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CASE REPORT

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Recurrent fungal endocarditis of the aortic valve: A challenging clinical scenario

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Key Clinical Message

Fungal endocarditis is a rare but potentially fatal infection with significant diagnostic and management challenges. Antifungal therapy and surgical debridement are the preferred treatments in these cases. Antimicrobial therapy with multiple antifungal agents may be required in high-risk patients presenting with prolonged fever suspected of having fungal endocarditis.

Abstract

Recurrent fungal endocarditis, particularly involving Candida parapsilosis, is a rare and challenging clinical entity with limited management guidelines. We present the case of a 44-year-old female with a history of intravenous drug use and treatment-resistant chronic hepatitis C who developed recurrent Candida parapsilosis endocarditis. Initially, she presented with native aortic valve fungal endocarditis, which was managed with antifungal therapy and surgical aortic valve replacement. Despite this intervention, she experienced a subsequent episode of prosthetic valve Candida parapsilosis endocarditis, further complicated by prolonged fungemia. This case underscores the complexities of managing recurrent fungal endocarditis and highlights the need for ongoing research to refine treatment strategies for this challenging condition.

KEYWORDS

aortic valve, Candida parapsilosis, endocarditis, fungal endocarditis

1 | INTRODUCTION

Fungal endocarditis, though only responsible for about 2%–4% of all infective endocarditis, is associated with a significantly higher mortality risk.[1,2] Candida species are responsible for most cases of fungal endocarditis, with *C. albicans* being the most common fungus identified, followed by *C. parapsilosis*.[3] *C. parapsilosis* is especially common in intravenous drug users (IVDU) and patients receiving parenteral nutrition.[4] Prosthetic heart devices, prolonged central venous lines, and immunocompromised hosts are also established risk factors.[5] Its tendency to form biofilms on foreign bodies may explain its relationship with vascular devices and pathogenic potential.[6] In the literature, up to 60% of cases of *C. parapsilosis* endocarditis involved a prosthetic valve, while the remaining

40% involved a native valve.[4] We present a rare instance of a 44-year-old woman with a history of intravenous drug abuse who presented with relapsing *C. parapsilosis* endocarditis that initially affected the native aortic valve, followed by relapse with persistent C. parapsilosis fungemia, septic embolization to the spleen, and involvement of the bioprosthetic aortic valve.

2 | CASE PRESENTATION

This is the case of a 44-year-old woman who initially presented in August 2020 for evaluation of worsening dyspnea and bilateral lower extremity swelling for 2 weeks. She also complained of unintentional weight loss of about 7.3 kilograms (16 pounds) in the preceding 3 months. The patient reported a remote history of intravenous opioid abuse; she quit 7 years before and was enrolled in a methadone program for recovery. She also had a long-standing history of asthma and Hepatitis C infection with unsuccessful treatment 20 years ago due to medication intolerance. At the time of her presentation, her vitals were significant for tachycardia of 113 beats per minute and a low-grade fever of 99.7 degrees Fahrenheit. Her physical examination revealed a distended abdomen, marked splenomegaly, and bilateral lower extremity pitting edema. Heart and lung sounds were normal, with normal jugular venous pressure, no pericardial friction rub, and no stigmata of endocarditis. Her laboratory reports revealed pancytopenia, elevated transaminase levels, elevated creatinine suggestive of acute kidney injury, and a deranged coagulation profile (Table 1). The Hepatitis C antibody tested was positive; however, the Hepatitis C quantitative polymerase chain reaction for ribonucleic acid was negative. Human immunodeficiency virus (HIV) testing and other serologies were negative.

