How to manage the aspergillus skull base osteomyelitis when it is only a probable diagnosis?

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Abstract

Purpose:Aspergillus basicranial infection is a rare disease, often associated with delayed or unproven diagnosis, the management of which is unclear. Methods:We report a probable case of otogenic skull base aspergillus osteomyelitis,review invasive basicranial osteomyelitis,manage and follow up the patient by galactomannan(GM) test and magnetic resonance imaging(MRI) during the treatment of voriconazole. Results:

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Introduction

Fungal skull base osteomyelitis(SBO) is a rare and life-threatening opportunistic infection that predominantly occurs in immunocompromised hosts.However, the diagnosis and therapeutic management are poorly defined. We report a probable case of Aspergillus basicranial infection in a senile diabetic patient. The purpose is to illustrate the importance of fungal serology examination in the diagnosis and therapeutic management.

Case report

An 84-year-old diabetic patient was admitted on January 19, 2021. presenting with right peripheral nerve palsy, intolerable otalgia, hearing loss, dysphagia, hoarseness, and bucking. Three months prior to admission, fungal clumps were found in his right external auditory canal and were treated with triamcinolone acetonide and econazole nitrate cream. Subsequently, he was diagnosed with otitis media and underwent multiple courses of antibiotic and steroid therapy.

Magnetic resonance imaging (MRI) and computed tomography (CT) revealed temporal bone osteomyelitis (Fig. 1). The patient underwent a mastoidectomy and experienced relief from otoalgia. Histological examination of intratemporal tissue showed hyperplastic fibrous tissue with partial hyalinization and calcification; no fungi were detected following methenamine silver staining (Fig. 2). High-throughput sequencing did not yield any reliable positive results. The 1-3-β-D-glucan (BDG) assay and Galactomannan test (GM test) results were 55.45 pg/ml and 1.85.Concurrently,the patient developed a fever with a productive cough,Baumanii

and Candida were isolated from a sputum analysis. Antibiotic treatment, combined with voriconazole, was administered and discontinued after 10 days.

All the symptoms improved, but the patient began experiencing pain in the occiput and left otalgia over the following four months, eventually developing left hearing loss. An enhanced MRI showed skull base osteomyelitis (SBO), small abscesses in the prevertebral space, and enhanced thickened dura (Fig. 3). The values of the BDG assay and GM test increased to 70.7 pg/ml and 4.5, respectively. The patient was diagnosed with basicranial Aspergillus infection and treated with voriconazole. Blood drug concentration and GM test were monitored monthly. The GM test value gradually declined to below 0.5 in 6 months, with clinical and radiological remission and no change in liver and renal function. The patient attempted to change or stop voriconazole, but had to resume the medication due to an increased GM test value. To date, the patient has remained in clinical remission for over 22 months (Fig. 4).

Discussion

Galactomannan is a polysaccharide component of Aspergillus cell walls,and it is released during tissue invasion by Aspergillus hyphae. Beta-D-glucan (BDG) is present in the cell walls of almost all pathogenic fungi, such as Candida, Aspergillus, and several other genera (except Mucorales and Cryptococcus). These two serologic biomarkers have been introduced for the diagnosis of invasive aspergillosis (IA) over the last four decades.

The concentration of serum GM in vivo is determined not only by the rate of production and secretion by the growing fungus but also by the rate of uptake in the bloodstream, as well as the rate of elimination from the circulation. A meta-analysis from Mayo Clinic in 2018 shows that serum GM had a moderate mean sensitivity of 0.71 and high specificity of 0.89. Increasing the cut-off index increased specificity and decreased sensitivity. A serum GM cut-off of 1.0 seems to provide optimal sensitivity of 0.79 and specificity of 0.88[1]. In another study, the sensitivity, in particular, was very heterogeneous at the cut-off values of 0.5, 1.0, and 1.5 optical density index. Currently, due to the large number of false positives, a higher cut-off of 1.0 is proposed[2]. Even so, the GM test is difficult to be considered a gold standard of IA diagnosis.The major sources of circulating BDG are invasive fungal disease, iatrogenic contamination, intestinal translocation, intestinal contents: mycobiome and BDG translocation, hepatic function, bacterial infections, and manufacturing-associated contamination. A meta-analysis showed that the BDG assay in ICU patients at risk for IC or candidemia had a mean sensitivity of 0.81 and mean specificity of 0.60[1]. The negative predictive value of BDG is very high,and it could not identify Aspergillus infection.So the BDG test is clearly less close to being a diagnostic gold standard of invasive fungal disease than the GM testThe limitation of BDG-based tests lies in their inability to identify pathogenic microbial species.

