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CASE REPORT

Triple-Valve Endocarditis in a Diabetic Patient: Case Report and Literature Review

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Abstract: ***Background*:** Despite major advancements since its first description in the 19th century, infective endocarditis remains a significant medical challenge. Although commonly involving a single valve, multiple valve involvement may occur, complicating matters even further. Triple-valve endocarditis is a very rare phenomenon. Poorly studied and described only a handful of times in the literature, little is known about the optimal therapeutic and management options in dealing with this complex entity.

***Conclusion*:** In this paper we describe the case of a 48-year-old male who was diagnosed with triple-valve endocarditis and provide a review of the literature to delineate what is already known and improve our understanding of this rare phenomenon.

Keywords: Triple-valve, endocarditis, diabetic patient, therapeutic and management options, phenomenon.

1. INTRODUCTION

Infective Endocarditis (IE) involves inflammation of the endocardium and was first described in the 19th century [1]. To this day, despite major advancements in both diagnostic and therapeutic procedures, it continues to have a significant impact on morbidity and has a high mortality rate [2]. The majority of IE cases involve one valve. Two valve involvement is less frequently seen and triple or quadruple valve involvement is extremely rare [3]. Mortality rate is seemingly similar between single and multiple valve endocarditis, however multiple-valve disease appears to be associated more frequently with heart failure and surgery [3-5]. Here we present the case of a diabetic patient who was found to have triple-valve endocarditis, complicated by septic emboli to the brain and lungs, acute kidney injury and acute hypoxic respiratory failure.

2. CASE REPORT

A 48-year-old gentleman with a history of insulin dependent diabetes mellitus type 2 and morbid obesity presented to our hospital as a transfer from an outside hospital for fever and altered mental status. He had recently been seen by his Podiatrist for a pressure ulcer over the plantar surface of his left foot which was aspirated with culture yields of *Methicillin Sensitive Staphylococcus Aureus (MSSA)*. He was prescribed Augmentin which he did not take due to GI upset. At the outside hospital, altered mental status and concerns of hemiplegia on physical exam prompted a CT scan which revealed an acute/subacute infarct in the right frontal area. Upon arrival to our hospital, vital signs revealed a temperature of 102.8 Fahrenheit (F), pulse of 128 bpm, respiratory rate of 38 and a blood pressure of 133/78 mmHg. He was alert and oriented but mildly confused. Cranial nerves were grossly intact, and strength was 3/5 in his left arm, 5/5 in the right arm and 1/5 in bilateral lower limbs. Chest ausculation revealed tachycardia, but no murmurs, rubs or gallops were appreciated. Three ulcers over the plantar surface of his left foot were noted. Electrocardiogram showed sinus tachycardia. Lab-work was notable for leukocytosis with a white blood cell count of 13,000/mm^3 and a hemoglobin level of 11.1gm/dl. Repeat head CT revealed right sided frontal and parietal subacute to acute infarcts. Lumbar puncture was negative for underlying infection. He was then continued on Intravenous (IV) Oxacillin.

A Neurology consult was obtained and recommended a brain MRI which revealed subacute infarcts of the right MCA and left frontal territories with intermixed foci of subacute hemorrhage and mild mass effect with some of the lesions (Fig. **1**). On the day following admission, the patient went into atrial fibrillation with rapid ventricular. He denied any cardiovascular complaints. He had never seen a Cardiologist before and never had any cardiovascular workup or testing done. TTE then revealed normal left ventricular size and thickness with an EF of 55-65% and no regional wall motion abnormalities. However, a 1.8 x1.3 cm mobile vegetation was seen attached to the atrial side of the the anterior leaflet of the tricuspid valve, causing trace tricuspid valve regurgitation. A Trans-Esophageal Echocardiogram (TEE) the following day revealed a 10 x 7.5mm thickening on the