Ultrasound Duplex Doppler of the lower extremities bilaterally was negative for deep vein thromboses. Computed tomography (CT) of the abdomen and pelvis and CT angiogram with pulmonary embolism protocol on her presentation ruled out pulmonary embolism. It was significant for two small nodules on the liver (likely hemangiomas), severe splenomegaly with several nonspecific splenic nodules, and mild biliary tree dilatation. She was admitted for further evaluation and management. During the initial days of her admission, blood cultures taken on her presentation were found to be positive for *Candida parapsilosis*, and she was started on liposomal Amphotericin B and fluconazole (see Table 2 for sensitivity results of the organism). A 2-D transthoracic echocardiogram (TTE) revealed a large vegetation on the left aortic cusp protruding into the left ventricular outflow tract. A transesophageal echocardiogram (TEE) confirmed it to be an 11 × 4 mm soft tissue mobile mass on the ventricular surface of the left coronary cusp of the aortic valve (Figure 1). She remained persistently pancytopenic during her admission, and a bone marrow biopsy done for further evaluation revealed a monocellular bone marrow with trilineage hematopoiesis and megakaryocytic atypia. Discussion with hematology derived that these bone marrow changes were likely multifactorial due to her chronic hepatitis C and the underlying systemic inflammation due to infective endocarditis.

Her cultures remained positive for *C. parapsilosis* for 4 weeks despite maximal therapy with different antifungals, limited by her underlying liver disease (Child-Pugh class B), including caspofungin 150 mg daily and micafungin 140 mg daily. A repeat TEE showed increased vegetation size to 11 × 16 mm. Due to the absence of concrete clinical trial data, it was difficult to frame a definitive therapeutic strategy, especially considering the need for valvular surgery. Based on the recommendations of published observational, she ultimately had an aortic valve replacement with a number 23 bovine Edwards aortic valve studies after clearing her fungemia. Cultures of the valve taken during the procedure were positive for *Candida parapsilosis*. Her postoperative stay was complicated by recurrent atrial flutter with a 4:1 atrioventricular block. She was started on anticoagulation and subsequently cardioverted to sinus rhythm with intravenous amiodarone given as an initial loading dose of 150 mg over 10 min, followed by an infusion of 1 mg per minute for 6 h, then 0.5 mg per minute for 18 h. She received 6 weeks of antifungal therapy post-procedure with intravenous micafungin 150 mg once daily, after which her blood cultures remained negative for fungal growth. She was eventually discharged home on oral fluconazole 400 mg daily for 3–6 months with outpatient follow-up. However, she was noncompliant with therapy and noncompliant with follow-up.

In November 2022, she returned to the emergency department with a 3-day history of sudden onset, constant, severe left upper quadrant pain associated with multiple episodes of non-bilious, non-bloody emesis. She denied fever, chills, diarrhea, constipation, hematemesis, hematochezia, bloating, or abdominal distension. She also reported poor oral intake and a decreased appetite. Vitals included a blood pressure of 138/91 mmHg, a pulse rate of 88 beats per minute, a respiratory rate of 18 per minute, a temperature of 97.8 degrees F, and oxygen saturation of 97% at room air. Her physical exam was significant for left upper quadrant tenderness without clinical features of localized or generalized peritonitis. Other aspects of the physical exam were within normal limits. Her initial laboratory investigations were significant for mild normocytic anemia, leucopenia, elevated aspartate and alanine aminotransferases, and alkaline phosphatase (Table 1).

TABLE 1 Laboratory Investigations.

