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Cerebral phaeohyphomycosis caused by *Alternaria* spp.: A case report

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ABSTRACT

Phaeohyphomycosis is a group of infections caused by pigmented, black, dematiaceous fungi and is responsible for cutaneous, superficial and deep mycoses, disseminated infection and brain abscesses. The primary agents involved include *Alternaria* spp., *Exophiala* spp. and *Cladophialophora* spp. Invasive systemic presentation is rare and in most cases is associated with immunosuppression; for this reason, reported cases of *Alternaria* spp. infection are scarce. This report describes the case of a 66-year-old man with a history of renal transplantation from a cadaveric donor 1 year ago, which was considered as the primary risk factor. The characteristics of the infection, procedures performed, microbiological findings and treatment provided are described.

1. Introduction

The term 'phaeohyphomycosis' (derived from the Greek phaios 'black' or 'dark' and mykes 'fungi'), which was introduced by Ajello et al [1], refers to human infections caused by pigmented filamentous fungi. In 1996, Rinaldi established a list of the aetiological agents involved, totalling 57 genera and 104 species [2]. In recent years, the list has increased to include more than 70 genera and 130 species. Some are limited to the corneal layer and subcutaneous cellular tissue, whereas others are neurotropic or disseminate [3,4]. *Alternaria alternata* belongs to this group—it is a saprophyte filamentous fungus belonging to the phylum *Ascomycota,* family *Pleosporaceae* and group *dematiaceae*. It is known for its high distribution and allergenic capacity (it is one of the common causes of asthma) [5]. However, systemic invasive presentation is rare and is associated in most cases with immunosuppression [4,6]. Reported cases of *Alternaria spp.* infection are rare; the most common presentations are mucocutaneous, ocular disease, rhinosinusitis and onychomycosis [4,6]. Brain involvement is rare and poorly reported in the literature.

2. Case

A 66-year-old man was evaluated at the emergency department in March 2016 because of clinical symptoms which started on the previous day before (Day 0); the symptoms included asthenia, adynamia, mild dyspnoea, dry cough, chills, fever and diaphoresis, with alteration of the consciousness state marked by disorientation and episodes of agitation, great respiratory difficulty and desaturation despite O_2 substitution under a high-flow system. He had a history of hypertensive nephropathy and polycystic kidney disease, had undergone renal transplantation from a cadaveric donor 1 year ago, and was under immunosuppressive treatment with tacrolimus (2 mg/day), prednisolone (40 mg/day) and azathioprine (100 mg/day). A chest x-ray was performed, which revealed a consolidation in the middle third of the left pulmonary field.

On day 1, he was shifted to the intensive care unit because of respiratory failure, which required invasive mechanical ventilation support, and septic shock with multiple organ failure syndrome. The neurological compromise was striking, with progression to stupor. Given the presence of signs of systemic inflammatory response, described pulmonary findings, history of immunosuppression and the risk of infection by opportunistic germs, empirical antibiotic treatment with piperacillin/tazobactam, vancomycin, clarithromycin, fluconazole and oseltamivir were established.

On day 2, he was assessed by the Departamento de Infectología (Department of Infectious Diseases), which considered it pertinent to rule out infection due to *Histoplasma, Cryptococcus* or *Aspergillus,* and they requested urinary antigen testing for *Histoplasma* and *Cryptococcus*

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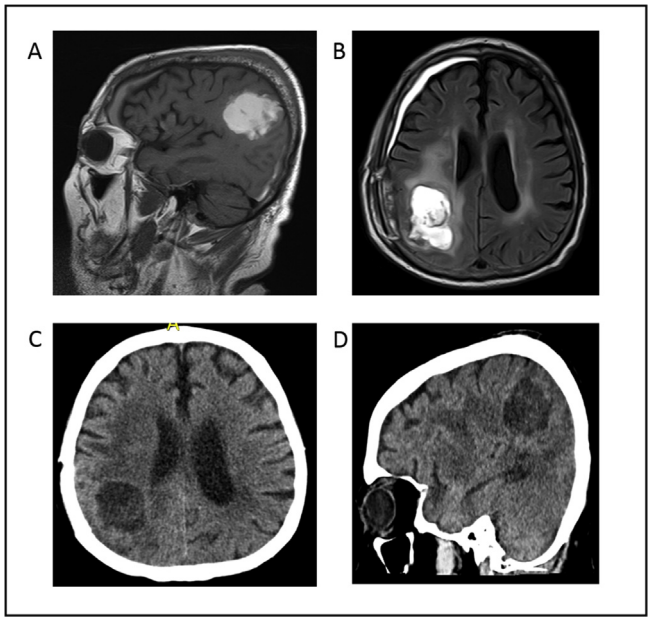

