IDCases 29 (2022) e01567

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Orthostatic hypotension as the initial presentation of disseminated cryptococcosis in a kidney transplant recipient

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ARTICLE INFO

Keywords:
Infectious disease
Cryptococcus
Fungal disease
Transplant recipient
Transplant, medicine
Orthostatic hypotension

ABSTRACT

Background: Solid organ transplant recipients are immunocompromised and at risk for invasive viral, fungal, and bacterial pathogens. *Cryptococcus neoformans* is the third most common invasive fungal infection in transplant recipients, and the clinical presentation of Cryptococcus neoformans infection can vary widely. Cryptococcal disease can affect the brain, lungs, skin, or vasculature, and it is frequently disseminated. Meningitis typically presents with fever, headache, and altered mental status. Solid organ transplant recipients with cryptococcosis tend to have poorer outcomes than HIV patients with cryptococcosis.

Case presentation: In this case report, we describe the case of a 69 year-old man with a past medical history of a deceased donor kidney transplant who presented with severe orthostatic hypotension and was found to have disseminated cryptococcosis.

Conclusions: This case report emphasizes the importance of broadening the differential diagnosis in transplant recipients who present with non-specific chief concerns.

Availability of data and materials: No datasets were used in the preparing of this manuscript. All patient information comes from the electronic health record and authors personal care of this patient.

Background

The prevalence of cryptococcal infection worldwide has been steadily increasing over the past 50 years. The incidence of cryptococcosis increased significantly after the HIV/AIDS era as severe immunodeficiency predisposes patients to fungal infections. However, with the advent of highly active anti-retroviral therapy (HAART), incidence of cryptococcosis among HIV/AIDS patients has been decreasing over the past two decades. Solid organ transplant and bone marrow transplant patients have become a new cryptococcosis population of interest with increased transplantation success. Due to chronic immunosuppression, these patients can often present with non-specific and atypical signs and symptoms contributing to delayed diagnosis. Atypical (non-infectious) presenting symptoms may be more common including hyponatremia, sinusitis, and vertigo [5–7]. Several studies have shown that there are worse outcomes associated with cryptococcosis in transplant recipients when compared to patients living with HIV [1–4]. Cryptococcosis with meningeal involvement typically presents with fever, headache, neuropsychiatric abnormalities, and respiratory symptoms if there is pulmonary involvement. However, the threshold for consideration of cryptococcal infection in an organ transplant patient should be lowered. In this case report, we report, to the best of our knowledge, the first documented case report of orthostatic hypotension as the presentation for disseminated cryptococcosis.

Case presentation

History

A 69-year-old man was transferred to our hospital from an outside hospital, where he presented following a 4-week history of dizziness and generalized weakness. The patient had visited the emergency room a month prior for uncontrolled hyperglycemia and hypotension to 70/50 mmHg, and his blood pressures at home over the past month ranged from 85/51 mmHg to 117/54 mmHg. On history, he reported a 6-week history of pre-syncope and lightheadedness when sitting upright or standing, making it difficult for him to walk unassisted. He also reported poor appetite, occasional nausea, generalized weakness and denied

Abbreviations: HAART, Highly active anti-retroviral therapy; TRANSNET, Transplant-Associated Infection Surveillance Network; IRIS, immune reconstitution inflammatory syndrome.

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https://doi.org/10.1016/j.idcr.2022.e01567
Received 31 March 2022; Received in revised form 3 July 2022; Accepted 9 July 2022
Available online 11 July 2022

headache, fevers or chills, cough, and shortness of breath. He had a medical history of end-stage-renal-disease status post deceased donor kidney transplant three years previously (managed with prednisone 12.5 mg daily, everolimus 0.75 mg twice a day, monthly belatacept infusions, and trimethoprim/sulfamethoxazole prophylaxis), type II diabetes mellitus, coronary artery disease, hypertension, and hyperlipidemia. His chronic conditions were managed with insulin glargine 35 units daily and 3 units insulin lispro with meals, metoprolol succinate 50 mg daily, and losartan 50 mg daily. There had been no recent changes to the patient's immunosuppressive regimen.

