Overwhelming cryptococcosis complicated by cryptococcal endocarditis

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SUMMARY

Cryptococcal species endocarditis is infrequently described, carries high mortality and nearly always occurs in immunocompromised states or on prosthetic valves. We report the case of a man in his 70s with multiple recent hospitalisations for pneumonia, hypercalcaemia and septic tank exposure who presented with intermittent fevers, progressive weakness,and worsening encephalopathy, manifested as confusion and word-finding difficulties for 3 weeks. Workup revealed cryptococcal species on blood serum gram stain, native aortic valve endocarditis and meningitis. Cerebrospinal fluid analysis demonstrated lymphocytosis, ultimately found to be secondary to chronic lymphocytic leukaemia. Surgical valve replacement was deemed medically contraindicated and antifungal therapy was initiated. Though poorly understood with very few documented cases, management of cryptococcal endocarditis relies on prompt diagnosis, early surgery when indicated, long-term antifungal therapy and treatment of underlying immunocompromising states where possible.

BACKGROUND

We report a case of cryptococcal infective endocarditis (IE) involving the native aortic valve with a previously undiagnosed underlying immunodeficiency. Cross-disciplinary collaboration proves critical for delivering optimum care to patients.

IE occurs as a result of surface endocardial infection, most commonly via *Staphylococcus aureus* (31% of cases worldwide), involving the mitral or aortic valve.[1 2] Incidence has been rising since the year 2000 and shows higher prevalence in patients with pre-existing valvular disease, valve protheses and immunosuppressed states.[1] This often carries multisystem engrossment, with common cardiac manifestations including valvular abscesses, vegetations or pericarditis. However, few reported cases have involved fungal species.

IE mortality overall remains high, with in-hospital rates estimated around 20%, in contrast to 44% for cryptococcal IE.[3 4] These outcomes have remained largely unchanged over the past few decades, when compared with more common pathology, such as myocardial infarction, elucidating a need for better description and study.[5 6]

CASE PRESENTATION

A man in his 70s with pertinent medical history of hypertension, diabetes mellitus type 2 and prior cerebrovascular infarct, presented with intermittent fevers, progressive weakness and worsening encephalopathy, described as confusion and word-finding difficulties, for 3 weeks. Notably, the patient had been hospitalised at an outside facility 6 months ago for multifocal pneumonia, bilateral pulmonary emboli and sepsis secondary to methicillin-susceptible *S. aureus* bacteraemia with a negative transthoracic echocardiography for endocarditis. He recovered from this hospitalisation and had returned to his occupation as an installer of septic tanks in the local community. His last project repairing an uncovered septic tank took place 3 weeks prior to the current admission, shortly after which he became excessively weak and experienced multiple episodes of chills with accompanying expressive aphasia.

Based on the overall clinical picture of titre of serum cryptococcal antigen (1:1280), cerebrospinal fluid (CSF), cryptococcal antigen (1:320), CT findings and significant exposure history, the patient was diagnosed with overwhelming cryptococcosis with chronic pneumonia, cryptococcaemia, meningitis and cryptococcal aortic valve endocarditis, complicated by perivalvular abscess, in the context of newly diagnosed chronic lymphocytic leukaemia (CLL). The diagnosis of endocarditis was made using modified Duke criteria.[7]

INVESTIGATIONS

MRI of the head (figure 1) on presentation revealed a new 2 cm subacute right putamen intracranial haemorrhage, sequalae of prior bilateral occipital strokes and acute sinusitis, for which amoxicillin/clavulanic acid was initiated. CT of the chest (figure 2) showed chronic bilateral lower lobe necrotising pneumonia, with both airspace disease and cavity formation. Infectious disease, neurology and pulmonary medicine were consulted. Given the patient's reported occupation of installing septic tanks, the differential diagnosis for infectious agents included dimorphic fungi, atypical mycobacteria, *Nocardia* and *Cryptococcus* species. Non-infectious aetiology of progressive lung disease, such as lymphoma, was also considered.

Urine and serum fungal antigen assays were obtained to evaluate for *Blastomyces* and *Cryptococcus* infection, as well as sputum fungal smear, acid–fast bacillus stain and culture. COVID-19 PCR resulted negative on both day of admission and 5 days later again on repeat testing. Further analysis for underlying immunocompromised states, which resulted in negative screening tests, included human T-lymphotropic virus type 1 and 2 antibodies, cytomegalovirus PCR, Epstein-Barr viral PCR, herpes simplex virus types 1 and 2, varicella zoster PCR, a complete respiratory viral panel (ie, influenza

