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Case Report

Stereotactic biopsy of a brain lesion caused by *hormographiella aspergillata*

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ABSTRACT

Background: Invasive fungal infections are an increasing problem in immunosuppressed patients. In patients with the central nervous system involvement, there is a high case fatality rate. There is a very limited experience with infections caused by *Hormographiella aspergillata* (HA) in such cases and most often diagnosis is only confirmed postmortem.

Case Description: We report the case of a 53-year-old woman with acute myeloid leukemia. After primary therapy with daunorubicin, cytarabine, and gemtuzumab ozogamicin, the patient developed pneumonia and later neurological symptoms caused by multiple gadolinium-enhancing brain lesions in magnetic resonance imaging (MRI). Stereotactic biopsy of a frontal precentral lesion was performed and revealed HA infection. The patient died in the further course secondary to cardiopulmonary problems.

Conclusion: Stereotactic biopsy is a safe way to establish the diagnosis of unclear lesions such as HA infection. We recommend to perform stereotactic biopsy early in immunocompromised patients with brain lesions to guide further treatment.

Keywords: Cerebral fungal infection, *Coprinopsis cinerea*, Hematopoietic stem cell transplantation, *Hormographiella aspergillata*, Invasive fungal infection, Stereotactic biopsy

INTRODUCTION

Invasive fungal infections (IFI) are an increasing problem regarding the growing number of people at risk. They cause more than 1.5 million deaths globally every year.[3] In contrast to superficial, cutaneous/mucosal, and subcutaneous fungal infections, IFIs affect organs such as heart, lung, brain, kidneys, or liver, especially in immunocompromised patients. The most common IFIs are Candidiasis, Aspergillosis, and Cryptococcosis which are caused respectively by *Candida*, *Aspergillus,* and *Cryptococcus*.[15] In the past decade, fungal infections of the central nervous system have been described more frequently, but often the diagnosis is confirmed only postmortem.[9]

Hormographiella aspergillata (HA) is known as the asexual form of *Coprinopsis cinerea* which is a species of the basidiomycete mushroom genus.[8,10] It may cause invasive infections in

immunosuppressed patients, but overall, such infections are rare. While HA infections are associated with a very high case fatality rate, the choices of diagnostic and therapeutic procedures are still debated. Here, we present a patient with acute myeloid leukemia (AML) in whom stereotactic biopsy established the diagnosis of HA-related cerebral IFI. We also review previous cases and suggest to consider a shift in diagnostic algorithms.

CLINICAL PRESENTATION

A 53-year-old woman was admitted to Hannover Medical School after developing left-sided paresthesias and hemiparesis. Her medical history was remarkable for high-risk AML, which had been diagnosed 2 months earlier, with initially over 80% of blasts in bone marrow. In addition, she suffered from a chronic anxiety disorder and depression with a history of tranquilizer and antidepressant drugs intake.

The primary therapy had consisted in medication with daunorubicin, cytarabine, and gemtuzumab ozogamicin (DA + GO). On day 15, a good response to therapy was registered (<5% blasts in bone marrow). Nevertheless, the patient had a persistent cytopenia with prominent leukopenia (up to 0.1 $10^3/\mu L$). Thereafter, she developed pneumonia with recurring fever and an increasing CRP (up to 430 mg/L). A computed tomography (CT) scan of the chest performed on day 35 showed multiple nodules in both lungs, matching with a fungal pneumonia. Bronchoalveolar lavage (BAL) cultures however tested negative for fungi and tuberculosis. In particular, no *Aspergillus* antigen could be detected. Initial antifungal prophylaxis with Voriconazole was switched to Caspofungin. Subsequent bone marrow examination revealed no relapse of AML.

After the occurrence of paresthesias and hemiparesis, brain magnetic resonance imaging (MRI) showed multiple gadolinium-enhancing cerebral lesions [Figure 1a]. Differential diagnosis included metastases, lymphoma, bacterial, and fungal granulomatous lesions. Stereotactic biopsy was recommended for further diagnosis and to tailor therapy but was refused by the patient. The situation was complicated by a psychotic episode with limited judgment. Despite weekly white blood cells transfusions and antimycotic therapy escalation to Posaconazole and Amphotericin-B, neurological symptoms deteriorated and the patient became increasingly somnolent. A second brain MRI was carried out and showed progress of the lesions with involvement of the meninges. The lesions were characterized by signs of microhemorrhages and perifocal edema [Figures 1b-e]. The patient's family finally agreed to obtain a stereotactic biopsy and the patient was transferred to the department of neurosurgery.