Laboratory test	Results of August 2020 admission (initial presentation)	Results of 2022 admission	Results of 2023 admission	Normal range
Hemoglobin (g/dl)	11.2 (L)	11.6 (L)	10.5 (L)	14–18
Mean corpuscular volume (fl)	79.0	80.5	79.6	80.0–100.0
Platelets (K/UL)	53 (L)	130	102 (L)	130–400
White blood cells (K/UL)	2.2 (L)	3.4 (L)	3.2	4.5–11.0
Prothrombin time (sec)	16.1 (H)	12.1	12.1	12–15.1
International normalized ratio	1.31 (H)	1.02	1.03	0.85–1.14
Partial thromboplastin time (sec)	52.4	33.2	35.1	25.4–36.7
Fibrinogen (mg/dl)	109	174		244–550
Sodium (mmol/L)	138	141.0	137	136–145
Potassium (mmol/L)	4.1	4.4	4.4	3.5–5.1
Chloride (mmol/L)	110.0 (H)	110.0 (H)	108	98–107
Serum bicarbonate (mmol/L)	22	22	24	20–31
Blood urea nitrogen (mg/dl)	26 (H)	22	20	9–23
Creatinine (mg/dl)	1.76 (H)	1.08	1.20	0.70–1.30
Calcium (mg/dl)	7.6 (L)	8.3 (L)	8.5 (L)	8.7–10.4
Aspartate aminotransferase (Units/L)	109 (H)	94 (H)	61 (H)	8–34
Alanine aminotransferase (Units/L)	81 (H)	109 (H)	53 (H)	10–49
Alkaline phosphatase (Units/L)	249 (H)	138 (H)	121 (H)	46–116
Total bilirubin (mg/dl)	1.1	0.7	0.4	0.3–1.2
1,3-Beta-D-Glucan (Fungitell) (pg/mL)	>500 (H)	>500 (H)	>500 (H)	<60

Note: (L)—indicates a value below the normal reference range; (H)—indicates a value above the normal reference range.

TABLE 2 Table showing the antimicrobial sensitivity results of the *C. parapsilosis* isolated in the blood.

	Minimal inhibitory concentration (mcg/mL)		
Antifungal	*C. parapsilosis* isolated in August 2020 (first presentation)	*C. parapsilosis* isolated in November 2022 (second presentation)	*C. parapsilosis* isolated in January 2023 (third and most recent presentation)
Amphotericin B	0.250 (S)	0.250 (S)	0.250 (S)
Caspofungin	0.500 (S)	0.500 (S)	0.500 (S)
Fluconazole	1 (S)	1 (S)	1 (S)
Micafungin	1 (S)	1 (S)	1 (S)
Voriconazole	0.015 (S)	0.015 (S)	0.015 (S)

3 | INVESTIGATIONS AND TREATMENT

A chest radiograph cleared the chest for any significant infiltrates. A right upper quadrant ultrasound scan was significant for a benign, small liver hemangioma with no evidence of gallstones and a normal common bile duct. A computed tomography (CT) of the abdomen and pelvis was significant for splenomegaly with a large splenic infarct, a dilated splenic vein, two small hemangiomas within the liver, and a right ovarian cyst (Figure 2). Given her prior history of endocarditis with aortic valve replacement and a new finding of splenic infarction, there was a high clinical suspicion of endocarditis. Blood cultures were sent on admission, and an echocardiogram was ordered. A 2-D TTE showed no valvular vegetation, no regional wall motion abnormalities, and a normal left ventricular ejection fraction of 60%–65%. Blood cultures taken on admission were negative for 2 days. The patient had resolution of her left lower quadrant pain and vomiting, remained afebrile with a normal white cell count, and was discharged to follow-up outpatient with cardiology for a transesophageal echocardiogram in the next 3 days, follow-up with hematology for hypercoagulable workup, and follow-up with infectious diseases. One day after discharge,

