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Case report

Cryptococcus laurentii meningitis in a non-HIV patient★

Miriams T. Castro-Lainez[a], Rafael Deliz-Aguirre[b], Daphne Antunez[a], Marco Cruz-Codina[a], Lizbeth Cahuayme-Zuniga[c], Karla Vitale[d,*], Miguel Sierra-Hoffman[e], John K. Midturi[c]

[a] Universidad Nacional Autónoma de Honduras, Facultad de Ciencias Médicas, Hospital Escuela Universitario, Boulevard Suyapa, Tegucigalpa, Honduras
[b] Independent Researcher, Charitéstraße, 10117 Berlin, Germany
[c] Department of Internal Medicine, Division of Infectious Disease, Baylor Scott & White Healthcare, Temple, TX 76508, USA
[d] Texas A&M Detar Family Residency Program, Victoria, TX 77901, USA
[e] Post Acute Medical, 506 E. San Antonio St, 3rd Floor, Victoria, TX 77901, USA

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ABSTRACT

Cryptococcus species (other than *Cryptococcus* neoformans) have been labeled as saprophytic and nonpathogenic in immunocompetent individuals in the past. In recent years, infections caused by non-neoformans *Cryptococcus* species have been recognized. *Cryptococcus laurentii* is known to be a rare human pathogen. In this case report, we present a 59-year-old man who did not have HIV infection with meningoencephalitis caused by *Cryptococcus laurentii*. No significant underlying immunosuppressive disorder was found. The only identifiable risk factors were that the patient was a farmer with previous exposure to pigeon droppings. Here, we describe what we believe to be the fifth reported case of meningitis caused by *Cryptococcus laurentii*.

Introduction

Cryptococcus is an encapsulated budding yeast found in the environment. It can potentially cause fatal disease, especially among immunocompromised hosts. *Cryptococcus neoformans* and *Cryptococcus gattii* represent the two most clinically significant species for humans [1]. Recently, there has been increasing clinical recognition of species other than *C. neoformans* and *C. gattii*. Most of these different presentations are opportunistic in immunosuppressed hosts [2,3]. Among the uncommon agents of cryptococcosis is *Cryptococcus laurentii*. The former is usually found in pigeon droppings.

Case report

A 59-year-old Hispanic male, a farmer from Cuero, Texas came with a history of controlled type 2 diabetes mellitus (Hemoglobin A_{1C} of 5.9%), controlled hypertension, mild asthma and hyperlipidemia who presented to his primary care physician complaining of persistent and worsening headache of six months in duration. He was diagnosed with frontal sinusitis and was started on antimicrobial, an antihistamine and a non-steroidal anti-inflammatory drug (NSAID). Eight days after the initial outpatient visit, the patient went to the emergency room due to worsening headache, blurred vision, dysequilibrium and photophobia. During the interrogation, the patient disclose that he worked at a local prison which had an agriculture operation. Several months prior to his hospitalization, the patient was assigned to clean a barn which was grossly contaminated with pigeon droppings.

His vital signs upon presentation were: temperature of 36.8 °C, heart rate 80 beats per minute, respiratory rate 18 breaths per minute, and pulse oximetry (SpO_2) 96%. His physical examination showed that he was intermittently confused and in significant distress due to his headache and photophobia. His pupils were equal and round, reactive to the light and accommodation and his eye movement was extremely painful. Nuchal rigidity, a positive

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* Corresponding author at: 309 Edinburgh St, Victoria, TX 77904, USA.
E-mail addresses: mtcastrolainez@gmail.com (M.T. Castro-Lainez), Rafael.deliz.aguirre@gmail.com (R. Deliz-Aguirre), daphneantunez@gmail.com (D. Antunez), mtcruzcodina@gmail.com (M. Cruz-Codina), Lizbeth.cahuaynezuniga@bswhealth.org (L. Cahuayme-Zuniga), kvitale97@midwestern.edu (K. Vitale), msh.xatracho@gmail.com (M. Sierra-Hoffman), john.midturi@bswhealth.org (J.K. Midturi).

