CASE REPORT

Cryptococcal meningitis in a daily cannabis smoker without evidence of immunodeficiency

Bryan B Shapiro,[1,2] Rebecca Hedrick,[2] Brigitte C Vanle,[2] Courtney A Becker,[3] Chris Nguyen,[3] David M Underhill,[3] Margie A Morgan,[4] Joel D Kopple,[5,6,7] Itai Danovitch,[2] Waguih William IsHak[2,6]

[1]Department of Psychiatry and Human Behavior, UC Irvine Medical Center, Orange, California, USA
[2]Department of Psychiatry and Behavioral Neurosciences, Cedars-Sinai Medical Center, Los Angeles, California, USA
[3]F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA
[4]Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA
[5]Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA
[6]David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[7]UCLA Fielding School of Public Health, Los Angeles, California, USA

Correspondence to
Bryan B Shapiro MD and MPH, bryan.shapiro@uci.edu

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SUMMARY

Cryptococcal meningitis is a life-threatening condition most commonly observed in immunocompromised individuals. We describe a daily cannabis smoker without evidence of immunodeficiency presenting with confirmed *Cryptococcus neoformans* meningitis. An investigation of cannabis samples from the patient's preferred dispensary demonstrated contamination with several varieties of *Cryptococcus*, including *C. neoformans*, and other opportunistic fungi. These findings raise concern regarding the safety of dispensary-grade cannabis, even in immunocompetent users.

BACKGROUND

Despite the widespread deregulation of cannabis for medical and recreational use, long-term risks of chronic cannabis smoking have not been fully elucidated. Of concern, fungal contaminants have been identified in dispensary-grade cannabis[1–3] and exposure to contaminated cannabis smoke has been linked to invasive pulmonary aspergillosis in immunocompromised hosts.[4–6] Here we describe a daily cannabis smoker presenting with cryptococcal meningitis but lacking evidence of immunodeficiency. As the first reported case linking daily cannabis smoking to a life-threatening fungal infection of the central nervous system, this case was thought to be of considerable public health importance.

CASE PRESENTATION

In mid-July of 2016, a 48-year-old African-American woman from Bakersfield, California was brought to the emergency department at Cedars-Sinai Medical Center (CSMC) by her sister with a 2-month history of progressive fatigue, dizziness, memory impairment, ataxia and left-sided numbness and weakness. Medical and social histories pertaining to this case were obtained from interactions with the patient and her sister, and/or extracted from previous medical records.

The patient, a high school graduate of lower socioeconomic standing, has lived in Bakersfield since 2003 and was recently removed from her job as an administrative assistant due to poor performance and aggressive behaviour. She describes herself as a social drinker and has enjoyed going to parties and other social events. She possesses a California medical cannabis card prescribed by a physician and reports smoking three to six cannabis 'blunts' (hollowed out tobacco cigars filled with cannabis) nearly every day since the age of thirteen. She denies excessive use of alcohol, tobacco or other recreational drugs. She has chronic hypertension but she does not take any medicines including herbal medicines or other supplements and denies past use of oral or inhaled corticosteroids. She has no history of cancer and has not had any surgical procedures.

Four weeks prior to admission, she was admitted to a hospital in Bakersfield for sudden-onset paraesthesias and numbness in the left face and left hand and was admitted again one week later for recurrent syncopal episodes. Extensive medical evaluation during these two admissions was inconclusive and persistent symptoms prompted her visit to CSMC for further care.

