Medical Mycology Case Reports 36 (2022) 23–26

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Rhino-orbital entomophthoramycosis in pediatric patients: Report of two cases

Javier Ordoñez-Ortega [a], Ana María Borbolla-Pertierra [b], Yolotl Sánchez-Carrillo [a], María de los Ángeles Costta-Michuy [a], Mónica Mirabal-García [c], Marlen Luengas-Bautista [c], Deborah Palacios-Reyes [a,*]

[a] Infectious Disease Department at Instituto Nacional de Pediatría, Mexico City, Mexico
[b] Ophthalmology Division at Instituto Nacional de Pediatría, Mexico City, Mexico
[c] Microbiology Laboratory at Instituto Nacional de Pediatría, Mexico City, Mexico

ARTICLE INFO

Keywords:
Entomophthorales
Pediatric cases
Atypical disease
Rhino-orbital
Coenocytic hyphae

ABSTRACT

Here we present two cases of entomophthoramycosis in young children, these were the first cases ever diagnosed at our center. Both cases represented a diagnostic and treatment challenge. Surgical treatment was key in the management of both patients. Even though atypical disease was encountered, clinical response was obtained after surgical excision and antifungal treatment for a few months.

1. Introduction

Entomophthorales are fungi that infect insects (entomophthoramycosis: from the Greek language translated as "insect destroyer") and also can be found colonizing soils rich with decaying vegetation and organic matter, almost exclusively in regions with tropical and subtropical climates [1,2]. These fungi can cause infection in mammals, so far only the genus *Conidiobolus* and *Basidiobolus* have been reported as human pathogens [1,2]. They usually cause localized chronic subcutaneous infections. *Conidiobolus* typically affects rhino-facial structures leading to important deformity whereas *Basidiobolus* causes infection in limbs, thorax and back.

Even though this mycosis affects principally immunocompetent adults principally related with exposure to high inoculum inocula during agricultural activities, cases affecting infants and children have been described. Diagnosis can be challenging in pediatric patients because it is a rare entity that requires the presence of histopathologic features and culture growth to differentiate from other infections including other fungi. Here we present the first two pediatric cases of entomophthoramycosis ever diagnosed in our center.

2. Case series

2.1. Case 1

A 19-month-old male from Zacapuato, in Guerrero, Mexico (tropical climate) who begins with epiphora, erythema in the right eye (day 0). On day +4 topical treatment with unspecified eye drops was started with no improvement. On day +5 swelling in both eyelids appeared, so he was admitted in a local hospital (day +8) and started with parenteral antibiotics (ceftriaxone and clindamycin). The patient presented with low grade fever and the swelling of both eyelids progressed, so an intracranial computed tomography (CT) was performed (day +11) showing a mass in the anterior-medial part of the right orbit. He was referred to our center with a preliminary diagnosis of orbital sarcoma on day +13. Antibiotic therapy with vancomycin and ceftriaxone was initiated, and biopsy was performed on day +16. Histopathology showed broad hyphae within an inflammatory infiltrate that consisted of eosinophils and neutrophils (Fig. 1). On day +19 antifungal treatment was added with liposomal amphotericin B (L-AmB) at 5mg/kg/day due to a high suspicion of mucormycosis. Culture was obtained in a second biopsy performed on day +20 and direct microscopy stained with potassium hydroxide (KOH) at 20% showed broad hyaline pauciseptated hyphae. On day +23 after incubation at 30 °C in Sabouraud dextrose

* Corresponding author.
E-mail address: palacios.deborah@gmail.com (D. Palacios-Reyes).

https://doi.org/10.1016/j.mmcr.2022.03.003
Received 16 December 2021; Received in revised form 26 January 2022; Accepted 2 March 2022
Available online 7 March 2022

agar (SDA), powdery, creased white colonies were evident, and microscopy displayed hyphae and conidia with prominent papillae. Three weeks later (day +45) zygospores were present (Fig. 1). The strain was sent to the Microbiology Laboratory of *Universidad Autónoma de Nuevo León* (UANL) where sequencing of the D1/D2 region was performed. The strain had an 89.47% identity with *Conidiobolus* spp. (RCEF4924, GenBank: KP218521) and 87.58% with *C. incongruus*.

