

Aspergillosis of the middle ear in 37 immunocompetent patients

Aspergiloza ucha środkowego – analiza 37 pacjentów

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Abstract

Introduction: *Aspergillus* spp. constitute the most common causative agents of fungal otitis. In the literature, only few manuscripts concerning middle ear infection with this pathogen can be found.

Objective: To evaluate a series of 37 consecutive immunocompetent patients with chronic otitis media (COM) co-infected with *Aspergillus* spp.

Material and methods: Detailed analysis of the clinical course, risk factors and results of treatment was performed.

Results: In all cases, persistent ear discharge was a dominant symptom. Two patients were hospitalized and operated on due to the complications of otogenic origin. *A. niger* complex constituted 50% of all isolates, *A. flavus* complex – 29%, while *A. fumigatus* complex – 21%. In 60% of cavities after canal wall-down mastoidectomies, *A. fumigatus* complex was cultured. In all cases with cholesteatoma and granulation, surgical removal of the lesions (during tympanomastoidectomy procedures) was performed. In all patients treated by closed technique, voriconazole was administered just after initial microbiological confirmation of conidial fungi in microscopic examination. In patients after canal wall-down tympanomastoidectomies, regular cleansing of mastoid cavities followed by topical boric acid was the first-line and effective treatment method.

Conclusions: Surgery accompanied and followed by systemic antifungal therapy seems to be the best treatment option in the middle ear aspergillosis. In unstable canal wall down mastoid cavities infected with *Aspergillus* spp., regular cleansing and boric acid are an effective treatment choice.

Key words: *Aspergillus*, aspergillosis, fungal otitis, middle ear infection, voriconazole.

Streszczenie

Wprowadzenie: *Aspergillus* spp. to jeden z najczęstszych patogenów wywołujących grzybicze zapalenie ucha. W piśmiennictwie dostępne są tylko nieliczne publikacje dotyczące infekcji ucha środkowego o takiej etiologii.

Cel pracy: Analiza 37 immunokompetentnych pacjentów z przewlekłym zapaleniem ucha środkowego (COM), zakażonych *Aspergillus* spp.

Materiał i metody: Dokonano szczegółowej analizy przebiegu klinicznego, czynników ryzyka i wyników leczenia.

Wyniki: We wszystkich przypadkach dominującym objawem był uporczywy wyciek z ucha. Dwóch chorych było hospitalizowanych i operowanych z powodu powikłań usznopochodnych. *A. niger* stanowił 50% wszystkich izolatów, *A. flavus* – 29%, a *A. fumigatus* – 21%. U 60% pacjentów operowanych techniką otwartą wyhodowano *A. fumigatus*. We wszystkich przypadkach COM z perlakiem i ziarniną zapalną przeprowadzono operację ucha środkowego z usunięciem patologicznych zmian. U wszystkich chorych leczonych techniką zamkniętą włączono systemowo worykonazol. Pacjentów po operacjach radykalnych uszu skutecznie leczono kwasem bornym stosowanym miejscowo.



Wnioski: Najlepszą opcją terapii aspergilozy ucha środkowego jest leczenie operacyjne oraz worykonazol. W przypadku otomykozy jam po technikach otwartych o tej etiologii skuteczny schemat terapeutyczny stanowi ich regularne oczyszczanie z mas grzybiczych oraz miejscowe stosowanie kwasu borowego.

Słowa kluczowe: *Aspergillus*, aspergiloza, otomykoza, zakażenie ucha środkowego, worykonazol.

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Introduction

Aspergillus spp., together with *Candida* spp., are the most common causative agents of fungal otitis [1, 2]. It is still controversial whether fungi are the true pathogens or rather a result of the compromised immune system after the bacterial infection [3]. In fact, most of the otomycosis cases are related to a prolonged topical antibiotic and steroid use. Other causative factors of fungal otitis include humid climate, immunodeficiency syndromes, diabetes and history of prior otologic procedures [2, 3]. Most patients with external otitis require only local treatment – otic drops or creams together with mechanical debridement [4]. However, if the infection is localized in the middle ear, systemic antifungal treatment and surgical procedures are very often needed [5].