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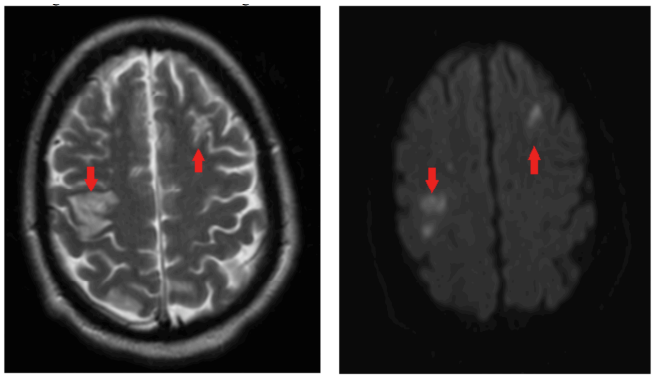

Fig. (1). T2 (left) and diffuse-weighted (right) magnetic resonance imaging scans of the brain showing subacute infarcts of the right MCA and left frontal territories.

aortic surface of the non-coronary cusp (Fig. **2**), and an 8 x 6mm slightly mobile mass attached at the medial commissure of the mitral annulus on the left atrial side (Fig. **3**), both consistent with vegetation. A large 34mm multi-lobulated mass associated with the anterior tricuspid valve leaflet consistent with vegetation was also seen (Fig. **4**), along with mild to moderate tricuspid valve regurgitation. Blood cultures returned positive for *Methicillin-Sensitive Staphylococcus Aureus (MSSA)*. Despite antibiotic coverage with IV Oxacillin since admission, the patient was clinically deteriorating and had worsening leukocytosis. He also remained persistently bacteremic with culture yields of *MSSA* 7 days later. He was then continued on IV Nafcillin due to drug shortage of Oxacillin. A CT scan of the chest and abdomen was obtained to look for other sources of infection or possible abscesses and revealed multiple bilateral cavitary nodules in the lungs compatible with septic emboli, along with bilateral pleural effusions with adjacent consolidations for which bilateral chest tubes were placed (Fig. **5**). A cardiothoracic surgery consult was then made for the findings on TEE but given his recent stroke with hemorrhagic components and findings on chest CT, he was not deemed a suitable candidate for surgery and recommended continuing with antibiotic therapy and reevaluation down the line.

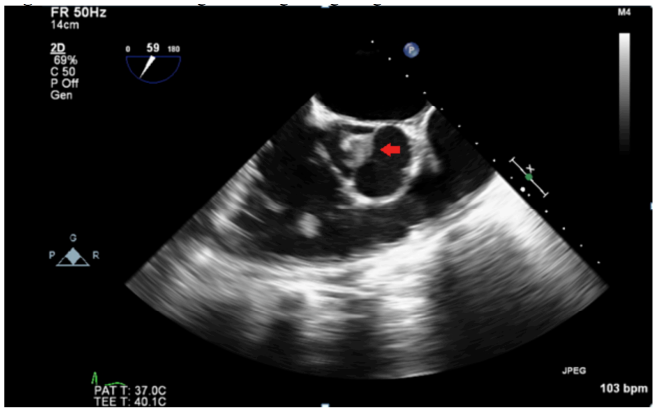

Fig. (2). TEE 2-D image showing a large vegetation on the aortic valve.

Clinical course was complicated by Acute Kidney Injury (AKI), worsening anemia requiring multiple blood transfusions and acute hypoxic respiratory failure requiring BIPAP,

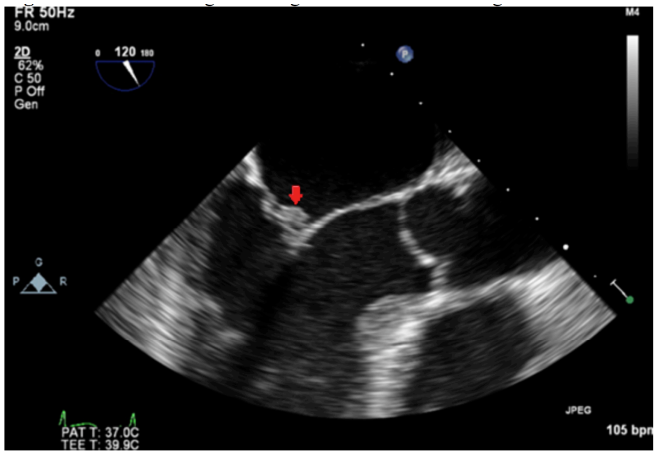

Fig. (3). TEE 2-D image showing a small non-mobile vegetation on the mitral valve.