Examination

On admission, the patient was intermittently hypertensive with blood pressures ranging from 114/65–209/93 mmHg, with a pulse rate of 75 beats per minute, an oxygen saturation of 99% on room air, and a temperature of 36.7 °C. Generally, the patient was resting supine in no acute distress, appeared comfortable, and was alert and oriented. Lungs were clear to auscultation bilaterally with no increased work of breathing, cranial nerves II-XII were intact, strength in the right lower extremity was 4/5 and the left lower extremity was 5/5, and reflexes and sensation were intact bilaterally in upper and lower extremities. Additionally, there were scaling erythematous plaques present on the medial right ankle which had been present for about 6 weeks. Laboratory findings revealed a white blood cell count of 6.8×10^8/L, hemoglobin of 13.4 g/dL, creatinine of 2.1 mg/dL (baseline creatinine was ~2.0 mg/dL), and a serum bicarbonate of 21 mEq/L, with remaining electrolytes within normal limits. C-reactive protein was 5.9 mg/dL, erythrocyte sedimentation rate 6.0 mm/h, and creatinine kinase 53 units/L. Everolimus level was slightly supratherapeutic at 7.1 ng/mL (goal 3–5 ng/mL). The patient had significant orthostatic hypotension with a blood pressure of 230/115 mmHg (pulse 75) when supine which decreased to 114/65 mmHg (pulse 73) when sitting upright, along with an associated pre-syncopal sensation.

Investigation

Although the patient had no focal infectious signs or symptoms, urinalysis was obtained and unremarkable and blood cultures were sent. Orthostatic hypotension in the setting of long-standing diabetes led the team to consider adrenal insufficiency (less likely given chronic prednisone) and diabetic autonomic neuropathy. On endocrine testing, the cosyntropin stimulation test was normal, morning cortisol was normal, thyroid-stimulating-hormone low at 0.23 mU/L, free T4 elevated at 2.0 ng/dL, likely due to euthyroid sick syndrome. The patient was given IV fluid boluses and a trial of fludrocortisone 0.1 mg daily to treat diabetic autonomic neuropathy which did not improve orthostatic symptoms.

On day 5 of hospitalization, the outside hospital called with results of blood cultures drawn 6 days prior growing yeast with speciation pending. A CT chest-abdomen-pelvis revealed multiple areas of nodular and linear consolidations within bilateral upper and lower lung lobes, consistent with pneumonia. The following day, the yeast was identified as *Cryptococcus neoformans* and serum cryptococcal antigen was positive with antigen titer greater than 1:2560. A CT head revealed age-appropriate findings and subsequent lumbar puncture was performed with opening pressure 15 cm CSF (normal 10–25 cm CSF) and clear cerebrospinal fluid with 14 WBC/uL (34% monocytes, 66% lymphocytes), glucose of 14 mg/dl (normal range 40–70 mg/dl) and a protein of 81 mg/dL (normal range 15–45 mg/dL). Serum glucose at the time was 184 mg/dL. Cerebrospinal fluid cryptococcal antigen was positive with antigen titer was greater than 1:2560 and CSF cultures grew *Cryptococcus neoformans*. A lumbar MRI was ordered to evaluate his right lower extremity weakness which revealed focal L5 findings suggestive of chronic foraminal stenosis. The patient was diagnosed with disseminated *Cryptococcus neoformans* infection with blood, cerebrospinal, and pulmonary involvement.

Treatment

Liposomal amphotericin B and flucytosine treatment were initiated and everolimus was held. After four days, the patient's liver enzymes began uptrending and flucytosine was switched to oral fluconazole. As patient's infection was treated, pre-syncopal symptoms improved remarkably and orthostatic hypotension resolved. Lower extremity weakness and right lower extremity rash improved as well. After 14 days of antimicrobial treatment, a repeat lumbar puncture was performed and cerebrospinal fluid culture grew no yeast, the most sensitive and specific marker of cerebrospinal cryptococcal clearance.

Outcomes

At the end of the two-week induction therapy (liposomal amphotericin B + fluconazole), the patient was no longer orthostatic and his functional status had greatly improved. The patient was transitioned to oral fluconazole 400 mg for the consolidation phase of therapy for the next 8 weeks, to be followed by maintenance therapy for at least a year. At four-week follow-up, the patient was doing well with improving functional status, no neurological deficits, and liver enzymes were within normal limits. Unfortunately, 7 weeks after discharge the patient was admitted for delirium and died after a 3-week hospital course due sepsis from pseudomonas osteomyelitis. Although the patient did respond to therapy and the immediate cause of death was not cryptococcosis, the delay in cryptococcal diagnosis may have contributed to his subsequent clinical decline.

Discussion and Conclusions

This case illustrates two important points, (1) orthostatic hypotension may be a presenting symptom of cryptococcosis, and (2) in patients with solid organ transplants (vs. patients with HIV/AIDS), the presentation of cryptococcosis is more insidious and the threshold for clinical consideration of cryptococcal infection should be lowered.