Objective

The study aimed to analyze a series of 37 patients with chronic otitis media (COM) and *Aspergillus* spp. middle ear infection treated in our Department in 2014–2020. Clinical course, risk factors and results of treatment were evaluated.

Material and methods

The prospective analysis of 37 consecutive patients with chronic otitis media of *Aspergillus* spp. origin treated in our Department in 2014–2020 was conducted. In the analyzed period of time 589 ear swabs were taken for microbiological testing in patients with COM altogether (276 in post-operative time).

In the study group the following details were estimated: symptoms of the disease, prior local/systemic treatment, history of ear surgeries, general history including additional diseases (diabetes, allergies, immunodeficiency syndromes), epidemiological data like age and gender. They were correlated with the mycological and treatment results.

In all cases middle ear discharge, granulomatous tissue or fungal hyphae were collected (with cotton swabs or sterile forceps using a sterilized otoscope to prevent contact with the external auditory canal): intraoperatively from middle ear spaces or after middle ear surgery from the tympanic membrane perforations/mastoid

cavities (after canal wall down tympanoplasties) in an outpatient department. The specimens were inoculated onto Sabouraud medium and incubated at 37°C for 24 h and at 25°C for the next 7–14 days until the growth was obtained. *Aspergillus* spp. were identified and differentiated by microscopic characteristics and colony morphology. In the study period we did not have the possibility to use more advanced diagnostic methods (including current identification gold standard, that is the analysis of the nucleotide sequence of the partial BTUB gene or MALDI-TOF MS with an adequate reference spectra library).

The paper was prepared in accordance with the ethical standards of the Institutional Review Board (approval protocol number KB-1315/18) and with the Declaration of Helsinki (1964, amended most recently in 2008) of the World Medical Association.

Results

Patient characteristics

In the study group there were 22 men and 15 women at a median age of 56 years (age range: 15–74 years). All patients suffered from different forms of COM. In that number 26 patients were diagnosed with cholesteatoma, 6 with granulation, while 5 patients presented central perforation with purulent discharge. Thirty two patients have been operated before, including 17 more than once. All patients had a history of prolonged topical antibiotic and steroid use. In 15 patients *Aspergillus* spp. was cultured from the cavities after canal wall-down mastoidectomies. In all patients persistent discharge from the ear (unresponsive to empiric antibacterial local treatment) was a dominant symptom. Two patients were hospitalized and operated on due to the complications of otogenic origin (mastoiditis and meningitis in the course of cholesteatoma, respectively). Two patients with COM with granulation suffered from diabetes and one patient with COM with cholesteatoma had polytrauma before. There were no patients with diagnosed immunodeficiency syndromes in the analyzed group.

Mycological results

Most cultures were monomicrobial. *Aspergillus* spp. was isolated in 56 specimens taken from 37 patients.



A. niger complex constituted 50% of all isolates, *A. flavus complex* – 29%, while *A. fumigatus complex* – 21%. In the probes with granulation and in cholesteatomas the strains of *A. niger complex* dominated (64% and 49%, respectively) while in otitis media with perforation – *A. flavus complex* (60%) (Table 1). In most cavities after canal wall-down mastoidectomies (60%) *A. fumigatus complex* was isolated. In 2 patients with diabetes, *Pseudomonas aeruginosa* was additionally cultured. Susceptibility testing was not routinely performed (all cases requiring systemic antifungal treatment were “locally invasive”, potentially life-threatening and responded well to administered treatment as recommended in the literature [4]).

