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Case report

Case report: Disseminated cryptococcus gattii in an immunocompetent patient

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ABSTRACT

Background: Cryptococcosis is an opportunistic fungal disease, caused by Cryptococcus grubii, C. neoformans, and infrequently by C. gattii. [1], [2] Infection occur in patients with immunosuppression or with intact immunity. Dissemination mostly occurs in the lungs and meninges, but also the skin, bones and the prostate, with very high mortality rates reported for cryptococcal meningitis ranging from 27% to nearly 100%. [2], [3]
Case presentation: We report the case of a healthy, immunocompetent male presenting with a six-month history of weight loss, a chronic cough, recent-onset haemoptysis and a lung mass. The differential diagnosis included pulmonary Tuberculosis, bacterial or fungal pneumonia and lung carcinoma. The patient was subsequently diagnosed with disseminated C. gattii, which remains very rare. Risk factors for this infection included a distant history of cigarette smoking, as well as travel to central Africa for a recreational trip several months prior.
Discussion and conclusion: Fungal infections should be considered in any patient presenting with respiratory or neurological symptoms suggestive of Tuberculosis, pneumonia or lung carcinoma, regardless of immunocompetency. Our case highlights the importance of taking a thorough travel history in all patients, as the differential diagnosis would need to include atypical pathogens that could be endemic in the area of travel. It also highlights the significant morbidity associated with cryptococcosis and drug-related toxicities and the methods to prevent complications.

Background

Cryptococcosis is an opportunistic fungal disease that occurs predominantly in patients with immunosuppression. The Infectious Disease Society of America Clinical Practice Guidelines (2010) on cryptococcal disease, outlined three groups at risk:

(1) patients with HIV infection, (2) organ transplant recipients, and (3) HIV-negative non-transplant patients [1].

The WHO African Region, including South Africa, is one of the most affected regions, with more than 25.7 million people living with HIV in 2018 [4].

In South Africa (SA), cryptococcus surveillance performed in Gauteng Province (2002), reported incidence rates of 15.6 cases per 100,000 population [2]. Similarly, mortality rates from cryptococcal meningoencephalitis in SA are 27% and nearly 41% in countries such as Papua New Guinea [5].

Worldwide, the major species involved in cryptococcosis are Cryptococcus grubii and C. neoformans, with a small proportion caused by C. gattii in a more restricted habitat [2].

The lungs are the primary locus of infection, with extra-pulmonary dissemination occurring mainly to the central nervous system (CNS), skin, bones and the prostate. Among non-HIV patients, *C. gattii* infection, presentation mostly includes pulmonary nodules or meningoencephalitis, whereas, in HIV-infected patients, it is mostly meningitis (with or without fungaemia) [2].

Identification of *Cryptococcus* species does not appear to be necessary for routine management in the HIV population, as *C. gattii* infection does not impact the management or outcome more severely than other

Abbreviations: AIDS, Acquired immune deficiency syndrome; AKI, Acute Kidney injury; AmBd, amphotericin B deoxycholate; RBC, Red-blood cell; CDC, Centre for disease control; CLAT, Cryptococcal latex agglutination tests; CT, Computed tomography; ECG, Electrocardiogram; ELISA, Enzyme-linked immunosorbent assay; FNAB, Fine needle aspiration biopsy; HIV, Human immunodeficiency virus; ICP, Intracranial pressure; Kg, kilogram; LFAmB, Lipid-formulation Amphoteracin B; LP, Lumbar puncture; PAS, Periodic acid-Schiff; ROSE, Rapid onsite cytology examination; SAHIVSoc, Southern Africa HIV Clinicians Society; TB, Tuberculosis; QTc, Corrected QT time on electrocardiogram.

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species [2].

The case report describes a rare case of disseminated cryptococcosis in an immunocompetent patient referred with suspected lung carcinoma, after presenting with non-resolving pneumonia. The author discusses the importance of obtaining a travel history, the morbidity associated with cryptococcal disease and the management of several complications related to the toxicity of the treatment of disseminated cryptococcosis disease.

Case presentation

A 63-year-old Caucasian male was referred from a local emergency centre as an outpatient with weight loss, chronic cough and blood-stained sputum. A chest radiograph done two weeks prior showed a round opacity in the posterior left lower lobe. This was treated as a bacterial pneumonia with oral levofloxacin with symptom progression prompting representation. The patient recalled that no previous travel history had been taken.

