Prosthetic valve endocarditis caused by multidrug-resistant *Candida albicans* in a patient with myelodysplasia syndrome: A case report and literature review

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**Abstract**

**Background and Purpose:** Candida endocarditis is an infrequent disease with a high mortality rate, which commonly occurs in immunosuppressed patients with cardiac valve replacement. We reported a 70-year-old woman diagnosed with *Candida* prosthetic valve endocarditis (PVE). This study also involved a review of all published cases of *Candida* PVE from 1970.

**Case Report:** Herein, we reported a 70-year-old woman with the history of severe mitral stenosis and myelodysplasia syndrome. She underwent mitral valve replacement for two times. The blood cultures were positive, and phenotypic identification of the isolates at the species level was performed based on microscopic and macroscopic characteristics. In the second prosthetic valve replacement, huge fungal white and creamy vegetation was observed which was identified as *Candida albicans* based on the conventional and molecular methods. Despite the administration of antifungal treatments, the patient passed away probably due to the multidrug-resistant *Candida* PVE.

**Conclusion:** As PVE is a late consequence of prosthetic valve replacement, extended follow-up visits, early diagnosis, repeating valve replacement surgeries, and timely selective antifungal treatments are warranted.

**Keywords:** Amphotericin B, Antifungal resistant, Azoles, *Candida* endocarditis, Multidrug resistant, Myelodysplasia syndrome, Prosthetic valve replacement

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**Introduction**

*Candida* endocarditis is an infrequent disease with a high mortality rate, ranging within 23-46%. This disease is commonly reported in patients with cardiac valve replacement [1, 2]. The potentiality of *Candida* species, mainly *Candida albicans*, to form biofilms on native cardiac tissue and prosthetic valve causing increasing resistance to antifungal treatment, has a great impact on patient outcomes [3]. As *Candida* species have various degrees of susceptibility to currently available antifungals, it is very important to identify the causative agents and prescribe the effective treatment [3].

The major risk factors for this condition include indwelling central venous catheters, long-term broad-spectrum antibacterial therapy, and previous heart surgery. Other risk factors, such as long-term usage of corticosteroids, cytotoxic drug consumption, intravenous drug abuse, and immunosuppression, are implicated as the causes of increasing the incidence of fungal endocarditis [4, 5]. In recent years, the emergence of drug-resistant *Candida* species has complicated the treatment of different diseases and adoption of the proper medication regimen.

Herein, we reported a case of *Candida* prosthetic valve endocarditis (PVE) caused by multi-azole and amphotericin B resistance in a patient with myelodysplasia syndrome (MDS) for the first time in Iran. We also briefly reviewed the reports of PVE caused by *Candida* species in patients with different types of cancers.
Case report

A 70-year-old woman with a severe headache, vertigo, fever, and arrhythmia, suspected with Parkinson’s disease was admitted to Mazandaran Heart Center, Sari, north of Iran, in 2017. She had a history of symptomatic sever mitral stenosis probably due to rheumatic heart disease in her childhood for which she underwent mitral commissurotomy when she was 25 years old. After her first surgery, she administered penicillin G benzathine 1.2 million units IM once a month up to her last admission. She was also subjected to echocardiography every 6 months.

In 2010, the patient suffered from persistent fever, which was unresponsive to antibiotics for 2 weeks. Echocardiography revealed infective endocarditis; however, no microbial strain was isolated from blood culture. After treatment, symptoms reduced; nonetheless, a few days after discharging from the hospital, her blood cell profile was deteriorated gradually. The diagnosis of MDS was eventually confirmed after performing bone marrow aspiration for three times. Thereafter, the patient was subjected to androgen therapy with danazol (10 mg/kg b.w./day), and Prednisolone (1 mg/kg b.w./day). When the white blood cell count became normal, danazol was discontinued; however, the consumption of prednisolone (5 mg/day) was continued. During the long-term use of prednisolone, she was afflicted with steroid-induced diabetes and oral lichen planus due to the impairment of immune system.

On October 2015, due to the deterioration of patient’s general condition, she was transferred to Tehran Heart Center for further evaluation. Transesophageal echocardiography (TEE) revealed severe mitral valve (MV) stenoses; as a result, she was subjected to percutaneous transvenous mitral commissurotomy.

On May 2016, the patient was admitted to hospital due to persistent fever and general weakness, and was detected with MV regurgitation. She was prescribed vancomycin (20 mg/kg), gentamicin (1 mg/kg), and ciprofloxacin (10 mg/kg). She had a fever of up to 40°C that was unresponsive to antibiotics and persisted after a week. Imipenem was replaced with ciprofloxacin (10 mg/kg b.i.d) and gentamicin (1 mg/kg b.i.d) were administered. However, 48 h later, the patient presented with dyspnea, decreased consciousness, and decreased blood cells, resulting in a coma. The patient passed away due to sepsis probably related to the candidemia and Candida PVE with antifungal-resistant Candida albicans.

