



A-28-Years-Old Immunocompetent Man Having Post Prosthetic Aortic Valve Infective Endocarditis with Severe Aortic Regurgitation Due to Multi-Drug Resistant *Burkholderia Cepacia*: Lessons Learned

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Abstract

A-28-years-old immunocompetent man had prolonged fever for two months. He had prosthetic valve replacement to aortic valve and mitral valve repair (ring annuloplasty) for rheumatic mixed aortic and mitral valve disease (severe aortic regurgitation and mitral regurgitation); and, surgical closure to congenital ventricular septal defect 5 years ago. He was treated as infective endocarditis with ceftazidime and Piperacillin/ Tazobactam according to first blood culture and sensitivity which revealed *Acinetobacter* spp. For para-valvular leakage in aortic valve and failed medical treatment, previous prosthetic aortic valve was replaced again with mono-leaflet mechanical valve. Second blood culture revealed *Burkholderia cepacia*, resistance to all antibiotics (quinolone, cephalosporin, aminoglycosides, trimethoprim- sulphamethoxazole, tigecycline and colistin). Autopsy findings were reported.

Keywords: infective endocarditis; *Burkholderia cepacia*; prosthetic aortic valve; mitral valve repair; ventricular septal defect

Introduction

Infective endocarditis is a life-threatening microbial infection of native and prosthetic heart valves, endocardial surface, and/or indwelling cardiac device. Despite technological advances, the prevalence of infective endocarditis is increasing; and its mortality has not significantly improved.

Burkholderia cepacia is a rare cause of infective endocarditis. *Burkholderia cepacia* prosthetic valve endocarditis (PVE) is extremely rare, with few cases in the literature [1].

Case presentation

A-28-years-old man had prolonged fever for two months. He suffered central chest pain at the peak of fever; he also had dyspnea on exertion and palpitation. He had surgical aortic valve replacement (SAVR) (mechanical) for severe aortic regurgitation (rheumatic etiology); mitral valve repair (ring annuloplasty) for rheumatic mitral regurgitation; and, surgical closure to congenital ventricular septal defect 5 years ago. There was no history of orthopnea, paroxysmal nocturnal dyspnea and dyspnea at rest. There was no recent surgery or dental procedure. As his nasopharyngeal swab for SARS-CoV-2 was positive, he received remdesivir for 5 days.

He continued to have undue tachycardia and fever; temperature 101°F; tachycardia 106/minutes; blood pressure 110/60 mmHg; wide pulse pressure; SaO₂ 96% on air; apex beat displaced and heaving; and, early diastolic murmur was heard in the aortic area.

Transthoracic echocardiogram revealed severe aortic regurgitation, prosthetic aortic valve was functioning well; vegetation (0.5 x 0.9 cm) was found; para-valvular leakage was seen; and, LVEF was 66%. Blood culture done on Day '0' showed *Acinetobacter* spp; and sensitive to Ceftazidime, Cotrimazole, Piperacillin/ Tazobactam. Vigorous medical treatment was given according to blood culture report.

Regarding the progress of disease, temperature was swinging; the patient was unwell; and, serum creatinine was rising. Therefore, consultation with nephrologist was done; he suggested conservative management. Two sets of blood culture were repeated on Day '6' and Day '24'; and, they were sent to two separate microbiology laboratories. And both were sterile.

In view of refractory fever, para-valvular leakage of aortic prosthetic valve with vegetation, severe aortic regurgitation and

sterile culture, previous prosthetic aortic valve was replaced on Day '42'. The endothelial surface of aorta was normal. Valve dehiscence was found at NCC and RCC annular area measuring 30 % of the circumference. There was no vegetation over the previous prosthetic aortic valve. Old prosthetic valve was excised and removed. Calcified debris were removed too. Then, it was replaced with mono-leaflet mechanical valve (TTK Chitra 25 mm).

Hemodynamic status was stable during surgery as well as post-operative period. However, the patient continued to have fever with chills and rigors. Blood culture done on Day '46' showed *Burkholderia cepacia*, it was resistance to all antibiotics (quinolone, cephalosporin, aminoglycosides, trimethoprim-sulfamethoxazole trimethoprim- sulfamethoxazole, tigecycline and colistin. Blood cultures on Day '48' and Day '54' did not isolate organism.

Fever was swinging. One week after surgery, he had febrile fits; and, temperature was 104°F. He was managed with multidisciplinary team- cardiac surgeon, cardiologist, intensive care physician and neurologist. Non-contrast CT Head was normal. Blood biochemistry was normal.

