J Infect Chemother 25 (2019) 901–905

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Cryptococcus endocarditis: A case report and review of the literature☆

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ARTICLE INFO

Article history:
Received 10 January 2019
Received in revised form
23 March 2019
Accepted 7 May 2019
Available online 8 June 2019

Keywords:
Cryptococcal neoformans
Fungal endocarditis
Cardiac device associated infection

ABSTRACT

Introduction: *Cryptococcus neoformans* is known to be a cause of meningitis. However, as cryptococcal endocarditis is rare, it is not well understood. Here, we describe a case with Implantable Cardioverter Defibrillator associated endocarditis and meningitis caused by *Cryptococcus neoformans* and we review the literature associated cryptococcal endocarditis.

Case presentation: A 72 years old Japanese male presented in emergency department with non-productive cough and respiratory discomfort. His past medical history was ischemic heart disease four years ago and ICD was implanted. Physical examination was unremarkable. Chest computer tomography revealed ground glass opacity in the right lung. He received a diagnosis of amiodarone-induced interstitial pneumonitis and high dose steroid pulse therapy. Septic shock and acute respiratory failure occurred after steroid therapy. *Cryptococcus neoformans* was identified by blood culture and cerebral spinal fluid. Intravenous liposomal Amphotericin B and oral flucytosine were initiated. Transesophageal echocardiography revealed vegetation on the lead of the ICD. Diagnosis of cryptococcal endocarditis was made. The patient died despite antifungal therapy was continued.

Discussion: We analyzed our case and 8 cases of cryptococcal endocarditis in the literature for 40 years. Almost all of the patients had previous valve replacement surgery or immunocompromised state. Three cases had meningitis. Surgery performed in 3 cases. The overall mortality rate were 44.4%.

Conclusions: Cryptococcal endocarditis is rare and carries a high mortality. Almost all of the patients had underlying diseases. Diagnosis needs repeating blood culture and echocardiogram, sometimes. Cryptococcal endocarditis needs lumber puncture for rule out meningitis.

1. Introduction

Cryptococcus neoformans is an encapsulated oval-shaped yeast fungus that is well known as an opportunistic pathogen. *Cryptococcus neoformans var neoformans* has been isolated from various sources in nature and especially from avian guano [1]. Cryptococcosis is initiated by inhalation of the fungus into lung and remain dormant depending on the host immunity. Cryptococcal infection develop through reactivation of such latent infection in the lung like tuberculosis [2]. Clinical presentation has a wide variety from asymptomatic pulmonary involvement to hematogenous spread to the brain and meninges.

Fungal endocarditis is reported in 2% of all infectious endocarditis (IE) [3]. *Candida species* and *Aspergillus species* are relatively common pathogens of fungal IE [4]. Cryptococcal endocarditis is extremely rare and its risk, clinical course and prognosis were unknown. To our knowledge, there have been no previous reports on Cardiovascular Implantable Electronic Device (CIED) associated endocarditis caused by *Cryptococcus neoformans*. In this report, we described a patient with ICD lead associated cryptococcal endocarditis and reviewed the available literature on cryptococcal endocarditis.

☆ All authors meet the ICMJE authorship criteria.

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https://doi.org/10.1016/j.jiac.2019.05.003
1341-321X/

2. Case presentation

A 72 years old Japanese male presented in emergency department with non-productive cough and respiratory discomfort. He had previously diagnosed with ischemic heart disease and an ICD was implanted 4 years ago as a secondary prevention cardiac arrest due to ventricular fibrillation. Past medical history were hypertension, dyslipidemia, diabetes mellitus, and chronic hepatitis B. On arrival to emergency department, body temperature was 36.7 °C, blood pressure 110/60 mmHg, heart rate 70 beats per minute, respiratory rate 20 breaths per minute, and oxygen saturation 97% while the patient was breathing on oxygen nasal canule 2 L/min. Cardiac examination revealed no murmurs. Other physical examination are unremarkable. High resolution CT revealed bilateral diffuse ground glass opacities and septal thickening and traction bronchiectasis in the lung (Fig. 1). He was admitted to our hospital. Community acquired pneumonia and drug induced pneumonitis were suspected. Blood culture was obtained. Intravenous cefotaxime 2 g q8h and oral doxycyclin 200 mg/day were started. Amiodalone was discontinued. However, on hospital day 3, he was intubated due to deterioration of respiratory status, then antibiotics was changed to levofloxacin 500 mg q24h. At that time, bronchoscopy was performed. On the 8th hospital day, we diagnosed patient as amiodarone-induced interstitial pneumonitis because bronchoalveolar lavage fluid revealed foamy macrophage and no organisms and blood culture on the hospital day was negative. Then, high dose pulse steroid therapy (methylprednisolone 1 g/day for 3 days followed by maintenance dose of prednisolone 60 mg/day) was performed after we diagnosed amiodarone induced pneumonitis. Respiratory distress improved. On hospital day 11, he was extubated and levofloxacin was ceased.