On day +24, with the preliminary results of culture, trimethoprim/sulfametoxazol (TMP/SMX) at 10mg/kg/day was added to L-AmB. On day +28 the patient underwent debulking surgery with resection of the remaining mass. Adjuvant treatment with hyperbaric oxygen was started on day +30 and kept during two weeks. Treatment with L-AmB was completed for 45 days and TMP/SMX for 20 days. Due to clinical improvement, the patient was discharged on day +45 to complete treatment with oral itraconazole at 10mg/kg/day for four months. A six-month follow-up CT scan showed an important decrease of inflammation and the patient remained with no visual or eye movement impairment.

2.2. Case 2

A three-year-old boy who lived in Poza Rica, in Veracruz, Mexico (tropical climate). On day 0 he presented with swelling and pain of the right lower eyelid. On day +10 he had purulent discharge from the right lower eyelid, so topical antibiotic and oral dicloxacillin were indicated by a primary care physician who also performed a surgical incision. On day +11 through +20 the swelling and pain worsened, so the family sought medical attention at our center. He was admitted on day +22, physical exam showed proptosis with important bipalpebral edema and erythema, therefore it was not possible to assess eye movements. Blood work-up showed leukocytosis and thrombocytosis. Brain MRI was performed on day +25, T2/Flair sequence revealed a mass that spared the eyeball and optic nerve, extending through inferior and medial soft tissue in the middle and anterior orbit, without involvement of paranasal sinuses (Fig. 2). Because of high suspicion of neoplastic etiology, a surgical resection was performed on day +30. Direct microscopy of biopsy stained with KOH at 20% showed coenocytic hyaline hyphae, and histopathology on day +34 revealed the presence of thick pauciseptate hyphae with *Splendore-Höeppli* phenomenon (Fig. 2). Culture was negative after four weeks of incubation. With pathology preliminary results (day +34), L-AmB was started at 5mg/kg/day along with TMP/SMX at 10mg/kg/day and methylprednisolone at 0.7mg/kg/day. After five weeks, treatment with L-AmB and TMP/SMX ended (day +69), and itraconazole was started at 10mg/kg/day as ambulatory treatment and continued for four months. Steroid treatment was prolonged for four weeks followed by dose-reduction. Follow-up evaluation at seven months showed edema and erythema of the right lower eyelid, with difficulty to assess visual acuity. MRI findings were concordant with relapse of edema, so itraconazole and steroid treatment were restarted and continued for eight weeks with dosage-reduction after four weeks of prednisone. Follow-up at 15 months showed improvement with no impairment of eye movements and better visual acuity.