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Kernig sign and bilateral hyperreflexia with increased patella reflexes were also found during the physical examination. A lumbar puncture (LP) revealed normal opening pressure (150 mm H_2O), white blood cell count of 702 cells/μL with neutrophilic predominance (58%), cerebrospinal fluid (CSF) glucose 51 mg/dL, serum glucose level 166 mg/dL, with CSF/serum ratio 0.37, and a CSF protein 88 mg/dL.

The patient tested negative for *C. neoformans* and *C. gattii* using the BioFire® FilmArray® Meningitis/Encephalitis Panel. In the CSF the fungal smear reported rare fungal elements. A serum cryptococcal antigen was positive (*Crypto* AG titer 1:10). *Cryptococcus laurentii* was isolated and identified using the yeast identification system (Api 20 Aux) bioMerieux. The CSF fungal culture grew *Cryptococcus laurentii* at 48 h. Both a computed tomography (CT) head scan without contrast and MRI with gadolinium did not report any abnormal findings.

The patient was initiated on liposomal amphotericin (LAMB) B at 3 mg/kg/day and on fluconazole 400 mg IV q12 hours. The patient remained in the intensive care unit (ICU) for seven days. He improved clinically, therefore the patient declined a repeat lumbar puncture. The patient completed six weeks of induction therapy and was discharged on oral fluconazole 400 mg PO BID. The latter was done because *Cryptococcus* is generally thought of as an opportunistic yeast, hence it was thought initially that he had an underlying suppressive disorder, but despite the multiple laboratory tests done and images sent, an immunosuppressive disorder was not found. It was felt that it would be safer for the patient to be treated with combination therapy and left for a longer period on fluconazole. While on dual therapy, the highest blood urea nitrogen (BUN) and creatinine measurement were 39 mg/dL and 1.7 mg/dL respectively. After a year, the patient was transitioned to a maintenance dose of 200 mg PO BID, which he still takes. His liver functions has been monitored his liver function monthly, no abnormality has been identified. As of this writing, the patient remains well, and he went back to work 15 months later.

Discussion

Cryptococcal meningitis is the most common cause of fungal meningoencephalitis worldwide and the most common cause of fungal central nervous system infection in the immunosuppressed host [4]. Until the early 1970s, it was considered a rare infection. Its rapid epidemiological expansion was matched with advances in immunosuppressive therapy, initiation of organ transplantation, and improvement in chemotherapy for hematological malignancies [4]. It was not until the 1980s with the onset of the human immunodeficiency virus (HIV) world epidemic that cryptococcal meningitis became known as the leading cause of CNS infections—a status which it retains to date despite the major improvements in the control of the HIV epidemic [2,5,6]. The most common and virulent species have been *Cryptococcus neoformans* and *Cryptococcus gattii*. On the contrary, *Cryptococcus lauretii* and *Cryptococcus albidus* have historically been labeled as saprophytic, non-pathological or clinically irrelevant [5].

Epidemiologically, *C. neoformans* is present worldwide. *C. gatii* is endemic to Africa and Australia, although some cases have been reported in the Pacific Northwest of North America [5,7]. Less commonly seen is the saprophytic *C. laurentii*, spread worldwide.

It is worth mentioning that some genetically identical fungi have different taxonomical (i.e., species) names. While some

Table 1
Previously published case reports of *Cryptococcus laurentii* meningitis.

Age/ Gender	Comorbidities	Associated Risk Factors	Blood culture	Symptoms	Diagnostic Method	Treatment	Outcome	Reference
35/M	HIV	Low CD4 count	Yes	• Fever • Headache • Vomiting	• CSF culture • India Ink • Blood culture • Vitek System	Amphotericin B, followed by fluconazole	Resolved	[5]
30/F	None	Postpartum woman (Cesarean 21 days before symptoms began; immune reconstitution syndrome)	No	• Headache • Altered sensorium • Drowsiness • Vomiting	• CSF culture • India Ink • Vitek system	Amphotericin B	Death	[6]
34/F	• HIV • Kaposi Sarcoma	Low CD4 count	No	• Dyspnea • Dry cough • Fever • Anorexia • Weight loss • Headache • Hypotension • Bradycardia	• CSF culture • India Ink • Vitek system	Amphotericin B, followed by fluconazole	Resolved	[2]
34/M	HIV	Low CD4 count, IV Drug use, prior antifungal therapy	Yes	• Fever • Headache	• CSF culture • India Ink • Blood culture • Vitek system	High 1os1 fluconazole	Resolved	[14]
54/M	Control Diabetes, controlled hypertension, hyperlipidemia	Contact with pigeon droppings, farmer	Yes	• Headache • ● Night sweats • Blurred vision • Tinnitus • Unintended weight 1os	• India Ink • CSF culture	Amphotericin B, followed by fluconazole	Resolved	[a]

