

## Case report

## *Cryptococcus neoformans* infective endocarditis of native valves in an immunocompetent host

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### ABSTRACT

With the emergence of Human immunodeficiency virus (HIV) and the resulting immunocompromised state, *Cryptococcus neoformans* infections have gained more importance in clinical practice. Cryptococcal infections in immunocompetent hosts continue to be uncommon. We present a rare case of *Cryptococcus neoformans* infective endocarditis (IE) in a young immunocompetent male. As per our literature review, this is the first reported case of native valve *Cryptococcus neoformans* endocarditis in an immunocompetent host. All cases till date have been reported in patients with underlying immunocompromised state or prosthetic valve.

### Introduction

*Cryptococcus* belongs to the fungal phylum of Blastomycota. It is an encapsulated yeast, found in soil. Systemic infections usually result from inhalation of spores or desiccated yeasts leading to primary pulmonary infection [1]. The pathogen shows tropism to the central nervous system. It rarely causes IE with most reported cases involving a cardiac prosthetic valve after surgery. This case presents a rare scenario of native valve infection in an immunocompetent host.

### Case presentation

A 26 year old homeless smoker male with no other significant personal history was initially admitted after cardiac arrest related to drug overdose with development of acute renal failure following the event. Patient was started on dialysis but while the workup was pending, he left the hospital against medical advice. Patient was readmitted at another outlying facility within a week, with acute shortness of breath and left against medical advice again after improvement of symptoms following few sessions of hemodialysis. No significant family history was reported. Social history was significant for intravenous heroin, cocaine and methamphetamine use. He decided to seek care within a week and was admitted at our facility for further evaluation and management. Patient denied any recent camping or exposure to pigeon droppings through occupational or recreational exposure.

Physical examination was significant for tachycardia (heart rate 123 beats per minute) and tachypnea (respiratory rate of 25 breaths per minute). He had jugular venous distension, bilateral lower extremity and scrotal edema. Needle track marks were noted over the upper

extremities. Chest radiograph showed cardiomegaly with pulmonary edema.

Complete blood count on admission showed white blood cell count of 13,000/uL, hemoglobin of 10.4 g/dL, and platelet count of 100,000/uL. A basic metabolic profile on admission was significant for potassium of 5.5 mmol/L and serum creatinine of 7.08 mg/dL. Nephrology was consulted and patient underwent emergent dialysis. Electrocardiogram showed sinus tachycardia with frequent ventricular complexes, no atrioventricular nodal block was noted. A transthoracic echocardiogram (TTE) was obtained due to clinical findings suggestive of heart failure. It showed a large mobile vegetation on the atrial surface of the tricuspid valve with severe tricuspid regurgitation. (Fig. 1) Severe global hypokinesis with systolic ejection fraction of 25% was also noted. An echogenic non-mobile structure was noted on the posterior mitral leaflet with moderate mitral regurgitation (Fig. 1). Transesophageal echocardiography (TEE) confirmed a 2.2 × 1 centimeter (cm) mobile vegetation on anterior leaflet of tricuspid valve and 1.5 × 0.8 cm mobile density on the posterior tricuspid valve. A 0.5 × 0.6 cm sessile echodensity was noted attached to posterior mitral valve that appeared calcified and consistent with old vegetation on the TEE. (Figs. 2 and 3). Records of care at outlying hospitals were finally obtained a few days after hospitalization at our facility. Blood cultures from other hospital showed 2 out of 2 sets of blood cultures positive for *Cryptococcus neoformans* from the initial facility, followed by 1 out of 2 sets positive for the same organisms 5 days later from patient's second admission. Repeat fungal blood cultures at our facility remained negative. Laboratory testing was done to rule out HIV and other underlying immunodeficiency with test results shown below in Table 1.