Fig. 1. Magnetic resonance images: intra-axial lesion with expansive behaviour, 28 mm in diameter, with ring enhancement and associated vasogenic oedema, located in the right parietal lobe; area of right anterior subinsular vasogenic oedema without enhancement.

and a bronchoalveolar lavage galactomannan test. These tests were negative. Liposomal amphotericin B (300 mg/24 h as day 4 to day 26) was initiated on suspicion of opportunistic fungal infection. Because the patient had a recent history of positive viral load for cytomegalovirus, ganciclovir was initiated (2.5 mg/kg/day, as day 2 to day 16; when viral load for cytomegalovirus was undetectable).

Reports of viral load for cytomegalovirus showed reactivity but with decreasing loads; therefore, cytomegalovirus infection was not considered to be the cause of the pulmonary and neurological findings or the cause of the severity of the present decompensation. Blood cultures, and oral tracheal secretion cultures for common aerobic germs were negative.

From the neurological perspective, despite suspending sedation, the patient persisted with an altered state of consciousness. Therefore, brain tomography was performed, which revealed an intra-axial lesion with expansive behaviour that was 28 mm in diameter, with ring enhancement, and associated vasogenic oedema located in the right parietal lobe; the area of right anterior subinsular vasogenic oedema was without enhancement. Lesions were identified as foci of cerebritis (Fig. 1).

An open biopsy was performed, which identified a subcortical mass with a lumpy consistency. The mass was yellowish and partially vascularised and without cleavage planes, which were suggestive of a secondary tumour. No purulent material or signs of cerebritis were observed; however, samples were taken for microbiological (culture for common aerobic germs, fungal culture, Gram staining, BK staining, KOH test and fresh examination) and histopathological studies; the latter were not conclusive. Upon fresh examination of the samples taken during surgery, the microbiology laboratory reported the presence of large, irregular, septate and dematiaceous hyphae, which resulted in continued and optimizing antifungal management directed at mycelial fungi with amphotericin B and voriconazole (6 mg/kg BID). The decision by the infectiology group was to extend the treatment for 42 days in combination and then, for 6 months to 1 year only with voriconazole (Fig. 2A).

Following neurosurgical intervention, the patient's condition improved, ventilation support was discontinued, and alertness was restored. Days later, on Sabouraud agar, growth of flat, cottony, grey-white colonies was initially observed, with the colour subsequently turning to greenish black (Fig. 2B).

The back of the colony had a dark brown colour. The strain was sent for identification, based on morphology employing a compound microscope at 40× magnification evidencing septate dematiaceous hyphae with septate conidiophores following standard manuals [7,8]. Microbiological typing of the mycelial fungus was achieved, which concluded that the patient presented with phaeohyphomycosis, which was disseminated by *Alternaria spp.* (Fig. 2C).

On day 5, an MRI scan revealed collection on the surgical bed with the persistence of oedema in the right subinsular region without defined collection. Considering that the purpose of the excision was tissue preservation, the excision of the lesion was not radical, so it was decided to optimise dematiaceous treatment with the inclusion of terbinafine treatment (250 mg/day until to death). Subsequently, its progress was satisfactory, without evidence of new neurological deficits. Subsequent computed tomography (CT) scans showed no significant changes in brain lesions. There was no progression of mycosis nor were other organs compromised.

Four months later, the patient dies from a cause other than the fungal infection.

3. Discussion

The term phaeohyphomycosis is used to describe infections caused by pigmented fungi (dematiaceous) [9]. More than 100 species have been associated with this disease in humans. Generally, presentation is non-invasive and is associated with varying degrees of morbidity and low rates of mortality [10]. The literature on phaeohyphomycosis in transplant patients is scarce, and the majority corresponds to case reports [10]. When the central nervous system is compromised, the most common presentation is brain abscess, which occurs in over half of immunocompetent patients, and the mortality rate is up to 73%. *Cladophialophora bantiana* is the etiologic agent in approximately 50% of cases, and *Alternaria alternata* is the most common agent in subcutaneous infections [9].

In patients with solid organ transplantation, neutropenia has been documented as one of the factors most commonly associated with invasive fungal infection, and during clinical presentation, fever (18%), respiratory symptoms (13%) and changes in chest CT (24%) are very frequently observed. However, altered mental status occurs in approximately 2% of patients [4–6].

In the present case, the patient had the afore mentioned clinical features, including the presence of neutropenia, since admission. The imaging findings (CT and cerebral MRI in this case), although usually non-specific, revealed the presence of an intraparenchymal abscess from the first approach. Histopathological examination of the samples ruled out the presence of a secondary tumour, and the existence of irregular hyphae was confirmed by the fresh study. Finally, the culture revealed the presence of *Alternaria spp.*, which has not been reported as a causative agent of brain abscesses.

