Cryptococcal endocarditis of native valves without immunodeficiency or drug abuse: a case report

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Abstract
Cryptococcal endocarditis has rarely been reported. Most patients with this condition are associated with risk factors, such as structural heart disease/valve replacement, immunodeficiency/immunosuppression or drug abuse. We report a case of cryptococcal endocarditis of the native valves without any risk factors. A 50-year-old Chinese man was admitted to hospital with fever for 1 month without any underlying heart disease, immunodeficiency, or drug use. He was diagnosed as having Cryptococcus neoformans infective endocarditis and was discharged after valve replacement surgery and long-term antifungal therapy.

Keywords
Cryptococcus, endocarditis, native valve, aortic valve replacement, heart failure, fever

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Introduction
Infectious endocarditis is a difficult disease to treat. Fungal endocarditis, which is mainly caused by Candida species and Aspergillus species, accounts for only 2% of all cases of endocarditis.1,2 Cryptococcal endocarditis has rarely been reported. Only a few reported cases of this condition were associated with risk factors, 1Department of Cardiovascular Medicine, Nanjing Chest Hospital, Nanjing, China
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such as heart valve disease/valve replace-
ment, immunodeficiency/immunosuppres-
sion, or drug abuse. We present a case of
cryptococcal endocarditis of native valves
without immunodeficiency or drug abuse.

Case presentation
A 50-year-old Chinese man was admitted
with recurrent fever 1 month after removal
of internal fixation after fracture of the left
clavicle 4 months previously. He had
received intravenous infusion of various
antibiotics (e.g., cefuroxime, moxifloxacin,
cefoperazone and sulbactam) in local hos-
pitals, but still had intermittent fever (peak
temperature was nearly 40°C), accompa-
nied by progressive aggravation of chest
tightness and shortness of breath. His med-
ical history was lacunar cerebral infarction
and chronic hepatitis B. No major social
and family history was reported. On admis-
sion, his body temperature was 36.4°C,
heart rate was 78 beats per minute, respira-
tory rate was 18 breaths per minute, and
blood pressure was 113/55 mmHg. A phys-
ical examination was unremarkable, except
that conjunctiva of both eyes was obviously
congested and there was a sigh-like murmur
in the aortic valve area.

A laboratory examination showed the
following: white blood cell count of 2.1 ×
10^9/L, red blood cell count of 2.58 ×
10^12/L, hemoglobin level of 78 g/L, mean
corpuscular volume of 93 fL, platelet count
of 98 × 10^9/L, high-sensitivity C-reactive
protein level of 58.72 mg/L, D-dimer level
of 2.93 mg/L, N-terminal-pro-brain natri-
uretic peptide level of 12,072 ng/mL, and
fungal D-glucan level of 109.9 pg/mL.
Anti-tuberculosis LAM antibody, anti-
tuberculosis 38 kD antibody, Mycoplasma
pneumoniae immunoglobulin (Ig) M, influ-
enza B virus IgM, and anti-Ro-52 antibody
were positive, and a human immunodefi-
ciency virus test was negative. A chest com-
puted tomography (CT) scan showed a
small amount of bilateral pleural effusion
and pericardial effusion, while a brain CT
scan was unremarkable. Transthoracic
echocardiography showed additional echo
of the aortic valve, aortic valve vegetation
(17 × 15 mm), and moderate aortic valve
insufficiency. The left ventricular internal
diameter during diastole was 63 mm and
the ejection fraction was 50%. There were
mild mitral and tricuspid valve insufficien-
cy, mild pulmonary hypertension, and a
small amount of pericardial fluid (Figure 1).

After obtaining the patient’s consent, we
initiated intravenous vancomycin 1 mg once
every 12 hours, levofloxacin 500 mg once a
day, and fluconazole 400 mg once a day.
Intermittent fever was still present, with a
thermal peak of 39°C. Blood cultures were
performed immediately after admission and
at the peak of the fever on the next day.
Both results, which were obtained after
5 days, showed Cryptococcus neoformans
(Figure 2). Because of the poor medical
treatment and the high risk of shedding
and embolization of valve vegetation, emer-
gency aortic valve replacement was per-
formed (Figure 3). C. neoformans was
also isolated from extracted cardiac tissue
by periodic acid-silver methenamine
(Figure 4). Postoperative anti-infection
strategy was adjusted to cefminox 2 g once
every 12 hours, amphotericin B 50 mg once
a day, and fluconazole 0.8 g once a day. The patient’s chest tightness and wheezing symptoms greatly improved, but he still had intermittent fever, with a peak temperature of 38.2°C. Four times of postoperative blood cultures were negative. One month later, the antifungal strategy was switched to flucytosine (1.5 g, every 6 hours) + fluconazole (0.8 g, once a day) for approximately 10 weeks. He was discharged after 1 week of a normal body temperature. After discharge, fluconazole (0.4 g, once a day) was orally administered. The patient was followed up for approximately 6 months, with no obvious discomfort, such as fever (the patient’s details have been de-identified).