[a] Case presented here.

mycologists wish to get rid of this confusing system, it still exists. Clinicians should exercise caution while reviewing information on the pathogen. *Cryptococcus* may also be called *Filobasidiella.* The difference lies in the location and reproductive stage. *Cryptococcus* is the pathogenic stage which resides in animals, including humans. It reproduces asexually; therefore, it cannot be transmitted between humans or animals [8]. *Filobasidiella*, is the reproductive stage of this budding yeast, that is, teleomorph, found on the soil.

Not only does *Cryptococcus* have dual nomenclature, but it also has had many other names. The species in this case report, *C. laurentii*, also appears in the literature as *Torula laurentii* (1920), *Torulopsis laurentii* (1934), *Cryptococcus laurentii* var. *Laurentii* (1952), *Rhodotorula laurentii* (1960), *Rhodotorula nitens* (1963) [9] and more recently, *Papiliotrema laurentii* [10]. While most of these names are old and only relevant while researching historical case reports, the last one mentioned, *P. laurentii*, is a recent development born in 2015. Therefore, the name of this yeast may change during the next decade.

Focusing on the histology, the capsule can be readily seen by applying India ink to cerebrospinal fluid. Similarly, mucicarmine stain can be used for localization of the cells in tissues [11]. To our knowledge, the only commercially available molecular diagnostic tools available to date for the identification of *Cryptococcus* is the Meningitis/Encephalitis (ME) Panel of BioFire® FilmArray® Multiplex PCR System (bioMérieux) and GenMark's ePlex Blood Culture Identification (BCID) panel. While both panels can detect *C. neoformans* and *C. gatii*, they lack the ability to identify *C. laurentii*. Interestingly, there seems to be cross-reactivity between parainfluenza virus and *C. laurentii* on the BioFire® respiratory panel according to the Food and Drug Administration (FDA) [12].

We report a patient who presented with chronic headaches for six months. A lumbar puncture and CSF analysis confirmed the presence of cryptococcal infection. The CSF cryptococcal antigen and India ink tests suggested *Cryptococcus* the day the LP was performed. The BioFire® FilmArray® Meningitis/Encephalitis Panel was negative, which was consistent with the diagnosis. The definite diagnosis was given by the fungal culture 48 h later.

An online search was done, including MedLine, Google Scholar, and PubMed. We found four other cases of *Cryptococcus laurentii* meningitis (Table 1). We compared presentation and diagnostic methods, treatment, outcome and immune status. Three had HIV as a risk factor. One other patient reported no major immunodeficiency at the time of diagnosis, the same as the patient we are presenting. The patient had a two-year follow-up, and he remains immunocompetent. The mortality rate seen in this review was 20%. The only patient who passed away had a delayed diagnosis. All patients received treatment with amphotericin B as induction and later were given fluconazole, except for one who received fluconazole alone.

For this case report, we speculate that previous exposure to pigeon droppings and working in an agricultural setting were the risk factors. It is known that *Cryptococcus laurentii* is used as a biological pesticide to prevent the decay of fruits in some areas of the world [13]. Also, retrospectively, we agree we expanded the treatment longer than what guidelines suggest; this was due to our inexperience with the cryptococcal strain and the initial critical state that the patient was in.

Cryptococcus laurentii meningitis is extremely rare. It is usually seen in immunocompromised patients; therefore, a high index of suspicion is needed. It is important to emphasize that the current medical community relies on high-tech methods for faster results. Even though access to the latest technological advances are helpful, clinicians should not forget to individualize each patient according to the history and physical exam and order lab tests accordingly. Traditional microbiological tests, such as India ink, CSF culture and the CSF cryptococcal antigen by the lateral flow assay, provided the answer to our case. Combining biotechnology and molecular biology with more traditional approaches like staining is an important step in reducing false negatives.

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