Initial workup at CSMC demonstrated a positive urine test for cannabinoids (446 ng/mL 11-nor-9-carboxy-tetrahydrocannabinol). HIV antigen-antibody combination tests and a rapid plasma reagin test for syphilis were negative. A complete blood count indicated red blood cells 5.15×10^12/L, haemoglobin 12.3 g/dL, platelets 334x10^9/L, white blood cells 7.1x10^9/L with 53% neutrophils, 35% lymphocytes (absolute lymphocyte count 2.5x10^9/L) and 10% monocytes. An analysis of lymphocyte subsets in a subsequent blood sample indicated normal absolute and per cent CD3, CD4 and CD8 cell counts with a normal CD4/CD8 cell ratio. Blood chemistry tests indicated serum glucose 110 mg/dL, sodium 142 mmol/L, potassium 3.6 mmol/L, chloride 103 mmol/L, carbon dioxide 24 mmol/L, blood urea nitrogen 13 mg/dL, creatinine 0.7 mg/dL, total protein 6.8 g/dL and serum albumin 3.6 g/dL. An MRI of the brain indicated evidence of infarction in the left corpus callosum and left internal capsule, consistent with previous stroke, but it was the opinion of the neurologist that these lesions were unlikely to account for her current symptoms. An abdominal CT demonstrated a 1.4 cm lesion in the right hepatic lobe possibly representing a haemangioma or small cyst, and a small indeterminate lesion in the right kidney.

A psychiatrist was consulted on day 6 of admission because of an episode of increased confusion and agitation in which the patient assaulted a floor nurse. Over the next several days, the patient

became increasingly lethargic and confused and eventually without spontaneous movement or speech, but would answer questions when prompted. During this time, insurance through her former employer was terminated and she was transitioned to Medi-Cal, California's Medicaid programme.

A lumbar puncture was performed on day 20 of admission based on suspicion of meningitis. Cerebrospinal fluid (CSF) contained leucocytes 1.7x10^8/L (62% neutrophils, 37% lymphocytes and 1% monocytes), red blood cells 1x10^6/L, protein 131 mg/dL and glucose <5 mg/dL with a concomitant serum glucose of 100 mg/dL. *Cryptococcus neoformans* capsular antigen was detected in the CSF and blood plasma with an original value of 1/1024 and 1/2048, respectively. Microscopic analysis of the CSF revealed encapsulated yeast morphologically consistent with *Cryptococcus* and the fungal culture grew a yeast, found to be *C. neoformans*. The identification of *C. neoformans* was established using matrix-assisted laser desorption/ionisation time of flight mass spectrometry analysis by the Bruker Biotyper V.3.2.12.[7]

INVESTIGATIONS

The patient's confirmed *C. neoformans* meningitis without evidence of being immunocompromised was puzzling. Her history of daily cannabis use and residence in a region of California known to harbour *Coccidioides immitis* (the cause of 'Valley fever') in its soils[8] raised suspicion that the medical cannabis she routinely smoked may have been contaminated with fungi including *Cryptococcus* and hence was the source of the cryptococcal meningitis.

After her mental status improved, the patient identified a dispensary in Bakersfield, California, where she has almost exclusively obtained medical cannabis for the past several years. She reported a preference for the less expensive, outdoor-grown strains. Nine 1 g samples of different outdoor-grown strains were collected from this dispensary. These samples were transferred to the F Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute at CSMC for fungal DNA sequencing.

DNA for fungal internal transcribed spacer (ITS1) sequencing was isolated from the samples as described previously.[9] Fungal ITS1 amplicons were generated, subjected to next-generation sequencing and processed.[10] High-quality reads were aligned to the UNITE database (https://unite.ut.ee/) using BLAST v2.2.22 in the QIIME (software V.1.6) wrapper with an identity percentage ≥97% for operational taxonomic unit picking. According to these analyses, *Cryptococcus* sp comprised 0.02%–0.66% of the total fungal load in the nine cannabis samples. All samples were contaminated with at least one species of *Cryptococcus*, and six distinct species of *Cryptococcus* were identified (*C. arrabidensis*, *C. heimaeyensis*, *C. laurentii*, *C. neoformans*, *C. victoriae* and *C. wieringae*). Three out of the nine samples demonstrated presence of *C. neoformans*. Several opportunistic fungal genera were also identified in at least one of the samples: *Aspergillus* (*A. flavus*), *Fusarium, Rhodotorula*, *Zygomycetes*, *Acremonium*, *Trichoderma*, *Bipolaris*, *Exophiala* and *Chladophialophora.*

OUTCOME AND FOLLOW-UP

After four weeks of treatment with 330 mg of intravenous amphotericin B and 400 mg of oral fluconazole daily, she demonstrated marked improvement, and eventually no growth of *Cryptococcus* in her CSF. She was discharged in early November of 2016 on a continued oral regimen of 400 mg of fluconazole taken daily.