Background history included relapsed atrial fibrillation with a previous atrial ablation, on sotalol and rivaroxaban. Social history included distant cigarette use. Travel history included a work-related trip to the United Kingdom, as well as a trip to Angola six months prior, which included recreational cave-exploration activities. The patient had several months of chronic fatigue and headache, a non-productive cough and intermittent fever. This led to multiple primary care visits and repeated sputum testing for tuberculosis (TB) with negative results. More recent symptoms included unintentional weight loss of more than 10 kg and anorexia for 4 – 6 weeks, progressive chronic headaches without visual disturbance, 2 weeks of streaky haemoptysis and night sweats. No reported skin lesions, or urological or gastrointestinal symptoms.

The initial outpatient examination revealed an acutely unwell, afebrile, cachectic male patient. On general inspection, there was no clubbing, pallor or lymphadenopathy. Chest findings were unremarkable, except for a respiratory rate of 22 bpm (without hypoxia). On neurological examination, no nuchal rigidity or papilledema was present. The patient was admitted to the hospital from the outpatient clinic and isolated in the medical ward pending an infectious disease screen.

A repeat radiograph showed a well-defined mass in the posterior basal region of the left lower lobe. On biochemistry, the white cell count was elevated at 9.92×10^9 ($3.9 – 9.8 \times 10^9$) with a normal haemoglobin, and renal and liver function. Sputum for acid-fast bacilli and TB Gene Xpert was negative. Two HIV 4th generation ELISA tests were non-reactive.

Computed tomography (CT) showed a lobulated mass of 38 × 44×42 mm in the posterior basal segment of the left lower lobe, abutting the pleural space. Features included a hypodense lesion with necrotic areas and an inferior pleural-based nodule of 21 × 20×25 cm and no cavitation. Sub-centimetre pre-carinal lymph nodes of 5 × 7 mm and mild central bronchiectasis were noted. Imaging of the brain with a contrast CT was normal.

The presumptive diagnosis was that of a malignant lung mass with superimposed infection, however, pulmonary TB and atypical infections needed to be excluded.

The patient developed an in-hospital fever of 38.5 °C and neck stiffness with severe headaches after 72 h in the hospital. The rest of the neurological examination, including fundoscopy, was normal. A repeat CT brain was normal, showing no evidence of raised intracranial pressure or a space-occupying lesion. A lumbar puncture (LP) was performed for cerebrospinal fluid (CSF) collection and empiric antimicrobial therapy was started with ceftriaxone pending the results. The opening pressure was 49 cmH2O.

Results of the lumbar puncture was total white cells = 560 cells/uL, polymorphs = 0 cells/uL, mononuclear cells = 560 cells/uL, total protein = 1115 mg/L (140 – 450 mg/L) and glucose = 2.7 mmol/L (2.2 – 3.9 mmol/L).

The following day, a fine needle aspiration biopsy (FNAB) was performed on the pulmonary lesion with rapid onsite cytology (ROSE). The pathologist detected numerous fungal yeasts with budding, which were strongly positive for mucin, and positive on PAS and Grocott stains, suggestive of Cryptococcus species.

Cryptococcal latex agglutination test (CLAT) was positive on serum and CSF. Microbiological culture of the lung mass, blood culture and CSF confirmed Cryptococcus gattii species and a diagnosis of disseminated cryptococcal disease was made.

The patient was commenced on induction amphotericin B (AmBd) and fluconazole 400 mg daily, in discussion with an infectious disease specialist from the nearest Tertiary centre.

The ophthalmological and urological assessment was normal. Subsequent fungal cultures detected Cryptococcus gattii species from the pulmonary lesion, the CSF and blood culture.

The patient experienced significant drug-related toxicities due to the AmBd, including renal failure up to 285 μmol/L (45 – 90 μmol/L), hypokalaemia and hypomagnesaemia) which was managed with aggressive fluid rehydration and intravenous (IV) electrolyte replacement.

During the induction phase, thrombophlebitis was managed initially with peripheral access and subsequently with central venous access. Intractable headaches occurred within the first 15 days, leading to near-daily LPs and opioid analgesia. Transfusion rigors were managed with IV paracetamol and a reduced rate of the AmBd and fluid rehydration. Ongoing monitoring for drug interactions between fluconazole and sotalol was continuous cardiac monitoring and measurement of QTc.