On hospital day 18, laboratory data showed WBC elevation to 14.8 $\times$ 10^3 μL/ml. Blood culture and urine culture was obtained. Hospital acquired pneumoniae was suspected and piperacillin/tazobactam 2.25 g q6h was started. Blood culture was negative.

On the 22nd hospital day, respiratory failure recurred and he was intubated again. Blood culture was submitted at this timing. A chest CT scan revealed exacerbation of consolidation and traction-bronchiectasis (Fig. 1). We suspected amiodarone induced pneumonia recurred and started high dose pulse steroid therapy again as previous review. On the 24th hospital day, a yeast like fungus was isolated in one blood culture, then intravenous micafungin 150 mg q24h was started. On hospital day 26, the fungus revealed susceptibility of fluconazole was sensitive. Antifungal drug was switched to fluconazole 700 mg q24h for loading dose, followed by fluconazole 350 mg q24h. On the 28th hospital day, body temperature elevated to 39.6 °C. Drug fever due to piperacillin/tazobactam was suspected and antibiotics changed to ceftazidime 1 g q8h and clindamycin 600 mg q8h.

On the 29th hospital day, the yeast was identified as *Cryptococcus neoformans* using VITEK@2 -YST card (bioMérieux, Marcy l'Etoile, France). Physical examination revealed petechiae on right bulbar conjunctiva and Janeway lesion on left plantar surface. Lumber puncture was performed. Opening pressure was 12 mmHg and final pressure was 8 mmHg. Analysis of cerebrospinal fluid (CSF) revealed cell count 0/mm^3, protein 38 mg/dL, glucose 110 mg/dL, CSF/blood glucose ratio was 0.43. Yeast like fungus was identified using Indian ink stain in the CSF (Fig. 2) and later confirmed as *C. neoformans* on the culture. Cryptococcal antigen was positive in the CSF and serum at the titer of 10 and 1000, respectively. Fluconazole was changed to intravenous liposomal Amphotericin B (L-AMB) 250 mg ($\approx$4 mg/kg) and oral flucytosine (5-FC) 6000 mg/day (100 mg/kg). No vegetation was found on initial transesophageal echocardiography (TEE). *C.neoformans* was isolated again from blood culture 2days after initiation of antifungal therapy. On 34th hospital day, ceftazidime and clindamycin was ceased because these antibiotics continued for 7 days. *Corynebacterium striatum* (Blood culture was drawn on the 30th hospital day) was isolated in two sets of blood culture. Susceptibility of *C. striatum* were VCM: S

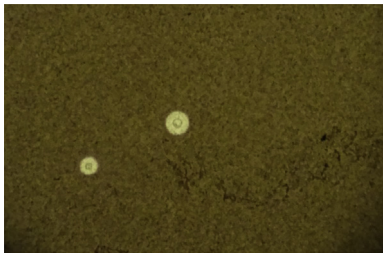

Fig. 2. Cryptococcus in cerebrospinal fluid.