There are no comparative studies of antifungal treatment in phaeohyphomycosis; however, high success rates have been reported with several agents, including: voriconazole, itraconazole and amphotericin B [11–13]. Current recommendations according to the American Society of Transplantation Infectious Diseases Community of Practice [13] and the European Fungal Infection Study Group of the European Society of Clinical Microbiology and Infectious Diseases [14] list in their 2012 and 2014 guidelines for the treatment of phaeohyphomycosis, respectively, that amphotericin B, posaconazole, and voriconazole remain first-line medications. Echinocandins and flucytosine have been used less frequently [15]. In our case, the patient received treatment with liposomal amphotericin B and voriconazole, and although the initial treatment included anidulafungin, it was discontinued early on. Subsequently, the persistence of an injury despite antifungal management with amphotericin b liposomal, voriconazole

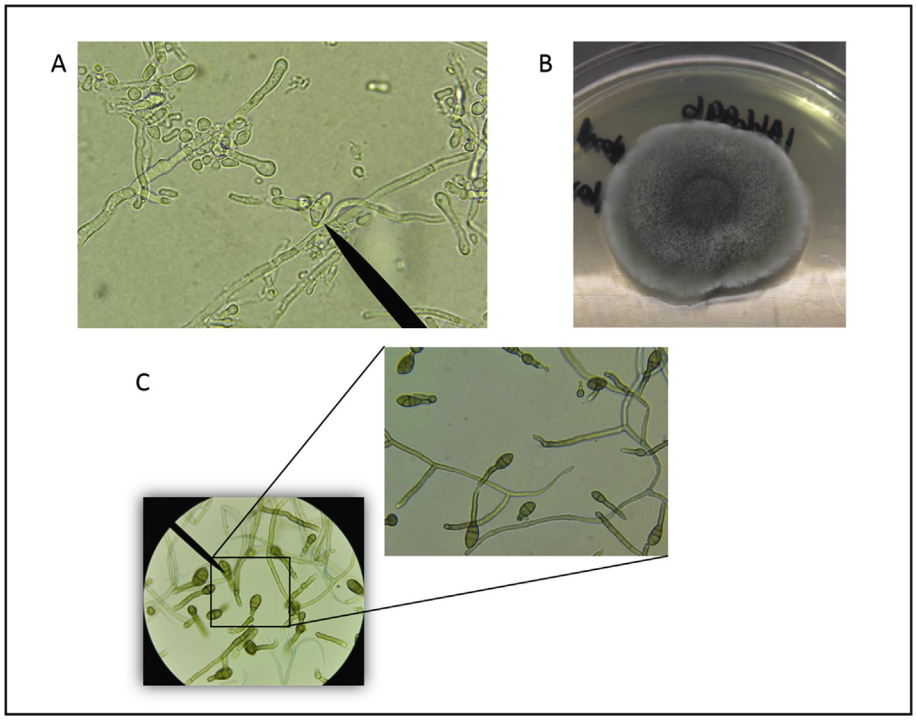

Fig. 2. Micro and macroscopic phenotypic characterisation of *Alternaria spp.* A: fresh examination revealed the presence of large, irregular, septate hyphae, B: Sabouraud dextrose agar culture, villous grey colony. C: Septate dematiaceous hyphae. Septate conidiophore and macroconidia.

and surgical management led us to consider the combination of terbinafine therapy. Terbinafine has a broad antifungal spectrum, with adequate in vitro performance against dematiaceous fungi [16]. The use of terbinafine has been poorly reported in the management of invasive fungal infections. The report of the management of subcutaneous mycosis (sporotrichosis, maduromycosis, chromoblastomycosis) prevails, but its use in central nervous system infections has hardly been reported. It is the case of the use of terbinafine in cerebral abscess due to *Scedosporium apiospermum, Pseudallescheria boydii* and in central nervous system mucormisosis successfully treated [17–19].

The clinical results were satisfactory, with neurological recovery and improvement in resonance imaging and tomography scans, with no evidence of relapse. Thus, timely diagnosis and early and aggressive therapy with amphotericin B, voriconazole and finally, terbinafine showed a favourable response.

Although compromise of the central nervous system by a fungal agent is rare, its incidence is on the rise because of the increase in the number of patients with immunosuppressed states, and among them, those in a post-transplant condition. Further studies are required to establish timely diagnostic and treatment guidelines. We hope that our experiences in this case will be a valuable contribution in this regard.