DISCUSSION

To the authors' knowledge, this is the first report linking the smoking of cannabis obtained from a dispensary that sold cannabis contaminated with small amounts of *Cryptococcus* to the development of cryptococcal meningitis. A daily cannabis smoker, who did not have evidence of immunodeficiency, presented with *C. neoformans* meningitis, and we identified small amounts of six *Cryptococcus* species, including *C. neoformans*, in cannabis samples retrieved from her preferred medical cannabis dispensary. These findings raise the possibility that *C. neoformans* in the cannabis may have caused the systemic fungal infection in this immunocompetent patient.

A variety of fungal contaminants have been identified in dispensary-grade cannabis, including *Cryptococcus*.[1–3] However, only *Aspergillus* infections of the lung have been linked to the chronic smoking of cannabis and these were exclusively reported in immunocompromised patients.[4–6] It is relevant that *A. flavus* was also identified in one of the nine samples of cannabis obtained from the patient's preferred dispensary. While *C. neoformans* meningitis is classically observed in immunocompromised individuals (eg, late-stage HIV infection, transplant recipients), it may uncommonly occur in individuals without evidence of immunodeficiency.[11] Nevertheless, as *Cryptococcus gattii* is most commonly implicated in cryptococcal meningitis in immunocompetent persons, the finding of *C. neoformans* in this relatively healthy patient prompted further interest in this case.

Several factors may predispose cannabis smokers to invasive fungal infections. Fungal spores are common contaminants of cannabis cigarettes, endure in cannabis cigarette smoke and can be inhaled.[1 12] Cannabis cigarette smoke may impair the function of pulmonary alveolar macrophages which may facilitate the colonisation of organisms into the lung prior to haematogenous dissemination.[13] Moreover, Δ(9)-tetrahydrocannabinol (THC), the most widely studied active ingredient in cannabis, may independently suppress immune function in the central nervous system by inhibiting the migratory capacity of microglia.[14] Indeed,a large body of in vitro and in vivo studies demonstrating a constellation of immunosuppressive effects of THC, including suppressing the function of macrophages and macrophage-like cells, T lymphocytes, natural killer cells and cytokines.[14] While both active and passive tobacco smoking has been consistently associated with an increased risk of bacterial meningitis,[15] no large-scale epidemiological studies to our knowledge have investigated associations between cannabis smoking and fungal meningitis irrespective of immune status. As data suggest that

Learning points

- Cryptococcal meningitis and other disseminated fungal infections usually occur in immunocompromised individuals (eg, late-stage HIV infection).
- Several studies, including the present case report, have identified opportunistic fungal contaminants of cannabis products, including cannabis smoke.
- This is the first report linking the smoking of outdoor-grown cannabis obtained from a dispensary to the development of cryptococcal meningitis in an individual without evidence of immunodeficiency.
- Further research determining whether chronic smoking of cannabis may be associated with an increased risk of disseminated fungal infections, such as cryptococcal meningitis, appears indicated.

tobacco cigarettes are also commonly contaminated with fungal spores,[1] it would be interesting to explore whether an association exists between chronic tobacco smoking and the incidence of disseminated fungal infections such as meningits.

As the first report linking contaminated cannabis to a life-threatening systemic fungal infection, these findings call into question the safety of cannabis for use by the general population. The widespread deregulation of medical cannabis has coincided with increased acceptance of its medicinal and recreational use—the number of adults in the USA who report using cannabis has doubled between 2013 (7%) and 2016 (13%)[16] and according to a recent global survey of clinicians, 76% were in favour of the use of cannabis for medicinal reasons.[17] Based on the potentially life-threatening risks of developing fungal infections by smoking cannabis and the rapidly increasing popularity and use of this activity in the USA, a comprehensive investigation of the safety of inhaled cannabis products would seem warranted.

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Competing interests None declared.

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