Ongoing intolerance by day seven, prompted a Section 21 application for Liposomal Amphoteracin B (LFAmB) and oral flucytosine (5-FC) with the South African Health Products Regulatory authority (SAHPRA). This application took nearly 10 days for approval, with an additional four days for the arrival of the LFAmB from the supplier.

The patient had completed approximately two weeks of interrupted Amphoteracin B and fluconazole therapy when the LFAmB was commenced.

The LFAmB was better tolerated by the patient, but there were ongoing problems with renal impairment, cholangitis and transfusion reactions, requiring discontinuation for up to 48 h at a time. The patient also experienced oesophagitis and vomiting, related to the pill burden of flucytosine at a dose of 6000 mg per day (12 tablets per day in divided doses every 6 h), which was managed with pantoprazole and metoclopramide. Recurrent anaemia required the transfusion of packed RBC every two weeks.

After a protracted hospital stay with treatment interruptions and treatment-related complications, the patient completed six weeks of induction therapy and was successfully discharged home. Treatment comprised of induction with AmBd+fluconazole and later LFAmB + 5-FC totalling six weeks.

Repeat Chest CT at the end of induction, demonstrated a reduction in the size of the pulmonary mass to 30 × 32×33 mm. The creatinine remained mildly elevated at 105 μmol/L (45 – 90 μmol/L), but all other biochemical parameters had returned to normal. All symptoms had resolved on discharge.

The consolidation phase of treatment was oral fluconazole 400 mg daily for 8 weeks, with a biochemical and clinical review every two weeks, followed by maintenance phase treatment of fluconazole 200 mg daily for 6 months, with a monthly review.

At the 6 & 12- month review, no relapse occurred and the CT chest only had a residual pulmonary nodule that will be followed annually.

Discussion

Clinical manifestations

C. neoformans and *C. gattii* mainly lead to lung infections (e.g., pulmonary nodules, pneumonia) and central nervous system infections

(meningoencephalitis, cranial neuropathies, lethargy and seizures). Other less frequent body sites of infection include skin, prostate (which can serve as a reservoir), eyes, bone marrow and joints.

Restoration of immunity in HIV-infected patients can also result in paradoxical immune reconstitution inflammatory syndrome (IRIS), following initiation of antifungal and antiretroviral therapy.

Laboratory diagnosis

A definitive diagnosis of cryptococcosis is confirmed by direct examination of the yeast from various sites with India ink-staining, isolation by culture and serology [6]. Tissue cultures include cytological and histological staining from the skin, lungs, CSF, bone-marrow and gastro-intestinal tract.

The organism is observed as yeast with narrow-based budding and identified by special stains that label the polysaccharide capsule including mucicarmine, periodic acid-Schiff (PAS), and Alcian blue stains [6].

Treatment and drug-toxicities

There is a paucity of prospective studies to investigate the treatment of cryptococcal disease in the immunocompetent host. The recommendations are similar to the Southern African HIV Clinicians Society (SAHIVSoc) guideline on cryptococcal disease in HIV-infected persons (2019) [3].

Similarly, the Infectious Disease Society of America and the Centre for Disease Control (CDC), recommend a 3-stage regimen of induction, consolidation, and maintenance treatment for meningoencephalitis in all patients, irrespective of host risk factors [5,6].

Induction

1. AmBd (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg daily) for at least 4 weeks
2. For AmBd toxicity issues, LFAmB may be substituted in the second 2 weeks.
3. If a patient is AmBd intolerant, substitute liposomal AmB (3–4 mg/kg daily IV).

Consolidation

4. Followed by consolidation with fluconazole (400 mg daily) for 8 weeks.
5. If flucytosine is not given or treatment is interrupted, consider lengthening AmBd or LFAmB induction therapy for at least 2 weeks.

Maintenance

6. Use maintenance therapy with fluconazole (200 mg daily) for 6–12 months.

Flucytosine (5-FC)

Flucytosine causes bone marrow toxicity leading to anaemia, neutropenia and thrombocytopenia [3]. In addition, it is cleared by the kidneys, necessitating renal dose adjustment in AKI [3].