Computed tomographic images of the lungs and abdomen showed

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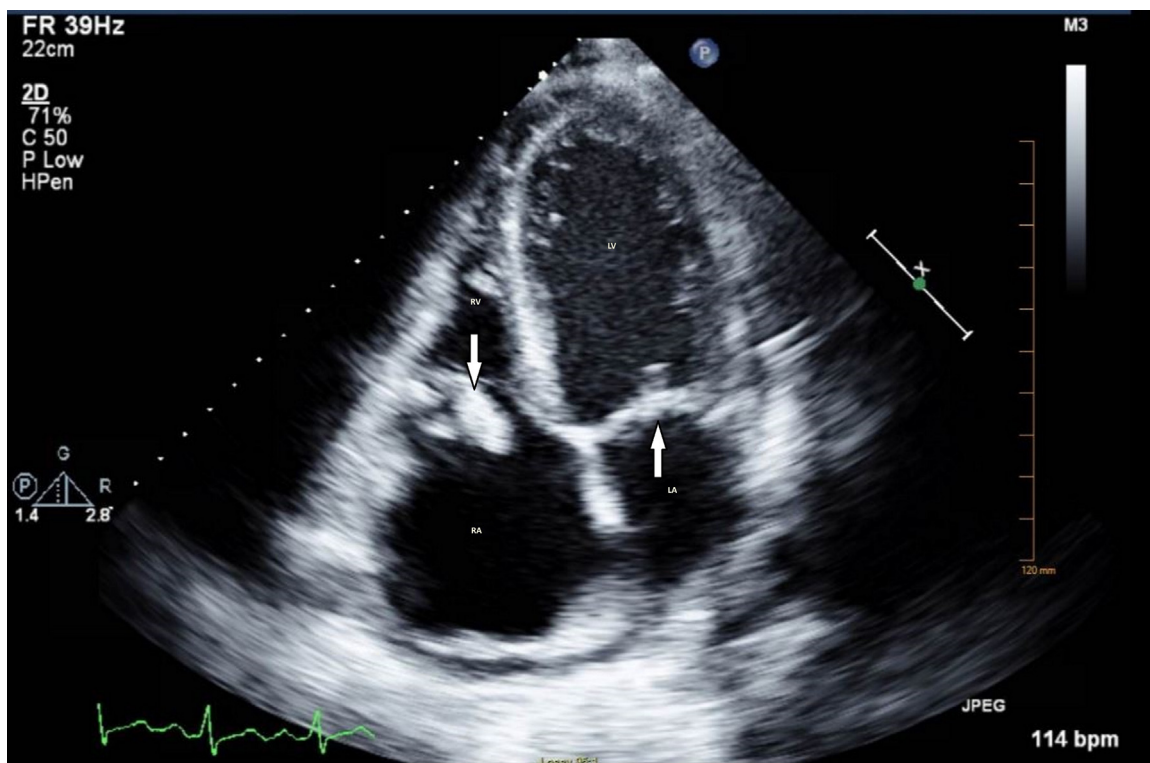


Fig. 1. Transthoracic echocardiogram (TTE) showing tricuspid and mitral vegetations noted on apical fourchamber view. (RA-Right atrium, LA- Left Atrium, RV- Right ventricle, LV- Left ventricle, upward arrow showing mitral vegetation, downward arrow showing tricuspid vegetation).

