Recurrent Fungal Endocarditis of the Aortic Valve: A Challenging Clinical Scenario

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Ethical Approval and Consent to Participate

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 for Publication

Written informed consent was obtained from the patient or the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Background

Fungal endocarditis, a rare but severe infection of the cardiac valves, is associated with significant morbidity and mortality. Recurrent aortic valve fungal endocarditis is an even rarer clinical entity with limited literature on management strategies. The condition is typically caused by the spread of fungal spores through the bloodstream, which can occur due to various factors, such as intravenous drug use, dental procedures, or intravascular or intracardiac medical devices. Symptoms of aortic valve fungal endocarditis may include

fever, fatigue, shortness of breath, chest pain, and a new or changing heart murmur. Diagnosis typically involves a combination of blood tests, imaging studies, and cardiac catheterization.

Case Presentation

We present a challenging case of relapsing *Candida parapsilosis*endocarditis in a 44-year-old female with a history of intravenous drug use and chronic hepatitis C infection with portal hypertension and splenomegaly. The index presentation of her endocarditis involved a native aortic valve requiring aortic valvular replacement, with the subsequent presentation involving the patient's bioprosthetic valve necessitating a redo aortic valve replacement.

Conclusion

Recurrent aortic valve fungal endocarditis is a complex and life-threatening condition that demands a high index of clinical suspicion, timely diagnosis, and aggressive treatment. A multidisciplinary approach involving infectious disease specialists, cardiologists, and cardiothoracic surgeons is essential for optimal patient outcomes. Cases of fungal endocarditis due *to Candida albicans* are the most commonly reported and studied case of fungal endocarditis. Limited data exists on the appropriate management of endocarditis caused by other candida species such as *Candida parapsilosis* . Further studies are needed to establish standardized treatment protocols and improve patient prognosis.

Keywords: Candidemia, candidiasis, fungal infection, endocarditis, aortic valve, prosthetic valve

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 its pathogenic potential [6]. Most cases of C. parapsilosis recorded thus far have either isolated prosthetic valve involvement or, less frequently, isolated native valve involvement [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 C. parapsilosis fungemia, septic embolization to the spleen, and involvement of the bioprosthetic aortic valve.

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 two weeks. She also complained of unintentional weight loss of about 7.3 kilograms (16 pounds) in the preceding three months. The patient reported a remote history of intravenous opioid abuse; she quit seven years before and was enrolled in a methadone program for recovery. She also had a long-standing history of asthma and chronic Hepatitis C infection with unsuccessful treatment twenty years ago due to medication intolerance. At the time of her presentation, her vitals were significant for tachycardia of 113 beats per mins and a low-grade fever of 99.7F. 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. 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 were 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 and were significant for two small nodules on the

liver (likely hemangiomas), severe splenomegaly with several non-specific splenic nodules and mild dilatation of the biliary tree. 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 echo 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 x 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.

Her cultures remained positive for *C. parapsilosis* for four weeks despite maximal therapy with different antifungals, limited by her underlying liver disease (Child-Pugh class B), including caspofungin and micafungin. A repeat TEE showed an increase in the size of vegetation to 11 x 16 mm. Due to the absence of concrete clinical trial data, it was difficult to frame a definitive therapeutic strategy, especially the need for valvular surgery. Based on the recommendations of published observational studies, 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 post-operative stay was complicated by recurrent atrial flutter with a 4:1 atrioventricular block, which was adequately ablated, and she was subsequently started on anticoagulation. She received six weeks of antifungal therapy post-procedure with intravenous micafungin, after which her blood cultures remained negative for fungal growth. She was eventually discharged home on oral fluconazole for three to six months with outpatient follow-up. However, she was non-compliant with therapy and non-compliant with follow-up.

In November 2022, she returned to the emergency department with a three-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 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**).

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 valvular repair and a new finding of splenic infarction, there was a high clinical suspicion of endocarditis, and blood cultures were sent on admission, and an echocardiogram was ordered. A 2-D transthoracic echocardiogram 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 two 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 three days, follow-up with hematology for hypercoagulable workup, and follow-up with infectious diseases. One day after discharge, blood culture resulted positive for the growth Candida species at three days. The patient was called and readmitted to the hospital, where she was started on antifungal therapy with caspofungin. 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 5mm x 5mm 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. Isavuconazole commenced because it can shorten the QT-interval, unlike the older azole antifungals. 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 x 8mm 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 forty-eight hours, and with three consecutive negative blood cultures, she was discharged in December 2022 to complete six weeks of therapy with isavuconazole and to follow up with Cardiology and Infectious Diseases outpatient.

