Medical Mycology Case Reports 34 (2021) 27–31

Contents lists available at ScienceDirect

Medical Mycology Case Reports

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

Invasive fungal infection of the brain caused by *Neoscytalidium dimidiatum* in a post-renal transplant patient: A case report

Maha Alamri [a,*], Heba Alghamdi [b], Sahar Althawadi [b], Maysoon Mutabaggani [b], M. Anas Dababo [c], Fahad Alajlan [d], Maha Alzayer [e], Michel Doumith [e,f], Majed Alghoribi [e,f], Reem S. Almaghrabi [a]

[a] Section of Infectious Diseases, Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
[b] Microbiology Laboratory, Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
[c] Anatomic Pathology, Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
[d] Adult Neurology, Neuroscience Department, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
[e] Infectious Diseases Research Department, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
[f] King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

ARTICLE INFO

Keywords:
Scytalidium
Neoscytalidium dimidiatum
Fungal
Infection
Transplant
Immunocompromised

ABSTRACT

Neoscytalidium is a phytopathogen that is often found in plants and soil. It mostly leads to skin and nail infections, and invasive diseases of the sinuses, lung, and brain have been described mostly in immunocompromised patients. We report a case of a post-renal transplant patient who received anti-thymocyte globulin for induction immunosuppression. A month after her transplant, she presented with fever and new-onset seizures, and computed tomography revealed a brain abscess with mass effects and herniation. The patient underwent abscess drainage and craniectomy. The pathological findings showed filamentous septate hyphae. The surgical culture rapidly grew wool-like colonies with a black reverse on Sabouraud agar. Lactophenol cotton blue staining showing septate branched hyphae with one to two arthroconidia cells with flattened ends. The patient was given a combination of amphotericin B and voriconazole but unfortunately died ten days after the diagnosis. This case highlights *Neoscytalidium* as a cause of invasive fungal disease in immunocompromised patients that is difficult to treat and is often fatal, even when combined surgical and medical therapies are used as treatment modalities.

1. Introduction

The Neocytalidium genus is a phytopathogen found in plants and soil. It includes more than 15 species; two are usually pathogenic in humans, *Neoscytalidium dimidiatum* and *Scytalidium hyalinum* [1]. These pathogens are usually geographically distributed in tropical and subtropical areas, with the highest incidence in Africa, South America, India, and Asia, accounting for 0.7% of onychomycosis and 0.2% of skin infections on the soles [1,2]. The clinical manifestations are diverse, and most reported cases are related to skin and nail infection mimicking dermatomycosis and onychomycosis; however, there are cases of invasive disease, mainly in patients with immunocompromising conditions [1]. Invasive ophthalmological disease affecting healthy and immunocompetent adults has been described in several cases, leading to endophthalmitis and keratitis.

In most cases, the disease was refractory to systemic and topical antifungals requiring enucleation [3–7]. Disseminated and invasive diseases involving the brain and sinuses have been described in multiple post-solid organ transplant patients [8–11]. As the pathogen rarely presents with invasive disease, the diagnosis is often delayed, resulting in a poor outcome; we describe a case of invasive Neoscytalidium brain infection in a post-renal transplant patient.

2. Case

A 55-year-old female known to have hypertension, a history of stroke with residual weakness, carotid artery stenosis post right carotid endarterectomy, diabetes mellitus, and end-stage renal disease (ESRD) started hemodialysis in 2018. She underwent a living related renal transplant on Day 0, in which her daughter was the donor. She received anti-thymocyte globulin (ATG) and methylprednisolone for induction immunosuppression and was maintained on prednisolone, tacrolimus,

* Corresponding author. Section of Infectious Diseases, Department of Medicine King Faisal Specialist Hospital and Research Centre, Riyadh, 11211, Saudi Arabia.
E-mail address: malamari70@kfshrc.edu.sa (M. Alamri).