In vitro antifungal susceptibility testing of Candida albicans isolate was carried out based on the clinical and laboratory standards institute (CLSI) M27-A3 [7] and M27-S4 guidelines [8]. Based on the breakpoint, the isolate was resistant to voriconazole (16 μg/ml), itraconazole (16 μg/ml), fluconazole (64 μg/ml), posaconazole (16 μg/ml), and amphotericin B (4 μg/ml). Furthermore, it was susceptible to anidulafungin (0.008 μg/ml) and micafungin (0.008 μg/ml), and intermediate to caspofungin (0.5 μg/ml).

Ethical considerations

The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran.

Discussion

Over the past few years, there has been an
increasing number of reports on fungal endocarditis [9] showing the high morbidity and mortality rate of this condition, ranging within 30-80% [10]. Although *Candida* endocarditis accounts for about 1-2% of infective endocarditis, it can be very fatal. This medical condition is usually diagnosed postmortem because of its nonspecific clinical symptoms. *C. albicans*, followed by *C. parapsilosis*, are the common *Candida* species causing endocarditis [9].

According to the Duke criteria, PVE is classified as "early" when it happens within 60 days of valve replacement and "late" when occurring more than 60 days post-replacement [11, 12]. In this report, our case was classified as a late *Candida* endocarditis because symptoms manifested 300 days after the first valve replacement.

In our patient, the major predisposing factors included a congenital heart disease, malignancy such as myelodysplastic syndromes (formerly described as pre-leukemia or smoldering acute leukemia), long-term use of corticosteroids for MDS treatment, prosthetic cardiac valves, and long-term broad-spectrum antibiotic therapy after cardiac surgery.

To review the cases of prosthetic valve endocarditis caused by *Candida* species in patients with different types of cancers, a search was performed on the English articles published from 1970 onward in two databases, namely Google Scholar and PubMed. The key words and medical subject headings used for the search were as follows: “*Candida* endocarditis”, “Prosthetic valve endocarditis”, and “Cancer”. Table 1 summarizes the demographic features, risk factors, treatment strategies, and outcomes in reported cases of prosthetic valve endocarditis caused by *Candida* species in patients with different types of cancers.

### Table 1. Demographic features, risk factors, treatment, and outcome in reported cases of prosthetic valve endocarditis caused by *Candida* species with different types of cancers

| Reference | Country | Age/ gender | Type of cancer | Treatment | Diagnosis method | Causative agent | Risk factors | Observation | Outcome |
|-----------|---------|-------------|----------------|-----------|------------------|----------------|--------------|-------------|---------|
| Ihde, 1978 [13] | USA | <20/ NS | Lymphoma, carcinoma of the cervix | Corticosteroids, antibiotics | B/C (+), CFSE (+), Microscopic examination | *C. albicans* | Chemotherapy, central venous catheter, corticosteroids | Abscesses in the left ventricular myocardium | Died |
| Maeno, 1990 [14] | Japan | 83/ NS | Pancreatic cancer | Anti-fungal agents | B/C (+), mannan antigenemia, D-阿拉伯initol creatinine ratio, Echo | *C. albicans* | NS | Vegetation at the aortic valve | Died |
| Johnston, 1991 [15] | USA | 31/M | Testicular carcinoma | 5-FC+AMB, surgery | B/C (+), TEE | *C. albicans* | NS | Recurrent embryonal cell testicular carcinoma | Mitrail valve vegetation | Died |
| Hamada, 1996 [16] | Japan | 63/M | Gastric cancer | Anti-fungal agents, surgery | B/C(+) | *C. albicans* | Liver abscess | Aortic and tricuspid regurgitation | Survived |
|  | Japan | 65/M | Bile duct cancer | Anti-fungal agents, catecholamine, digoxin, surgery | B/C(+) | *C. albicans* | NS | Aortic regurgitation | Died |
| Inoue, 1998 [17] | Japan | 57/M | Gastric cancer | FLC, surgery | NS | *C. parapsilosis* | Chemotherapy, central venous catheter | Cardiac valve vegetation | Survived |
| Azrifi, 1999 [18] | Malaysia | <1/NS | ALL | AMB , surgery | Echo | *C. albicans* | Immunodeficiency | NS | NS* |
| Jagernauth, 2007 [19] | UK | 54/M | Carcinoid disease | Antifungal drug, Surgery | NS | *Candida* spp | Surgery for pulmonary and tricuspid valve replacement | Vegetation | Survived |
| Ozkizaz, 2007 [20] | Turkey | <1/ NS | AML | FLC, AMB , surgery | Echo, B/C(+), pathological examination | *C. albicans* | NS | Vegetation at the outlet of the right ventricle | Died |
| Block, 2009 [21] | Australia | 64/F | Carcinoma of the lung | FLC, 5FC thrombolytic therapy, surgery | B/C (+), U/C(+), TEE | *C. albicans* | NS | Fungal ball | Survived |
| Chopra, 2010 [22] | USA | 74/F | Cardiomyopathy | MFG, surgery | B/C, U/C(+), TEE | *C. kefyr* | Diabetes type II | Mitrail valve vegetation | Survived |
| Reyes, 2015 [23] | Peru | 36/F | Ovarian cancer | AFG, VRC , FLC, antibiotics, surgery | B/C(+), TEE | *C. parapsilosis* | Chemotherapy | Vegetation in the aortic valve | Died |
| Present case | Iran | 70/F | MDS | AMB deoxycytate, CAS, VRC | B/C(+), TEE | *C. albicans* | Spectrum antibiotic therapy, diabetes | Mitrail valve vegetation | Died |

