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Molecular Identification of *Fonsecaea monophora*, Novel Agent of Fungal Brain Abscess

Appendix

Appendix Table. *Fonsecaea monophora* cases reported in the literature

Year/ Author	Age/Sex with Immune status and Exposure history	Symptoms	Radiology	KOH/ Direct Microscopy	Culture	Histopathology	Molecular	AFST	Therapy	Outcome/ Follow-up	Comment
1954/ Lucasse (*1*)	10/M	4 mo of back pain refractory to quinine and penicillin; mild neck stiffness and occasional low-grade temperature; *Mansonella perstans* seen in blood smear	NA	small black filaments floating in clear CSF at autopsy	a black fungus thought at the time to represent *Cladosporium trichoides*	multiple small peripheral cerebral abscesses with a granulomatous response in autopsy specimen; some containing hyphal and spore-like forms	sequencing confirmed at CBS, Utrecht (CBS 100430)	NA	progressive neurologic deterioration despite empiric penicillin, streptomycin and antiparasitic therapy	death after 5 mo	Described as *Cladosporium trichoides*
2003/ Nobrega (*2*)	28/M with history of knife wound in right inguinal area with granuloma sixteen years back and noticed a visual defect in the left eye at that time; previous data for schistosomiasis and Chagas disease; more recently, manifested a pulmonary granulomatous lesion in the right lung with a single non-pigmented form of a fungus	severe bitemporal headache accompanied by fits of dizziness with nausea and vomiting, right ocular pain and loss of the temporal field of the right eye; right homonymous inferior quadrantopsy defect and a left homonymous hemianopsy; macrocytic anemia probably of nutritional origin	tumoral mass measuring 2 × 2 x 1.5 cm involving the right temporo-occipital area and another smaller apparently healed lesion at the left occipital lobe	elongated septate pigmented hyphae	velvety, dark olive gray colonies developing radial grooves and a central elevation when old; LPCB showing light brown septate hyphae ≈3 µm in diameter and straight conidiophores bearing frequently branched one-celled chains of conidia	granulomatous inflammation; golden brown round or oval forms 10–12 µm in diameter and septate hyphal forms 6–7 µm in diameter observed inside giant cells or isolated in necrotic areas (“chromoblastomycosis”); capillary hyperplasia and perivascular lymphocytic cuffing	sequencing confirmed at CBS, Utrecht	NA	IV amphotericin B started after pathology report; right temporal craniotomy and surgical enucleation after 20 d; discharged with oral itraconazole	initially responded to surgery and antifungals; expired few months after due to complications of the previous neuro-surgery; no residual fungal disease at autopsy	Described as *F. pedrosoi*
2005/ Surash (*3*)	53/M with diabetes, previous exposure to tropical fish and plants	1 week history of right-sided weakness, slurred speech and constant	3.6 × 2.3 cm ring-enhancing lesion in left frontal lobe with surrounding edema;	septate fungal hyphae on Gram stain	dematiaceous fungus after 1 week incubation provisionally	brown, septate, branching hyphae with occasional bulbous elements	sequencing confirmed at CBS, Utrecht (CBS 117238)	amphotericin B 0.5 µg/mL, itraconazole 0.03 µg/mL,	IV amp B for 1 week; IV voriconazole+flucytosine followed by switch to oral; surgical excision of frontal	stable and slowly improving	1st described case of CNS *F. monophora* (3rd overall)

