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Case Report

Invasive cerebral phaeohyphomycosis in a Chinese boy with CARD9 deficiency and showing unique radiological features, managed with surgical excision and antifungal treatment

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ABSTRACT

We report this rare case of cerebral phaeohyphomycosis in a previously healthy Chinese boy, who was found to have caspase recruitment domain family member 9 (CARD9) deficiency. Initial radiological features suggested a neoplastic cerebral lesion, while histopathological examination supplemented by internal transcribed sequencing (ITS) of cerebral tissue confirmed the diagnosis of phaeohyphomycosis. He was treated with intravenous (IV) liposomal amphotericin B and voriconazole, guided by plasma and cerebrospinal fluid (CSF) level monitoring at drug initiation. At the 1 year follow-up, the patient demonstrated near complete neurological and radiological recovery.

Introduction

Phaeohyphomycosis is an infection caused by a group of dematiaceous fungi. Invasive infection most commonly affects the respiratory tract, while the central nervous system (CNS) is the least common site. The pathogenesis is presumed to be hematogenous dissemination from a subclinical pulmonary focus, although most cases of cerebral infection have shown no evidence of previous pulmonary involvement (Arcobello and Revankar, 2020). Whilst other life-threatening fungal infections occur in immunocompromised individuals, more than half of phaeohyphomycosis patients are not immunodeficient. *Cladophialophora bantiana* was the most commonly isolated species in the CNS, with mortality of up to 70%. Whilst treatment remains unstandardized, combinations of antifungals and complete excision were associated with better outcome (Revankar et al., 2004).

Recently, CARD9 deficiency has been increasingly reported in patients, with 58 otherwise healthy individuals presenting with isolated fungal infections. Ten of the 58 had phaeohyphomycosis, of which two had invasive infections (Corvilain et al., 2018).

We report the first Chinese pediatric patient with isolated CNS phaeohyphomycosis with underlying CARD9 deficiency. We also highlight a unique radiological feature not previously described. Furthermore, we share our treatment strategy of paired CSF and serum voriconazole, with dosing levels guided at drug initiation, combined with surgical excision, achieving good recovery after 1 year.

Abbreviations: CADD, combined annotation-dependent depletion; CARD9, caspase recruitment domain family member 9; CNS, central nervous system; CSF, cerebral spinal fluid; DANN, deleterious annotation of genetic variants using neural networks; ITS, internal transcribed spacing; IV, intravenous; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

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Case presentation

A 6-year-old previously healthy Chinese boy, born to non-consanguineous Chinese parents, presented with a 1-day history of headache and left upper limb seizure. Magnetic resonance imaging (MRI) of the brain showed a right parietal 2.1 × 2.4 × 2.2 cm focal enhancing mass, with surrounding vasogenic edema and leftward midline shift. Magnetic resonance spectroscopy (MRS) showed elevated choline peak, choline-to-creatine ratio, and lactate/lipid peak, reduced N-acetylaspartate, and no increase in cerebral blood flow; these findings led to suspicion of a high-grade CNS neoplasm.

Emergency craniotomy was performed, with gross lesion resection of a well-circumscribed, non-vascular, firm lesion. Histopathological examination revealed predominant macrophages and obtuse branching pigmented septate hyphae. Melanin production was confirmed by Masson-Fontana staining and bleaching by potassium permanganate (Figure 1a and b), distinct from Aspergillosis, which usually demonstrates dichotomous, right-angle branching, with wide and irregular hyphae and preferential vessel invasion. Resected specimens were not submitted for fungal cultures, based on the initial suspicion of malignancy. ITS sequencing identified melanin-producing fungi suggestive of *Alternaria* species, consistent with a diagnosis of phaeophyphomycosis. The CSF was sterile. With a fungal etiology demonstrated, retrospective radiological reviews of the MRI images identified hyperintense finger-like projections on T2W images similar to intracavitary projections (Figure 1c), which are otherwise not seen in tumors. Furthermore, T2W hypointensity and T1W hyperintensity reflect the paramagnetic nature of the underlying melanin.