Ns: not specified, TTE: transthoracic echocardiography, TEE: transesophageal echocardiography, ALL: acute lymphoblastic leukemia, MDS: myelodysplasia syndrome, Echo: echocardiography, FLC: fluconazole, AMB: amphotericin B, AFG: anidulafungin, CAS: caspofungin, VRC: voriconazole, MFG: micafungin, 5FC: flucytosine, U/C: urine culture, U/C: urine culture, CSF: cerebrospinal fluid culture
The main factor that made treatment unresponsive was associated with multi-azole and amphotericin B-resistant *Candida* endocarditis. Multiple risk factors in our patient might be more likely to cause fungal endocarditis and have a fatal outcome. The combination of risk factors, clinical features, and echocardiography findings may help the clinical diagnosis of endocarditis. The TEE is a modality of choice with high sensitivity (87-100%) and specificity (83-94%) in the initial evaluation of the patients with high risk for infective endocarditis [24].

The blood culture as a traditional gold standard for the detection of candidemia has some limitations, including low sensitivity and high turnaround time [25]. Blood culture was positive in the first valve replacement surgery, but it was negative in the second one, while TEE showed a large vegetation on the mitral valve leading to endocarditis. The accurate diagnosis of *Candida* endocarditis is a challenge since its symptoms are very similar to those of bacterial infections. Negative blood culture results can lead to delayed anti-fungal therapy that contributes to an increased risk of hospital mortality. This explains why most of *Candida* PVE cases are diagnosed on autopsy or very late [2].

*Candida* species have wide ranges of virulence factors, such as adhesion, invasion, and biofilm formation on medical devices, such as bioric or artificial cardiac valves. They can have detrimental effects on patient’s life, because they lead to the failure of the prostheses and result in the persistent presence of organism in bloodstream as a source of fungemia episodes [26].

Azole-resistant *Candida* species is regarded as a considerable problem for patients undergoing long-term fluconazole treatment. There are only four drug classes for *Candida* infections, including azoles, polyenes, echinocandin, and pyrimidine analogue of cytosine (5-fluorocytosine). Multidrug-resistance is defined as the non-susceptibility of the isolate to ≥ 1 agent in ≥ 2 antimicrobial categories [27].

In this case, we reported *C. albicans* that was resistant to multi-azoles and amphotericin B.

Hematologic disorders, such as MDS, are reported as risk factors for invasive *Candida* infections [28]. Long-term use of corticosteroids for the treatment of MDS and prolonged use of broad-spectrum antibiotics (e.g., penicillin over 35 years) can severely lead to the conditions predisposing a patient to candidemia and *Candida* endocarditis. Candidemia after heart valve replacement is a powerful predictive factor for late PVE, even more than one year, after the first episode of infection. Therefore, patients should be checked with an extended follow-up.

*Candida* endocarditis is an uncommon but devastating infection that affects the elderly with a weakened immune system as a late consequence of prosthetic valve replacement. The extended follow-up visits, early diagnosis, repeating valve replacement surgeries, and timely selective antifungal treatments are warranted.

**Conclusion**

This report highlighted that *Candida* PVE can occur as a late consequence of valve replacement in elderly patient with suppressed immune system. The extended follow-up visits, early diagnosis, repeating valve replacement surgeries, and timely selective antifungal treatments are warranted.

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**Author’s contribution**

T. S. contributed to study concept and managed the project, F. K. wrote the first draft of the manuscript, and T. S., M. A., L. D., S. Z. T. and R. J. performed the critical revision of the manuscript. S. M. and R. M provided practical support.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

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None.

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