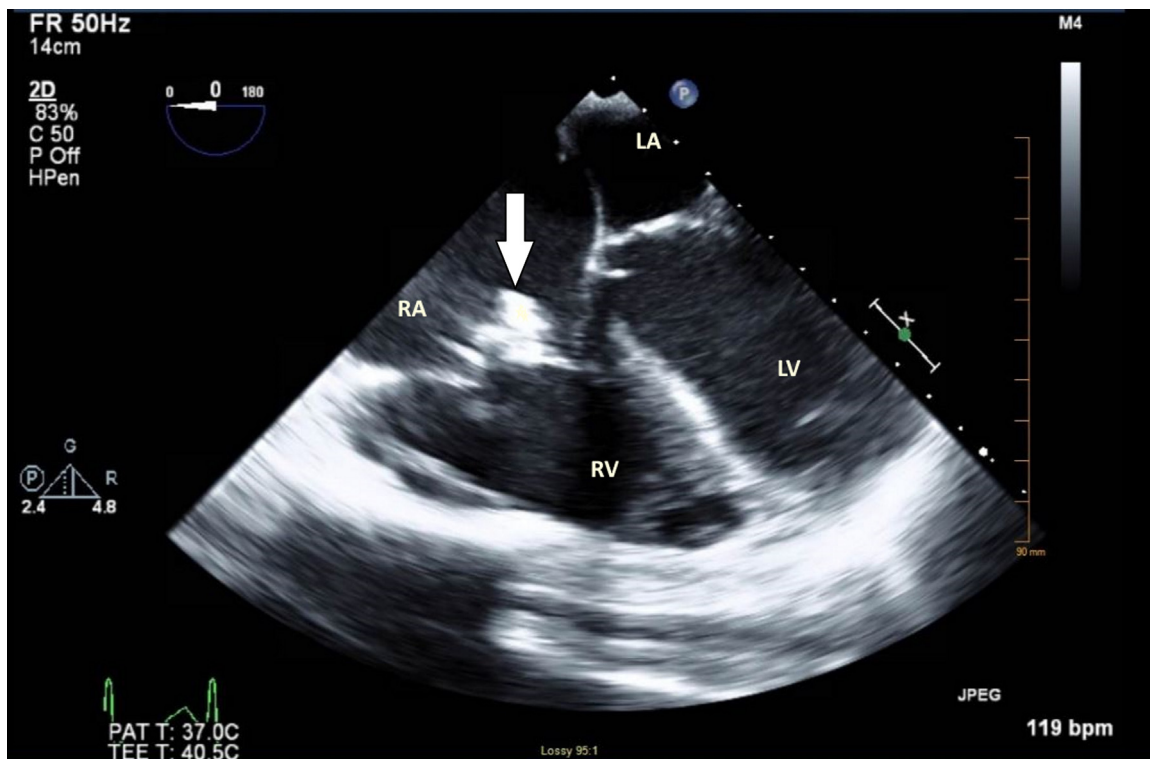


Fig. 2. Transesophageal echocardiogram (TEE) showing large tricuspid vegetation on Midesophageal four-chamber view. (Downward arrow showing tricuspid vegetation).

patchy confluent opacities of bilateral lungs suggestive of septic emboli. A 2.2 cm hypo dense sub-capsular lesion was seen in spleen which possibly presented a septic emboli as well. Lumbar puncture was performed to rule out central nervous system cryptococcal disease with findings as shown in Table 2.

Records confirmed that patient was treated with liposomal Amphotericin-B for three days at outlying hospital before he had left against medical advice. On admission at our facility, while waiting to obtain records from other hospital, patient was started empirically on vancomycin 1000 mg and gentamicin 80 mg intermittent intravenous