Overall, serologic examination is not considered sufficient for a proven diagnosis. Microscopic examination, culture, and PCR sequencing are also required, according to the recent EORTC/MSG guidelines[3]. Invasive fungal diseases do not have specific symptoms, signs, or imaging findings. Some studies have evaluated the early diagnostic value of serum GM tests combined with computed tomography for invasive pulmonary aspergillosis. The diagnostic and follow-up performance of the two biomarkers were further improved by using them as a combination of tests (parallel analysis improves sensitivity and negative predictive value) or continuous monitoring (serial analysis improves specificity and positive predictive value). In this report, pain appeared earliest and persisted in the progression of the disease; imaging studies provided localization but were not diagnostic. At the early stage of the disease, the BDG assay and GM test showed a slight increase, but the presence of Candida in the sputum examination made us consider them as false positives. Fortunately, we persisted in monitoring the serological changes dynamically and made the decision to treat with voriconazole. Serological tests were sensitive and varied with the severity of the illness and remained valuable for observation even after the disappearance of symptoms and imaging changes.

It is known that treating Aspergillus infections in the central nervous system requires longer periods of drug therapy[4]. When the patient stopped taking the medication, the GM test values began to rise, raising concerns about a possible resurgence of aspergillosis. The current guidelines do not exhaustively describe

these rare clinical cases, and the optimum duration of antifungal treatment and follow-up remains uncertain.

Only about half of all invasive fungal infections are diagnosed pre-death,the value of the GM test is not sensitive and specific enough to be considered a diagnostic gold standard, according to many sources.However, when used it in combination with BDG, CT, and MR imaging and observed dynamically,it demonstrates significant value during the course of Aspergillus infections and therapeutic management.

Abbreviation

SBO:Skull base osteomyelitis

MRI:Magnetic resonance imaging

CT:Computed tomography

BDG:1-3-β-D-glucan assay (β-D-glucan assay)

GM test:Galactomannan test

IA:Invasive aspergillosis

Fig.1

A : Computed tomography(CT) showed right mastoiditis with extensive bony erosions of the temporal bone,osteomyelitis and involvement of the nasopharynx,petrous apex,inferior temporal fossa,Eustachian tube.

B : CT scan showed postoperative surgical cavity 17 days after mastectomy.

Fig.2

A: Otoscopy images show external auditory canal after treatment of triamcinolone acetonide and econazole nitrate cream cream.

B : Images of surgical cavity 5 weeks after mastoidectomy respectively.

C : Histological examination in mastoid mucosa shows hyperplastic fibrous tissue with partial hyalinization and calcification.

D : No fungi were found after methenamine silver staining.

Fig.3

A : On admission

B : 5 month after right mastoidectomy,before voriconazole treatment

C : 11month after right mastoideductomy,6 month after voriconazole treatment

D : 17month after right mastoidectomy,12month after voriconazole treatment

Axial and sagittal post contrast T1-weighted enhanced MR scan around Eustachian tube scan confiffirming SBO extending from the right to the left along cranial base bone, prevertebral space(red arrow) with little abscesses (green arrow),enhancement of the thickened dura(blue arrow)and parapharyngeal tissue.Meningeal enhancement is a evidence of convincing intracranial extension.Images shows the diffuse infective lesions improved by both of mastoidectomy(yellow arrow)and voriconazole(pink arrow),but the extending lesions cannot be prevented by surgery.

Fig.4

The upper limits of GM test and BDG assay are 0.5 and 37.5 (pg/ml) respectively.

The negative result of BDG assay is labelled as 37.5((pg/ml) in Table.

Pain(1: No pain;2:Mild pain,need no painkiller;3: Moderate pain, need painkiller;4:Severe pain,poor effective of painkiller)

O :Operation

V :Treatment with voriconazole

C :Chose voriconazole from another manufacturer

W :Drug withdrawal of voriconazole

R : Retreatment of voriconazole

Declarations

Ethical Considerations :The patient gave their informed consent to participate and consent to publish , and the treatment was approved by the institute's committee on human research.

Competinginterests :The authors declare that they have no conflicts of interest.

Authors'contributions :The data were collected by Zhenwen Zhu and Yating Wang.Xihong Cao analysed all the data,and provided the treatments with Jie Huang.The pathological analysis was done by Lijuan Chen.Qingyu Zhang helped in imaging analysis.

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