CLINICAL CASE REPORT

The first described case of *Lodderomyces elongisporus* meningitis

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We describe the first documented case of meningitis caused by *Lodderomyces elongisporus*. Identification of *L. elongisporus* was made on the basis of an arachnoid biopsy with pathology samples sent for fungal internal transcribed spacer sequencing after multiple central nervous system (CNS) fungal culture specimens were negative. After final diagnosis, treatment was transitioned from amphotericin to fluconazole, which, combined with insertion of lumbar drain followed by a permanent ventriculopleural shunt, resulted in significant clinical improvement. Our report reviews the literature of (1) cases of *L. elongisporus*, which almost exclusively describe fungemia or endocarditis; (2) CNS infections caused by *Candida parapsilosis*, an organism with which *L. elongisporus* was previously conflated; and (3) management of fungal meningitis–associated hydrocephalus.

KEYWORDS: fungal meningitis, ITS sequencing, *Lodderomyces elongisporus*

Les chercheurs décrivent le premier cas répertorié de méningite causée par le *Lodderomyces elongisporus*. Ils ont dépisté le *L. elongisporus* après avoir effectué une biopsie de l'arachnoïde et envoyé les prélèvements pathologiques au séquençage de l'espaceur transcrit interne fongique après l'obtention de multiples cultures fongiques négatives. Après le diagnostic définitif, le traitement d'amphotéricine a été remplacé par du fluconazole qui, combiné à l'insertion d'un drain lombaire suivie par l'installation d'une dérivation ventriculopleurale permanente, a favorisé une amélioration clinique évidente. L'analyse bibliographique a permis d'extraire 1) des cas de *L. elongisporus*, qui ont été observés presque exclusivement dans des cas de fongémie auparavant, 2) des infections du système nerveux central causées par le *Candida parapsilosis*, un organisme avec lequel le *L. elongisporus* a déjà été confondu et 3) la prise en charge de l'hydrocéphalie associée à la méningite fongique.

MOTS-CLÉS : méningite fongique, séquençage ITS, *Lodderomyces elongisporus*

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CASE PRESENTATION

A 62-year-old man presented to a peripheral hospital with a 2-week history of headache and dizziness. His medical history included T3bN+ adenocarcinoma of the rectum, hypertension, hyperlipidemia, and chronic lymphopenia (0.3×10^9 g/L). One year before presentation, he was treated with neoadjuvant capecitabine and pelvic radiation for his rectal adenocarcinoma. This treatment was followed by surgical resection of his malignancy, and finally five cycles of adjuvant oxaliplatin and capecitabine, completed 2 months before his presentation.

On presentation, his initial vital signs were within normal limits. Computed tomography scan of the head showed hydrocephalus. One day after admission, gait ataxia, urinary

incontinence, and confusion were noted. Neurology was consulted, and he was subsequently transferred to a larger peripheral hospital for further workup and treatment while awaiting transfer to an inpatient neurology unit at a tertiary referral centre. MRI showed diffuse dilation of the ventricular system, consistent with evidence of worsening communicating hydrocephalus. Lumbar puncture was performed, which showed a neutrophilic-predominant cerebrospinal fluid (CSF) pleocytosis (344×10^6/L; 52% neutrophils, 41% lymphocytes, 7% monocytes), hypoglycorrhacia (1.1 mmol/L), and significantly elevated protein (4.152 g/L). An opening pressure was 28.5 cm H_2O (seated position). He was started on empiric coverage for meningitis with ceftriaxone, vancomycin, and acyclovir.

He was subsequently transferred to our institution under the neurology service 4 days later (7 d after initial admission). At the time of transfer, he had a decreased level of consciousness (one-word responses, obeying one-step commands) without focal or lateralizing deficits. The Infectious Disease Service raised concern for fungal meningitis on the basis of his clinical presentation, imaging, and CSF profile, and the patient was started on liposomal amphotericin.