The typical presenting symptoms of cryptococcal meningitis are fever, headache, photophobia, neck pain, and/or altered mental status. Unusual presentations can delay diagnosis and treatment significantly. Some of the unusual presenting symptoms for cryptococcal meningitis in transplant patients include headache without neurological signs [8], vertigo [7], sinusitis [6], and hyponatremia [5]. Atypical and non-specific presenting symptoms result in delayed diagnoses, exemplified by our patient who visited the emergency room several times with orthostasis and pre-syncope prior to being admitted.

In our patient, no other infectious source was identified on labs or imaging and other causes of orthostatic hypotension including adrenal insufficiency, diabetic autonomic neuropathy, and hypovolemia were ruled out. As a result, the patient's orthostatic hypotension is best explained by the disseminated cryptococcal infection. Of note, the patient had no classic infectious signs and symptoms including fevers, headache, chills, and cough, and labs were without leukocytosis or elevated inflammatory markers, making the diagnosis challenging.

The maintenance of postural normotension depends on a normal plasma volume, intact baroreflexes, and reasonable vasomotor tone [16]. The mechanisms to maintain these physiologic parameters are complex. The adrenergic pathway runs through similar brainstem structures to the thoracic spinal cord and then to the autonomic ganglia of the heart, arterioles, and venules [17]. Autonomic instability is associated with other infectious neurological processes such as herpes simplex encephalitis [9], pneumococcal meningoencephalitis [10], and HIV [13]. Theoretically, any of the above mechanisms could be involved in the pathophysiology of orthostatic hypotension associated with cryptococcal disease. Elucidation of the mechanism of orthostasis in cryptococcal disease will require further research.

According to the Transplant-Associated Infection Surveillance Network (TRANSNET), cryptococcosis is the third most common

invasive fungal infection in organ transplant recipients (behind candidiasis and aspergillosis) [11]. Additionally, the median time from solid organ transplant to diagnosis was 20 months with a significant proportion of patients presenting 3 years after transplant, like our patient. Of note, there is significant disease burden and mortality as cryptococcal infection causes fatal cryptococcosis in 25–80% of immunocompromised patients who get infected [12].

One study which used population-based administrative billing data to investigate the association between missed diagnosis and mortality risk found that missed opportunities to diagnose cryptococcosis are common, particularly in HIV-negative patients. In HIV-negative patients, missed opportunities for diagnosis resulted in an absolute increased 90-day mortality risk of 8.8% [14]. In the month prior to transfer to our hospital, our patient had visited the emergency department with hypotension and weakness. These presentations were likely missed opportunities to diagnose cryptococcus. Given that serum cryptococcal antigen testing is an affordable and reliable marker for cryptococcal infection there should be a lower threshold to obtain it in any patients with symptoms suggestive of cryptococcus [15,16].

The key components of managing cryptococcosis in transplant recipients are management of the increased intracranial pressure, antifungal therapy, adjunctive therapies, and immunosuppression reduction [17]. In this case, the opening pressure was not elevated enough to warrant therapeutic lumbar punctures (>25 cmH2O) and treatment included amphotericin B as well as holding everolimus and belatacept. One major treatment concern is Immune reconstitution inflammatory syndrome (IRIS) which is characterized by rapid Immune reconstitution after reduction in immunosuppression and potent antifungal treatment. IRIS has a particularly poor prognosis warranting exclusion of clinical failure with a repeat lumbar puncture before transitioning to maintenance therapy [17].

Several features are associated with increased mortality in transplant recipients with cryptococcal meningitis including altered mental status, absence of headache, liver failure, and renal failure at baseline [18]. One key to identifying cryptococcosis in transplant recipients is lowering the threshold for clinical suspicion in patients with non-specific concerns. This case study of a patient presenting with orthostatic hypotension found to have disseminated cryptococcosis illustrates why clinicians should lower the threshold for testing in transplant recipients.

Funding

No grants or funding was used to complete this manuscript.

Ethics approval and consent to participate

Not applicable, this manuscript does not report a study with human participants, human data, or human tissue.

Consent to publish

Written informed consent was obtained from the patient's next of kin (daughter) for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

CRediT authorship contribution statement

SG made substantial contributions to the conception, acquired and interpreted data, drafted the work, revised the work. SB and CF made substantial contributions to the conception and revised the work. SG, SB, and CF approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the manuscript.

Declaration of Competing Interest

These authors have no financial or non-financial competing interests to disclose.

Acknowledgements

Not applicable.

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