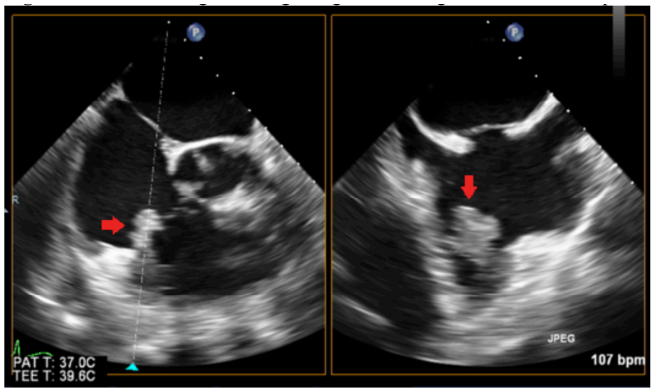

Fig. (4). TEE 2-D image showing a large mobile vegetation in the tricuspid valve.

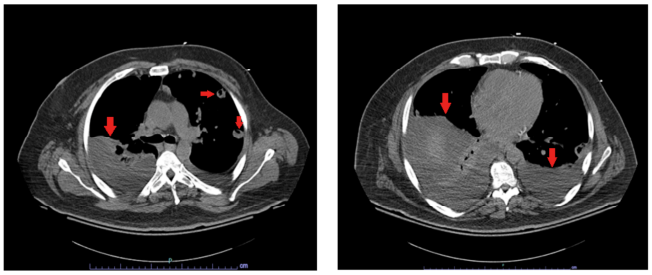

Fig. (5). CT scans of the chest revealing multiple bilateral cavitary lesions in the lungs compatible with septic emboli. Bilateral pleural effusions are also noted.

concerning for an underlying pneumonia. Embolic phenomena to the fingers and toes were also noted (Fig. **6**). Worsening renal function and new rash development prompted switching to Cefazolin and then Daptomycin. Three weeks after presentation, a repeat TEE was done that showed worsening of the tricuspid regurgitation that had initially been seen, with probably perforation of the tricuspid valve. Cardiac surgery re-evaluation continued to deem the patient as a poor candidate for surgery given his decompensated respiratory status with concerns of Acute Respiratory Distress Syndrome (ARDS). At no point did the patient develop signs

Fig. (6). Embolus to the tip of the 5th toe on the right foot, associated with sloughing and a small amount of yellow discharge. *(The color version of the figure is available in the electronic copy of the article).*

concerning for heart failure. Over the course of the next couple of weeks, there was marked improvement in the patient's clinical status. His white cell count normalized; fevers, AKI and ARDS had all resolved. The plan was to continue IV Daptomycin for a total of 6 weeks followed by a repeat echocardiogram and evaluation for cardiac surgery. The patient had presented from out-of-state and opted for medical follow-up nearer to his home.

3. DISCUSSION

The aforementioned report presents a challenging case of uncommon triple-valve endocarditis requiring a prolonged hospital stay and multidisciplinary approach. It was further challenged by our patient's comorbidities and evidence of multi-organ involvement at presentation.

3.1. Incidence

The rarity of triple-valve endocarditis precludes large scale studies or series from studying its incidence, characteristics, prognosis, and management approach. One series sited an incidence of multi-valve endocarditis at 18%, among a cohort of 77 cases of IE studied. However, none of the cases involved three or more valves [3]. In another series of 25 opiate addicts with echocardiographic evidence of vegetations, no cases of triple-valve involvement was found [6]. Nonetheless, data from studies on Multi-Valve Endocarditis (MVE) may provide insight into nature and of this complex entity.

3.2. Presenting Features

Up to 90% of patients with IE present with fever, often associated with chills, anorexia and weight loss [7]. Heart murmurs are also audible in 85% of patients [7]. Emboli to the brain, lungs or spleen occur in 30% of patients. Our patients altered mental status and hemiplegia on physical exam, along with fever, raised concerns for underlying meningitis. Neurological manifestations in IE are not uncommon, with neurological events developing in 20-40% of all patients with IE, mainly being the consequence of vegetation embolism [7]. 75% of emboli also occur before beginning antibiotic therapy [8]. The concerns behind this lay in delaying the diagnosis of underlying IE, resulting in delays in proper treatment and management of the underlying culprit. In one series, Epaulard *et al*. retrospectively reviewed IE related strokes and found that 26/34 cases presented with stroke before diagnosis of IE. There was a median delay of 8 days in diagnosis but this had no influence on survival [9]. In our case, a transthoracic echocardiogram was obtained 3 days after admission, which ultimately led to the diagnosis of IE.

