Case report

Candida dubliniensis chronic meningitis in an immunocompetent patient: Case report and literature review

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ABSTRACT

Chronic meningitis due to *Candida* species is a rare presentation generally associated with immunocompromise. We present a case of chronic meningitis due to *Candida dubliniensis* in an immunocompetent systemically well man who presented with 32 months of headache and visual changes. This is the fourth reported case in an immunocompetent patient. Injecting drug use was identified as a risk factor in all cases which presented similarly, with prolonged headache and papilloedema. A significant delay to diagnosis is common to all the reported cases. Candidal chronic meningitis in immunocompetent patients may be underdiagnosed due to lack recognition of risk factors, timely cerebrospinal fluid sampling and appropriate culture.

Introduction

Chronic meningitis, persistent inflammation of the meninges lasting greater than 4 weeks, is a rare entity with a challenging evaluation and a cause not determined in up to a one-third of all patients [1]. There is a broad differential of infectious, malignant and inflammatory etiologies. The most common pathogens isolated vary by geographic region, as well as host factors such as immunocompromise and predisposing procedures. In regions where tuberculosis is endemic it is the most common cause of chronic meningitis, but in people with Human Immunodeficiency Virus (HIV) the most common cause is cryptococcosis [2]. *Candida dubliniensis,* closely related to *Candida albicans,* is predominantly an opportunistic pathogen of the immunocompromised in whom it can cause invasive and fatal disease [3].

Case

A 30-year-old Australian Indigenous man presented with 32 months of progressive headaches. These were described as a sharp pain across the top of his head, without lateralisation or radiation. Initially his headaches were infrequent but increased in frequency, intensive and duration; causing incapacity, lasting up to 8 h occurring 3–5 times per week. There was occasional associated blurred vision, nausea, photophobia and vertiginous symptoms. He was systemically well, with no fevers or weight loss. He had a history of injecting drug use, previously treated hepatitis C, former heavy ethanol intake and was on an opioid substitution programme. There was no history of immune compromise. He was using shared needles and two weeks prior to onset he reported a transient febrile illness in the context of injected sublingual Buprenorphine/Naloxone tablets taken out of his mouth then crushed and diluted with tap water.

Physical examination was unremarkable except for bilateral optic disc swelling consistent with Frisen grade 3 papilloedema. Humphrey visual field testing suggested some mild, non-specific peripheral visual field loss. There was normal central visual acuity and no evidence of uveitis or endophthalmitis. These findings were stable over 10 months, with the cause unknown. A brain MRI (Magnetic Resonance Imaging) was reported as normal and the patient proceeded to lumbar puncture.

Initial lumbar puncture demonstrated a high opening pressure of 31 cmH_2O (normal <20 cmH_2O) with a markedly elevated white cell count of 1300×10^6/L (normal $<5 \times 10^6$/L), leucocyte differential was 67% polymorphic and 33% mononuclear, protein 3400 mg/L (150–500 mg/L) with a low normal glucose of 2.3 mmol/L (2.2–3.9 mmol/L). Gram stain showed no organisms and initial cultures were negative. Given the chronicity of his presentation and lack of systemic features the decision was made to leave him off all antimicrobials whilst awaiting further investigations.

Blood tests demonstrated a normal white cell count of 9.7×10^6/L ($<10.0 \times 10^6$/L), ESR (Erythrocyte Sedimentation Rate) 9 mm/hr (<15 mm/hr) and a marginally elevated CRP (C-reactive protein) 11 mg/L (<5 mg/L). Serial blood cultures were negative. Serology was negative for HIV, with normal lymphocyte counts and immunoglobulin levels