3. Discussion

Even though Entomophthorales are ubiquitous fungi found in soils

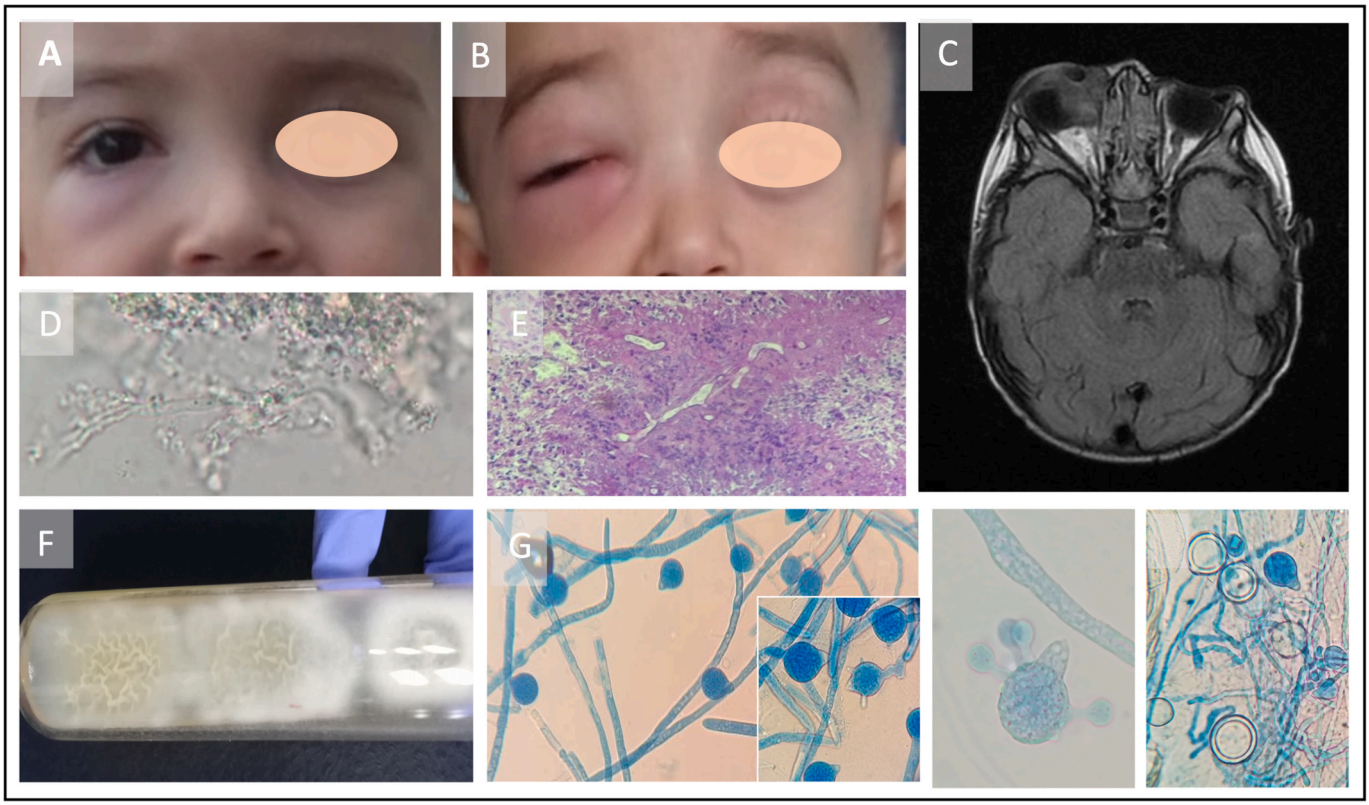

Fig. 1. Case 1. Images (A) and (B) show the evolution of the case through 22 days from the onset of the disease. (C) Brain MRI axial T2/Flair showing a right extraconal orbital mass, with pre and postseptal, medial and inferior location with areas of central necrosis, infiltrating the papyraceous lamina and extending to the ipsilateral lacrimal duct, with displacement, compression, and molding of the eyeball. (D) Direct microscopy of biopsied tissue with hyaline macrosiphonate hypha without septa, with intracytoplasmic granules, and in (F) Splendore-Höeppli phenomenon in PAS staining. (G) SDA after 3 days of incubation at 30 °C with folded, glabrous, beige colonies, with scarce and short mycelia. (H) Direct microscopy of colony with lactophenol blue stain, displaying primary conidia with pointed papillae, (I) also some primary conidia with the presence of replicative secondary conidia. (J) After 3 weeks of incubation zygospores were found suggesting *C. incongruus* as the etiology. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