Discussion

C. neoformans belongs to the fungal phylum of Blastomycota with no capsule or only a small capsule in vitro. However, C. neoformans forms a thick capsule quickly after entering the human body with significantly enhanced pathogenicity. Cryptococcus species can infect any tissue and organ of the human body. The central nervous system is the most commonly affected organ, followed by the lungs and skin. Systemic infections are usually due to lung infections caused by inhalation of spores or dried yeast. Cryptococcus species are opportunistic pathogens. The infection rate of C. neoformans in patients with acquired immune deficiency syndrome can be as high as 30%, while this rate is only approximately 1 in 100,000 in people without immunodeficiency.

Infective endocarditis caused by Cryptococcus species is extremely rare. In retrospect, only 12 cases of cryptococcal endocarditis have been reported worldwide since 1957, mostly in patients with immunocompromised or prosthetic valve replacement. Six cases of cryptococcal endocarditis occurred in native valves (one vegetation occurred on the implantable cardiac
Table 1. Brief review of reported cases of cryptococcal endocarditis from 1957 to 2020.

| Authors            | Year | Sex | Age (years) | Underlying disease                              | Vegetation | Surgery | Antifungal strategies | Prognosis          |
|--------------------|------|-----|-------------|-------------------------------------------------|------------|---------|-----------------------|-------------------|
| Lombardo TA et al.  | 1957 | Male | 44          | RHD                                             | MV+AV      | No      | Actidione, sulfadiazine | Died              |
| Colmers RA et al.  | 1967 | Male | 55          | Mitral stenosis, DM                             | MV         | No      | AMB                   | Survived (1 year) |
| Child JS et al.    | 1979 | Male | 56          | Hematological disorder (prednisone, azathioprine)| MV         | No      | AMB                   | Died              |
| Blanc V et al.     | 1996 | Male | 12          | RHD, mitral valve plasty                        | MV         | Yes     | AMB + FLCZ            | Survived (1 year) |
| Roy M et al.       | 2018 | Male | 26          | Intravenous drug user                           | TV         | No      | L-AMB + FLCZ          | Survived (6 months) |
| Kowatari R et al.  | 2018 | Male | 4           | Acute leukemia, chemotherapy                    | MV         | Yes     | Voriconazole + capsofungin | Survived (3 years) |
| Nakajima T et al.  | 2019 | Male | 72          | ICD implantation, DM, interstitial pneumonitis (prednisone) | Lead  | No      | Micafungin + FLCZ + L-AMB + flucytosine | Died |

*The survival time was known at the time of publication.

Abbreviations: RHD, rheumatic heart disease; MV, mitral valve; AV, aortic valve; DM, diabetes mellitus; AMB, amphotericin B; L-AMB, liposomal amphotericin B; FLCZ, fluconazole; TV, tricuspid valve; ICD, implantable cardiac defibrillator.
defibrillator lead) (Table 1). Unlike previous cases, our case is the first report of cryptococcal endocarditis of native valves without a complex history of valvular disease/valve replacement, immunodeficiency/immunosuppression, or drug use. Although some pathogens, such as bacteria, a virus, and immune indicators were positive after admission, the diagnosis of cryptococcal infection was quickly confirmed by blood culture and vegetative pathology.

Fungemia is usually considered to be an opportunistic disease. Advances in medicine have led to prolonged survival of immunocompromised patients as well as to development of opportunistic fungal infections. In recent years, fungal infection has gradually become the principal component of nosocomial infection. Although our patient did not have acquired immune deficiency syndrome, a tumor, or other risk factors of fungal infections, he underwent surgery for removal of internal fixation for the clavicle 4 months previously. He also repeatedly received intravenous infusion treatment before he was admitted to our hospital. Consequently, the invasive operation or intravenous line used might have led to hospital-acquired fungemia.

Previous studies have reported that 71% of cryptococcal infection is associated with meningitis. Related guidelines also recommend that routine lumbar puncture should be performed, even if there is no evidence of encephalitis in cryptococcal infections. No obvious meningeal signs of irritation were detected in our case and a complete cerebrospinal fluid etiological examination after valve replacement was negative. Fortunately, the pathogen may fail to invade the central nervous system, and this result also provides a basis for the selection of antifungal strategies.

Our patient received aortic valve replacement after 1 week of anti-inflammatory and antifungal treatment, which was in accordance with the recommendations of the 2015 European Society of Cardiology infective endocardial treatment guidelines. Our patient had all of the indications for active surgery, such as heart failure, infection, and vegetation >15 mm, which is an independent risk factor for a new embolism. Surgical methods quickly corrected the gradually worsening heart failure, and prevented embolism and inflammatory spread of the cryptococcal mass, laying a foundation for a good final prognosis.

Cryptococcal endocarditis has a low incidence and lacks standardized antifungal management recommendations. Using the recommendations of lung and central nervous system infections, the antifungal strategy for non-human immunodeficiency virus patients is amphotericin B combined with flucytosine fortification, followed by fluconazole. Because of the lack of experience and considering the side effects, we adopted an amphotericin B + fluconazole regimen for our patient. After the 1-month induction period, the long-term regimen of flucytosine and fluconazole also achieved good results.

In summary, we report a case of cryptococcal infective endocarditis of native valves with no history of immunodeficiency, drug use, or underlying heart disease. Prompt diagnosis, timely surgery, and long-term antifungal strategies may be important for a good prognosis.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Ethics statement
No ethical approval was required for this case report. Patient details were de-identified. Therefore, consent for publication by the patient was not required.

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