Ethical form

The ethics committee of the Fundación Clínica Shaio approved this study (Act 281)

Declaration of competing interest

None of the authors have anything to declare.

References

[1] C. W, L. Ajello, L.K. Georg, R.T. Steigbigel, A case of phaeohyphomycosis caused by a new species of Phialophora, Mycologia (2018) 490–498, https://doi.org/10.1080/00275514.1974.12019630.
[2] R. MG, Phaeohyphomycosis, Dermatol. Clin (1996) 147–153, https://doi.org/10.1016/S0733-8635(05)70335-1.
[3] D.A. S, S.G. Revankar, Melanized fungi in human disease, Clin. Microbiol. Rev. (2010) 883–928, https://doi.org/10.1128/CMR.00019-10.
[4] L.V. Gómez, N. Cardona-Castro, Feohifomicosis, una infección fúngica oportunista emergente, CES Med (2016) 66–77.
[5] J. Lazaro L.J., Alergia a hongos y asma grave, Media Res. 8 (1) (2015) 7–15.
[6] T. W, D.P. Kontoyiannis, K.A. Marr, B.J. Park, B.D. Alexander, E.J. Anaissie, Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the transplant-associated infection surveillance network (TRANSNET) database, Clin. Infect. Dis. (2010) 1091–1100.
[7] M.B. Ellis, More Dematiaceous Hyphomycetes, Commonwealth Mycological Institute, Kew, Surrey, UK, 1976.
[8] E.G. Simmons, Alternaria: an Identification Manual, CBS Biodiversity Series, Utrercht, the Netherlands, 2007, pp. 1–775 6.
[9] B.T. JA, Micología Médica Básica, fourth ed., McGraw Hill, 2012.
[10] T.F. P, Silveira CJC, J. Amaral, R.P. Gorayeb, J. Cabral, Meningoencephalitis caused by Alternaria: a clinical case, Clin. Drug Investig. 33 (2013) 27–31, https://doi.org/10.1007/s40261-012-0016-2.
[11] J. P, P.K. Sharkey, J.R. Graybill, M.G. Rinaldi, D.A. Stevens, R.M. Tucker, Itraconazole treatment of phaeohyphomycosis, J. Am. Acad. Dermatol. (1990) 577–586, https://doi.org/10.1016/0190-9622(90)70259-K.
[12] I. M, N. Singh, F.Y. Chang, T. Gayowski, Infections due to dematiaceous fungi in organ transplant recipients: case report and review, Clin. Infect. Dis. (1997) 369–374, https://doi.org/10.1093/clinids/24.3.369.
[13] L. W, N. Singh, S. Huprikar, S.D. Burdette, M.I. Morris, J.E. Blair, Donor-derived fungal infections in organ transplant recipients: guidelines of the American society of transplantation, infectious diseases community of Practice, Am. J. Transplant. (2012) 2414–2428, https://doi.org/10.1111/j.1600-6143.2012.04100.x.
[14] A. U, O.A. Cornely, M. Cuenca-Estrella, J.F. Meis, European society of clinical microbiology and infectious diseases (ESCMID) fungal infection study group (EFISG) and European confederation of medical mycology (ECMM) 2013 joint guidelines on diagnosis and management of rare and emerging fungal diseases, Clin. Microbiol. Infect. 1 (2014) 4.
[15] S. S, S. Huprikar, Emerging fungal infections in solid organ transplantation, Am. J. Transplant. (2013) 262–271, https://doi.org/10.1016/j.idc.2013.02.004.
[16] H.G. de, D.M. Li, Cerebral phaeohyphomycosis—a cure at what lengths? Lancet Infect. Dis. (2009) 376–383, https://doi.org/10.1016/S1473-3099(09)70131-8.
[17] A.F. Henao-Martinez, J.R. Castilla-Mancilla, M.A. Barron, Combination antifungal therapy in the treatment of Scedosporium apiospermum central nervous system infections, Case Reports in Infectious Diseases (2013), https://doi.org/10.1155/2013/589490.
[18] T.S.R. Jensen, M.C. Arendrup, C. von Buchvald, Successful treatment of rhino-orbital-cerebral mucormycosis in child with leukemia, J. Pediatr. Hematol. Oncol. 39 (4) (2017 May) e2111–e2215 10.1097/MPH. 0000000000000701.
[19] Mursch Kay, Behnke-Mursch, Svorad Trnovec, Successful Treatment of Multiple Pseudallescheria Boydii Brain Abscesses and Ventriculitis/ependymitis in a 2-Year-Old Child after a Near-Drowning Episode, (2014, October), https://doi.org/10.1007/s00381-005-1151-3.