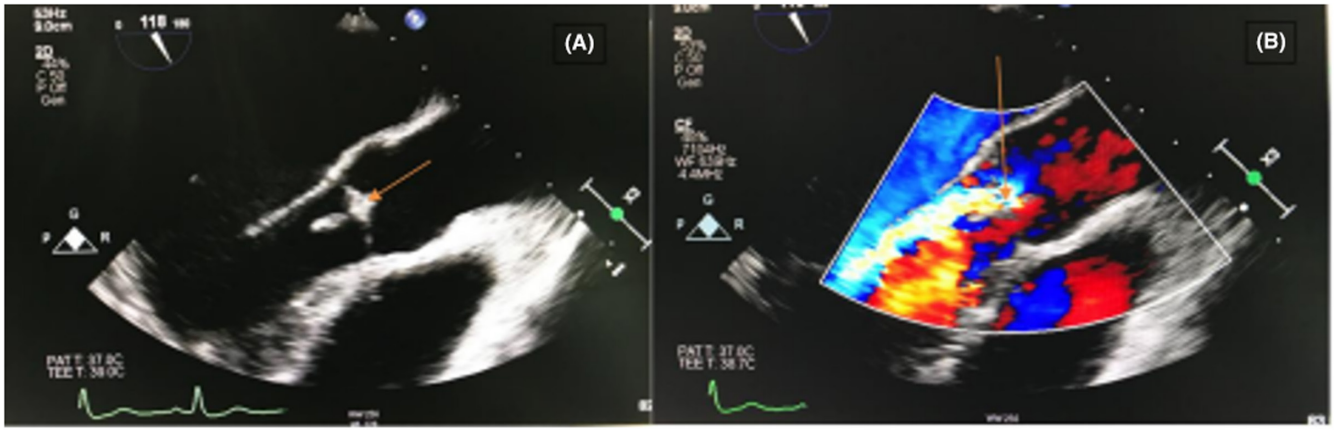

FIGURE 1 Transesophageal echocardiogram on the first admission in August 2020. A transesophageal echocardiogram shows large vegetation on the left aortic cusp protruding into the left ventricular outflow tract with moderate aortic regurgitation. The orange arrow in Figure A shows the vegetation, and the orange arrow in Figure B shows the aortic regurgitation.

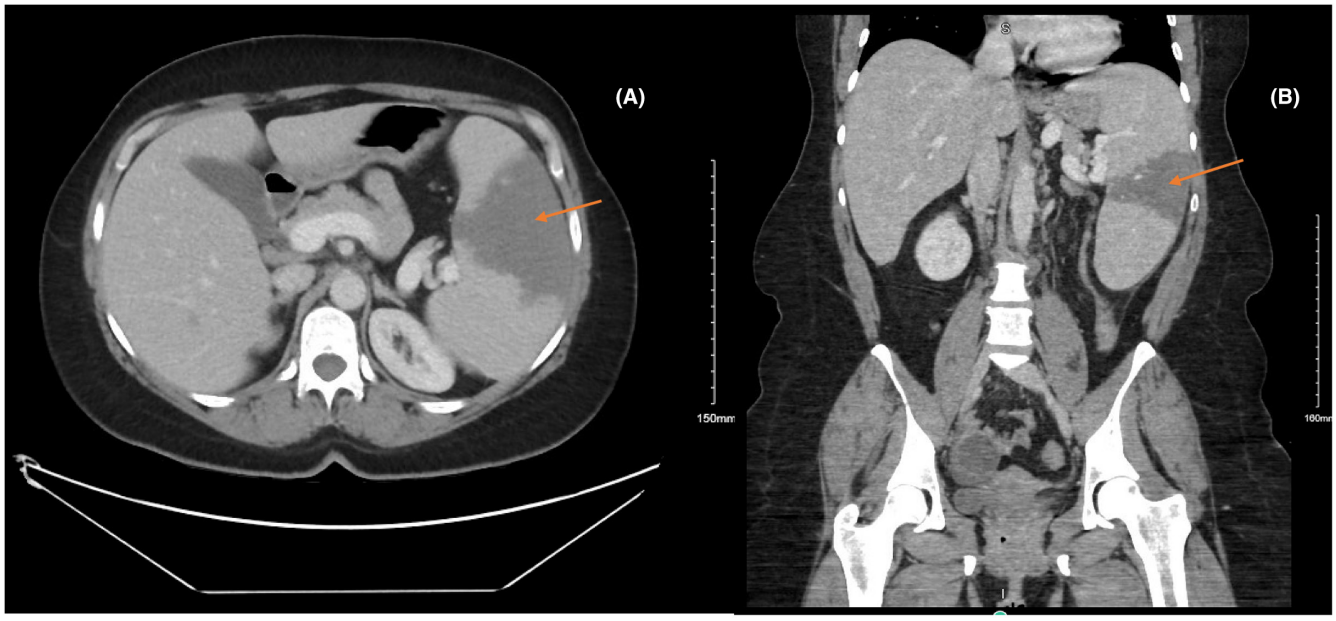

FIGURE 2 CT of the abdomen done on her second hospitalization in November 2022. (A) axial view and (B) coronal view of the abdomen showing splenomegaly and a large splenic infarct. The orange arrows point to a hypodensity within the enlarged spleen, which represents the splenic infarct.