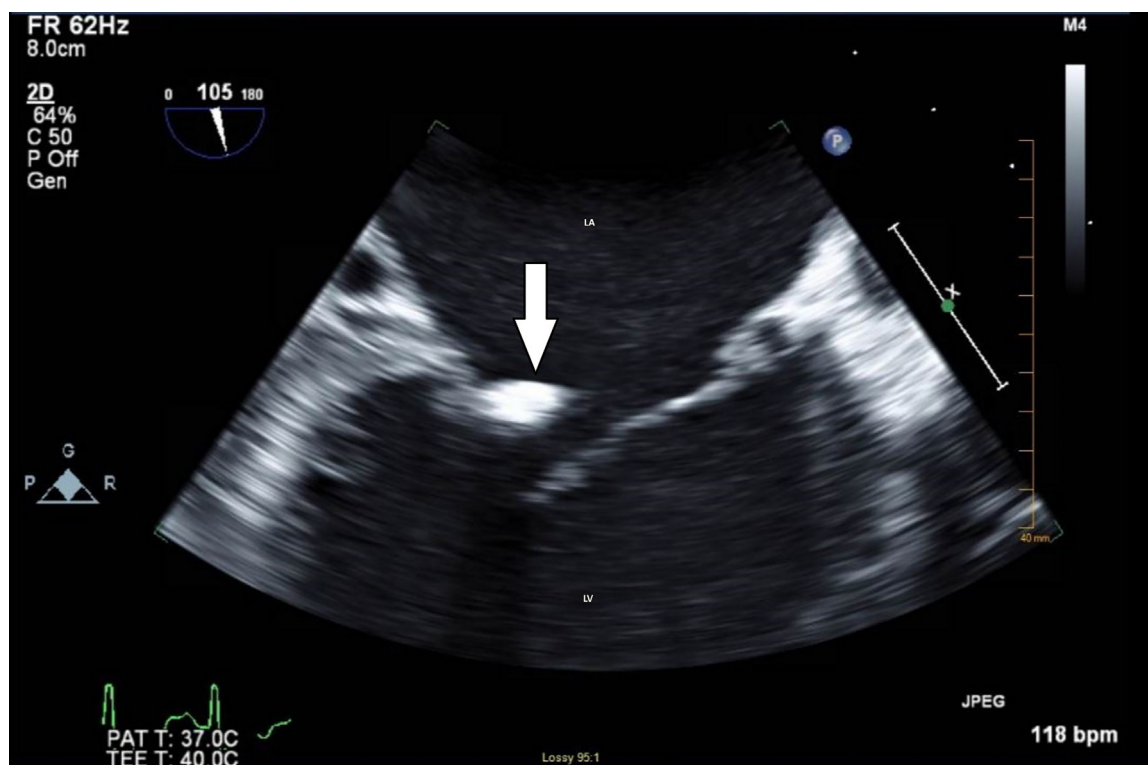


Fig. 3. Transesophageal echocardiogram (TEE) showing mitral vegetation on Midesophageal mitral commissural view. (Downward arrow showing mitral vegetation).

Table 1

Laboratory test results to rule out underlying immunodeficiency and other pertinent test results.

HIV 1,2 screen HIV-1 RNA PCR	Negative	Non detectable
C-Reactive Protein	3.32 mg/dL	
Absolute CD4 count	1328/cubic milliliter	
Serum Cryptococcal Antigen	Negative	
Brucella Serology	IgG, IgM negative	
Q fever Serology	negative	
C3 complement level	114 mg/dl	
C4 complement level	25.4 mg/dl	
Hepatitis C antibody Hepatitis C RNA PCR	Positive	Non detectable
Immunoglobulin G	1589 mg/dL	
Immunoglobulin A	295 mg/dL	
Immunoglobulin M	137 mg/dL	

Table 2

Lumbar Puncture result.

Component	value	Reference	units
CSF Total Nucleated cells	10	0–5	/mm <sup>3</sup>
CSF Neutrophils	1%		%
CSF Lymphocytes	98%		%
CSF Cryptococcal PCR	Negative	Negative	–
CSF Cryptococcal Antigen	Negative	Negative	
CSF glucose	52	40–70	mg/dl
CSF Protein	20.5	12–60	mg/dl
CSF Gram stain	Negative		
CSF Culture	Negative		

(IV) therapy with dialysis for suspected bacterial endocarditis. Liposomal Amphotericin-B 6milligram/kg and Fluconazole 400 mg IV once daily was started once fungal cultures with growth of *Cryptococcus* were obtained. Cardiothoracic surgery was consulted who recommended against emergent surgery due to patient’s social situation and high operative risk.

Due to high risk for being lost to follow up, patient completed 6

weeks of liposomal Amphotericin-B treatment while inpatient. Prior incomplete treatment with Amphotericin-B at outlying hospital was likely the cause of negative serum Cryptococcal Antigen testing at our facility and made the diagnosis very challenging. After completing intravenous Fluconazole therapy while inpatient, he was discharged home on oral Fluconazole 400 mg every 48 h after hemodialysis for 6 months. Flucytosine therapy was recommended but patient refused to take the medication due to concerns about side effects. On subsequent follow-up, patient was noted to be compliant with treatment and did not need any surgical intervention. Patient was seen at the infectious disease follow up clinic 3 months after discharge with weekly follow up of C-Reactive protein that trended down within normal range. Repeat fungal and bacterial blood cultures done one month after discharge showed no growth. Repeat transthoracic echocardiogram in one month showed anterior tricuspid valve vegetation 1.2 × 2.4 cm in size and septal vegetation was 0.9cmx1.9 cm in size. The mitral valve vegetation size on repeat echocardiogram was 1cmx0.5 cm. Another transesophageal echocardiogram done approximately nine months after initial presentation showed ejection fraction of 60%.Small dense lesion on posterior mitral leaflet and a 1.3 × 0.3 cm lesion on anterior leaflet of tricuspid valve was seen with significant calcification, likely representing healed vegetation.