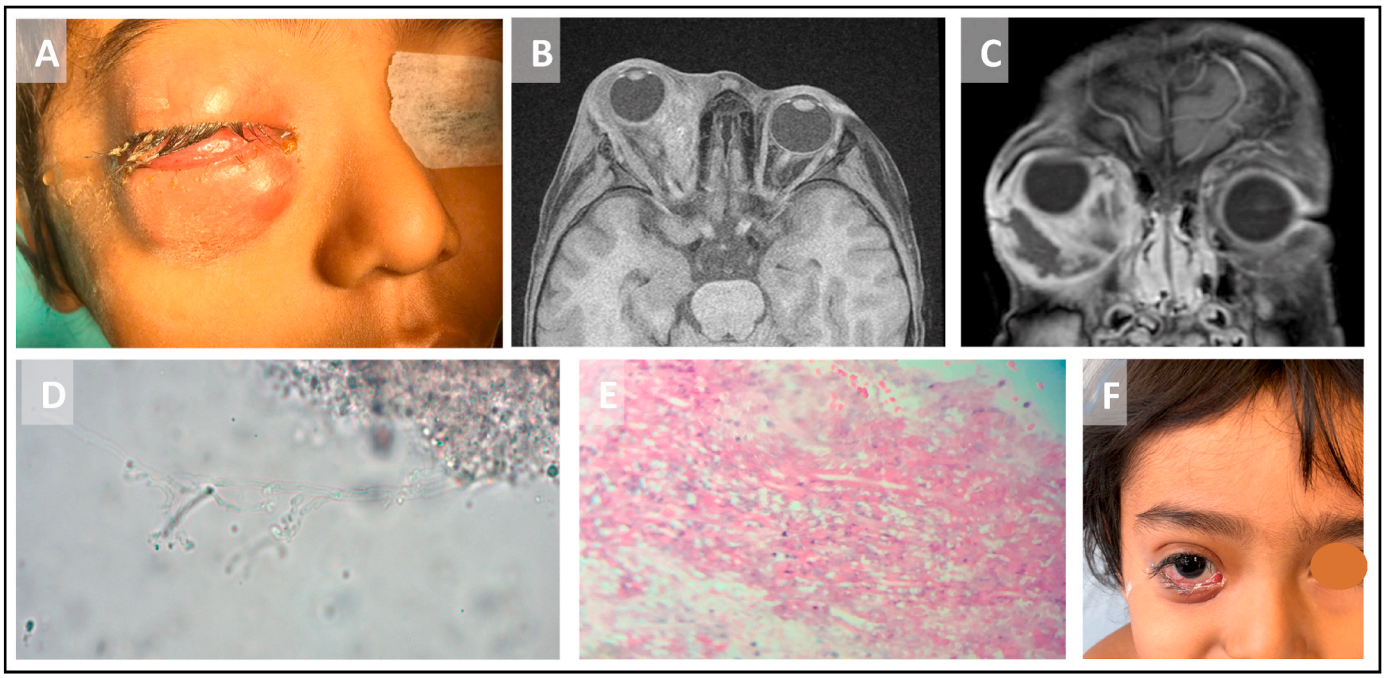

Fig. 2. Case 2. (A) Clinical picture taken during surgical procedure in our center, six weeks since symptoms started. Right eye with proptosis, limiting palpebral opening, and conjunctival chemosis. Brain and orbital MRI: (B) axial FAST SPGR and (C) coronal FAST SPGR FS + C with extra-conal infiltrative mass that compresses, deforms, and causes proptosis of the eyeball. (D) Direct microscopy of biopsied orbital tissue with potassium hydroxide (KOH) at 20% showing broad, hyaline pauciseptated hyphae. (E) biopsy stained with hematoxylin/eosin (HE) showing hyphae surrounded by an important eosinophilic infiltrate known as Splendore-Höeppli phenomenon. (F) Clinical image of patient before hospital discharge, after 5 weeks of antifungal treatment and surgical excision.

from tropical and subtropical regions, infections in pediatric patients are considered rare. For entomophthoramycosis, direct inoculation in exposed or damaged skin or mucosa has been proposed as the main infecting mechanism, some authors also propose inhalation of fungal spores or propagules, and insect bites [2].