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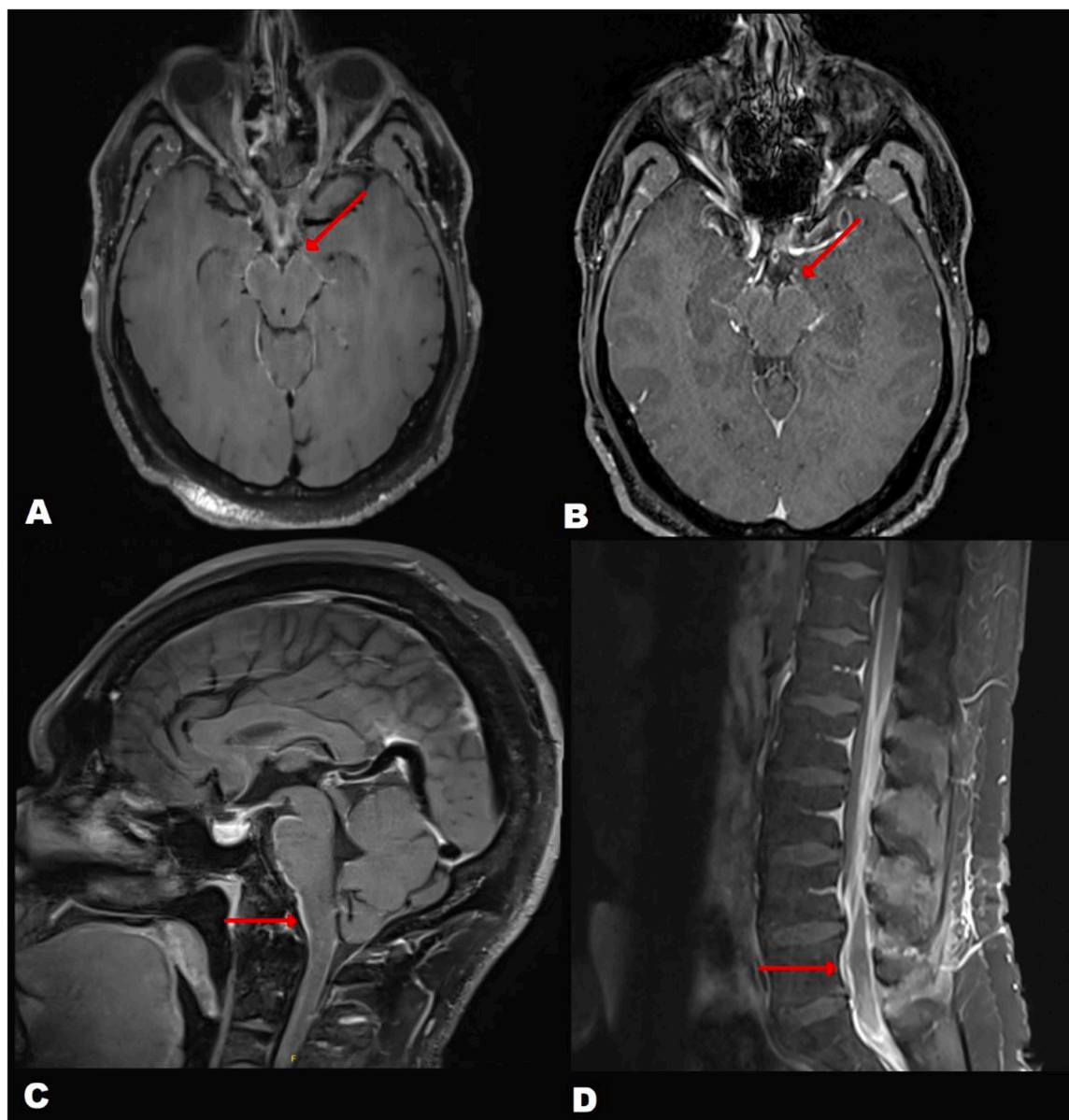*E-mail address:* codyfrancisprice@gmail.com (C. Price).

Fig. 1. Leptomeningeal enhancement on post contrast T1 MRI sequences (A+C using dark blood sequences). A Leptomeningeal enhancement around the midbrain, compared to B from 10 months prior. C Leptomeningeal enhancement around the medulla and pons. D. Enhancement of the cauda equina with adherence to the anterior spine.

including IgG subsets. Transthoracic echocardiography did not demonstrate any valvular vegetations. Chest, abdomen and pelvis CT (Computed Tomography) did not show any evidence of inflammatory or neoplastic disease. Repeat brain and whole spine MRI with gadolinium contrast revealed diffuse leptomeningeal enhancement particularly around the pons and cerebral peduncles and posterior fossa contents, this extended to involve the leptomeninges of the spine including the nerve roots in the cauda equina which were adhered anteriorly (Fig. 1). Retrospective review of the brain MRI 10 months prior to diagnosis demonstrated early leptomeningeal enhancement around the midbrain (Fig. 1), although this had progressed substantially by the time of his admission. There was no evidence of sinusitis, mastoiditis or otitis.

His CSF (cerebrospinal fluid) fungal cultures subsequently isolated *C. dubliniensis* on two separate samples. Susceptibility testing was conducted using Sensititre Yeast One microdilution plate (ThermoFisher Scientific, USA) with the following results: anidulafungin 0.12 mg/L, micafungin 0.03 mg/L, caspofungin 0.06 mg/L, 5-flucytosine < 0.06 mg/L, posaconazole 0.06 mg/L, voriconazole < 0.008 mg/L,

itraconazole 0.06 mg/L, fluconazole 0.25 mg/L and amphotericin B 0.25 mg/L. Treatment commenced with intravenous liposomal amphotericin B 3 mg/kg daily and oral fluconazole 800 mg daily for two weeks, followed by four weeks of oral fluconazole monotherapy. His treatment was complicated by amphotericin B induced acute kidney injury which improved with intravenous fluid administration without requiring early cessation or dose reduction of the amphotericin B. CSF culture clearance was demonstrated at the first lumbar puncture post commencement of therapy, at 2 weeks. Therapeutic large volume lumbar punctures were performed every 2 weeks to reduce his intracranial pressures and reduce his risk of further visual field loss. These continued until opening pressures normalised at 6 weeks and also demonstrated a reducing white cell count and protein concentration. His headaches resolved.