An initial CSF specimen was collected in the absence of administration of antifungal therapy, but the fungal culture was negative. Bacterial, mycobacterial, and fungal culture investigations were negative for multiple CSF specimens collected after the initiation of antibacterial and antifungal therapy. Cryptococcal antigen and enterovirus, herpes simplex virus, and varicella zoster virus polymerase chain reaction (PCR) investigations were also negative. Cytology did not detect any evidence of leptomeningeal carcinomatosis. Repeat MRI showed extensive leptomeningeal enhancement with signal abnormality in the brain, especially at the pontomedullary junction (Figures 1, 2, 3), where a complex

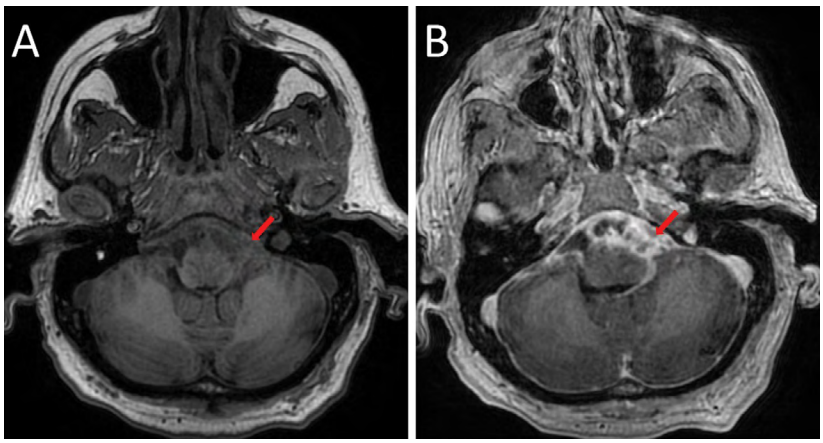

Figure 1: Axial T1-weighted images pre– (A) and post– (B) contrast administration demonstrating extensive, complex, multiseptated enhancement through the pre-pontine cistern and along the leptomeningeal surface of the brainstem. There is mass effect, with effacement of the ventral brain stem

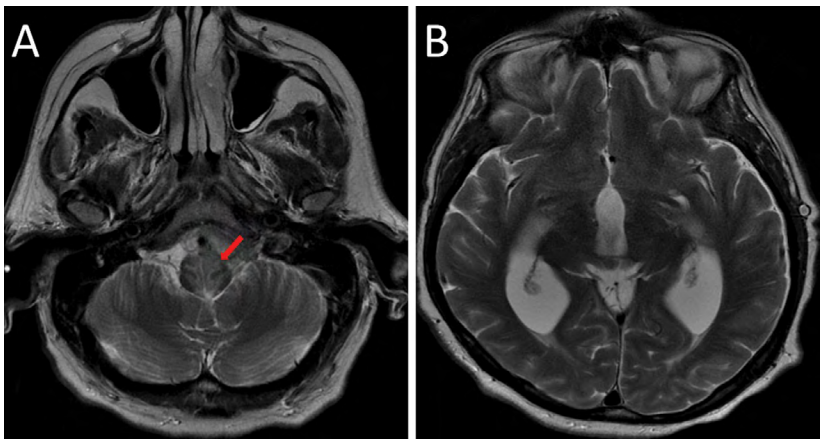

Figure 2: Axial T2-weighted images: (A) shows abnormal signal hyperintensity within the upper medulla, adjacent to the areas of cisternal enhancement; (B) demonstrates hydrocephalus with expansion in the caliber of the third and lateral ventricles

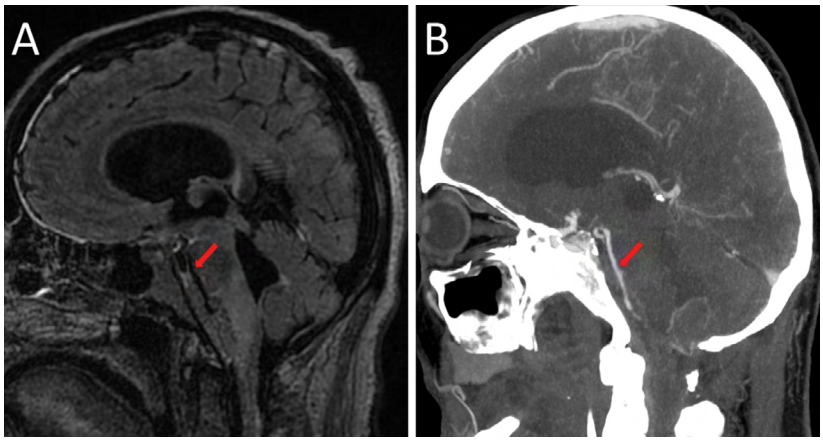

Figure 3: (A) Sagittal fluid-attenuated inversion recovery image demonstrating the full extent of abnormal signal material throughout the pre-pontine cistern, surrounding the expected course of the basilar artery; (B) sagittal reconstruction of a computed tomography angiogram demonstrating multifocal luminal caliber narrowing of the basilar artery