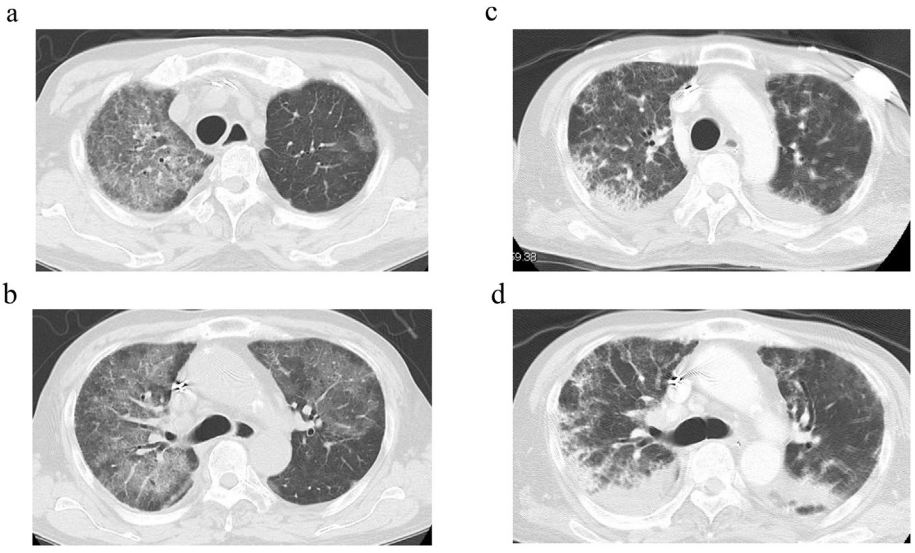

Fig. 1. Representative chest Computed Tomography findings. a, b) Chest CT shows diffuse ground glass opacities and septal thickening and traction bronchiectasis on the admission day. c, d) Chest CT on shows bilateral exacerbation of consolidation and traction-bronchiectasis the 22nd hospital day.

(MIC: 0.5) and Daptomycin MIC = 0.064. Daptomycin 350 mg (≈6 mg/kg) also initiated. On hospital day 39, second TEE revealed a vegetation on the lead of ICD in the right atrium (Fig. 3). Diagnosis of cryptococcal endocarditis was made by modified Duke criteria. Although we recommended the extraction of ICD for radical treatment, he rejected the surgery. The patient died on hospital day 54, an autopsy was declined by his family. The clinical course illustrated in Fig. 4.

3. Patients and methods

We performed a literature review of cryptococcal endocarditis using the Pub Med/MEDLINE database and google scholar. Cryptococcal endocarditis research has been conducted since 1973, the year in which vegetation was first observed by echocardiogram [5]. Using research term were 'cryptococcus and endocarditis'. Only English-articles were included.

Cases were included in this analysis if they met criteria for definite or probable modified Duke criteria [6] and *Cryptococcus* spp were identified by culture or cryptococcal antigen.

Total 8 cases of cryptococcal endocarditis were found in the literature [7–14]. We analyzed the 8 cases and our case and outlined about predisposing factor, diagnosis, treatment, complication and prognosis of the illness (Table 1).

4. Results

All cases of Cryptococcal endocarditis consisted of men. Mean age was 37.4 years old. All species were *Cryptococcus neoformans*. Predisposing factors are previous valve surgery (6/9, 66.7%) and immunosuppressive therapy (5/9, 55.6%). There was no case of HIV patient in the literature. Majority of patients had fever (6/9, 66.7%) and CNS symptoms was 3/9 (3/9, 33.3%). Vegetation involved aortic valves (3/9, 33.3%), mitral valves (3/9, 33.3%), tricuspid valve (1/9, 11.1%) and ICD-lead (1/9, 11.1%). No vegetation was found in 1 case (1/9, 11.1%).

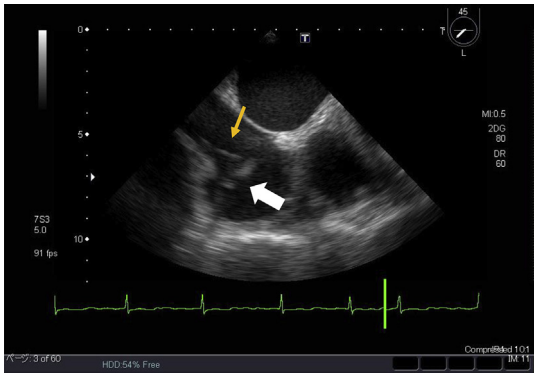

Fig. 3. TEE shows vegetation (yellow arrow) on the atrial lead (white arrow).

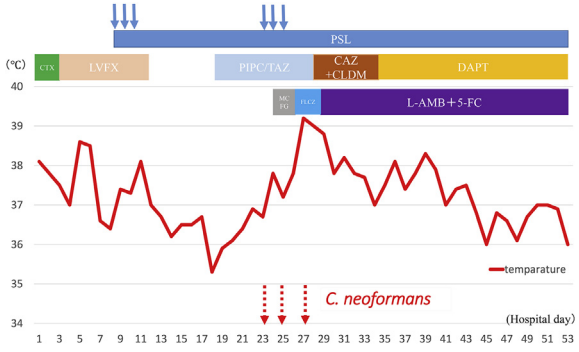

Fig. 4. Blue arrow showed steroid pulse therapy. Red arrow showed blood culture of *Cryptococcus neoformans*.