https://doi.org/10.1016/j.mmcr.2021.09.001
Received 10 April 2021; Received in revised form 30 August 2021; Accepted 7 September 2021
Available online 16 September 2021

and mycophenolate-mofetil. The patient had delayed graft function requiring dialysis. Biopsy of the transplanted kidney showed acute tubular necrosis (ATN). On Day +34 during her clinic follow-up appointment, the patient presented with a fever of 38.2 °C and had a tonic-clonic seizure lasting for 1 min. She was admitted for further examination and treatment. A social history was then taken from the family. She had been a housewife living on a farm for the past three months. She had direct contact with sheep and rabbits. She had a skin rash attributed to an allergic reaction. On physical examination, she was afebrile with normal vital signs. She was confused, and her pupils were reactive and equal in size bilaterally. Motor and sensory functions were intact. Deep tendon reflexes were normal in the upper limbs, and absent tendon reflexes were normal in the lower limbs with a mute bilateral plantar reflex. Meningeal signs could not be elicited.

The systemic examination was unremarkable. Laboratory investigations were remarkable for a white blood cell count was slightly elevated to 12.66 10^9/L, with a normal absolute neutrophil count of 9.849.84 10^9/L, severely suppressed absolute lymphocyte count of 0.21 10^9/L, significantly increased creatinine 536 μmol/L, low sodium level of 127 mmol/L, elevated procalcitonin of 2.59 ng/ml, elevated C-reactive protein of 102 mg/L, and a normal tacrolimus level of 14.9 ng/ml. Brain computed tomography (CT) without contrast was performed on the day of admission and showed a subacute infarction in the right cerebral hemisphere following anterior circulation in the arterial territories with few focal areas of calcifications (Fig. 1). Hypodensity was seen within the right parieto-occipital lobes, with no significant mass effect presenting as a subacute ischemic event. The patient's neurological status deteriorated with a worsening level of consciousness (LOC),

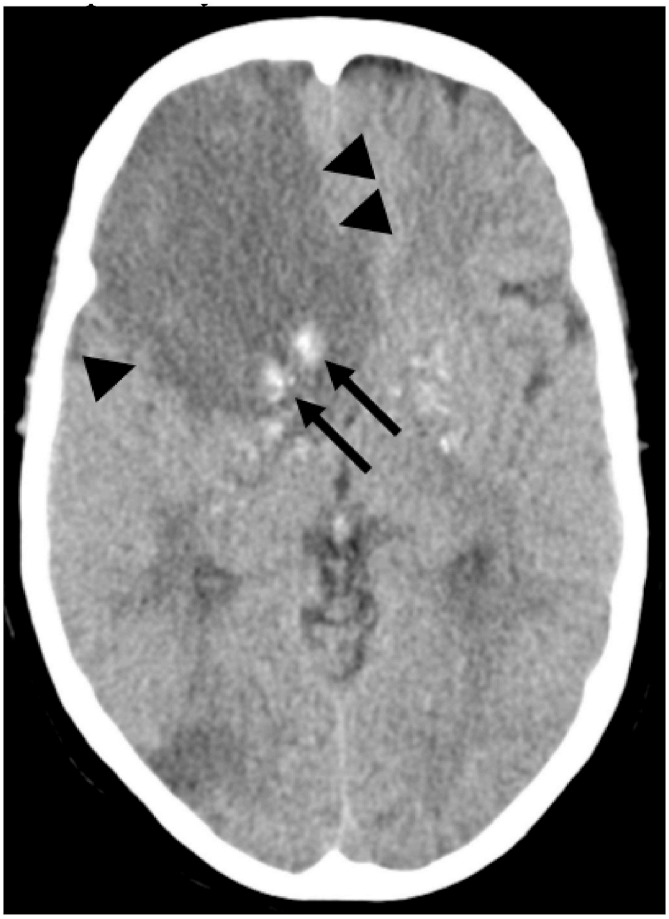

Fig. 1. Axial non-contrast CT of the brain cerebrum that revealed subacute infarction (black arrowheads) in the right cerebrum with few areas of calcifications (black arrows).