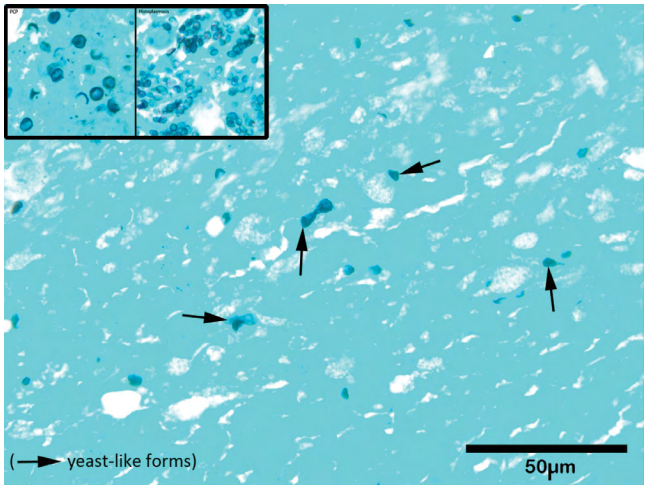

Figure 4: Silver methenamine stain; fungal fragments seen (marked with arrows)

Pneumocystis jirovecii and histoplasmosis control images are provided in left corner

septated abscess-like collection was visualized anterior to the brain stem in the prepontine cistern and where there also appeared to be intraparenchymal involvement of the upper medulla. For management of hydrocephalus, the patient required two large-volume lumbar punctures, followed by lumbar drain insertion, and he showed clinical improvement after this intervention (Glasgow Coma Scale improved to 14 from 8 immediately post-insertion on one occasion). Five lumbar drains were sequentially inserted and removed, with revisions needed as a result of frequent drain occlusions that caused a parallel decline in clinical status on each occasion.

Because of the lack of a diagnosis, a C1 laminectomy and biopsy of arachnoid tissue at the cervicomedullary junction was performed approximately 3 weeks into his admission. Repeat bacterial, fungal, and mycobacterial cultures were negative, and pathology showed a mixed inflammatory infiltrate with some multinucleated giant cells. Argyrophilic particles noted on silver methenamine stain were suspicious for yeast-like fungal forms (Figure 4).

Internal transcribed spacer (ITS) PCR and sequencing performed on the tissue biopsy specimen identified the presence of *Lodderomyces elongisporus*. After identification of the argyrophilic particles, voriconazole was added to the patient's regimen. Once *L. elongisporus* was identified, the patient was transitioned to intravenous fluconazole for 2 weeks, followed by an indefinite course of oral fluconazole. During his stay, complications included a left hemispheric convexity subdural collection likely secondary to anticoagulation needed for

a line-associated upper limb deep vein thrombosis and a small medullary stroke secondary to vertebrobasilar arterial narrowing arising from adjacent effect of the fungal abscess (Figure 3), with resultant mild left hemiparesis.

CLINICAL OUTCOME

Four months after admission, the patient was transferred to a rehabilitation facility on oral fluconazole. At the time, he was alert and conversational but non-ambulatory and dependent on all activities of daily living owing to physical and cognitive deficits. In the following 3 months, his recovery plateaued; he remained unable to sit up or walk unassisted despite near-full recovery from his stroke-related hemiparesis and absence of any limb ataxia. Follow-up MRI at 6 months after initial presentation showed similar appearance of the prepontine collection, a slight increase in hydrocephalus, and resolution of the subdural collection. Repeat lumbar puncture showed near normalization to a nucleated cell count of 6×10^6/L (97% lymphocytes), protein of 0.84 g/L, and glucose of 2.7 mmol/L. Because the persistent hydrocephalus was suspected to be causing the plateau in recovery and sufficient time had elapsed that shunt infection risk was adjudged by neurosurgery to be acceptably reduced, a permanent shunt was inserted at 10 months after presentation. A ventriculo-pleural shunt was preferred to a ventriculo- (or lumbo-) peritoneal shunt given his rectal cancer history. Despite a postoperative complication of right-sided subdural hematoma that required craniotomy and subdural drain, he has resumed ambulatory status with a cane and described subjective memory improvement 1 month after drain insertion. He has rejoined his wife at home.