On admission, the patient was in a poor general condition. She was obtunded and had a marked left-sided hemiparesis. Stereotactic serial biopsies were obtained (Riechert Mundinger frame with Zamorano-Dujovny application) targeting the right precentral lesion under general anesthesia. The collected samples were sent for microbiological and neuropathologic analyses. After surgery, the patient was transferred to the intensive care unit. Postoperative CT scan was unremarkable. Nevertheless, the patient had increasing cardiorespiratory problems, which led to her death on day 70. Autopsy was declined by her family.

Microscopic examination of the stereotactic biopsy specimen revealed gliotic central nervous system (CNS) parenchyma with sparse lymphomonocytic infiltrates. In addition, there were necrotic areas. Within the necrotic zones, fungal hyphae were detected by periodic acid Schiff (PAS) staining [Figure 2]. Some of these had a string-like appearance and developed bulbous beads. The hyphae branched and septations within the hyphae were visible. After deoxyribonucleic acid (DNA) extraction from the tissue, consensus primers for the 18S-Ribonucleic acid (RNA) gene were used to amplify the most important members of the fungal genera *Aspergillus*, *Candida*, *Mucor*, *Rhizopus*, *Cryptococcus*, *Paecilomyces*, *Scedosporium,* and *Absidia* and to specify them by hybridization of the polymerase chain reaction (PCR) product. Since the PCR product was strong but the hybridization signal was absent, the PCR product was sequenced directly. The resulting DNA sequences were then clearly assigned to the HA fungus species.

DISCUSSION

Stereotactic biopsy in fungal brain infections

Stereotactic cerebral biopsy is a routine neurosurgical procedure with a diagnostic yield of more than 90% at a relatively low risk, which allows to obtain specimen of lesions before tailored therapy. Alternative options are frameless or neuronavigated techniques. Stereotactic biopsy is mostly performed in patients with deep-seated lesions, unresectable lesions, or in tumors suspected to be radio- or chemosensitive such as cerebral lymphoma or germinoma.[17] More rarely stereotactic biopsy is performed in patients with lesions suspected to have an infectious origin, especially in immunosuppressed patients. For example, it has shown high diagnostic efficacy in human immunodeficiency virus-infected patients with unclear brain lesions.[12] Stereotactic biopsy has only rarely been used to specify lesions caused by suspected fungal infections. In general, in the limited number of reported cases, biopsy was successful and microbiological examinations of the specimen revealed the particular fungus, such as *Candida albicans* or *Blastomyces dermatitidis*.[14,19] Interestingly, some reports even noted complete remission when stereotactic biopsy was performed to obtain a diagnosis allowing specific treatment.[14,19,21]