The patient was treated with 4 months of intravenous voriconazole and liposomal amphotericin B (AmBisome), followed by oral voriconazole for 1 year at the time of reporting. Serum and CSF voriconazole levels were established with one application of tandem mass spectroscopy on drug initiation, giving a CSF/serum ratio of 0.57. Voriconazole dosing was titrated using the serum levels and the established ratio, aiming for more than 2 mg/L in the CSF (Chen et al., 2012). Rapid trio exome sequencing revealed compound heterozygous missense mutations (NM_052813: exon13:c.G1526A:p.R509K from the father and NM_052813:exon4:c.A586G:p.K196E from the mother) in CARD9. Homozygotes of these mutations are not evident in population genome control databases, and have not been reported in the literature. The mutant allele from the father yielded a combined annotation-dependent depletion (CADD) score of 21.2 and a deleterious annotation of genetic variants using neural networks (DANN) score of 0.913. For the mother, the CADD score was 23.8 and the DANN score 0.997. According to ACMG guidelines, the father's mutation is classified as a variant of uncertain significance and the mother's mutation is likely pathogenic (Richards et al., 2015). Given the history of isolated CNS fungal infection in a child with previously good health, his mutations are likely disease causative. At the 1 year follow-up, the patient showed near complete recovery of left limb weakness, while serial MRI brain images showed resolving contrast enhancement and reduced lesion size.

Discussion

CARD9 deficiency is currently the only known primary immunodeficiency predisposing individuals to isolated fungal disease. In a case series of 58 individuals, phaeohyphomycosis was reported in ten patients, where eight were subcutaneous and two were invasive infections. Out of the two invasive cases, one was reported to have CNS involvement. Nine were alive at the time of reporting and one had died from bone and pulmonary disease. Whilst the two invasive cases demonstrated multiorgan involvement by *Exophilia* species (Corvilain et al., 2018), our case had isolated CNS phaeohyphomycosis caused by *Alternaria* species.

Reviewing treatment for phaeohyphomycosis within this CARD9 series, oral itraconazole with or without IV liposomal amphotericin B appears to have been the most popular regimen. Voriconazole was given orally in the case of CNS infection, and intravitreally in the other invasive case. Only one case of subcutaneous phaeohyphomycosis required surgical excision (Corvilain et al., 2018). Due to the high mortality rate for CNS phaeohyphomycosis, surgical removal is recommended, together with a longer duration of combined systemic antifungal treatment. Voriconazole, with its ability to achieve good CSF levels, supersedes other azoles in treating CNS infection by dematiaceous fungi (Revankar et al., 2004; Azarpira et al., 2008). Therapeutic drug monitoring of voriconazole may play an important role in optimizing treatment efficacy, due to its inter- and intrapatient variability and markedly reduced oral bioavailability in children (Chen et al., 2012). Limited studies have looked at CSF and plasma level correlation, with reported ratios from 0.22 to 0.57 (Lutsar et al., 2003; Wiederhold et al., 2014; Kobayashi et al., 2016; Furudate et al., 2020); our finding of a ratio 0.52 was consistent with these results. Currently, no standardized treatment guideline exists for CNS phaeohyphomycosis; nor have there been studies correlating clinical outcome with plasma and CSF voriconazole drug levels.