3.3. Diabetes and Endocarditis

According to a multinational database, diabetes was found to be an independent predictor of mortality in IE, especially in male patients [10]. *S. Aureus* was also isolated more often in the diabetic group. Mohaved *et al*. revealed that patients with type 2 diabetes mellitus have significantly higher prevalence of IE independent of renal failure or valvular abnormalities [11]. A separate series by Chirillo *et al*. on 309 patients showed a worse clinical outcome and course of IE in those with diabetes mellitus [12]. Among patients undergoing hemodialysis, diabetes as a cause of end-stage renal disease is a prognostic factor for late mortality among hemodialysis patients with infective endocarditis [13].

3.4. Treatment

According to the latest American guideline for the management of patients with valvular heart disease [14], early surgery is *indicated* during initial hospitalization before completion of a full therapeutic course of antibiotics in patients with IE who present with:

- Valve dysfunction resulting in symptoms of HF.
- Heart block, annular or aortic abscess, or destructive penetrating lesions.
- Left-sided IE caused by *S. aureus*, fungal or other highly resistant organisms.
- Persistent infection as manifested by persistent bacteremia or fevers lasting longer than 5 to 7 days after onset of antibiotics.
- Prosthetic valve endocarditis and relapsing infection without other identifiable source for portal of infection.

Operation without delay may be considered in patients with IE and an indication for surgery who have suffered a stroke but have no evidence of intracranial hemorrhage or extensive neurological damage. Delaying valve surgery for at least 4 weeks may be considered for patients with IE and major ischemic stroke or intracranial hemorrhage if the patient is hemodynamically stable.

Despite our patient meeting criteria for vegetation size, duration of bacteremia and possible perforation of the tricuspid valve as seen on repeat TEE, his surgery was understandably delayed given evidence of subacute infarcts with hemorrhagic components. Upon re-evaluation by a different cardiac surgeon, he was still not deemed a suitable candidate for surgery given the relatively preserved function of both mitral and aortic valves, recent stroke with hemorrhagic components and some mass effect, along with the picture of ARDS as seen on CT scan of the chest. The number of valves involved appears not to influence the necessity for surgery. The plan set in place upon discharge was to proceed with surgery given clinical stability and completion of a 6 week course of antibiotic treatment.

3.5. Literature Review

We conducted an extensive literature review using the PubMed and Scopus databases and identified only 15 other triple-valve endocarditis cases (excluding ours) (Table **1**).

Table 1. Triple-valve endocarditis cases reported in the literature.

