Case report

Beware of covert enemies: *Candida orthopsilosis* malignant otitis externa with base of the skull osteomyelitis, a case report and review of literature

Junais Koleri\textsuperscript{a,}*\textsuperscript{,}, Ahmad Al Bishawi\textsuperscript{a}, Israa' Al-Sheikh\textsuperscript{b}, Salman Qureshi\textsuperscript{c}, Muna AlMaslamani\textsuperscript{d}, Hamad Abdelhadi\textsuperscript{d}

\textsuperscript{a} Department of Infectious Diseases, Communicable Diseases Centre, Hamad Medical Corporation, Qatar
\textsuperscript{b} Department of Internal Medicine, Hamad Medical Corporation, Qatar
\textsuperscript{c} Department of Neuroradiology, Hamad Medical Corporation, Qatar

\textbf{A R T I C L E  I N F O}

\textbf{Article history:}
Received 6 February 2021
Received in revised form 25 April 2021
Accepted 16 May 2021

\textbf{Keywords:}
Malignant otitis externa
MOE
*Candida orthopsilosis*
Osteomyelitis

\textbf{A B S T R A C T}

\textbf{Background:} Malignant otitis externa (MOE) is a serious infection of the external auditory canal that is frequently associated with skull base osteomyelitis (SBO) as well as secondary neurological sequelae. Patients with poorly controlled diabetes mellitus or immunosuppression are at increased risk of developing such critical infection for multiple local and systemic factors. While most cases are secondary to bacterial infections particularly *Pseudomonas aeruginosa*, fungal infections are also occasionally encountered, often associated with delayed diagnosis and high morbidity and mortality.

\textbf{Case report:} We report a case of a 63 years old man with uncontrolled diabetes mellitus who presented with symptoms and signs of MOE, supported by radiological assessments. The patient was treated presumptively with a prolonged course of antibiotics without clinical improvement, coupled with progression of radiological findings and significant disease extension. Reassessment with biopsies and tissue cultures from external auditory meatus, tempo-mandibular bone, as well as base of the skull grew *Candida orthopsilosis*. The patient received induction treatment with high dose liposomal amphotericin followed by fluconazole to control disease progression and complications.

\textbf{Conclusion:} *Candida* MOE with secondary skull base osteomyelitis is rare and difficult to diagnose with no clear guidance on assessment and management. Clinicians should be aware of the unusual presentations where microbiological and histopathological evaluations are essential for proper management.

\textcopyright{} 2021 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Case report

A 63 years old man presented to our emergency department with a right sided headache and vertigo of one week duration along with right sided decreased hearing. There was no ear discharge. Review of systems were unremarkable. The past medical history was significant for a long-standing type 2 diabetes mellitus with secondary complications of retinopathy, dyslipidemia, and systemic hypertension. Drug history included insulin in addition to linagliptin, perindopril, and rosuvastatin. The patient has no history of smoking or alcohol consumption. Family history included diabetes mellitus and hypertension.

Vital signs were within normal limits. Physical examination was unremarkable apart from partial left sixth cranial nerve palsy with no associated nystagmus or other cerebellar signs. Local examination of the ears, nose, and throat showed no significant tenderness, color change, or pre or postauricular swelling in affected ear. Tympanic membranes were intact. Neck and head examination revealed no associated swellings or palpable lymph nodes, and the temporomandibular joint were normal.

Initial tests showed WBC of $8.8 \times 10^{3}$/L, C-reactive protein of 15.3 mg/L, HbA1C of 7.2%, normal kidney function tests, and a negative HIV serology. Radiological assessment with CT head (Fig. 1) demonstrated thickening of the external auditory canal and middle ear with an ill-defined soft tissue mass pacifying the right mastoid air cells cavity. Subsequent MRI (Fig. 2 and Fig. 3) showed an extensive diffuse multi-compartmental enhancement with bone involvement suggestive of osteomyelitis.

A provisional diagnosis of MOE with SBO was made and the patient was commenced presumptively on antipseudomonal
therapy in the form of parenteral then high dose oral ciprofloxacin therapy at 750 mg BID.