Treatment results

Treatment schemes were dependent on the COM type (Table 1). In all patients after canal wall-down mastoidectomies (open cavities), local treatment with 3% solution of boric acid (6–8 drops twice a day every 12 hours) and regular debridement of the cavities (twice a week) until microbiological clearance of the swabs (range: 21–36 days) was administered. In all cases with cholesteatoma and granulation, surgical removal of the lesions (during tympanomastoidectomy procedures) was performed. In all patients treated by closed technique (15 patients), due to the higher potential risk of intracranial complications and inability to control middle ear spaces during follow-up visits (closed cavities), just after initial microbiological confirmation of conidial fungi in microscopic assessment, voriconazole was administered: 400 mg twice a day (intravenously) for 7 days as a loading dose and 200 mg (orally) twice

a day as a maintenance dose for 3–8 weeks (median: 29 days); control swabs were taken every 2 weeks (range: 12–18 days). Four patients with COM with granulation required prolonged antifungal treatment (median time: 42 days); in all of these cases pathologic inflammatory granulation was located in spaces which are difficult to debride (below the facial nerve canal, in the region of stapes or in the hypotympanum recess), in 3 cases *A. niger complex*, while in 1 – *A. flavus complex* were cultured. Two patients operated on due to the complications of otogenic origin recovered after surgery with cholesteatoma removal and 5-week intravenous voriconazole treatment. In all patients with central perforations, local treatment with boric acid was ineffective and had to be converted to systemic (oral) voriconazole (median time: 27 days). In 2 patients with diabetes and *Pseudomonas aeruginosa*, ciprofloxacin (500 mg twice a day for 2 weeks) was additionally used. All patients had favorable outcome (microbiological and clinical) and remain asymptomatic (follow up time: median 32 months, range: 12–52 months).

Discussion

Otomycosis is a relatively common problem. In most cases it is localized in the external auditory canal and presents as an accumulation of typical hyphae or thick, fibrinous debris [5, 6]. In comparison, not too much data related to fungal infections of the middle ear spaces can be found. They usually occur in immunocompromised patients and, if untreated, can lead to serious complications [7, 8].

We present a series of immunocompetent patients with aspergillosis of the middle ear in whom the clini-

Table 1. Mycological results and treatment schemes in different COM groups

Form of COM	Number of patients/number of isolates with <i>Aspergillus</i> spp.	Pathogens (number of isolates)	Treatment method	Treatment time
COM with cholesteatoma	26/37	<i>A. niger complex</i> (18) <i>A. flavus complex</i> (10) <i>A. fumigatus complex</i> (9)	1) tympanomastoidectomy: CWU – 11 patients, CWD – 15 patients + 2a) systemic voriconazole – in all patients after CWU technique 2b) regular cleansing + boric acid in patients after CWD technique	Range: 3–5 weeks CWU: median 31 days CWD: median 26 days
COM with granulation	6/14	<i>A. niger complex</i> (9) <i>A. flavus complex</i> (3) <i>A. fumigatus complex</i> (2)	1) tympanomastoidectomy: CWU – 6 patients + 2) systemic voriconazole	Range: 4–8 weeks Median: 34 days
COM with central perforation	5/5	<i>A. flavus complex</i> (3) <i>A. niger complex</i> (1) <i>A. fumigatus complex</i> (1)	1) boric acid – ineffective 2) systemic voriconazole	Boric acid – 14 days Voriconazole: median time 27 days

COM – chronic otitis media, CWU – canal wall up, CWD – canal wall down.



cal presentation of the infection was (excluding 2 cases with extra- and intracranial complication) rather mild and manifested as a purulent discharge from the ear. Eighty six percent of patients have been operated before, which, probably together with the prolonged topical antibiotic use prior to the surgical procedure, was the potential causative factor of the infection.

In the analyzed group, *A. niger complex* was found to be the most frequent (50%) isolate. In most publications concerning external otitis of *Aspergillus* spp. origin, it is reported as the most common species as well [3, 9, 10]. *A. fumigatus complex* is described as the second most prevalent etiological factor of otomycosis [3, 11]. However, in our population *A. flavus complex* dominated. It can probably be explained by the conidia size of the second mentioned pathogen (which are longer and facilitate adhesion to the epithelium lining middle ear spaces) and its higher virulence described in animal models. *A. flavus complex* is described as typical for infections with granulomatous inflammation [12]. In our group *A. niger complex* dominated.