Year/ Author	Age/Sex with Immune status and Exposure history	Symptoms	Radiology	KOH/ Direct Microscopy	Culture	Histopathology	Molecular	AFST	Therapy	Outcome/ Follow-up	Comment
		dull right-sided headache	new lesion within right supra-sellar cistern and adjacent anterior interhemispheric fissure after 4 mo of therapy; another lesion in left thalamus after 5 mo of therapy; good resolution after 12 mo of therapy		identified as *Cladophialophora spp.*			voriconazole 0.06 μg/mL and posaconazole <0.015 μg/mL	lesion after 3 mo; oral voriconazole replaced with IV itraconazole after 5 mo followed by switch to oral; 21 mo of antifungals		
2007/ Takei (*4*)	62/F post liver transplant 4 mo back	5-mo history of progressive left upper extremity numbness as well as a 1-mo episode of increasing pain and swelling in the left ankle	three ring-enhancing lesions in cortex and subcortical white matter: 16 mm in right parietal lobe, 15 mm in left parietal lobe (solid), 5 mm in left occipital lobe; 11 × 13 mm enhancing subchondral geographic marrow abnormality within the left medial malleolus	NA	*.F monophora* grown from brain and tibial lesions	granulomatous inflammation with fungal organisms: groups of oval to elongated yeast-like cells, chains of budding cells (toruloid hyphae) and rare septate hyphae; with golden-brown cell walls and observed inside giant cells or isolated in necrotic areas; scattered muriform cells	done but not specified; final identification done at University of Texas, San Antonio	NA	surgical excision of right parietal lesion; oral voriconazole started on post-operative day 1 and continued; discharged after 9 d	no recurrence 1.5 y after discharge	1st case involving multiple systems
2010/ Koo (*5*)	48/F post renal transplant 8 y back on prednisone, tacrolimus, mycophenolate mofetil and sulfamethoxazole for frequent urinary tract infection; previously two episodes of acute rejection, CMV reactivation; born and raised in Jamaica and emigrated to the U.S. 20 y back	progressively severe frontal headaches of two weeks duration, discomfort and stiffness of neck muscles and mild photophobia	irregular 3.1 × 3.4 cm ring-enhancing lesion in left frontal lobe with mass effect, an area of more solid-appearing enhancement	NA	velvety grayish-black mold showing septate hyphae with 4 types of conidial formations: *Rhinocladiella*-like, *Cladosporium*-like, *Phialophora*-like and thinner asterisk-like	granulomatous inflammation and numerous pigmented budding yeast-like and hyphal forms	sequencing confirmed at CBS, Utrecht (CBS 117542)	amphotericin B 0.25 μg/ml, voriconazole 0.125 μg/ml and posaconazole 0.03 μg/ml	surgical excision and empirical liposomal amphotericin B; voriconazole added after phaeohyphomycosis confirmed and both continued for 2 weeks; voriconazole monotherapy for 18 mo	no recurrence 4.5 y after discharge	(1→3) β-D-glucan (BG) levels >500 pg/ml with serial decrease
2014/ Doymaz (*6*)	71/F with chronic diabetes mellitus and hypertension	nausea, vomiting and headache	3 × 4 × 3 cm lesion in left temporal lobe, 3 mm midline shift to the right side, vasogenic edema in the left fronto-temporo-parietal area	NA	dematiaceous fungus on SDA by 1st week; velvety in texture; LPCB suggestive of *Fonsecaea spp.*- up to three and	hyphal elements with thick septations, suppurative inflammatory changes, necrosis, foreign body giant cells and gliosis in peripheral parenchymal tissues	sequencing confirmed	NA	surgical excision and liposomal amphotericin B; replaced with IV voriconazole after 40 d for 3 weeks; discharged on day 60 on oral voriconazole	no recurrence 10 mo after discharge; healthy and stable	4th described case of CNS *F. monophora*