Blumentrath et al. proposed a classification for rhinoentomophthoromycosis in atypical, early, intermediate, and late disease [3]. The definition for atypical disease was previously used by Choon et al. to name involvement of facial structures other than nose and maxillary sinuses or non-facial tissues [4]. The more recent definition for atypical disease includes involvement of the orbit, central nervous system (CNS), bones, visceral organs, and/or lymph nodes with a time lapsed of less than 11 months. In a meta-analysis performed by Blumentrath, atypical disease was more frequently presented at younger age and in immunocompromised patients [3]. Clinical characteristics of atypical disease were orbital cellulitis, the presence of fever, headache, vision impairment and limitation in eye movements [3]. So far, most published pediatric cases of entomophthoramycosis, specifically conidiobolomycosis, could be catalogued as atypical disease [5–8]. In a case report by Lithander et al., a 5-month-old female with pre-septal cellulitis and involvement of left lacrimal sac was treated with multiple topical and systemic antibiotics for two months with no improvement. Finally, biopsy revealed hyphae and culture was positive for *C. coronatus*. Treatment was stared with fluconazole with no improvement, so it was replaced for deoxycholate formulation of AmB (D-AmB). Excision of granulomatous lesion was necessary to achieve improvement as well as hyperbaric oxygen therapy [5]. A second case, published by Temple et al. of an 18-month-old girl who presented with induration and erythema of the left epicantal region, fever, and no improvement after antibiotic therapy. The progression of symptoms led to a biopsy of the lesion where fungal hyphae were found. D-AmB was started but a week after, the patient required endoscopic surgery to remove the mass. D-AmB was injected directly in the lesion and systemic steroid treatment was added. Later, treatment was changed to itraconazole. In this case disease relapsed after antifungal treatment and radical resection of the left eye was needed [6]. In 2011, Pornpanich et al. reported another pediatric case with similar clinical evolution. Treatment with D-AmB for four weeks followed by itraconazole for two months was stablished [7]. Immunologic work up was performed in all cases mentioned, including the ones from our center, with no evidence of immunity inborn errors (IIE) [5–7].

As shown in the two cases we presented, diagnosis for entomophthoramycosis is challenging, especially when atypical disease is encountered. As with most fungal infections, direct microscopy, culture, and histopathology are crucial for establishing diagnosis. The Splendore-Höeppli phenomenon consists of an eosinophilic reaction triggered by the presence of the invading hyphae [1]. This feature is not exclusive of entomophthoralean fungi and was initially described in schistosomiasis. It can also be found to a lesser extent in mucormycosis [9], but the presence of infarction and angioinvasion should lead towards this diagnosis rather than entomophthoramycosis [1,9].

Important to consider differential diagnoses with other tropical infections, as well as other fungal infections (mucormycosis). The presence of coenocytic hyphae in tissue samples should always raise the suspicion of mucormycosis, which requires aggressive surgical and antifungal treatment. Nevertheless, important features can help differentiate entomophthoramycota from mucormycota [1,2]. Time of onset is usually shorter for mucormycosis compared to entomophthoramycosis, even in pediatric patients [8]. Entomophthorales do not usually generate angioinvasion as Mucorales do, and rarely develop invasive disease in immunocompetent individuals. Mucorales are known to be opportunistic fungal agents which main predisposing factor is neutropenia and a ketoacidotic state [1,8].

So far, there are no treatment guidelines established for the management of entomophthoramycosis. Surgery combined with antifungals appears to be the most effective treatment strategy. In a retrospective study performed by Varguese et al. of 22 cases of adult patients with rhinofacial conidiobolomycosis, antifungal susceptibility test was performed in nine isolates, all with high MIC values for all azoles (itraconazole, voriconazole and posaconazole) and two for AmB. The lowest

MICs were for cotrimoxazole [10,11]. Previous authors have stated high MICs for azoles and AmB but with no clinical correlation. Clinical efficacy of itraconazole is reported in 73% and 22% for AmB [1]. Treatment using drug combinations like AmB with itraconazole or cotrimoxazole, or potassium iodine with itraconazole have proven to be effective [1, 12]. In the cases presented we decided on combination of antifungal treatment, as well as extensive surgical management, because of the advanced stage at diagnosis and atypical presentation.

The use of hyperbaric oxygen therapy was available for Case 1 after debulking surgery was performed. Hyperbaric oxygen therapy (HBOT) has been reported as adjunctive treatment for former zygomycosis since the 1970s. Pressurized hyperoxygenation leads to augment tissue oxygenation and specifically in mycoses, HBOT has been proved to increase antifungal action of AmB. It has been used as adjunctive therapy in mycosis that require surgical treatment or with involvement of deep tissues and necrosis [13]. For Case 2 the use of HBOT was not available.