DISCUSSION

L. elongisporus was revealed as a distinct fungal species via sequencing of the ribosomal RNA gene in 1994 (1). Before 1994, it was believed to be the teleomorph of *Candida parapsilosis* (2). Its role in human infection and disease has been reported only in case studies. Previous reports have documented six cases of *L. elongisporus* fungemia (3–8), one case of a catheter-tip infection in a patient with fungemia (9), and two cases of endocarditis (10,11). Early case studies share a common theme, with authors describing a delay in the identification of the fungal species as a result of limitations in the traditional fungal identification system (3,5,9). It is now recognized that cases of *L. elongisporus* may previously have been under-reported, because a molecular study characterizing isolates phenotypically identified as *C. parapsilosis* from a worldwide collection revealed that 10 isolates were actually *L. elongisporus* (12). Conventional biochemical methods are not able to reliably distinguish the four species of the *C. parapsilosis* complex, including *L. elongisporus*. However, recent reports demonstrate the accuracy of matrix-assisted laser desorption ionization–time of flight for the identification of *L. elongisporus* from cultured isolates (8,11).

In the case we have described, the arachnoid tissue biopsy was culture-negative, likely as a result of prolonged antifungal therapy at the time of biopsy, and ITS sequencing was required to identify *L. elongisporus*. Fungal PCR was performed using pan-fungus primers targeting ribosomal RNA genes in the ITS region followed by DNA sequence analysis. Testing was performed by the Department of Paediatric Laboratory Medicine at the Hospital for Sick Children in Toronto.

Previous case reports have documented infection with *L. elongisporus* in a variety of geographic settings (Table 1). Most cases identified clear risk factors for fungal infection, including the presence of central lines (4–6,9,10). In our case, the patient described had a history of chemotherapy on two occasions in the year before presentation and frequent contact with the health care system; however, he did not have a central line. In addition, he had chronic lymphopenia and prior gastrointestinal surgery. No other risk factors were identified. HIV serology, immunoglobulins, and autoimmune workup were negative. *L. elongisporus* was identified from ITS sequencing, and therefore susceptibility testing was not possible.

On the basis of previous case reports, isolated strains have shown similar susceptibility profiles, typically with low minimum inhibitory concentrations (MICs) to azoles (ie, fluconazole MIC 0.25–0.32 μg/mL), echinocandins (ie, caspofungin MIC 0.015–0.5 μg/mL), and amphotericin (MIC ≤0.12–0.5 μg/mL) (7, 9,12,13). There are no established break points for antifungal susceptibility testing for *L. elongisporus*, but those for *C. parapsilosis* are often applied as a surrogate (9). Our choice of antifungal therapy was influenced by these previous reports and the need for appropriate central nervous system (CNS) penetration (7,9,12,13).

C. parapsilosis CNS infection and risk factors for clinical disease

Although this is the first documented case of *L. elongisporus* meningitis, a review of the literature shows documented cases of meningitis (14–16) and device-associated CNS infections (17–20) caused by *C. parapsilosis*. This clinical entity has been described primarily among neonates, as well as among immunocompromised patients and those with indwelling devices (17,21). In contrast to other species of *Candida,* invasive *C. parapsilosis* infection can occur without previous colonization (21). It can be transmitted through contaminated external sources such as medical devices, fluids, parenteral nutrition, prosthetic devices, and health care workers' hands. Additional described risk factors include a central venous