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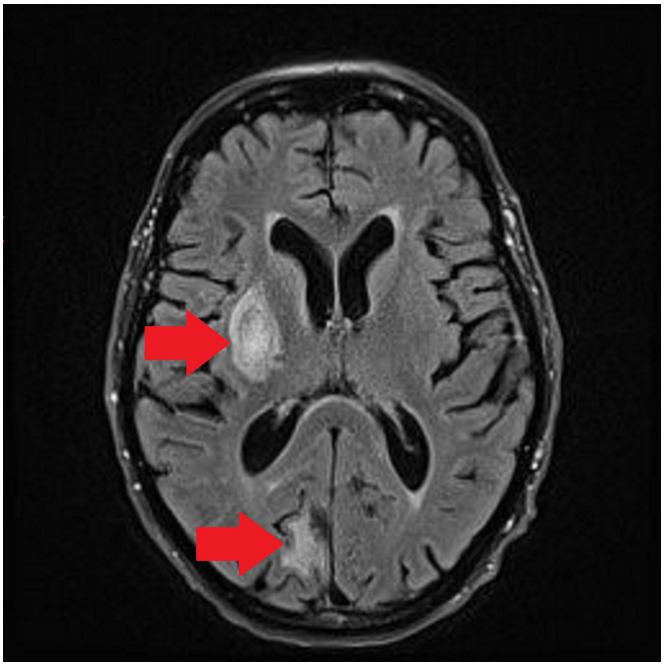

Figure 1 MRI of the brain showing 2 cm subacute right putamen intracranial haemorrhage (upper red arrow) and chronic infarction in the region of the right posterior cerebral artery (lower red arrow).

A, influenza AH1, influenza AH3, influenza B, human metapneumovirus, respiratory syncytial virus types A and B, adenovirus, rhinovirus, parainfluenza types 1–4, *Bordetella pertussis*, *B. parapertussis*/*bronchiseptica* and *B. holmesii*), hepatitis B and hepatitis C. A transthoracic echocardiogram demonstrated new severe aortic valve stenosis and a follow-up transoesophageal echocardiogram revealed native aortic valve endocarditis, with perivalvular extension and abscess cavity posterior to the valve (figure 3). Lumbar puncture showed normal opening pressure of 14 mm Hg, with lymphocytic predominance and lymphocytic pleocytosis on CSF analysis, suggesting an underlying lymphoproliferative disorder. A serum cryptococcal antigen lateral flow assay was positive with at titre of 1:1280, and CSF cryptococcal antigen lateral flow assay was also positive 1:320. Fungal blood cultures showed growth of *Cryptococcus neoformans*-susceptible to azoles, caspofungin and amphotericin B. Subsequent flow cytometry confirmed new diagnosis of CD5-positive kappa light chain restricted B-cell population consistent with

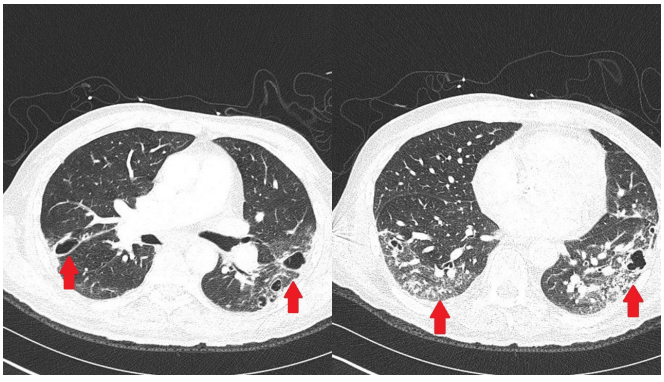

Figure 2 CT of the chest showing nodular (red arrows on the right) and cavitary lesions (red arrows on the left) predominantly in the lower lobes bilaterally.

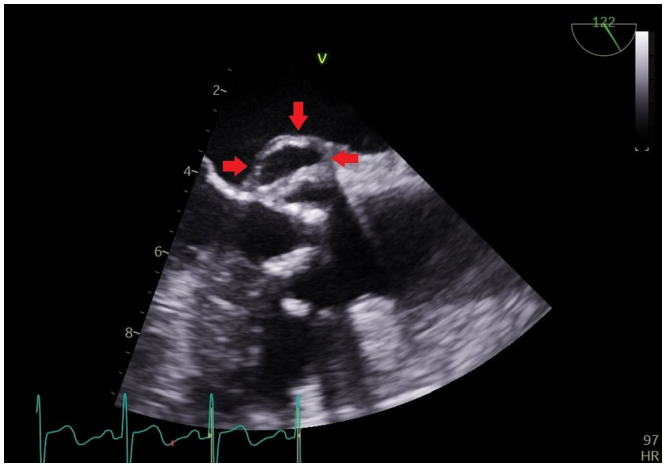

Figure 3 Transoesophageal echocardiogram showing native aortic valve endocarditis with perivalvular extension. An abscess cavity is posterior to the valve and is outlined by the red arrows.