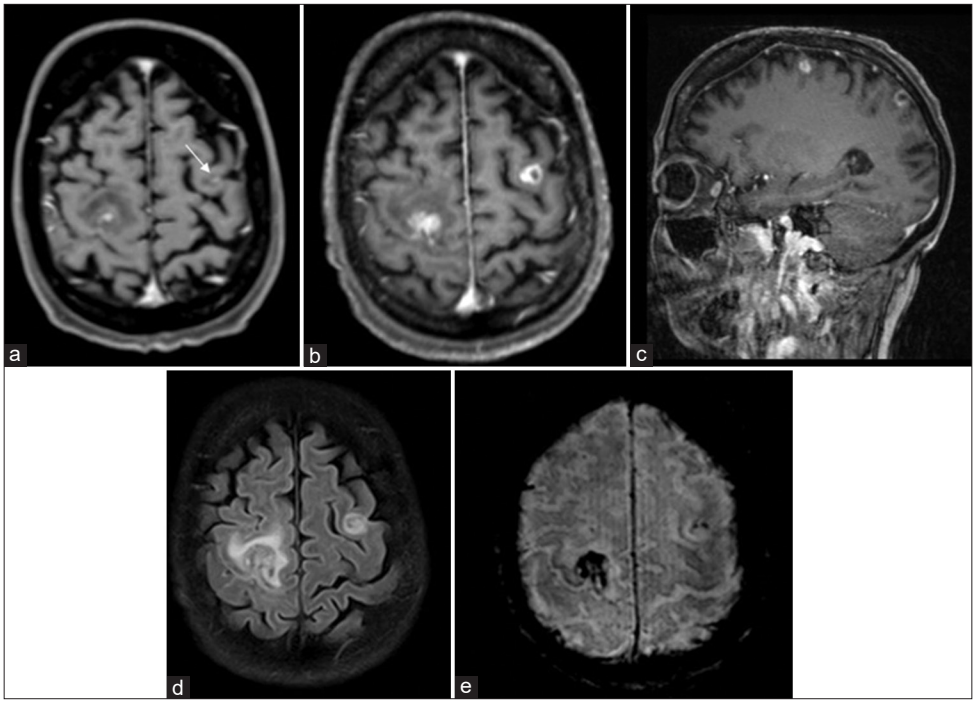

Figure 1: Brain magnetic resonance imaging findings of a 53-year-old woman with acute myeloid leukemia and multifocal cerebral lesions caused by *Hormographiella aspergillata*: (a) initial axial post contrast T1-weighted scan shows two gadolinium enhancing lesions in both frontal hemispheres with minor mass effect on the right side with a leptomeningeal enhancement on the left (arrow). (b-e) Follow-up imaging: (b) axial post contrast T1-weighted scan displays the progression of the gadolinium enhancing lesions compared to (a and c) sagittal post contrast T1-weighted scan showing a frontal as well as parietal lesion with the same lesion characteristic as in (a-d) The FLAIR image shows the amount of surrounding edema with different extent between the two lesions. (e) Susceptibility weighted imaging demonstrates signal loss due to paramagnetic effects caused by iron deposition/microhemorrhages.

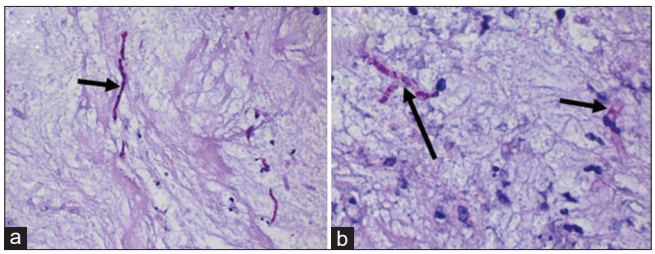

Figure 2: Microscopic examination of the stereotactic biopsy of the right-sided frontal lesion. Periodic Acid Schiff staining. (a) Hyphae with a string-like appearance and bulbous beads (arrow) on the background of necrotic CNS parenchyma; (b) focally branching hyphae (long arrow) and partly septate hyphae (short arrow) can be identified. Only single lymphocytes and macrophages are found within the necrosis.

Fungal cerebral infections

Fungal infections of the central nervous system are rare conditions but associated with high lethality, especially in immunocompromised patients. Common responsible fungi in CNS infections are *Candida* spp., *Cryptococcus neoformans*, *Aspergillus* spp., or *Mucoromycetes* spp.[9] The incidence of IFI caused by *Candida* species is estimated at 72–228 infections per million population. For *C. neoformans* and *Aspergillus* species, it is estimated at 30–66 and 12–34 infections per million inhabitants, respectively.[16]

The clinical presentation of fungal infections of the CNS is variable and may include meningitis, meningoencephalitis, stroke, cerebritis, vasculitis, and venous sinus thrombosis. Frequent symptoms are headache, fever, seizures, motor symptoms, progressive confusion, altered mental status, nausea, vomiting, visual impairment, papilledema, and focal neurological deficits.[4,18]

Radiological findings in fungal CNS infections are non-specific and vary from fungal meningitis, fungal cerebritis, brain abscess, and cryptococcoma to meningeal vasculitis.[7] These unspecific clinical and radiological findings make fungal brain infections a diagnostic challenge. In general, the diagnosis of IFI such as invasive candidiasis or invasive aspergillosis is difficult and requires biopsy, culture, and histopathological examination in combination by a molecular/microbiological workup of infected tissues.[2]

Table 1: Reported cases of cerebral infections caused by Hormographiella aspergillata.