4. Conclusion

These cases represented a diagnostic and therapeutic challenge at our center. Even though these are considered rare mycoses we must consider them in the differential diagnosis of rhino-facial, pre-septal and orbital cellulitis in children, specially where there is no improvement with conventional treatment.

Ethical Form

None of the authors has conflict of interests. Written consent has been obtained from the legal guardians of the patients whose cases are presented in this paper.

The statements on funding, conflict of interest and consent need to be submitted via our Ethical Form that can be downloaded from the submission site www.ees.elsevier.com/mmcr. **Please note that your manuscript will not be considered for publication until the signed Ethical Form**.

Declaration of competing interest

Please declare any financial or personal interests that might be potentially viewed to influence the work presented. Interests could include consultancies, honoraria, patent ownership or other. If there are none state ‘there are none.’

Acknowledgements

Mauricio Rojas chief of Pathology Department at *Instituto Nacional de Pediatría*.

Rogelio Treviño-Rangel Clinical Microbiologist Researcher at *Facultad de Medicina, Universidad Autónoma de Nuevo León (UANL)*

Gloria González González chief of the Microbiology Laboratory at *UANL*. Professor Alexandro Bonidaz from Dermatology Service and Mycology Department, Hospital General de México.

References

[1] R. Vilela, L. Mendoza, Human pathogenic Entomophthorales, Clin. Microbiol. Rev. 31 (4) (2018 Aug 29), e00014-18, https://doi.org/10.1128/CMR.00014-18. PMID: 30158298; PMCID: PMC6148186.

[2] N. Shaikh, K.A. Hussain, R. Petraitiene, A.N. Schuetz, T.J. Walsh, Entomophthoramycosis: a neglected tropical mycosis, Clin. Microbiol. Infect. 22 (8) (2016 Aug) 688–694, https://doi.org/10.1016/j.cmi.2016.04.005. Epub 2016 Apr 19. PMID: 27109491.

[3] C.G. Blumentrath, M.P. Grobusch, P.B. Matsiégui, F. Pahlke, R. Zoleko-Manego, S. Nzenze-Aféne, B. Mabicka, M. Sanguinetti, P.G. Kremsner, F. Schaumburg, Classification of rhinoentomophthoromycosis into atypical, early, intermediate, and late disease: a proposal, PLoS Neglected Trop. Dis. 9 (10) (2015 Oct 1), e0003984, https://doi.org/10.1371/journal.pntd.0003984. PMID: 26426120; PMCID: PMC4591341.

[4] S.E. Choon, J. Kang, R.C. Neafie, B. Ragsdale, M. Klassen-Fischer, J.A. Carlson, Conidiobolomycosis in a young Malaysian woman showing chronic localized fibrosing leukocytoclastic vasculitis: a case report and meta-analysis focusing on clinicopathologic and therapeutic correlations with outcome, Am. J. Dermatopathol. 34 (5) (2012 Jul) 511–522, https://doi.org/10.1097/DAD.0b013e31823db5c1. PMID: 22728716.

[5] J. Lithander, A. Louon, E. Worthing, A. Ganesh, Y.M. Al-Lawatia, A. Elamin, D. K. Sankhla, A.R. Al-Juma, Orbital entomophthoramycosis in an infant: recovery following surgical debridement, combination antifungal therapy and use of hyperbaric oxygen, Br. J. Ophthalmol. 85 (3) (2001 Mar) 374–375, https://doi.org/10.1136/bjo.85.3.371d. PMID: 11277105; PMCID: PMC1723885.

[6] M.E. Temple, M.T. Brady, K.I. Koranyi, M.C. Nahata, Periorbital cellulitis secondary to Conidiobolus incongruus, Pharmacotherapy 21 (3) (2001 Mar) 351–354, https://doi.org/10.1592/phco.21.3.351.34210. PMID: 11253859.