the right pupil was irregular in shape and nonreactive to light, and the right-side plantar reflex was upgoing. A repeat brain CT the following day showed a worsening mass effect on the right lateral ventricle and a mild leftward midline shift with subfalcine herniation. Accordingly, the patient underwent emergency decompressive craniectomy and right frontal lobe biopsy on the same day (Day +35). Pathology showed abundant thin septate fungal hyphae with angioinvasion (Fig. 2). The fungal culture on day 3 (Day +37) rapidly grew on Sabouraud agar (Fig. 3). Lactophenol cotton blue staining showed a morphological appearance consistent with *Neoscytalidium* spp., *showing* hyaline septate hyphae and contiguous rectangular arthroconidia (Fig. 4) [12]. Template DNA was extracted from the grown culture to prepare an Illumina sequencing library using the Nextera-XT library preparation kit according to the manufacturer's instructions. Whole-genome low coverage sequencing was performed on the MiSeq Illumina instrument with a 2 × 300 paired-end protocol. The reads generated were assembled with SPAdes software [1] using the default options. The sequence of the internal transcribed spacer (ITS) region commonly amplified with ITS-1 and ITS-4 primers was extracted *in silico* from the assembled genome and queried against GenBank (www.ncbi.nlm.nih.gov) and the CBS-KNAW fungal biodiversity center (www.cbs.knaw.nl). Sequence alignments showed the highest identities (99.47–100%) to the ITS regions of the ribosomal DNA from *Neoscytalidium dimidiatum*. Manual alignments of the assembled contigs with publicly available *N. dimidiatum* draft genomes confirmed the species identity.

The patient was started on dual antifungals on Day +37 (2 days after the surgery when the preliminary pathology results were obtained), liposomal amphotericin B 5 mg/kg once daily, and voriconazole 6 mg/kg as a loading dose for two doses and subsequently at 200 mg twice daily. After a week, the voriconazole level was checked and was in a therapeutic range (3.04 mg/L). A chest CT scan was performed to assess the extent of the disease and showed no changes suggestive of invasive pulmonary fungal infection. On Day +38, the patient's neurological condition deteriorated. Brain CT showed extensive ischemic changes along the Anterior cerebral artery and middle cerebral artery territory in the right cerebral hemisphere and the development of obstructive hydrocephalus. As the patient's prognosis was deemed poor, she was not taken to surgery, and her code status was changed to do not resuscitate. On Day+47, the patient died.

3. Discussion

This case describes a rare fungal pathogen that rarely presents as an invasive disease but caused a rapidly progressive and fatal invasive brain infection in a renal transplant patient. *Neoscytalidium* belongs to the saprophytic dematiaceous fungi group. It has a wide geographic distribution and is present mainly in soil and plants [13]. We postulate that the infection occurred before the transplant given the patient's prolonged stay on a farm and the suspicious skin lesions she developed. The rapid course of disease progression is likely related to poor cellular dysfunction following ATG administration.

Similar invasive diseases have been reported in renal transplant patients. The invasiveness of these diseases was described in 1996 when Rockett et al. [11] reported a case of subcutaneous phaeohyphomycosis in a renal transplant patient. Another case series by Garinet et al. [10] described invasive skin and soft tissue disease in 5 renal transplant patients. Invasive pulmonary infection and disseminated skin infection have been described in a renal transplant patient. In the latter case, the patient's skin biopsy culture was morphologically consistent with a diagnosis of *Neoscytalidium*. Amphotericin B followed by voriconazole was given and led to a good response and resolution of the skin and lung lesions [14]. This emphasizes that the combination of the two agents provides a reasonable choice for treatment.

Four cases have been published describing invasive diseases affecting the brain and are summarized in Table 1. Cerebral disease appears to be fatal in the three described cases irrespective of the