Reference	Age	Gender	Presenting Symptom (s)	Risk Factor(s)	Murmur (s)	Clinical Features of IE	Valves Involved	Microorganism (s)	Acute Heart Failure	Surgery	Death
Maturu *et al.* [26]	25	F	Fever	Second trimester abortion	Pansystolic Murmur	Splinter Hemorrhages/ Janeway lesions	MV, AV, TV	MSSA	Yes	No	No
Zea - Vera *et al.* [27]	15	M	Fever	Hemodia-lysis	Holosystolic murmur	Janeway lesions	MV, AV, TV	MRSA	Yes	Aortic valve: replacement (mechanical) Mitral/Tricuspid: repair	No
Khan *et al.* [28]	36	M	Fevers, rash weakness, chills	IV Drug Use/ Bicuspid AV	Diastolic murmur	Embolic lesions on hands and toes/Janeway lesions	MV, AV, TV	MSSA	Yes	Aortic valve replacement x 3 (first two replacements bioprosthetic valves, last replacement mechanical)	No
Shaikh *et al.* [29]	17	F	Fever, malaise, foot gangrene, hemiparesis	None	Pansystolic and early diastolic murmurs	Systemic Emboli	MV, AV, TV	Mycobacterium Tuberculosis	No	Mitral/Aortic valve: replacement Tricuspid valve: repair	No
Tomaszuk-Kazberuk *et al.* [30]	47	M	Abdominal pain, anorexia, night sweats, daily chills, weight loss	Alcohol Abuse	Systolic murmur	None	MV, AV, TV	Erysipelothrix rhusiopathiae	Yes	Mitral/Aortic valves: replacement (mechanical) Tricuspid: replacement (bioprosthesis)	Yes
Alloca *et al.* [31]	57	M	Fatigue, anorexia, dyspnea, fever spikes, weight loss	None	Systolic and diastolic murmurs	None	MV, AV, TV	Streptococcus Bovis Enterococcus Faecalis	Yes	Aortic valve: replacement (mechanical) Mitral/Tricsupid: replacement (bioprosthesis)	No
Bavunoglu *et al.* [32]	26	M	Fever, weight loss, abdominal pain	VSD	Pansystolic murmur	None	MV, AV, TV	Streptococcus Sanguinis	No	Aortic valve: replacement (mechanical)	No
Sakakura *et al.* [33]	45	F	Edema, dyspnea on exertion	VSD	Pansystolic murmur	None	PV, AV, TV	No growth	Yes	Aortic/Pulmonary valves: replacement (mechanical) Tricsupid: replacement (bioprosthesis)	No
Bortolotti *et al.* [34]	23	F	Fatigue, headache, cough, fever	None	Pansystolic/Diastolic Murmurs	None	MV, AV, TV	Staphylococcus Epidermidis	Yes	Mitral/Tricuspid valves: replacement (bioprosthesis) Aortic Valve: replacement (mechanical)	No
Araujo *et al.* [35]	41	M	Cough, fever, pleuritic chest pain	Diabetes, VSD	-	-	PV, AV, MV	E. Faecalis	No	Triple valve replacement (types of valves not specified)	Yes

(Table 1) Contd…

Reference	Age	Gender	Presenting Symptom (s)	Risk Factor(s)	Murmur (s)	Clinical Features of IE	Valves Involved	Microorganism (s)	Acute Heart Failure	Surgery	Death
Einav *et al*. [36]	28	F	Painful eruption on hands and feet, orthopnea, dyspnea	SLE	Holosystolic/Diastolic murmurs	Osler nodes	MV, AV, TV	- [Liebmann Sacks Endocarditis]	Yes	Aortic/Mitral valves: replacement (mechanical) Tricuspid: repair	No
Kontogiorgi *et al*. [37]	39	M	Fever, neck stiffness, headache	Drug Abuse	Aortic Valve murmur	None	MV, AV, TV	Staphylococcus Aureus	Yes	Aortic/Mitral valves: replacement (mechanical) Tricuspid: repair	No
Arslan *et al*. [38]	78	M	Dyspnea, night sweats, malaise, chills, fever	Coronary angiograpy/ureteral catheteri-zation 1 month prior	Pansystolic murmur	None	MV, AV, TV	E. Faecalis	No	No	Yes
Sibal *et al*. [39]	47	F	Fever	Bicuspid AV	Systolic Murmur	Splinter Hemorrhages	MV, AV, TV	Staphylococcus Lugdunensis	Yes	Triple valve replacement (mechanical)	No
Sheikh *et al*. [40]	48	M	Lethargy, anorexia, weight loss	Ex- IV Drug user	Pansystolic/Early diastolic murmur	-	TV, PV, AV	Streptococcus Mutans	No	No	Yes

IV: Intravenous; MV: Mitral Valve; AV: Aortic Valve; TV: Tricuspid Valve; PV: Pulmonary Valve; MSSA: Methicillin-Sensitive Staphylococcus Aureus; MRSA: Methicillin-Resistant Staphylococcus Aureus; VSD: Ventricular Septal Defect; SLE: Systemic Lupus Erythematosus.

In the cases identified, 11/15 of patients presented with fever as the main or one of the main chief complaints. Our patient also presented with documented fever and complaints of anorexia prompting him to discontinue his insulin use. In a series by Lederman *et al*., 123 patients treated for IE were reviewed. They deduced that endocarditis-associated mortality among patients who remained febrile after 1 week of therapy was 18%. Prolonged fever also identifies patients at higher risk of a fatal outcome [15].