Reference	Patient/Age (years)	Underlying disease	HA infection sites	Cerebral radiologic findings	Diagnostic confirmation of cerebral lesions	Therapy	Outcome
Verweij *et al.*, 1997[20]	F/24	AML	Brain and lung	No findings in CT	No confirmation	Itraconazole and Amphotericin-B	Died one week after first neurological symptoms
Abuali *et al.*, 2009[1]	F/14	AML	Brain, lung, and skin	Multiple lesions of the cerebral hemispheres and the cerebellum (CT)	No confirmation	Voriconazole, Caspofungin, Posaconazole, and Amphotericin-B	Died 2 weeks after first neurological symptoms
Conen *et al.*, 2011[6]	F/41	AML	Brain, lung, and eye	Cerebellar hemorrhage (CT)	Postmortem (Autopsy)	Voriconazole, Posaconazole, and Caspofungin	Died 4 days after first neurological symptoms
Heiblig *et al.*, 2015[11]	M/19	Myelodysplastic syndrome and AML	Sino-orbito-cerebral	Infratemporal abscess and intraorbitary infiltration and signs of local meningitis (MRI)	Postsurgery	Posaconazole, Amphotericin-B, and Voriconazole	Died. Time interval not reported
Nanno *et al.*, 2016[13]	M/51	Myelodysplastic syndrome	Brain, lung, and small intestine	Abscess in cerebellum and occipital lobe (MRI)	Postmortem (Autopsy)	Itraconazole, Caspofungin, Amphotericin-B, and Voriconazole	Died 17 days after first neurological symptoms
Chauhan *et al.*, 2019[5]	M/54	CML	Brain and lung	Acute infarct (MRI)	Postmortem (Autopsy)	Micafungin	Died. Time interval not reported
Hounchonou *et al.*, 2022 Current Study	F/53	AML	Brain and lung	Multiple gadolinium enhancing lesions in both hemispheres	Stereotactic Biopsy	Posaconazol, Voricinazol, and Amphotericin-B	Died 1 month after first neurological symptoms

MRI: Magnetic resonance imaging, AML: Acute myeloid leukemia, CT: Computed tomography, HA: Hormographiella aspergillata, M: Male, F: Female, CML: Chronic Myeloid Leukemia

Cerebral infections caused by HA

HA is a largely unknown pathogen and it is rarely identified. The number of documented cases is low and thus, no definitive treatment has been specified. Only six cases of cerebral infection related to HA have been reported until now [Table 1].

All these patients were immunosuppressed, aged between 14 and 54 years, and had underlying hematological malignancies (acute myeloid leukemia, chronic myeloid leukemia, or myelodysplastic syndrome). Most patients underwent hematopoietic stem cell transplantation. Neurological manifestations included epileptic seizures, anosmia, amaurosis, signs of intracranial hypertension, altered mental status, tingling, and hemiparesis. Radiologic examinations showed unspecific findings. In two cases, MRI findings corresponded to brain abscesses.[11,13] In one case, CT demonstrated multiple lesions in both hemispheres and in the cerebellum.[1] In another case, the CT scan only revealed an extensive cerebellar hemorrhage.[6] In our patient, brain MRI displayed multiple gadolinium-enhancing lesions in both hemispheres.

Since clinical and radiological findings were unspecific and histological examinations were not available, a definitive confirmation of cerebral HA infection could be confirmed only postmortem in the majority of the published patients.

Therapeutic interventions were based on administration of common antifungal drugs, namely, Posaconazole, Voriconazole, Caspofungin, Micafungin, and Amphotericin-B in various constellations. In all reported cases and in the patient reported here, the infection was fatal. Patients died within a period of 4 weeks after onset of neurological symptoms.[1,5,6,11,13,20]