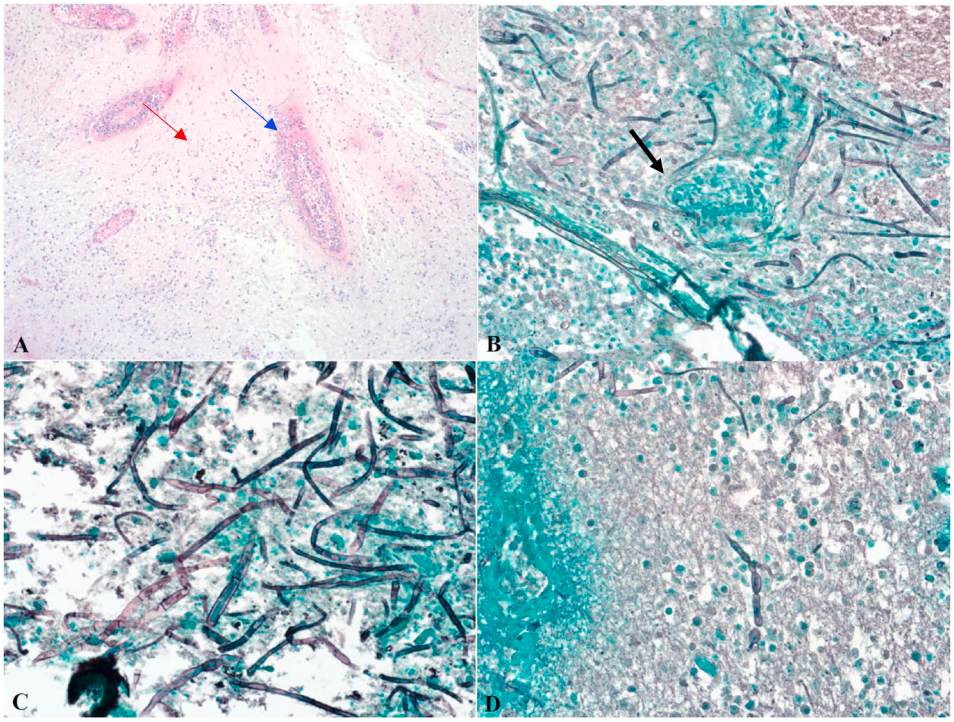

Fig. 2. A. H&E stained section 10X showing necrotic brain tissue (Red arrow) and necrotic inflamed vessels (Blue arrow). B. GMS stain shows fungal elements invading vessel (Black arrow) ×40 the fungal elements are mixed septated hyphae and nonseptate pseudohyphae. C. Numerous septated hyphae 60X. D. Nonseptate pseudohyphae elements 40x. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
*GMS: Grocott methenamine silver stain. H&E Hematoxylin and eosin.

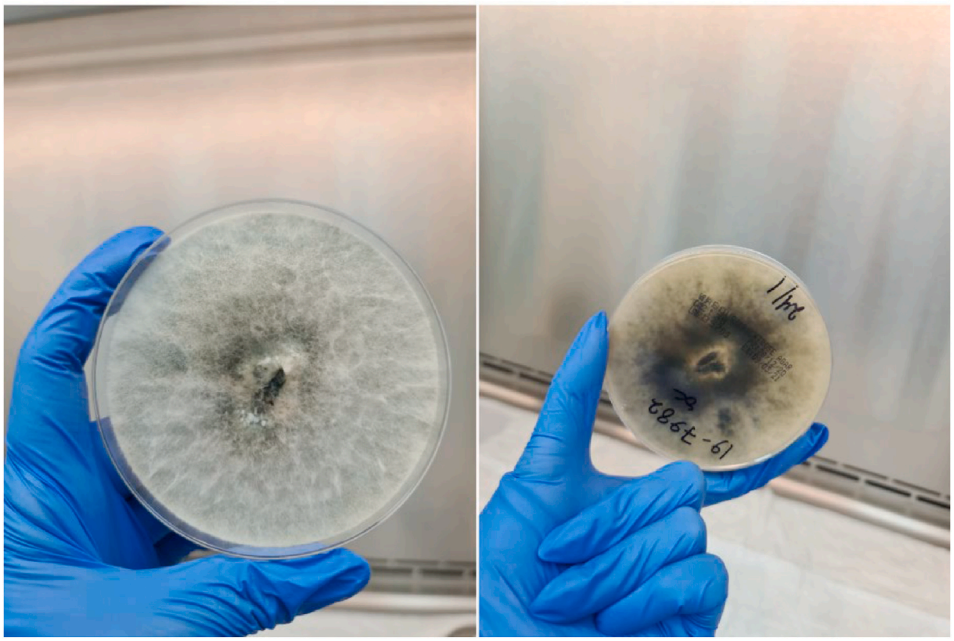

Fig. 3. A Sabouraud dextrose agar with chloramphenicol and cycloheximide showing a rapidly growing fungus that grew in 3 days with a characteristic wooly surface and dark gray reverse.