Despite being found in up to 85% of patients, our patient did not have a heart murmur on presentation [7]. This may be due to his underlying tachycardia, after which he developed atrial fibrillation. Once rate control was achieved, a systolic murmur was appreciated across the entire precordium. As shown in Table **1**, all cases of triple-valve endocarditis (except in one case report that did not mention any physical examination findings) presented with a murmur – diastolic, systolic or both. Common vascular and immunologic signs of this disease include splinter hemorrhages, Roth spots, and glomerulonephritis and were seen in 5/15 of the cases identified. Identification and recognition of these classical stigmata of IE may lead to a more rapid diagnosis and allow for early treatment of this deadly disease.

The majority of cases identified (Table **1**) ultimately required surgical intervention. One of the three patients who did not undergo surgery, a 78-year-old male, had refused surgery and ultimately died of complications despite appropriate antimicrobial treatment. The other two patients were successfully treated with medical management only. The case reported by Araujo *et al*. delineates the importance of adhering to the clinical and echocardiographic criteria available for surgical indications. In their case, a 41-year-old male with triple-valve endocarditis was taken for surgery without clear indications for surgical intervention and ultimately died due to septic shock. Surgical intervention on our patient was reasonably delayed given his subacute strokes and clinical instability.

There currently is no data dictating the benefits of mechanical vs bioprosthetic valve replacement nor valve repair vs replacement of multi-valve disease. As shown in Table **1**, all patients with triple-valve endocarditis had involvement of the aortic valve. Among those that underwent surgery, all had aortic valve replacements. Apart from 2 cases that did not specify the type of prosthesis used, the aortic valves were replaced using mechanical valves. Khan *et al*. describe the case of a patient who underwent three separate aortic valve replacement surgeries due to reinfection; the first two using bioprosthetic valves and the last one using a mechanical valve. The reasoning behind the use of bioprosthetic valves initially was due to the patients social and behavioral issues where he was unwilling to take Warfarin. It is important to note that all these patients were younger than 70 years of age. The current ACC/AHA guidelines lists the use of bioprosthesis as reasonable for patients aged greater than 70 years old [14]. As such, the use of a mechanical valve in the cases cited appears to be reasonable and is further supported by Nguyen *et al*., who analyzed 167 patients that underwent aortic valve replacement. They deduced that the use of a bioprosthetic valve was associated with lower overall 5-year survival than the use of a mechanical valve in patients up to 65 years old [16].

Mitral valve involvement was noted among 10 patients undergoing surgery. Only 1 patient had mitral valve repair, two other patients had vegetation on the mitral valve not requiring surgery and the remaining 7 patients had mitral valve replacements, the majority of which were mechanical valves. The same age cut-offs apply to mitral valve as for

aortic valve replacement, in terms of bioprosthetic *vs*. mechanical valves. A systematic review by Feringa *et al*. on 24 studies sought to compare mitral valve repair *vs*. replacement in infective endocarditis. They found that 39% of patients underwent repair and 61% underwent valve replacement, concluding that repair is associated with lower in-hospital and lower long-term mortality as compared to replacement surgeries [17]. However, as mentioned previously, these studies do not take into account triple-valve disease in which high-risk surgeries take place simultaneously on three different native valves. Patients selected for repair likely have less aggressive infections and fewer comorbidities, not truly representative of our patient characteristics.

Right-sided endocarditis primarily affects patients with IV drug use or those with central venous catheter access. It is less common than left-sided endocarditis, has a lower in-hospital mortality rate and can commonly be managed medically [18]. More surgical options exist when dealing with tricuspid-valve disease including repair, replacement or valve excision surgery. In the data we present, 3 patients had pulmonary valve involvement, 2 of which underwent replacement surgeries. 9 patients underwent tricuspid valve surgery, 4 of whom underwent repair surgeries and 5 had valve replacement surgeries. 80% of tricuspid valve replacement surgeries used bioprosthetic valves. Today, bioprosthetic valves are used in most cases of tricuspid valve replacement surgeries given that lower pressure and stress in the right heart provides higher durability for bioprosthesis [19, 20]. From our data it appears that multi-valve surgery does not seem to influence neither the choice of surgery performed nor the type of valve used on the native disease tricuspid valve.