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* . Isavuconazole was discontinued because of patient-reported side effects (persistent dizziness), and she was again started on intravenous micafungin. A repeat transesophageal echocardiography illustrated two 6mm mobile slender echocardiographic densities attached to the ventricular surface of the aortic bioprosthetic valve leaflets suggestive of endocarditis (**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 six weeks of IV micafungin; her blood cultures remained negative for fungal growth. Following completion of IV micafungin she was transitioned to oral fluconazole 400 mg daily. She followed up with infectious diseases in February and March 2023, where she remained asymptomatic and clinically stable.

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 conducted by Lefort et al. 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. reported a rise in the incidence of *C. parapsilosis*endocarditis, particularly in settings with high rates of prosthetic valve implantation [12]

C. parapsilosis is an opportunistic organism which 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 disease such as *C. tropicalis* and *C. albicans* , invasive infections with *C. parapsilosis* can occur in the absence of 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 various 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 non-specific symptoms [18, 19]. Candida endocarditis typically presents as subacute endocarditis, and *C. parapsilopas*endocarditis is frequently associated with septic emboli, which

may involve many organs due to its predilection for the aortic valve [19].

Definitive therapy for both native valve 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 six 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 [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, 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 the *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 is 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].

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.

C. parapsilosis endocarditis has a high mortality rate that approaches 40%. As the aortic valve is most commonly affected, there is often involvement of many organ systems due to septic embolization. High clinical suspicion and a multidisciplinary approach is needed in these cases to reduce morbidity and prevent mortality.

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Tables

Laboratory test	**Results of August 2020 Admission**	**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
(L) – indicates a value below the normal reference range; (H) – indicates a value above the normal reference range	(L) – indicates a value below the normal reference range; (H) – indicates a value above the normal reference range	(L) – indicates a value below the normal reference range; (H) – indicates a value above the normal reference range	(L) – indicates a value below the normal reference range; (H) – indicates a value above the normal reference range	(L) – indicates a value below the normal reference range; (H) – indicates a value above the normal reference range

Table 1 : Table of laboratory investigations on each admission to hospital

Table 2

Antifungal	**Minimal inhibitory concentration (mcg/ml)**	**Minimal inhibitory concentration (mcg**
	C. parapsilosis isolated in August 2020 (first presentation)	*C. parapsilosis* isolated in November 2022 (s
Amphotericin B	0.250 (S)	0.250 (S)
Caspofungin	0.500 (S)	0.500 (S)

Antifungal	Minimal inhibitory concentration (mcg/ml)	Minimal inhibitory concentration (mcg
Fluconazole	1 (S)	1 (S)
Micafungin	1 (S)	1 (S)
Voriconazole	0.015 (S)	0.015 (S)

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

Figures

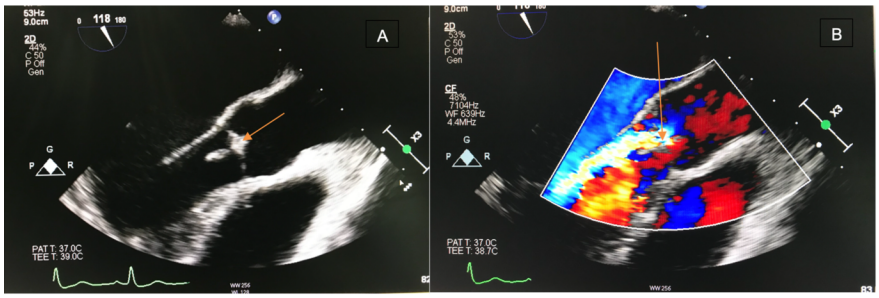
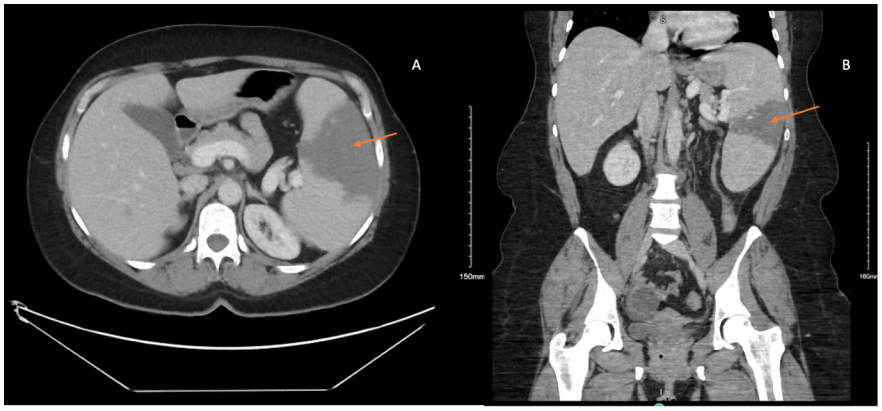