patient's immune status. All three reported cases progressed rapidly with hydrocephalus and death occurring shortly after diagnosis despite aggressive surgical intervention and treatment with amphotericin and/or voriconazole [8,15–17]. ATG use has also led to disease progression after an initial response to treatment, which appears to be a risk factor predisposing patients to more invasive disease [8].

The diagnosis was based on the morphological characteristics and rapidity of growth of wool-like colonies with a black reverse on Sabouraud agar and lactophenol cotton blue staining that showed septate hyphae with fission arthroconidia along with larger, more pigmented, brown-colored conidia [18].

There is no recommended treatment approach given the absence of standardized minimum inhibitory concentration (MIC) cutoffs. Amphotericin B, voriconazole, and terbinafine have the highest in vitro antifungal susceptibility [19]. Voriconazole has the lowest MIC of all antifungals, making it the most active drug. The MIC values for caspofungin, terbinafine, and posaconazole were variable for different isolates [20,21]. Most reported cases of invasive diseases were treated with a combination regimen of amphotericin B and voriconazole with little success, suggesting the aggressiveness of the disease and an inadequate

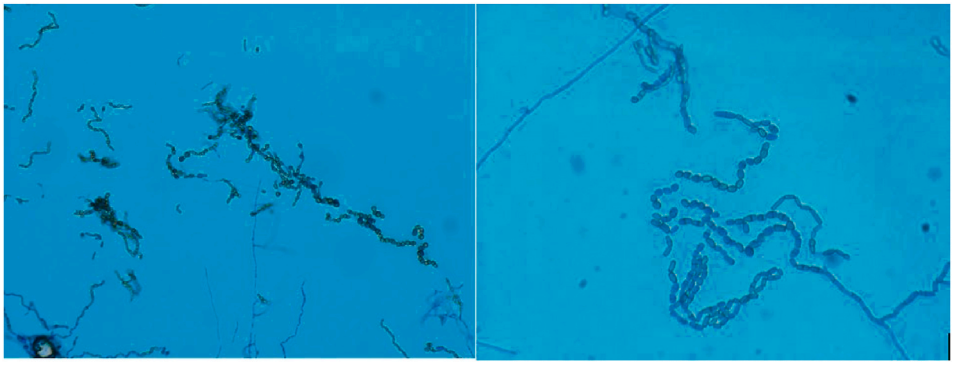

Fig. 4. Lactophenol cotton blue staining showing septate branched hyphae with 1–2 arthroconidia cells with flattened ends. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Summary of reported cerebral neoscytalidium infections.

Age (years) Reference number	Underlying disease	Presentation	Brain imaging findings	Surgical treatment	Antifungals	Outcome
31 [8]	Renal transplant complicated with acute cellular rejection requiring ATG.	Paranoid delusions and hallucinations.	Brain CT: right posterior temporal hypoattenuating lesion with surrounding edema measuring	EVD insertion for hydrocephalus.	Voriconazole.	Death.
17 [15]	Systemic lupus erythematosus with renal involvement.	Fever, seizure, neck rigidity.	Brain CT: hypodense lesion in the frontal lobe.	Craniotomy and abscess drainage.	Amphotericin B.	Death.
18 [16]	Healthy	Headache, fever, vomiting and right-sided weakness.	Brain CT: Hydrocephalus, with multiple white matter lesions in the right thalamus, internal capsule, globus pallidus and right cerebellum, with no significant contrast enhancement. Brain MRI: abscess in the left frontal lobe, with mild hydrocephalus.	Stereotactic abscess drainage. Theco-peritoneal shunt for hydrocephalus.	Amphotericin and fluconazole that was later switched to posaconazole.	Death.
62 [17]	Liver cirrhosis, hepatocellular carcinoma, diabetes.	Progressive dysarthria and generalized weakness.	Brain MRI: 1.8 cm brain abscess.	Stereotactic abscess drainage.	Amphotericin for one week then switched to voriconazole.	Alive after 15 months of follow up.