### Discussion

*Cryptococcus* endocarditis is a rare disease with very few cases reported in immunocompetent hosts. In 2009, Park et al. reported over 600,000 annual deaths from Cryptococcal infection in sub-saharan Africa alone [2]. *Cryptococcus neoformans* primarily lives in the yeast form and most people are exposed to it at young age in epidemic areas. Most cases are minimally symptomatic and the infection is rapidly cleared by immune system, though, in immunosuppressed patients, it has emerged as an important opportunistic infection [3]. The virulence of the organism is speculated to be due to a polysaccharide capsule that protects the pathogen in environment and within the host by several mechanisms such as downregulating inflammatory cytokines,

**Table 3**  
Brief review of reported cases.

Year	Authors	Prosthetic Valve	Native Valve	Immunosuppression	Treatment	Valves involved	Ref in Text
1957	Lombardo et al	No	Rheumatic Heart Disease	no	actidione,sulfadiazine	Mitral and Aortic	[26]
1967	Colmers et al	No	Yes	Yes	Amphoteticin B	Mitral, History of Mitral stenosis	[25]
1983	Boden et al	yes	no	Yes	Amphotericin B and Surgery	Aortic	[24]
1997	Bannerjee et al	yes	No	No	Amphotericin B	Mitral	[23]
2011	Alhaji et al	yes	No	No	Amphotericin B	Aortic	[27]

inhibiting antigen presenting capacity of monocytes, regulating phagocytosis by macrophages and also providing antioxidant property to protect the pathogen from reactive oxygen generated by the host [4–7].

The spectrum of disease due to the pathogen ranges from self-limiting skin infection to more devastating systemic infections in immunocompromised hosts. It most commonly causes central nervous system (CNS) infection such as meningoencephalitis. Disease in individuals with no apparent immunodeficiency is not very common [8–12]. Lui et al. performed a retrospective case series of *Cryptococcus* infections, reporting 20 out of 46(43.5%) cases were immunocompetent [13]. Other extra-pulmonary and extra-CNS cryptococcal infections reported include prosthetic joint infection, small bowel infection, bullous cellulitis, sarcoid like reaction, septic arthritis and palatal mass [14–20].

Cardiac involvement due to *Cryptococcus* infection can present with pericarditis, myocarditis and endocarditis, especially in immunocompromised host and in the presence of prosthetic valves [21,22]. Fungal endocarditis accounts for approximately 6% of cases of infective endocarditis [23]. *Cryptococcus* is a rare fungal pathogen to cause endocarditis, with *Candida*, *Aspergillus* and *Histoplasma* species being more commonly implicated in causing fungal IE. The risk factors for fungal endocarditis are the same factors as those identified for bacterial endocarditis, such as, intravenous drug use, prosthetic heart valves, structural heart disease and HIV. Our patient did have the risk factor of intravenous drug use, and a possible cause of cryptococcal bloodstream infection was needle contamination.

Cryptococcal endocarditis is extremely rare and has been reported in post-operative prosthetic valve infections [24–29]. Lombardo et al. reported the first case of *Cryptococcus* endocarditis in 1957 [25]. Clinical presentation of fungal endocarditis is usually the same as bacterial endocarditis but a high index of suspicion is needed to send the fungal blood cultures, otherwise the diagnosis can be delayed. Cultures in special media such as Sabouraud dextrose agar, brain-heart infusion agar, or canavanine-glycine-bromothymol blue are needed for isolation of fungi [30]. A single center study of fungal endocarditis reported much higher mortality with fungal pathogens as compared to bacterial counterpart [31].

Table 3 shows a brief review of reported cases since the first reported case in 1957. Three of the five cases had infection of prosthetic heart valves, with one case of rheumatic heart disease complicated with superimposed infection. There has been one reported case of native valve infection where the patient had known history of diabetes leading to immunosuppression and increased risk of infection [26]. Our case is the first reported case of *Cryptococcus neoformans* endocarditis of native valve with no known history of underlying immunosuppressed state.

Most case reports have emphasized the use of Amphotericin-B in the treatment of Cryptococcal endocarditis, with or without surgical intervention. Due to paucity of reported cases, no randomized trials(RCT) have been done to give clinicians a guideline based on RCTs to follow or to compare Amphotericin-B therapy with surgical management. Alhaji et al. in 2011 reported a case of prosthetic valve endocarditis successfully treated with Amphotericin-B [28]. Colmers et al. in 1967 reported success with medical therapy as well [26]. Our patient was considered a high risk for surgery, therefore medical management as chosen. The patient was successfully treated with IV liposomal Amphotericin-B

followed by a prolonged course of oral fluconazole without the need for any surgical intervention.

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