the blood culture resulted in positive growth of Candida species for 3 days. The patient was called and readmitted to the hospital, where she was started on antifungal therapy with caspofungin 150 mg once daily. Beta-D glucan was noted to be more than 500 pg/nL. The Candida species was later identified again as *Candida parapsilosis*. Transesophageal echocardiography demonstrated a bioprosthetic aortic valve with normal movement and a 5 mm × 5 mm nodular thickening of the right coronary cusp with no definitive endocarditis. Again, blood cultures remained positive for a prolonged period, and a long QT interval required the addition of a different, newer antifungal agent, isavuconazole was commenced because it can shorten the QT-interval, unlike the older azole antifungals. A loading dose of oral isavuconazole 372 mg every 8 h was given for 48 h, followed by a daily dose of 372 mg. A repeat transthoracic echocardiogram was done, which showed a bioprosthetic aortic valve with normal valvular motion, mild periventricular thickening (likely postoperative changes), and a 5 × 8 mm non-mobile echogenic density attached to the right coronary cusp, likely a calcification versus a healed vegetation. A repeated CT of the chest, abdomen, and pelvis showed no pulmonary findings and similar abdominal findings of splenomegaly and splenic infarct as the initial CT on admission. A CT of

the face showed no significant facial soft tissue swelling or abscess—mild paranasal sinus mucosal disease involving the maxillary sinuses and extensive dental disease. A gallium scan showed marked splenomegaly, and activity was identified in the region of the lower extremities, suggestive of marrow expansion, unchanged from previous imaging. Blood cultures were repeated every 48 h, and with three consecutive negative blood cultures, she was discharged in December 2022 to complete 6 weeks of therapy with isavuconazole and to follow up with cardiology and infectious diseases outpatient.

4 | OUTCOME AND FOLLOW-UP

One month later, in January 2023, the patient followed up with her primary care physician for complaints of dizziness, persistent nausea, and vomiting. She had repeated blood cultures that were positive for *Candida parapsilosis*. She had denied intravenous drug use. Isavuconazole was discontinued because of patient-reported side effects (persistent dizziness), and she was again started on intravenous micafungin 150 mg once daily. A repeat transesophageal echocardiography illustrated two 6 mm mobile slender echocardiographic densities attached to the ventricular surface of the aortic bioprosthetic valve leaflets suggestive endocarditis and aortic regurgitation (Figure 3). Cardiothoracic surgery was consulted, and she had a redo aortic valve replacement with a number 21 bovine Edwards bioprosthetic aortic valve. Cultures of the aortic valve done at the operation were again positive for *Candida parapsilosis*. Post-procedure, she received 6 weeks of IV micafungin 150 mg once daily; her blood cultures remained negative for fungal growth. Following completion of IV micafungin, she was transitioned to oral fluconazole 400 mg once daily. She followed up with infectious diseases in February and March 2023, where she remained asymptomatic and clinically stable.

