systemic anti-fungals; surgery for consideration (if no improvement)
III	Invasive mastoiditis with nerve VII palsy	Aggressive tissue invasion.	Amphotericin B; itraconazole; surgical debridement
IV	Invasive mastoiditis, nerve VII palsy, otogenic skull base osteomyelitis (SBO)	Angioinvasion; mild tissue granulomatous response	Amphotericin B; itraconazole; surgical debridement

culture should be repeated, and the possibility of fungal infection should be considered. If the patient has clinical features such as surrounding tissue pain, bone destruction, and the above imaging features, as well as diabetes and other high-risk factors for IA, invasive fungal infection of the middle ear should be excluded as soon as possible. The diagnosis of invasive fungal otitis media is greatly suspected when fungal hyphae are found in histopathology or fungal culture is positive, and the GM test or G test is positive at the same time.

Chen et al[14] proposed classification of fungal infections of the ear and temporal bone infections on the base of classification of paranasal sinuses mycoses. They divided mycotic infections into 4 types depending on the extension of the inflammation process and the presence of facial nerve palsy including their proper treatment (Table 2). Treatment of invasive fungal disease includes 3 aspects: control of immune status (e.g., regulation of blood glucose), surgical debridement, and antifungal drug therapy. In the limited data we consulted, there were no summary and evaluation of the treatment of invasive middle ear mold infection. Although a study on invasive Aspergillus otitis externa[15] pointed out that the efficacy of surgical debridement in the early stage is not significantly better than the use of antifungal drugs alone, the majority of clinicians still recommend deep surgical biopsy for early diagnosis and surgical debridement in the early stage for patients who do not respond to conventional antifungal therapy.[16,17] Regarding the timing of surgical debridement, Dominik et al[18] mentioned in the treatment of otogenic skull base osteomyelitis caused by invasive fungal infection that if empirical treatment fails, diagnostic radical mastoidectomy should be performed within 2 weeks. The prognosis of invasive fungal otitis media is closely related to the host's own immune status, early diagnosis, and relatively aggressive treatment.

CONCLUSION

Based on the above 2 cases and literature, we believe that an active treatment method should be taken for the first time when sufficient diagnostic evidence is obtained such as thorough surgical debridement and open surgery as early as possible and at the same time, ensuring a sufficient amount of antifungal therapy for a full course of treatment. In the future, we still need to expand the sample size to explore and summarize the optimal diagnosis and treatment of invasive fungal infection limited to the middle ear.

Informed Consent: Written informed consent was obtained from every patient before surgery. No further investigations or additional treatment was needed to write this article and anonymized patient information was published.

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Declaration of Interests: The authors declare that they have no conflict of interest.

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