[7] K. Pornpanich, M. Uiprasertkul, P. Luemsamran, B. Jantharaworamet, S. Vangveeravong, Entomophthoramycosis: a rare fungal orbital infection presenting with dacryocystitis, Orbit 30 (1) (2011 Jan) 21–23, https://doi.org/10.3109/01676830.2010.535640. PMID: 21281074.

[8] D. Palacios-Reyes, A. Bonifaz, Conidiobolomycosis in pediatric patients, Curr. Fungal Infect. Rep. 14 (2020) 203–208, https://doi.org/10.1007/s12281-020-00401-7, 2020.

[9] O.A. Cornely, A. Alastruey-Izquierdo, D. Arenz, S.C.A. Chen, E. Dannaoui, B. Hochhegger, M. Hoenigl, H.E. Jensen, K. Lagrou, R.E. Lewis, S.C. Mellinghoff, M. Mer, Z.D. Pana, D. Seidel, D.C. Sheppard, R. Wahba, M. Akova, A. Alanio, A.M. S. Al-Hatmi, S. Arikan-Akdagli, H. Badali, R. Ben-Ami, A. Bonifaz, S. Bretagne, E. Castagnola, M. Chayakulkeeree, A.L. Colombo, D.E. Corzo-León, L. Drgona, A. H. Groll, J. Guinea, C.P. Heussel, A.S. Ibrahim, S.S. Kanj, N. Klimko, M. Lackner, F. Lamoth, F. Lanternier, C. Lass-Floerl, D.G. Lee, T. Lehrnbecher, B.E. Lmimouni, M. Mares, G. Maschmeyer, J.F. Meis, J. Meletiadis, C.O. Morrissey, M. Nucci, R. Oladele, L. Pagano, A. Pasqualotto, A. Patel, Z. Racil, M. Richardson, E. Roilides, M. Ruhnke, S. Seyedmousavi, N. Sidharthan, N. Singh, J. Sinko, A. Skiada, M. Slavin, R. Soman, B. Spellberg, W. Steinbach, B.H. Tan, A.J. Ullmann, J. J. Vehreschild, M.J.G.T. Vehreschild, T.J. Walsh, P.L. White, N.P. Wiederhold, T. Zaoutis, A. Chakrabarti, Mucormycosis ECMM MSG Global Guideline Writing Group, Global guideline for the diagnosis and management of mucormycosis: an initiative of the European confederation of medical Mycology in cooperation with the mycoses study group education and research consortium, Lancet Infect. Dis. 19 (12) (2019 Dec) e405–e421, https://doi.org/10.1016/S1473-3099(19)30312-3. Epub 2019 Nov 5. PMID: 31699664; PMCID: PMC8559573.

[10] L. Varghese, R. Kurien, R. Diana Sahni, A. Manesh, L. Mary Cherian, D. Peter, D. Dayanand, J. Sarojini Michael, M. Thomas, V. Rupa, S. Pulimood, G. M. Varghese, Rhinofacial conidiobolomycosis: clinical and microbiological characterisation and shift in the management of a rare disease, Mycoses 64 (8) (2021 Aug) 882–889, https://doi.org/10.1111/myc.13294. Epub 2021 May 9. PMID: 33915007.

[11] A.B. Wankhade, P. Patro, R.D. Arora, N.M. Nagarkar, Nasofacial rhinoentomophthoramycosis: a report of two cases from Central India, J. Oral Maxillofac. Pathol. 24 (2020) S124–S127.

[12] M. Gupta, T. Narang, R.J. Kaur, A. Manhas, U.N. Saikia, S. Dogra, A prospective case series evaluating efficacy and safety of combination of itraconazole and potassium iodide in rhinofacial conidiobolomycosis, Int. J. Dermatol. 55 (2) (2016 Feb) 208–214, https://doi.org/10.1111/ijd.12966. Epub 2015 Jul 31. PMID: 26234812.

[13] A. Tragiannidis, A.H. Groll, Hyperbaric oxygen therapy and other adjunctive treatments for zygomycosis, Clin. Microbiol. Infect. 15 (SUPPL. 5) (2009) 82–86, https://doi.org/10.1111/j.1469-0691.2009.02986.x.