CONCLUSION

HA brain infection is a rare condition with unspecific clinical und radiological findings, which makes definitive diagnosis challenging. We here show that stereotactic biopsy and neuropathologic examination of the cerebral lesions is a valid option to establish the diagnosis of HA brain infection in the living patient. We strongly recommend to perform stereotactic biopsy early and more frequently in immunocompromised patients with unclear brain lesions. Such a regime allows to tailor treatment more specifically and might result ultimately in a better survival of these severely ill patients.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Abuali MM, Posada R, Del Toro G, Roman E, Ramani R, Chaturvedi S, *et al*. Rhizomucor variabilis var. regularior and *Hormographiella aspergillata* infections in a Leukemic Bone marrow transplant recipient with refractory neutropenia. J Clin Microbiol 2009;47:4176-9.
2. Arvanitis M, Anagnostou T, Fuchs BB, Caliendo AM, Mylonakis E, Molecular and nonmolecular diagnostic methods for invasive fungal infections. Clin Microbiol Rev 2014;27:490-526.
3. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. J Fungi (Basel) 2017;3:57.
4. Brumble LM, Reza MB, Dhakal LP, Cruz G, Saleh OM, Heckman, *et al*. Fungal infections of the central nervous system: Clinical, radiographic and laboratory manifestations. J Microbial Exp 2017;5:00167.
5. Chauhan A, Gruenberg J, Arbefeville S, Mettler T, Brent CH, Ferrieri P. Disseminated *Hormographiella aspergillata* infection with lung and brain involvement after allogenic hematopoietic stem-cell transplantation in a 54-Year-old man. Lab Med 2019;50:426-31.
6. Conen A, Weisser M, Hohler D, Frei R, Stern M. *Hormographiella aspergillata*: An emerging mould in acute leukaemia patients? Clin Microbiol Infect 2011;17:273-7.
7. Gavito-Higuera J, Mullins CB, Ramos-Duran L, Chacon CI, Hakim N, Palacios E. Fungal infections of the central nervous system: A pictorial review. J Clin Imaging Sci 2016;6:24.
8. Geno J, Guillamon JM, Guarro J, Pujol I, Ulfig K. Molecular characterization, relatedness and antifungal susceptibility of the basidiomycetous hormographiella species and Coprinus cinereus from clinical and environmental sources. Antonie Van Leeuwenhoek 1996;70:49-57.
9. Góralska K, Blaszkowska J, Dzikowiec M. Neuroinfections caused by fungi. Infection 2018;46:443-59.
10. Guarro J, Gene J, De Vroey C, Gueho E. *Hormographiella;* a new genus of hyphomycetes from clinical sources. Mycotaxon 1992;45:179-90.
11. Heiblig M, Bozzoli V, Saison J, Thomas X, De Croze D, Traverse-Glehen A, *et al*. Combined medico-surgical strategy for invasive sino-orbito-cerebral breakthrough fungal infection with *Hormographiella aspergillata* in an acute leukaemia patient. Mycoses 2015;58:308-12.
12. Luzzati R, Ferrari S, Nicolato A, Piovan E, Malena M, Merighi M, *et al*. Stereotactic brain biopsy in human immunodeficiency virus-infected patients. Arch Intern Med 1996;56:565-8.
13. Nanno S, Nakane T, Okamura H, Nishimoto M, Koh H, Nakamae H, *et al*. Disseminated *Hormographiella aspergillata* infection with involvement of the lung, brain, and small intestine following allogeneic hematopoietic stem cell transplantation: case report and literature review. Transplant Infect Dis 2016;18:611-6.
14. Neves N, Santos L, Reis C, Sarmento A. *Candida albicans* brain abscesses in an injection drug user patient: A case report. BMC Res Notes 2014;7:837.
15. Pathakumari B, Liang G, Liu W. Immune defence to invasive fungal infections: A comprehensive review. Biomed Pharmacother 2020;130:110550.
16. Pfaller MA, Pappas PG, Wingard JR. Invasive fungal pathogens: Current epidemiological trends. Clin Infect Dis 2006;43:3-14.
17. Reithmeier T, Lopez WO, Doostkam S, Machein MR, Pinsker MO, Trippel M, *et al*. Intraindividual comparison of histopathological diagnosis obtained by stereotactic serial biopsy to open surgical resection specimen in patients with intracranial tumours. Clin Neurol Neurosurg 2013;115:1955-60.
18. Sharma RR. Fungal infections of the nervous system: Current perspective and controversies in management. Int J Surg 2010;8:591-601.
19. Slomka M, Doub J. A rare case of Blastomyces dermatitidis brain abscess in an immunocompetent host. Med Mycol Case Rep 2020;18:8-11.
20. Verweij PE, van Kasteren M, van de Nes J, de Hoog GS, de Pauw BE, Meis JF. Fatal pulmonary infection caused by the basidiomycete *Hormographiella aspergillata*. J Clin Microbiol 1997;35:2675-8.
21. Zhu Z, Huang Z, Li Z, Li X, Du C, Tian Y. Multiple brain abscesses caused by infection with *Candida glabrata*: A case report. Exp Ther Med 2018;15:2374-80.

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