After 10 weeks of discharge, the patient represented with progression of symptoms complaining of worsening headache, dizziness, and double vision. Local examination showed swelling of the right ear canal and intact tympanic membrane with no accompanying discharge. In the view of disease progression while on treatment, PET-CT (Fig. 4) was arranged to rule out potential underlying neoplasms; but was furthermore supportive of an underlying infectious process. Subsequently, multiple microbiological and histological samples from the right ear canal, bone biopsies of the temporomandibular joint and soft tissues from the base of the skull demonstrated no evidence of malignancy or granulomas while extended culture yielded yeast eventually identified as Candida orthopsilosis matched from multiple sites. It was sensitive to amphotericin B (MIC 0.5 μg/mL) and fluconazole (MIC 0.5 μg/mL).

The patient was treated with two weeks induction course of liposomal amphotericin B (5 mg/Kg) followed by oral fluconazole (400 mg daily for a planned 6 months duration). Despite favorable initial response with the disappearance of the 6th nerve palsy, the patient had subsequent relapse with recurrent emergency visits and hospital admissions for worsening dizziness and vomiting. MRI was repeated and revealed persistent disease with increase in surrounding pachymeningeal enhancement. Accordingly, reinduction course of Amphotericin was considered followed by extended higher dose of fluconazole therapy of 800 mg daily scheduled for a prolonged duration of 12 months. During which, follow up MRI was repeated twice in 8 weeks interval, but showed no significant
New text content...
Candida parapsilosis MOE despite prolonged management with amphotericin B and flucytosine along with extensive surgery Table 1 [13].

From available limited evidence, following diagnosis of Candida MOE, prolonged antifungal therapy is warranted taking into consideration the associated SBO and potential central nervous system (CNS) involvement. Ideally, antifungal management should be guided by appropriate susceptibilities as well as bone and CNS penetration. While there are good supporting evidence for CNS penetration for amphotericin, flucytosine and azoles, there are limited data for echinocandins [16,17]. The IDSA recommendations for candida osteoarticular infection is surgical debridement, followed by lipid formulation amphotericin B or echinocandins for 2 weeks followed by a prolonged course of oral fluconazole for 6–12 months [18]. there is no specific mention of for fungal MOE or SBO in IDSA guidelines. Notably, surgery is no longer the mainstay of care for MOE except for bone biopsy and culture [8]. However, patients with more advanced disease may require debridement [19]. Our patient required prolonged treatment. He improved symptomatically and in terms of Vth nerve palsy, however radiologically remained stable disease.

Conclusion

We present a rare case of fungal MOE leading to skull base osteomyelitis caused by Candida orthopsilosis which was diagnosed on aggressive investigation following failure to respond to initial antimicrobial therapy. We advocate that if there is disease progression in spite of antibiotic therapy, one should promptly evaluate for alternative pathology including fungal infections, verification of which necessitates microbiological and histopathological confirmation. Despite prolonged appropriate antifungal therapy, substantial morbidity and mortality has to be expected. To the best of our knowledge, this is the first case of Candida orthopsilosis MOE and skull base osteomyelitis case to be reported.

Conflict of interest

No conflicts of interest.

Sources of funding

Hamad medical corporation.

Consent

Consent obtained from patient for case report publication

Ethical approval

Obtained from institutional ethical board.

Author contribution

Dr Junais Koleri – review of literature, collecting data, images, manuscript preparation
Dr Ahmed Bishawi – manuscript preparation
Dr Isra al shekh- review of literature

Dr Hamad abel hadi – review of literature, case preparation and analysis
Dr Salaman Qureshi – interpreting radiology, images
Dr Muna maslamani- manuscript preparation, guidance

Compliance with ethical standards

Ethics approval and patients’ consent was obtained for the publication of this case reports and all accompanying images. Permission was obtained to publish the case reports from institutional review board which is in line with international standards.