The dose recommended is 50 – 150 mg/kg/day given orally in 4 divided doses [3,5], The average dose would be 6000 mg (three 500 mg tablets four times daily), adding to an already high pill burden experienced.

Amphoteracin B (AmBd)

The major adverse effects of amphotericin B include acute kidney injury (AKI), hypokalaemia, anaemia, hypomagnesaemia, transfusion reactions and chemical phlebitis [1,3], In particular, AmBd causes renal potassium wasting requiring daily replacement.

Lipid-formulation Amphoteracin B (LFAmB)

Newer lipid-based AmB formulations significantly reduce renal toxicity in comparison with conventional AmBd, but transfusion reactions and AKI remain problematic [7,8].

These formulations have also been assessed for use in an outpatient setting and the researcher reported a 20% incidence of AKI, with only 5% hospitalisation, and a 90% renal recovery within 30 days [9].

Fluconazole

Alanine transaminase (ALT) levels should be checked if jaundice or hepatitis develops whilst using fluconazole, but routine ALT monitoring is not indicated [3].

Corticosteroids

The Southern Africa HIV Society Expert panel advises against the routine use of corticosteroids, and should be reserved for patients with severe IRIS (e.g. dexamethasone 1 mg/kg/day) [3].

Monitoring and treatment of adverse events

Routine monitoring

The SA HIV Society guidelines recommend regular monitoring:

- Days 0, 3 and 7: full blood count, creatinine, potassium and magnesium [3]
- Daily: Fluid input and output monitoring [7,10]
- Weekly: liver function counts

Prevention of renal impairment and electrolyte replacement

Various studies have confirmed that adequate hydration and electrolyte supplementation are inexpensive methods to reduce nephrotoxicity [7,10].

Infusion of normal saline (0.9%), Darrow's or Ringer's lactate before AmBd, is the most frequently cited [3].

Electrolyte disturbances are mostly anticipated and can be added to daily fluid infusions before administration to avoid hypokalaemia and hypomagnesaemia.

Intracranial hypertension

Approximately 15% of patients will develop raised intracranial pressure (ICP) and the patient should have daily monitoring for signs and symptoms, in particular during the induction phase of treatment. Strategies to reduce ICP include daily lumbar puncture, ventriculoperitoneal shunts and the use of dexamethasone [3,11].

Transfusion reactions

Febrile reactions (including rigors, headache, and thrombophlebitis) almost always occur and can be treated with paracetamol 1000 mg before infusion. Decreasing the rate of administration of AmBd over a prolonged period also reduced the incidence of transfusion reactions.

If the reaction is severe, premedication with hydrocortisone 25 mg IV and/or promethazine should be trialled [3,5].

Blood dyscrasias

Anaemia frequently complicates AmBd, but should prompt investigation for alternative causes of anaemia [3]. Flucytosine should be withheld or dose-reduced if neutropenia occurs. Alternatively, changing to fluconazole, but consideration of an extension of AmBd [3].

Transaminitis can be caused by all of the drugs used for cryptococcal disease and should be monitored weekly.

Conclusion

This report highlights the case of a healthy, immunocompetent patient presenting with weight loss, chronic cough, haemoptysis, and a lung mass. Recurrent treatment for non-resolving bacterial pneumonia

prompted the referral of this resident South African male patient whose differential diagnosis included TB, atypical or fungal pneumonia and lung carcinoma.

The patient was subsequently diagnosed with disseminated C. gattii, which remains rare and was not the primary diagnosis at initial presentation, given the immunocompetency status.

This case illustrates the effect of delayed diagnosis and the importance of taking a travel history and considering alternative infectious pathogens (other than TB) in South Africa.

It also highlights the significant morbidity associated with cryptococcal disease, drug-related toxicities and methods to reduce complications.

Ethical considerations

Ethics clearance was received from the University of Stellenbosch Health Research Ethics committee # C21/12/042.

Written informed consent was obtained from the patient for publication of this case report.

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I confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication.This manuscript, or part of it, has neither been published nor is currently under consideration by any other Journal.

The views and opinions expressed in this article are those of the author and do not necessarily reflect the official policy or position of any affiliated agency of the author.

Data availability

Data sharing does not apply to this article as no new data was created or analysed.

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