Table 1: Review of cases of *Lodderomyces elongisporus* infection

Case report	Demographics	Location	Comorbid conditions	Site of isolate	Method of identification	Presence of central catheter	Management	Clinical outcome
Present case	Male, aged 62 y	Canada	Rectal adenocarcinoma Lymphopenia	Arachnoid biopsy	Fungal ITS sequencing	No	Lumbar drain insertion Liposomal amphotericin + voriconazole followed by indefinite fluconazole	Survived
Al-Obaid et al (3)	Female, aged 71 y	Kuwait	Hypertension Coronary artery disease Peripheral vascular disease Stroke	Blood	Fungal ITS sequencing	No	Caspofungin	Died
Lee et al (6)	Female, aged 56 y	Korea	Lung cancer MRSA Bacteremia	Blood	MALDI-TOF Fungal ITS sequencing	Yes	None	Died
Fernandez-Ruiz et al (4)	Male, aged 79 y	Spain	Chronic obstructive pulmonary disease Diabetes End-stage renal disease	Blood	Fungal ITS sequencing	Yes	Caspofungin	Died
Hatanaka et al (5)	Male, aged 39 y	Japan	Thoracoabdominal aortic replacement complicated by aorto-esophageal fistula	Blood + catheter tip	Fungal ITS sequencing	Yes	Micafungin	Survived
Taj-Aldeen et al (7)	Male, aged 22 y	Qatar	Trauma	Blood	MALDI-TOF Fungal ITS sequencing	Unknown	Caspofungin Fluconazole	Died
Ahmad et al (9)	Male, aged 63 y	Kuwait	Cardiovascular attack Schizophrenic-like condition	Central catheter tip	Fungal ITS sequencing	Yes	Fluconazole	Survived
Daveson & Woods (10)	Male, aged 30 y	Australia	Endocarditis Embolic stroke Osteomyelitis Injection drug use	Aortic valve + blood	Fungal ITS sequencing	Yes	Aortic valve replacement Caspofungin x 2 wk pre-operatively Liposomal amphotericin + 5-flucytosine x 6 wk, then voriconazole x 7.5 mo	Survived

(*Continued*)

Table 1: Review of cases of Lodderomyces elongisporus infection *(Continued)*

Case report	Demographics	Location	Comorbid conditions	Site of isolate	Method of identification	Presence of central catheter	Management	Clinical outcome
Thompson et al (11)	Male, aged 46 y	United States	Mechanical aortic valve Hepatitis C Injection drug use	Blood	MALDI-TOF Fungal ITS sequencing	No	Cefepime + vancomycin + micafungin Switched to liposomal amphotericin + flucytosine x 6 wk	Survived
Koh et al (8)	Female, aged 54 y	Australia	Total colectomy + ileostomy Short gut syndrome Total parenteral nutrition	Blood	MALDI-TOF	Yes	Anidulafungin x 20 d (14 d after line removal) Central catheter removal	Survived

ITS = Internal transcribed spacer; MRSA = Methicillin-resistant Streptococcus aureus*; MALDI-TOF = Matrix-assisted laser desorption ionization-time of flight*

catheter, prolonged antibiotic use, immunosuppressive therapy, and malignancy (21). In a review on *C. parapsilosis*, Trofa et al suggest that immunocompromised individuals and surgical patients, particularly those undergoing surgery on the gastrointestinal tract, are at highest risk of infection (21). Although this clinical entity appears different than our case of *L. elongisporus* meningitis, there is overlap of risk factors, including frequent health care exposure, chemotherapy treatment, and surgery on the gastrointestinal tract 6 months before presentation.

MANAGEMENT OF FUNGAL MENINGITIS–ASSOCIATED HYDROCEPHALUS

In this case, a lumbar drain was inserted for management of communicating hydrocephalus. The hydrocephalus likely arose from the extremely elevated CSF protein, which can obstruct the arachnoid granulations and reduce resorption of CSF. Intracranial hypertension can be seen in fungal meningitis and is particularly common in cryptococcal meningitis. Clinical practice guidelines of the Infectious Diseases Society of America strongly recommend management of intracranial hypertension with repeated lumbar puncture, lumbar drain insertion, ventriculoperitoneal shunt, or pharmacological approaches (22). Cryptococcal meningitis is most prevalent among immunosuppressed patients and is often seen in those with HIV. Most studies on the use of a lumbar drain for management of intracranial hypertension have involved patients with HIV (23,24); however, Zhang et al show that lumbar drain insertion is an effective and safe alternative to repeated lumbar punctures in non-HIV cryptococcal meningitis (25). In the cases of *C. parapsilosis* meningitis described earlier, management of intracranial hypertension with repeated lumbar punctures or lumbar drain was not described.

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