Treatment schemes in aspergillosis of the middle ear are not well defined. Most articles assess the efficacy of topical or systemic drugs in the eradication of that pathogen from the external auditory canal [6, 9, 11, 13]. In the analyzed group only patients after canal wall-down mastoidectomies can be compared to that group. However, they significantly differ from typical otomycosis cases. As presented in the results, in 60% of probes taken from patients after this type of surgical procedure, *A. fumigatus complex* was identified and not *A. niger complex* like in most cases affecting the external auditory canal. Moreover, in Poland the only local antifungal drug registered in the ear is clotrimazole, which is not effective in otomycosis of *Aspergillus* spp. origin. Fortunately, in all patients after canal wall down procedures, regular cleansing of mastoid cavities followed by topical boric acid (as recommended in the literature in noninvasive *Aspergillus* otitis externa [4]), was effective and systemic treatment was not needed.

Not too much data concerning treatment of localized aspergillosis of the middle ear can be found in the literature. Ayçiçek *et al.* [14] evaluated the effectiveness of caspofungin and voriconazole in the treatment of experimental *Aspergillus* otitis media in the rabbit model. They were found as effective as amphotericin B and itraconazole. Arakawa *et al.* [15] examined the effect of intratympanic application of 10% solution of efinaconazole (a new triazole antifungal agent developed for the topical treatment of fungal infections of the nails) in the guinea pig ear. Unfortunately, the results of the experiment showed that it caused significant middle ear inflammation and severe hearing impairment. Tiwari *et al.* [16] presented a case of bilateral chronic suppurative otitis media of *Aspergillus terreus* which responded well to topical ketoconazole ther-

apy. In our opinion, all cases of middle ear aspergillosis in patients treated by means of closed techniques, due to the high risk of intratemporal and intracranial complications, should be considered as “locally invasive” so requiring systemic antifungal treatment (preferably with voriconazole according to the recommendations [4]). In our series, in all patients after canal wall-up techniques (closed cavities), voriconazole was administered. Amphotericin B was not used due to its high toxicity.

Middle ear is very often described as another paranasal sinus with its natural opening formed by the Eustachian tube. Based upon that the analysis of the most recent treatment recommendations in sinonasal tract aspergillosis should be presented. Rupa *et al.* [17] concluded that surgery followed by itraconazole or voriconazole for stage 1 (resectable sinonasal disease) and 2 (additional spread to the orbit/palate) disease and voriconazole for stage 3 (extensive) disease is recommended for a good outcome in chronic granulomatous fungal sinusitis. Amphotericin B is not recommended as the first-line therapy in such cases. Gupta and Gupta [18] analyzed the results of a postgraduate institute management protocol for invasive *Aspergillus flavus* sinusitis. They recommend surgical debridement followed by oral itraconazole in limited disease and by amphotericin B and itraconazole in extensive cases. Hachem *et al.* [19] studied the response to treatment in 39 neutropenic patients with invasive *Aspergillus* sinusitis. They found a significantly better outcome in the subgroup that underwent sinus surgery in addition to antifungal therapy than in the remaining control patients who received antifungal therapy alone. Based on our series, surgery accompanied and followed by antifungal therapy seems to be the best treatment option also in cases with COM with cholesteatoma and granulation.

In summary, we are aware of limitations of our study (small size and heterogenous character of the samples, the risk of low statistical power correlations) so we interpret our data and state conclusions very carefully. Nevertheless, as aspergillosis of the middle ear is not sufficiently explored, we think that the results of our research may be interesting and useful for many ENT clinicians and otosurgeons.

Conclusions

Aspergillosis of the middle ear should be considered in the differential diagnosis of the discharge in patients after tympanomastoidectomy procedures, especially those who are unresponsive to appropriate antibacterial therapy. *A. niger complex* is the most common isolate in such cases. Surgery accompanied and followed by systemic antifungal therapy seems to be the best treatment option in the middle ear aspergillosis. In unstable canal wall down mastoid cavities infected with *Aspergillus*



spp., regular cleansing and boric acid are the effective treatment method.

Conflict of interest

The authors declare no conflict of interest.

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