CLL. Additionally, cell counts for immune monitoring revealed low CD3 of 41% (normal range 58%–86%) and low CD4 of 25% (normal 32%–64%). However, the length of time that this patient had remained immunocompromised is unclear, as the diagnosis of CLL was incidental in the absence of any previous similar testing outside the duration of this admission.

TREATMENT

Empirical treatment was initiated for presumed fungal species with intravenous amphotericin 300 mg once per day and fluconazole 800 mg once per day. Intravenous linezolid 300 mg three times per day (history of vancomycin allergy), ampicillin 2 g every 4 hours and ceftriaxone 2 g two times per day were administered for empirical coverage of bacterial meningitis and were discontinued following negative CSF bacterial cultures. Additional supportive medications continued included intravenous acetaminophen 1 g as needed for fevers, pantoprazole 40 mg/day for gastro-oesophageal reflux disease and lisinopril 10 mg/day for primary hypertension in the converted form of intravenous enalaprilat (patient unable to tolerate home oral medications due to multifactorial encephalopathy) and intravenous fluids such as albumin, lactated ringers, normal saline and dextrose 5% in water as clinically indicated. Home medications held during admission included testosterone gel 1.62% for androgen replacement therapy, tamsulosin 0.4 mg/day for benign prostatic hypertrophy, metformin 500 mg two times per day, Eliquis 5 mg two times per day for segmental and subsegmental pulmonary embolism diagnosed at an outside facility 2 months prior to admission (held due to acute intracranial bleed on head imaging), and simvastatin 40 mg/day for treatment of hyperlipidaemia. Oncology was consulted and treatment of chemotherapy was not considered, given that there was presence of acute infection. Cardiothoracic surgery evaluated the patient for surgical aortic valve replacement and aortic root repair or replacement; however, this was deemed to be contraindicated due to the patient's recent intracranial haemorrhagic stroke. P-R interval via ECG was closely monitored, given location of the perivalvular abscess and remained stable. His mental status eventually declined, culminating in respiratory failure requiring intubation on day 11. Repeat CT of the head revealed new-onset hydrocephalus, leading to extraventricular drain placement on day 12.

OUTCOME AND FOLLOW-UP

The patient continued to be markedly delirious throughout the hospitalisation, although he responded to verbal and tactile stimuli. Unfortunately, the patient's clinical status failed to improve despite maximal possible therapy. The patient's family decided to withdraw care on day 15 and he subsequently expired.

DISCUSSION

Cryptococcal species are known to potentially affect any organ of the body, most commonly the central nervous system, leading to meningitis in nearly three-fourths of cases.[8] Pulmonary and cutaneous manifestations are also frequent, which can progress to systemic infection. IE caused by this fungal species is enormously rare and mostly described in case reports. This patient demonstrated overwhelming cryptococcal fungaemia, meningitis and endocarditis in the setting of an immunocompromising disease (CLL) and history of septic tank exposure.

Fungal endocarditis has historically only been reported in 2% of cases.[2] Of these cases, *Candida* and *Aspergillus* have highest prevalence,[6] compared with the rare cryptococcal endocarditis, whose clinical course and prognosis are described in only 13 case reports between the years 1973 and 2020.[4 8] All except one report involved patients with an immunocompromised state or prosthetic valve. Meningitis and embolism had been reported in 33.3%, with disseminated infection confirmed in a few cases. Therapy includes administration of antifungals and surgery with limited success.

Our patient was deemed not to be a candidate for cardiothoracic surgical intervention, given his tenuous clinical condition, and was limited to medical management. No standardised antifungal management currently is published for cryptococcal endocarditis, given its low incidence and potential side effects; thus, we adopted a combination therapy of intravenous amphotericin and fluconazole. Given extensive central nervous system manifestations, including eventual loss of consciousness and respiratory depression, along with ineligibility for native aortic valve replacement, the patient expired only 15 days following presentation, despite aggressive antifungal therapy. More research and documentation of similar cases are needed to optimise treatment for cryptococcal IE and its unique presentation.

We report a case of cryptococcal IE involving the native aortic valve with underlying immunodeficiency. While poorly understood with very few documented cases, outcomes may improve with prompt diagnosis, early surgery when indicated, long-term antifungal therapy and treatment of underlying immunocompromising states where possible.

Learning points

- This is a rare presentation of an infrequent causative agent for cardiac valvular pathology. cryptococcal infective endocarditis in a presumed immunocompetent patient should prompt investigation for undiagnosed underlying immunocompromising states.
- Complex cases of multiorgan failure should prompt appropriate relevant subspecialty involvement and a multidisciplinary approach early on to optimise outcomes.
- While poorly understood with very few documented cases, outcomes may improve with prompt diagnosis, early surgery when indicated, long-term antifungal therapy and treatment of underlying immunocompromising states where possible.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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