4.1. Diagnosis

Blood culture was positive on 6/9 cases (66.7%). However, 1 patient (No.5) needed 50 blood cultures and only 3 cultures isolated *Cryptococcus neoformans*. Transthoracic echocardiography (TTE) and TEE detected vegetation in 4/9 cases (44.4%), 2/9 cases (22.2%), respectively. Direct observation (surgery or autopsy) was needed in 2/9 (22.2%) cases. Vegetation was not proven finally in one case. Serum cryptococcal antigen test was all positive as long as they were tested. Patient No5 was diagnosed by cryptococcal antigen of CSF. The cases were classified as either definite cases (7/9, 77.8%) or possible cases (2/9, 22.2%).

4.2. Complication

Three of nine cases (33.3%) had meningitis. Three of nine cases (33.3%) had events of embolism (2 cerebral infarction, 1 coronary artery emboli). Disseminated infections (1 cerebral abscess, 1 pneumonia, 1 abdominal wall abscess and 1 myocardial abscess) were confirmed in some cases.

4.3. Therapy and prognosis

All patients received antifungal therapy: Voriconazole plus caspofungin (1/9 11.1%), Amphotericin B (AMB) (5/9, 55.6%), amphotericin B lipid complex (1/9, 11.1%), L-AMB plus FLCZ (1/9, 11.1%), and L-AMB plus 5-FC (1/9, 11.1%) were used. Fluconazole as maintenance therapy was used in two patients. Two patients with cryptococcal prosthetic valve endocarditis (PVE) and one patient with native valve endocarditis underwent surgery and survived. Two cases of PVE and one case of ICD-associated endocarditis without surgery died. Only one case of PVE without surgery survived. A case of native valve endocarditis without surgery died. The mortality rate of these infections was high (4/9, 44.4%) in our review of literature.

5. Discussion

In this case, Presumed cause of endocarditis were *C. neoformans* and *C. striatum*. However, he had petechiae and janeway lesion, that is, sign of endocarditis before *C. striatum* bacteremia was identified. So, we diagnosed causative organism of endocarditis was *C. neoformans*.

Cryptococcus endocarditis developed after steroid pulse therapy. At first, we suspected recurrence of amiodarone induced pneumonia. However, cryptococcus bacteremia was detected at the same time. So, we suspected pulmonary cryptococcosis developed after steroid pulse therapy. CT findings of pulmonary cryptococcosis are variable. Ground glass opacities and consolidation are included [15]. Pulmonary cryptococcosis should be included in differential diagnosis when respiratory distress and/or new CT findings develop after steroid therapy.

In our review, we could find only 8 cases of cryptococcal endocarditis. All most all of the cases have underling diseases and medical devices. It suggest that prosthetic valve or immunocompromised state would be major risk factors of cryptococcal endocarditis.

Blood culture is key test for diagnosis test for IE and, although negative blood culture remain a diagnostic challenge, its sensitivity

Table 1
Cryptococcal endocarditis cases reports in the medical literature between 1973 and 2018.

	paetient1	paetient2	paetient3	paetient4	paetient5	paetient6	patient 7	patient 8	paetient9
report year	2011	1997	1996	1983	1979	1974	2018	2018	this case
age	41	48	12	27	56	51	26	4	72
sex	M	M	M	M	M	M	M	M	M
symptom	fever, anorexia, cough, diziness	sternal dehiscence, fever	fever	fever seizure	dementia weakness	low grade fever lump in abdominal wall	acute shortness of breath	left hemiplegia	fever, respiratory failure
arhtifact	AVR	MVR	MVP	AVR	no	AVR	no	no	ICD
undelying disease	bicuspid valve HT, CKD	RHD	RHD	AR, nephrosis, PSL	hematologic disorder PSL, azathtioprine	pancytopenia→PSL α-streptococus IE	iv-drug user	acute leukemia, chemotherapy	VF, drug induced IP PSL, DM
identification	blood culture	thrombus culture	blood culture	blood culture	cryptococcal antigen	blood culture	blood culture	vegetation	blood culture
vegetation	AV	NA	MV	AV	MV	AV	TV	MV	lead
diagnostic modality	TEE	NA	TTE	surgery	TTE	autopsy	TTE	TTE	TEE
Duke criteria	definite	possible	definite	definite	possible	definite	definite	definite	definite
therapy	ABLC 4 weeks	AMB	AMB1 month→ AMB + FL 2 months→ FLCZ 6 months	AMB+5-FC 42 days	AMB about 2 months	AMB	L-AMB 3 days→ L-AMB + FLC 6 weeks→ FLCZ 6 months	VRCZ + capsofungin for 4 months	MCFG 2days→ FLCZ 2days→ L-AMB+5-FC 26 days
complication	none	cerebral infarction	cerebral abcess	meningitis、 myocardial abcess	meningitis, coronary artery emboli	pneumonia, abdominal wall abscess	none	multiple cerebral infarction	meningitis
surgery	no	no	yes	yes	no	no	no	yes	no
survive	survival (2 year)	death	survival (1 year)	survival (1.5 year)	death	death	survival (6 months)	survival (3 years)	death