Figure 1 : Transthoracic echocardiogram on the first admission in August 2020

Transthoracic echocardiogram showing a 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: Computed tomography of the abdomen done on the patient's second hospitalization in November 2022



- 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

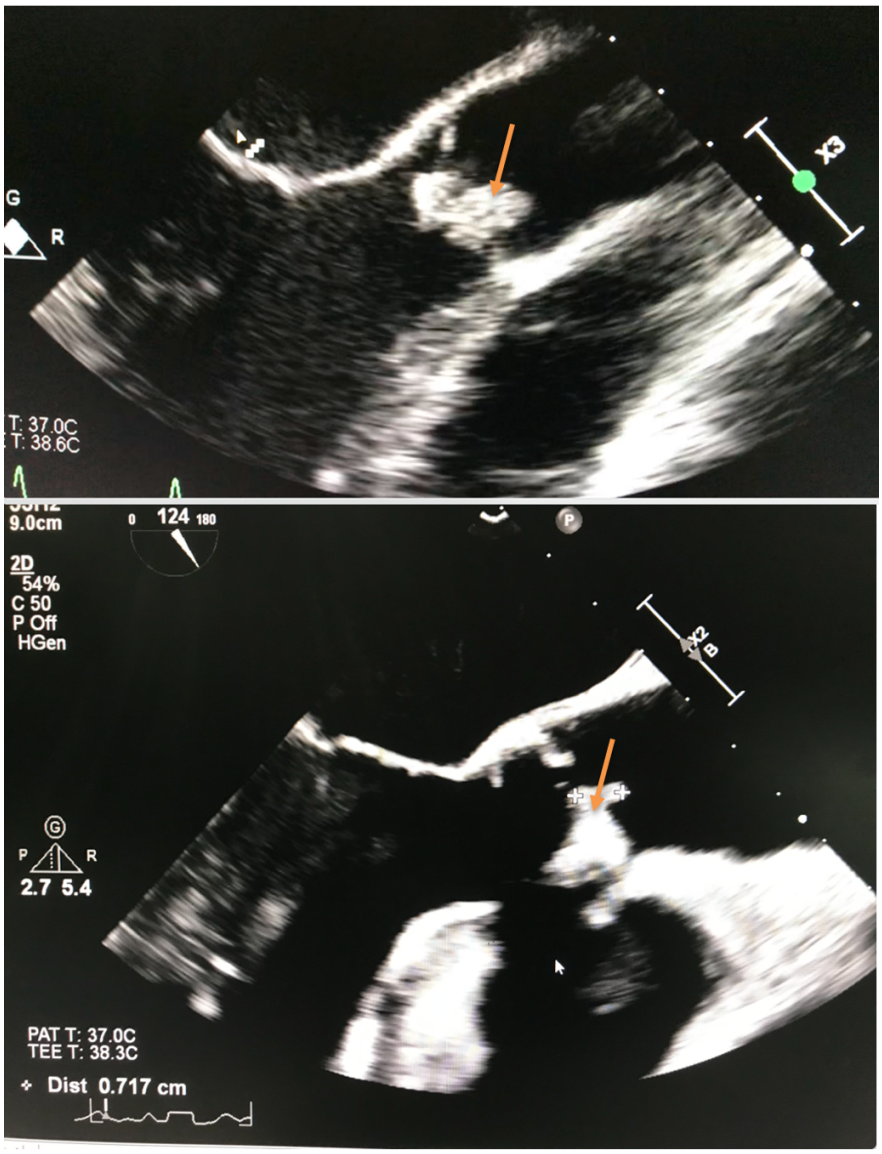


Figure 3 : Transesophageal echocardiogram done in January 2023

Transesophageal echocardiogram showing two 6mm mobile slender echocardiographic densities attached to the ventricular surface of the aortic bioprosthetic valve leaflets. The orange arrows indicate the vegetation on the aortic valve.