With the data we present, triple-valve endocarditis appears to always involve the aortic valve. Mechanical *vs*. bioprosthetic valve replacement appears to be based on traditional indications with no specific criteria based on multivalve involvement or severity of disease. The same conclusion is reached regarding tricuspid valve surgery where the use of bioprosthetic valve appears more common and unrelated to the number of valves involved or severity of infection. In the current literature, mitral valve repair appears to have better clinical outcomes compared to replacement surgeries. However, these studies do not take into account the severity of disease and patient comorbidities. In triple-valve endocarditis, the majority of mitral valve surgery appears to result in valve replacement. This is in conjunction with disease severe enough to preclude simple repair.

As previously mentioned, the leading cause of acute IE is *S. Aureus*. Of the 14 cases identified, 6 involved Staph species and 4 of which were *S. Aureus*. Increasing use of intravenous catheters and prosthetic devices have led to higher rates of healthcare-associated staphylococcal bacteremia, placing more patients at risk for IE [21]. Embolism is more likely to occur in IE caused by *S. Aureus* as compared to other organisms, 61% *vs*. 31% respectively [22]. During the course of his clinical stay, our patient was noted to develop embolic phenomena to his brain, lungs, feet and hands.

According to a series by Kim *et al*. who compared MVE to SVE, only congestive heart failure was found to be statistically more common in multi-valvular cases [3]. Another series by Lopez *et al*. found that multiple-valve disease was associated more frequently with heart failure, perivalvular complications and heart surgery; however in-hospital mortality was similar [5]. In addition, a series with a total of 90 patients undergoing valve surgery for IE found that multiple valve surgery was not an independent predictor of morbidity and mortality [4].

Surgical intervention in infective endocarditis commonly occurs. According to an International Collaboration on endocarditis studying 2781 adults with IE, surgical therapy was common, occurring in 48.2% of patients [23]. As delineated above, the number of valves involved is not an indication for surgical intervention. However, a series by Lopez *et al*. on 680 patients found that multiple-valve disease was associated more frequently with surgery, occurring in 70% of multiple valve endocarditis cases vs 54% in single valve IE cases [5]. In another series, 74% of patients with a contraindication to surgery died when compared with 16% with surgical treatment [24]. To this point, a series by Mihaljevic *et al*. on 63 patients with MVE showed that surgical treatment is associated with acceptable early and late mortality rates and excellent postoperative functional status, with early intervention prior to abscess formation providing the best chance for survival [25]. Given these findings, it may be reasonable, but premature, to infer that surgical intervention which is more commonly seen in MVE is the reason behind the relatively similar mortality rates in MVE compared to SVE.

There is evidence, though limited, that heart failure is more commonly associated with MVE [3, 5]. As shown in Table **1**, 67% of triple-valve endocarditis cases presented with or developed signs of acute heart failure; 90% of which underwent surgical intervention. Among all indications for surgical interventions, heart failure is the most crucial condition prompting intervention. The mortality rate of native valve endocarditis is 55-85% if heart failure is present in the case of medical treatment, and 10-35% if surgery is performed [8]. The high incidence of HF in MVE may thus be contributing to higher rates of surgical intervention in this group. This in turn, may be resulting in lower than expected mortality rates in a rather complex disease. At no point during our patient's hospital stay did he develop signs or symptoms concerning for heart failure. Across all four echocardiograms that the patient obtained, his left ventricular function was preserved and his hypoxic respiratory failure was related to ARDS secondary to underlying septic pulmonary emboli.

CONCLUSION

Triple-valve endocarditis is a rare occurrence that may pose a significant challenge to healthcare providers. Its rarity has precluded studies from providing insight into the incidence, management and outcomes of triple-valve disease; but it may be reasonable to extrapolate data from studies on endocarditis involving 2 or more valves. Despite available evidence showing comparable mortality trends between single and multi-valve disease, complications and

treatment options may be significantly different. A multidisciplinary approach may be necessary to tackle the systemic complications associated with this disease, and despite a higher rate of surgical intervention with favorable outcomes, optimal therapeutic management remains individualized to specific cases. No clear recommendations exist to best manage these complex patients and further research is necessary to explore and identify optimal management options.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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