5 | DISCUSSION

Aortic valve fungal infections, although rare, represent a critical and life-threatening complication in patients with predisposing risk factors such as intravenous drug use, prosthetic heart valve implantation, and immunosuppression.[7,8] Candida species have emerged as significant etiological agents of these infections, with Candida parapsilosis being increasingly reported in recent years.[9,10] For instance, a multicenter study by Lefort et al. (2012) found that *C. parapsilosis* accounted for 16% of all Candida species isolated from patients with fungal endocarditis.[11] Furthermore, a review by Pasha et al. (2016) reported a rise in the incidence

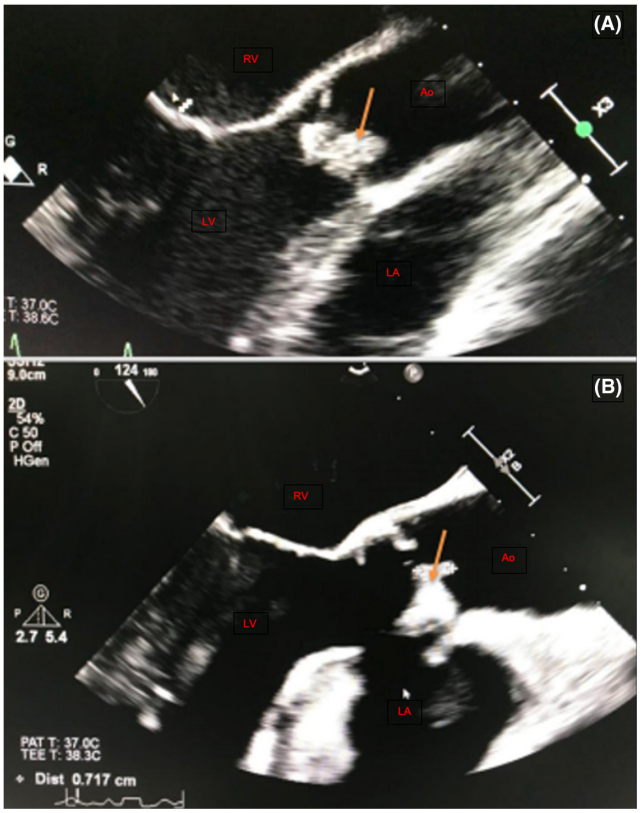

FIGURE 3 Transesophageal echocardiogram done in January 2023. A transesophageal echocardiogram showing two 6mm mobile slender echocardiographic densities attached to the ventricular surface of the aortic bioprosthetic valve leaflets. Orange arrows indicate the vegetation. Ao, aortic outflow tract; LA, left atrium; LV, left ventricle; RV, right ventricle.

of *C. parapsilosis endocarditis*, particularly in settings with high rates of prosthetic valve implantation.[12]

C. parapsilosis is an opportunistic organism that is a normal commensal of the human gastrointestinal tract and the human skin, commonly found underneath the nails of the hands.[13,14] Unlike other fungal causes of invasive diseases, such as *C. tropicalis* and C. *albicans*, invasive infections with *C. parapsilosis* can occur without prior colonization with the organisms. Notable risk factors in these cases are patients with preceding surgeries, usually of the gastrointestinal tract; immunocompromised patients such as those with human immunodeficiency virus/acquired-immunodeficiency disease syndrome; critically ill patients requiring long-term placement of invasive vascular lines; and neonates with very low birth weights.[13] Intravenous drug use is a known risk factor for invasive fungal infections with Candida species, particularly infections caused by *C. parapsilosis*.[13]

C. parapsilosis has been recognized as an important pathogen in invasive fungal infections, such as candidemia, meningitis, peritonitis, ocular infections, and endocarditis.[9] In cases of *C. parapsilosis* endocarditis, the aortic valve is most commonly affected, with a demonstrated

predilection for prosthetic aortic valves.[15,16] In the rare cases of *C. parapsilosis* endocarditis of a native valve, a history of intravenous drug use is usually present.[17] In both scenarios, endocarditis secondary to *C. parapsilosis* is usually preceded by fungemia.[16,17]

Distinguishing between candida and bacterial endocarditis during the initial assessment can pose significant challenges, as both can present with nonspecific symptoms.[18,19] Candida endocarditis typically presents as subacute endocarditis, and *C. parapsilosis* endocarditis is frequently associated with septic emboli, which may involve many organs due to its predilection for the aortic valve.[19]