References

[1] Lucente FE, Parisier SC, James R, Chandler: “Malignant external otitis.” (Laryngoscope. 1968;78:1257-1294). Laryngoscope 1996;106(7):805–7.
[2] Rubin J, Yu VL. Malignant external otitis: insights into pathogenesis, clinical manifestations, diagnosis, and therapy. Am J Med 1988;85(3):391–8.
[3] Weinroth SE, Schessell D, Tuazon CU. Malignant otitis externa in AIDS patients: case report and review of the literature. Ear Nose Throat J 1994;73(10) 772–4, 777–778.
[4] Cohen Atsmon S, Brenner A, Roth Y. Diabetes in the practice of otolaryngology. Diabetes Metab Syndr: Clin Res Rev. 2019;13(2):1141–50.
[5] Chandler JR. Malignant external otitis and osteomyelitis of the base of the skull. Am J Otol 1989;10(2):108–10.
[6] Mami N, Sudhoff H, Rajagopal S, Mollat D, Axon PR. Cranial nerve involvement in malignant external otitis: implications for clinical outcome. Laryngoscope 2007;117(5):907–10.
[7] Soudry E, Hamzany Y, Preis M, Joshua B, Hadar T, Nageris Bl. Malignant external otitis: analysis of severe cases. Otolaryngol–Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg 2011;144(5):758–62.
[8] Pichon M, Joly V, Argy N, Houze S, Bretagne S, Alanio A, et al. Aspergillus flavus malignant external otitis in a diabetic patient: case report and literature review. Infection 2020;48(2):193–203.
[9] Hamzany Y, Soudry E, Preis M, Hadar T, Hilly O, Bishara J, et al. Fungal malignant external otitis. J Infect 2011;62(3):226–31.
[10] Bae WK, Lee KS, Park JW, Bae EH, Ma SK, Kim NH, et al. A case of malignant otitis externa caused by Candida glabrata in a patient receiving haemodialysis. Scand J Infect Dis 2007;39(4):370–2.
[11] Bowles PF, Perkins V, Schechter E. Fungal malignant otitis externa. BMJ Case Rep 2017. [cited 2021 Apr 2]; 2017. Available from: https://www.ncbi.nlm.nih. gov/pmc/articles/PMC5372270/.
[12] Krishnamoorthy M, Orhanan N, Hassan NEB, Hitam SB. Candida Skull Base osteomyelitis: a case report and literature review. Acta Medica (Hadrec Kralove) 2020;63(2):82–5.
[13] Lancaster J, Alderson DJ, McCormick M. Non-pseudomonal malignant otitis externa and jugular foramen syndrome secondary to cyclosporin-induced hypertrichosis in a diabetic renal transplant patient. J Laryngol Otol 2000;114 (3):366–9.
[14] Lullo AMD, Russo C, Grimaldi G, Capriglione P, Conteane E, Vecchio W del, et al. Skull base fungal osteomyelitis: a case report and review of the literature. Ear Nose Throat J 2020, doi:http://dx.doi.org/10.1177/0145561320936006 [cited 2020 Nov 24]; Available from:.
[15] Chaudhary HA, Ibrahim WH, Yousef Z, Abuheker IV, Kartha A. Fungal malignant otitis externa involves a cascade of complications culminating in pseudoaneurysm of internal maxillary artery: a case report. Am J Case Rep 2019;21(20):562–6.
[16] Andes D. Optimizing antifungal choice and administration. Curr Med Res Opin 2013;29(Suppl 4):13–8.
[17] Chen Y-C, Lin Y-H, Chen K-W, Liu J, Teng H-J, Li S-Y. Molecular epidemiology and antifungal susceptibility of Candida parapsilosis sensu stricto, Candida orthopsilosis, and Candida metapsilosis in Taiwan. Diagn Microbiol Infect Dis 2010;68(3):284–92.
[18] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of america. Clin Infect Dis 2016;62 (4):e1–e50.
[19] MIÖN M, BOVO R, MARCHESE-RAGONA R, MARTINI A. Outcome predictors of treatment effectiveness for fungal malignant external otitis: a systematic review. Acta OtoLaryngolog Ital 2015;35(3):307–13.