ATG: Anti-thymocyte globulin. CT: Computed tomography. MRI: Magnetic resonance imaging. EVD: External ventricular device.

response to therapy. Early recognition and identification is important to guide targeted treatment and to improve outcomes.

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Please state any sources of funding for your research

There are none.

Conflict of 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'.

Please state any competing interests

There are none.

Consent

Please declare that you have obtained written and signed consent to publish the case report from the patient or legal guardian(s).

Please state that consent has been obtained from the patient or legal guardian(s)

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

No conflicts of interest exist.

References

[1] M. Machouart, P. Menir, R. Helenon, D. Quist, N. Desbois, *Scytalidium* and scytalidiosis: what's new in 2012? J. Mycol. Med. 23 (2013) 40–46, https://doi.org/10.1016/j.mycmed.2013.01.002.

[2] C.S. Lacaz, A.D. Pereira, E.M. Heins-Vaccari, L.C. Cucé, C. Benatti, R.S. Nunes, N. T. de Melo, R.S. de Freitas-Leite, G.L. Hernández-Arriagada, Onychomycosis caused by *Scytalidium dimidiatum*. Report of two cases. Review of the taxonomy of the synanamorph and anamorph forms of this coelomycete, Rev. Inst. Med. Trop. Sao Paulo 41 (1999) 319–323, https://doi.org/10.1590/S0036-46651999000500009.

[3] I.B. Cursi, L.B. Freitas, L. Neves Mde, I.C. Silva, Onycomychosis due to *Scytalidium* spp.: a clinical and epidemiologic study at a University Hospital in Rio de Janeiro, Brazil, an, An. Bras. Dermatol. 86 (2011) 689–693, https://doi.org/10.1590/s0365-05962011000400010.