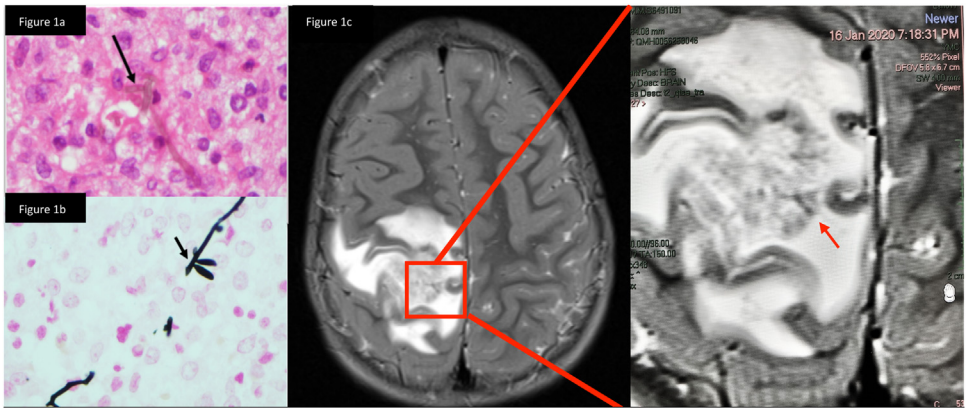

Figure 1. (a) (Hematoxylin and eosin staining, 400×): fungal hyphae of uniform thickness, displaying right-angle and sometimes obtuse-angle branching in a background of dense sheets of mixed but macrophage-predominant inflammatory cells. (b) (Masson Fontana, 400×): hyphae staining black with right-angle branching. (c) MRI brain; T2W image demonstrating intracavitary finger-like projections.

Finally, our case illustrates that fungal mass lesions can mimic malignancy and are indistinguishable according to MRI brain and MRS features. Numerous reviews have reported similar situations where radiological findings have confounded diagnosis, irrespective of the fungal identity, with MRS not proving useful in differentiating malignant lesions from phaeohyphomycosis (Hauck et al., 2008; Santosh et al., 2010; Jung and Kim, 2014; Goel et al., 2019; Magaki et al., 2019). Fungal etiology was only identified in these cases from later histopathological and microbiological examination. Retrospective reviews of MRI images with our radiologists revealed finger-like projections in the lesion (Figure 1c); such intracavitary projections are unique to fungal abscesses. This has not been previously reported in other cases of primary CNS phaeohyphomycosis.

In conclusion, CARD9 deficiency should be considered when a healthy individual presents with primary CNS phaeohyphomycosis. A combination regimen of liposomal amphotericin B and voriconazole, together with complete surgical excision, confers better prognosis. Paired CSF and plasma therapeutic drug monitoring of voriconazole can be useful. Radiological investigations cannot distinguish CNS fungal and malignant lesions; hence, tissue microbiological and histopathological examinations are vital in diagnosis.

Author contributions

Sophie HY Lai was involved in the clinical care, interpretation of results, and writing of the manuscript.

Jaime S Rosa Duque was involved in the clinical care and provided advice on voriconazole drug level monitoring and drug titration.

Brian Hon-Yin Chung was involved in whole exome sequencing for index patient and parents, and result interpretation.

Tom Wai-Hin Chung was involved in the interpretation of microbiological results and provided advice on clinical management.

Daniel Leung was involved in the interpretation of whole exome sequencing results.

Ronnie Siu-Lun Ho was involved in histopathological diagnosis and interpretation.

Raymand Lee was involved in radiological interpretation.

Rosana Wing-Shan Poon was involved in the interpretation of microbiological results.

Gilbert T Chua was involved in the clinical care and provided skills in investigating immune status.

Kai N Cheong was involved in the clinical care and provided skills in investigating immune status.

Mianne Lee was involved in whole exome sequencing and analysis of results.

Martin Man Chun Chui was involved whole exome sequencing.

Professor Sidney Tam was involved in tandem mass spectroscopy for CSF voriconazole level monitoring and interpretation of results.

Andrew Ho Cheuk Him was involved in the surgical excision of the lesion.

King-Fai Cheng was involved in the surgical excision of the lesion.

Wilson Wai-Shing Ho was involved in the surgical excision of the lesion.

Professor Kwok-Yung Yuen was involved in the interpretation of microbiological results and provided advice on clinical management.

Pamela Lee was involved in the clinical care and provided skills in investigating immune status.

Professor Yu Lung Lau was involved in the clinical care, and provided skills in investigating immune status, and in the drafting and revision of this paper (with Sophie HY Lai).

Conflicts of interest

All other authors declare no conflicts of interest.

Ethical approval

Consent was obtained and no approval was required for this case report.

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