Definitive therapy for native and prosthetic valve Candida endocarditis involves medical management, generally with long-term antifungal therapy and surgical management. The 2016 Infectious Diseases Society of America (IDSA) guidelines recommend amphotericin B with or without the addition of flucytosine or high-dose echinocandins (micafungin, caspofungin) as the initial therapy for Candida native valve and prosthetic valve endocarditis. Following this initial therapy, long-term therapy with fluconazole (400–800 mg per day) is recommended to ensure clearance of fungemia.[20] In addition to medical therapy, valvular replacement is also recommended, with continued antifungal therapy with fluconazole for at least 6 weeks following surgery or even longer in those patients with perivalvular abscesses for native valve endocarditis. Chronic suppressive therapy with daily high-dose fluconazole is recommended for patients with prosthetic valve endocarditis.[20] For those patients who are high-risk surgical candidates, long-term daily suppressive therapy with fluconazole in doses of 400–800 mg is recommended; however, the exact duration has not been determined.[20]

One of the challenges to definitive treatment in cases of Candida endocarditis, particularly with *C. parapsilosis*, is the increased risk of recurrence, which is most often due to inadequate clearance of fungemia (resulting in persistent fungemia) and the use of inappropriate antifungal therapy.[21] *C. parapsilosis* fungemia has been identified as a specific risk factor for the recurrence of endocarditis, as demonstrated in a retrospective case–control study by Munoz et al. (2015), mainly attributed to its ability to form biofilms.[22] Biofilms impede the therapeutic actions of antifungal agents, rendering organisms relatively resistant to antimicrobial agents.[23] Antimicrobial sensitivities obtained in our case revealed that *C. parapsilosis* was sensitive to the first-line antifungal therapies used in her treatment. Therefore, the persistent fungemia and relapsing endocarditis encountered in our case are likely the result of inadequate clearance of the organism due to its biofilm production, as supported in the literature.

One of the challenges experienced in this case is the limited evidence-based guidance on managing persistent Candidemia despite appropriate antifungal therapy and recurrent C. parapsilosis endocarditis, as seen in our case. Notably, recurrent aortic valve infections caused by *C. parapsilosis* are associated with high morbidity and mortality rates. The mortality rate of *C. parapsilosis* endocarditis approaches 40%, necessitating a comprehensive understanding of this pathogen and its propensity for recurrence.[18,24]

6 | CONCLUSION

C. parapsilosis is a rare cause of fungal endocarditis, commonly associated with IVDU. *C. parapsilosis* endocarditis has a predilection for the aortic valve and is more common in patients with bioprosthetic valves. It has a high mortality of about 40%. Our case presents a patient with risk factors for invasive fungal infection (IVDU and splenomegaly) who developed *C. parapsilosis* endocarditis, first of her native aortic valve and subsequently of her bioprosthetic valve. One of the challenging aspects of this case was the recurrent presentations *C. parapsilosis* candidemia and the persistent candidemia despite appropriate use of recommended first-line antifungal therapy, necessitating trials of multiple first-line therapies. The organism's ability to form biofilms is suspected to be the significant contributing factor to the persistent and relapsing nature of invasive infections caused by this organism.

As the aortic valve is most commonly affected, many organ systems are often involved due to septic embolization. High clinical suspicion and a multidisciplinary approach is needed in these cases to reduce morbidity and prevent mortality.

AUTHOR CONTRIBUTIONS

Shannay Bellamy: Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Mohammed Mirza:** Conceptualization; writing – original draft; writing – review and editing. **Muhammad Faiq Umar:** Conceptualization; writing – original draft; writing – review and editing. **Jacob Enyia:** Conceptualization; writing – original draft; writing – review and editing. **Khurram Malik:** Supervision; writing – review and editing. **Abdul Ameen:** Supervision; writing – review and editing. **Tyrone Krause:** Supervision.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethics approval is not applicable for this case report since it does not report or involve the use of animal or human tissue or data.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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