Discussion

This is the fourth reported case of *C. dubliniensis* chronic meningitis

Table 1

Comparison of clinical features of the four documented cases of *C. dubliniensis* chronic meningitis in patients not known to be immunocompromised.

	Case 1 [5]	Case 2 [6]	Case 3 [7]	Our case
Age	25	26	27	30
History of injecting drug use	Yes	Yes	Yes	Yes
History of hepatitis C infection	Unknown	Yes	Yes	Yes
Immunocompromised	No	Unknown	No	No
Duration of symptoms prior to diagnosis	12 months	12 months	10 months	32 months
Systemic features of infection	Absent	Unknown	Weight loss	Absent
Leptomeningeal enhancement on MRI	Yes	Yes	Yes	Yes
Neurological Deficit	Radiculopathy	Saddle anaesthesia and unilateral foot drop	Complete monocular loss of vision	Mild peripheral visual field loss
Method of microbiological diagnosis	CSF fungal Culture + dural tissue biopsy culture	CSF next generation sequencing	CSF fungal Culture	CSF fungal Culture

in an immunocompetent patient. Review of the other cases revealed striking similarities (Table 1). Particularly notable is that all patients had a history of injecting drug use and 3 of 4 of the cases had a history of hepatitis C. This and another reported case had a history of injecting sublingual buprenorphine. Our patient's description of injection of sublingual buprenorphine post removal from the oral cavity suggests a potential route of exposure. Our patient with his history of former heavy alcohol use may have had oral colonisation. In patients with psychoactive substance addiction, 13% isolated *C. dubliniensis* from the oral cavity and this frequency increased for patients with a longer duration of alcohol consumption [4].

The IDSA guideline recommends induction therapy for candida meningitis with amphotericin B with or without flucytosine [8]. Fluconazole was selected over flucytosine for combination induction therapy in this case for several reasons. The evidence for benefit with the addition of flucytosine is equivocal [8] and there are concerns around tolerance. There may be synergistic benefit with the combination of amphotericin B and fluconazole as summarised in a recent review [9]. While failure has been reported with fluconazole alone, failure has not been reported with combined therapy. This approach allowed a smooth transition to all oral therapy with fluconazole following induction.

If the time of onset of meningitis is considered our patient's onset of symptoms then this is a case of chronic meningitis of 32 months duration. The more conservative estimate from the first documented finding of papilloedema would be 10 months. He remained afebrile throughout his admission with only one marginally elevated serum marker of inflammation. Mild peripheral visual field loss was the only neurological deficit despite the extensive leptomeningeal involvement demonstrated on MRI.

Diagnosis was established by repeat culture of *C. dubliniensis* on 2 separate CSF samples which required 3 lumbar punctures and large volume CSF sampling. Diagnostic approaches in the setting of CSF culture negativity include non-species specific fungal assays such as B-D glucan [2] or next generation sequencing techniques [6]. Invasive dural tissue biopsy such as by [5] would provide another higher sensitivity culture avenue, but it would be challenging to justify meningeal biopsy and the risks entailed for this patient without features of progressive neurological decline.

By comparison, the cases of *C. dubliniensis* meningitis described in immunocompromised patients have a more florid illness. The first documented case was a 48 year old heart-lung transplant patient who had an initial treated *C. dubliniensis* fungaemia followed by meningitis 2 months later [10]. In the second case [11] a 60 year old diabetic and cirrhotic presented with acute meningitis and an altered level of consciousness and ultimately died despite initiation of antifungal therapy. Interestingly he also had a history of hepatitis C infection and substance use disorder.

The closely related *C. albicans* can also cause chronic meningitis although this manifestation is similarly rare and often fatal in the immunocompromised host [12]. *C. albicans* chronic meningitis in

immunocompetent hosts has a similar duration of many months prior to diagnosis, although these patients are reported to have systemic features unlike the more indolent course in our case of *C. dubliniensis* chronic meningitis [13].

The key points from this case of *Candida dubliniensis* chronic meningitis are the striking chronicity with relatively mild but progressive symptoms, absence of systemic features and lack of spontaneous resolution. All described cases in the literature in immunocompetent patients had a history of injecting drug use. This diagnosis should be considered in patients with evidence of chronic meningitis who are immunocompetent and systemically well.

CRediT authorship contribution statement

Cody Price: Writing – original draft. **Ian Wilson:** Writing – review & editing, Supervision. **Elizabeth Catchpoole:** Writing – review & editing, Supervision.

Ethical approval

Not required for case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available on request.

Competing interests

None.

Acknowledgements

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