[4] A.A. Al-Rajhi, A.H. Awad, S.S. Al-Hedaithy, R.K. Forster, K.C. Caldwell, *Scytalidium dimidiatum* fungal endophthalmitis, Br. J. Ophthalmol. 77 (1993) 388–390, https://doi.org/10.1136/bjo.77.6.388.
[5] U. Tendolkar, R. Tayal, S. Baveja, C. Shinde, Mycotic keratitis due to *Neoscytalidium dimidiatum*: a rare case, Community Acquir. Infect. 2 (2015) 142, https://doi.org/10.4103/2225-6482.172648.
[6] Q.A. Farjo, R.S. Farjo, A.A. Farjo, *Scytalidium keratitis:* case report in a human eye, Cornea 25 (2006) 1231–1233, https://doi.org/10.1097/01.ico.0000230323.28956.b9.
[7] R. Blázquez, M. Losada, A. Ruiz, C. Guerrero, J. Rodriguez-Tudela, A. Monzón, M. Segovia, Recurrent post-traumatic *Scytalidium dimidiatum* fungal Endophthalmitis, Clin. Microbiol. Newsl. 26 (2004) 44–46, https://doi.org/10.1016/S0196-4399(04)90018-9.
[8] D.H. Tan, L. Sigler, C.F. Gibas, I.W. Fong, Disseminated fungal infection in a renal transplant recipient involving *Macrophomina phaseolina* and *Scytalidium dimidiatum*: case report and review of taxonomic changes among medically important members of the Botryosphaeriaceae, Med. Mycol. 46 (2008) 285–292, https://doi.org/10.1080/13693780701759658.
[9] J.J. Dunn, M.J. Wolfe, J. Trachtenberg, J.D. Kriesel, R.R. Orlandi, K.C. Carroll, Invasive fungal sinusitis caused by *Scytalidium dimidiatum* in a lung transplant recipient, J. Clin. Microbiol. 41 (2003) 5817–5819, https://doi.org/10.1128/jcm.41.12.5817-5819.2003.
[10] S. Garinet, J. Tourret, S. Barete, N. Arzouk, I. Meyer, C. Frances, A. Datry, D. Mazier, B. Barrou, A. Fekkar, Invasive cutaneous *Neoscytalidium* infections in renal transplant recipients: a series of five cases, BMC Infect. Dis. 15 (2015) 535, https://doi.org/10.1186/s12879-015-1241-0.
[11] M.S. Rockett, S.C. Gentile, K.H. Zygmunt, C.J. Gudas, Subcutaneous phaeohypomycosis caused by *Scytalidium dimidiatum* in the foot of an immunosuppressed host, J. Foot Ankle Surg. 35 (1996) 350–354, https://doi.org/10.1016/s1067-2516(96)80086-x.
[12] G.W. Procop, Medically important fungi: a guide to identification – 5th edition, Lab. Med. 45 (2014) e68–e69, https://doi.org/10.1309/LMW8AT6W4EUIXYBP.
[13] S.J. Yang, C.Y. Ng, T.S. Wu, P.Y. Huang, Y.M. Wu, P.L. Sun, Deep cutaneous *Neoscytalidium dimidiatum* infection: successful outcome with amphotericin B therapy, Mycopathologia 184 (2019) 169–176, https://doi.org/10.1007/s11046-018-0308-z.
[14] B. Willinger, G. Kopetzky, F. Harm, P. Apfalter, A. Makristathis, A. Berer, A. Bankier, S. Winkler, Disseminated infection with *Nattrassia mangiferae* in an immunosuppressed patient, J. Clin. Microbiol. 42 (2004) 478–480, https://doi.org/10.1128/jcm.42.1.478-480.2004.
[15] M. Geramishoar, K. Zomorodian, F. Zaini, F. Saadat, B. Tarazooie, M. Norouzi, S. Rezaie, First case of cerebral phaeohyphomycosis caused by *Nattrassia mangiferae* in Iran, Jpn. J. Infect. Dis. 57 (2004) 285–286.
[16] R.S. Mani, Y.T. Chickabasaviah, S. Nagarathna, A. Chandramuki, M. R. Shivprakash, J. Vijayan, D.K. Prashantha, P.S. Vasudevan, A. Natarajan, J. Kovoor, Cerebral phaeohyphomycosis caused by *Scytalidium dimidiatum*: a case report from India, Med. Mycol. 46 (2008) 705–711, https://doi.org/10.1080/13693780802172017.
[17] S.Y. Jo, S. Lee, K.H. Kim, J. Yi, A case of brain abscess caused by the dematiaceous mold *Neoscytalidium dimidiatum* in a Korean Man, Ann. Lab. Med. 41 (2021) 247–249, https://doi.org/10.3343/alm.2021.41.2.247.
[18] M.K. Moore, The infection of human skin and nail by *Scytalidium* species, Curr. Top. Med. Mycol. 4 (1992) 1–42, https://doi.org/10.1007/978-1-4612-2762-5_1.
[19] L. Tonani, N.S. Morosini, H.D. de Menezes, M.E.N.B. da Silva, M. Wainwright, G. L. Braga, M.R. von Zeska Kress, In vitro susceptibilities of *Neoscytalidium* spp. sequence types to antifungal agents and antimicrobial photodynamic treatment with phenothiazinium photosensitizers, Fungal Biol 122 (2018) 436–448, https://doi.org/10.1016/j.funbio.2017.08.009.
[20] J. Dunand, A. Paugam, In vitro efficacy of voriconazole against clinical isolates of *Scytalidium* spp. from clinical lesions, Int. J. Antimicrob. Agents 31 (2008) 176–177, https://doi.org/10.1016/j.ijantimicag.2007.09.006.
[21] C. Lacroix, M.F. de Chauvin, In vitro activity of amphotericin B, itraconazole, voriconazole, posaconazole, caspofungin and terbinafine against *Scytalidium dimidiatum* and *Scytalidium hyalinum* clinical isolates, J. Antimicrob. Chemother. 61 (2008) 835–837, https://doi.org/10.1093/jac/dkn011.