Abbreviation; ABLC: amphotericin B lipid complex, AMB: amphotericin B, AV: aortic valve, AR: aortic regurgitation, AVR: aortic valve replacement, CCA: cerebral spinal fluid cryptococcal antigen, CKD: chronic kidney disease, DM: diabetes mellitus, FLCZ: fluconazole, 5-FC: flucytosine, HT: hypertension, IE: infectious endocarditis, IP: interstitial pneumonitis, L-AMB: liposomal amphotericin B, ICD: implantable cardioverter defibrillator, MCFG: micafungin, MV: mitral valve, MVP: mitral valve plasty, MVR: mitral valve replacement, MS: mitral stenosis, NA: data not available, PSL: prednisolone, RHD: Rheumatic heart disease, SCA: serum cryptococcal antigen, TEE: transesophageal echocardiography, TTE: transthoracic echocardiography, TV: tricuspid valve, VF: ventricular fibrillation, VRCZ: Voriconazole.

for cryptococcal endocarditis is not low, Serum cryptococcal antigen (SCA) has a high sensitivity and specificity in cryptococcemia and meningitis [16], so SCA should have high sensitivity also for cryptococcal endocarditis. In fact, all cases are positive in cases SCA are tested.

Echocardiography detected about 60% of vegetation. But, the patient No 6 was reported before echocardiography was not established as a diagnostic tool for IE. The sensitivity of TTE and TEE for cryptococcal endocarditis may be higher than this analysis, but negative echocardiography for IE may be observed in about 15% [17]. This case needed second TEE and several guidelines recommended TEE should be repeated if IE is highly suspected.

In our case, the patient did not have any meningeal sign. Immunocompromised state may mask symptoms. A case series reported that 71% of cryptococcemia is associated with meningitis [18]. In another literature, cryptococcemia is associated with high probability of meningitis [19]. We propose that lumber puncture should be performed for cryptococcal endocarditis even if patient don't have a sign of meningitis.

Due to the rare nature of this infection, there is no standard management and therapy for cryptococcal endocarditis. Antifungal therapy for cryptococcal endocarditis is based on other form of disseminated cryptococcosis. The recommended antifungal therapy for invasive cryptococcosis are AMB or L-AMB or amphotericin B lipid complex (ABLC), combined with 5-FC in non-HIV infected patients [20]. The role of surgery for cryptococcal endocarditis is not clear. Fungal endocarditis should be considered to be indication of combined therapy of antifungal drug and surgical debridement [4,21]. Like other type of fungal endocarditis, it is considered that cryptococcal endocarditis also required combined therapy.

The mortality of cryptococcal endocarditis is high, may be related to underlying disease, delay of diagnosis and decision regarding surgery. Reports were relatively old. Mortality of cryptococcal endocarditis may improve nowadays.

6. Conclusions

Cryptococcal endocarditis is very rare. Risk factors of cryptococcal endocarditis are valvular heart disease, especially prosthetic valve and immunosuppressive therapy. The sensitivity of blood culture for cryptococcal endocarditis is not low, but sometimes several blood cultures are needed. In the cases of cryptococcal endocarditis, meningitis must be ruled out. Therapy of cryptococcal endocarditis may need combination of antifungal agent and surgery.

Conflicts of interest

All authors declare no conflict of interest. The study was not funded by organization.

Acknowledgements

We would like to thank Editage (www.Editage.jp) for English language editing.

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