Year/ Author	Age/Sex with Immune status and Exposure history	Symptoms	Radiology	KOH/ Direct Microscopy	Culture	Histopathology	Molecular	AFST	Therapy	Outcome/ Follow-up	Comment
			- preliminary diagnosis of glioblastoma multiforme		very rarely small fourth conidia formed on the tips of the conidiophores						
2016/ Bagla (*7*)	54/F PLHA diagnosed 9 mo back; on ART with CD4 count 42 cells/mm3 and undetectable viral load; history of hepatitis C without cirrhosis and late latent syphilis; IV drug abuse 20 y back; smoking and alcohol addiction	intermittent headache, vomiting and episodes of left arm twitching for 1 week; confused and incontinent of stool and urine; diminished muscle strength and deep tendon reflexes in left arm	2 cm ring enhancing lesion with surrounding vasogenic edema in right parietal lobe	septate hyphae	dematiaceous mold	dematiaceous fungus in a background of granulomas with Langhans giant cells and central necrosis	sequencing confirmed at Associated Regional University Pathologists	amphotericin B 2 µg/mL, itraconazole 0.5 µg/mL, voriconazole 0.06 µg/mL and posaconazole 0.25 µg/mL	surgical excision on 7th day; started on IV voriconazole and liposomal amphotericin B on day 8; voriconazole changed to oral on day 12	initially improved on antifungals (possible response to steroids); worsening mental status from day 16 and expired within days	5th described case of CNS *F. monophora*
2016/ Varghese (*8*)	63/M with type 2 diabetes mellitus and decompensated chronic liver disease; past history of endoscopic esophageal variceal ligation	headache and progressive left-sided weakness for 3 weeks	2 × 2 cm hypodense cystic lesion in right lentiform nucleus region with significant perilesional edema	branched, septate hyphae with light brown pigmentation	olivaceous to black in color with velvety appearance; pigmented septate hyphae and pale to olivaceous smooth-walled conidia on sympodially branched conidiophores on LPCB	NA	sequencing confirmed-EMBL accession no. LN626652 (ITS) and LN651287 (D1/D2)	E-test: amphotericin B 4 µg/ml, flucytosine >32 µg/ml, itraconazole 0.19 µg/ml, voriconazole 0.004 µg/ml, posaconazole 0.032 µg/ml, caspofungin 0.25 µg/ml and anidulafungin 0.38 µg/ml	started empirically on IV fluconazole; replaced with oral voriconazole after 1 week; repeat aspiration and amphotericin B added for neurologic deterioration after 2 weeks	expired due to raised intracranial tension despite antifungals; caregivers refused surgical intervention	1st described case of CNS *F. monophora* from India
2017/ Stokes (*9*)	63/M South Sudanese immigrant with poorly controlled type 2 diabetes, liver cirrhosis due to chronic hepatitis B; recent travel to South Sudan for 1 y; admitted to an intensive care unit in Egypt for ≈1 mo with apparent malaria; progressive	headache and constitutional symptoms for weeks; febrile at his follow-up appointment 5 d later	CT head in the emergency was normal; 9 mm ring-enhancing lesion near the gray–white matter junction of the left parasagittal frontal lobe with a large amount of surrounding vasogenic edema on day 8; rapidly progressed to 20 mm on day 26	branched, septate hyphae	dematiaceous mold that was identified as *F. monophora*	extensive tissue and blood vessel necrosis with septate branching hyphae	sequencing confirmed	flucytosine 4 µg/mL, amphotericin B 0.25 µg/mL, itraconazole 0.06 µg/mL, micafungin 1 µg/mL, caspofungin 0.25 µg/mL and voriconazole 0.25 µg/mL	ceftriaxone and metronidazole for empiric therapy; anti-tubercular therapy added after day 12; continued to deteriorate; liposomal amphotericin B started on day 38; IV voriconazole added on day 42	right hemiplegia and worsening level of consciousness during admission; expired despite antifungals on day 64 from severe aspiration pneumonia	7th described case of CNS *F. monophora*

Year/ Author	Age/Sex with Immune status and Exposure history	Symptoms	Radiology	KOH/ Direct Microscopy	Culture	Histopathology	Molecular	AFST	Therapy	Outcome/ Follow-up	Comment
	fatigue, a 20 kg weight loss, decreased appetite, diarrhea and diffuse abdominal pain since then; had previously received epidural injections, the last one >6 y earlier; had worked for an Alberta slaughterhouse										
2018/ Dobias (*10*)	61/M from Moldova, living in the Czech Republic, who had worked as a locksmith on oil platforms in Turkmenistan, Kazakhstan, Sudan, and Iraq; myringotomy of both ear drums in 2010	sudden motion disorder of the right limbs, dysarthria, and hypomimia; confusion since 3 mo; right cranial nerves palsy	expansive focus of 3. 1 × 5. 2 cm size around the left lateral ventricle of the brain and a pronounced peripheral edema	NA	dark-pigmented fungal colonies with macro- and micromorphological characteristics typical of the genera *Cladophialophora*/ *Fonsecaea*	dark-pigmented hyphae	sequencing confirmed directly from brain tissue and culture; GenBank accession numbers LT984660 and LT984661	E-test: voriconazole 0.016 µg/mL, amphotericin B 4 µg/mL, itraconazole 0.25 µg/mL and posaconazole 0.016 µg/mL	surgical excision on day 5; liposomal amphotericin B; changed to voriconazole after AFST	improved significantly post-op, able to walk in 4 mo	(1→3) β-D-glucan (BG) levels 149 pg/ml with serial decrease
2018/ Helbig (*11*)	78/F with chronic obstructive pulmonary disease, presumably related to her work history as a baker	subacute right lower extremity paresis and facial nerve palsy	18 × 13 mm left thalamic mass with surrounding edema; enlargement of the ring-enhancing mass (24 × 20 mm) at 1 week	branching septate hyphae morphologically suggestive of *Aspergillus*	black velvet-like colonies	septate branching hyphae with chronic and acute inflammation and necrosis	sequencing confirmed at Robert Koch Institute, Berlin	Voriconazole 0.125 µg/mL	IV dexamethasone started after imaging; radical open excision at 1 week; voriconazole added after AFST	initially improving with voriconazole; died 4 mo post-surgery due to pneumonia	1st described case of CNS *F. monophora* from Germany

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