Echocardiogram showed as follows: LVEF was 55%; left ventricular hypertrophy; moderate to severe mitral regurgitation; prosthetic aortic valve was functioning well; no leakage; no vegetation; and, no pericardial effusion.

Urine culture report Day '48' isolated *Candida Albican*; the duration of indwelling urinary catheter was only five days. Blood culture done on Day '57' showed growth of *Enterococcus* spp; they were sensitive to ampicillin and levofloxacin. Therefore, levofloxacin was added. In spite of all efforts, the patient was deteriorating; hemoglobin dropped. Two units of packed cell was transfused.

On Day '62', the patient suffered sudden onset of excruciating central chest pain, palpitation and dyspnea. It was followed by fit attack; and, he became unconscious suddenly. Advance cardiopulmonary resuscitation was done; nonetheless, the patient did not recover. The immediate cause of death was possibly due to ventricular tachyarrhythmia; it provoked non-coronary angina.

Autopsy revealed a large area of ecchymosis over pericardium as shown in photo (1) Figure 1; it was related with cardiopulmonary resuscitation. Photo (2) Figure 2 demonstrates mitral valve; no vegetation. Photo (3) Figure 3 shows intact aortic prosthetic valve. Autopsy of brain, kidneys and coronary ostia were normal.



Figure 1: Autopsy of heart revealing a large area of ecchymosis over pericardium.



Figure 2: Autopsy of left atrium showing mitral valve without vegetation.



Figure 3(a): Autopsy of aortic valve showing intact prosthetic valve.



Figure 3(b): Autopsy of aortic valve with intact prosthetic valve.

Discussion

Prosthetic valve endocarditis (PVE) is one type of infectious endocarditis (IE); it accounts for 20% of all cases of endocarditis. Epidemiology of the aortic PVE is different if the valve replacement was done surgically (surgical aortic valve replacement SAVR) or

transcatheter aortic valve replacement (TAVR). In SAVR, the rate of incidence of PVE is 6 per 1000 cases. The rate of PVE is higher in patients who had bioprosthetic SAVR than patients with mechanical SAV. This patient had SAVR (mechanical) five years ago and he had good immunity; one reason for case reporting Table 1.

Table 1:

Day (D)	D 0	D 6	D 24	D 42	D 43	D 44	D 45	D 46	D 47	D 48	D 50	D 54	D 60
Hb (gm%)	7.9	10.3	9.3	9.2	7.8	10.1	8	8.9	9.8	8.5	7.1	7.8	
Hct (35-50%)	23	31	26	28	22	29	23	24	27	19		22	
TWBC	11.3	8	6.3	5.6	7.5	10.4	7.9	8.9	14.2	8.6	7.1	5.3	
Neutrophil	85	77	71	82								83	
Platelet	148	268	144	137	41	87	93	105	89	180	130	102	
Urea (10-50)	39		43	134		107	132	89	50	55	70		70
Creatinine (0-1.3)	1.12		1.5	4.6		1.5	1.7	1.3	1.3	1.3	1.5		1.5
Na	136		129	132		149	149	130	129	130	129		
K	2.9		4.8	4.2		5.0	5.2	4.0	4.6	3.9	4.8		
Cl	95.7		96.1	93.4		111	110	91	93	95	95		
PT (12-16)	32.4												
INR	3.0	1.1						1.2	1.6	1.6	3.8	3.8	
Total Bilirubin (mg/dl)	0.6	0.8									1.0		
AST (<40 IU/L)	66	19											
ALT (<41 IU/L)	72	14		31.9			15.5	12.3			48		
Alk phos (40-103 IU/L)	103	92		203			118	92			232		
ESR (mm1st hr)		60	80										
CRP(<0.5mg/dl)	13		12		8.2								
Total protein (62-80g/l)		71		50			47	50.8			53		
Albumin (38-54g/l)		37		27.7			28.7	29.2			27		
Cholesterol 140-200mg/dl		189									125		
Uric acid (3.4-7mg/dl)		7.1											

It is important to get an early diagnosis and treatment in PVE. This patient came to hospital late; only after two months history of fever. It may be one reason for having complications and mortality. Both echocardiographic and intraoperative findings pointed out poorly functioning prosthetic mechanical aortic valve; para-valvular leakage in transthoracic echocardiogram and prosthetic mechanical aortic valve dehiscence occupying 30 % of the circumference in intraoperative findings. As the patient had surgery 5 years ago and he was doing well till 2 months prior to admission, aortic valve dysfunction might be related with infective endocarditis. If the patient came early, one week after onset of fever, his prosthetic valve would not be damaged.

In the diagnosis of infective endocarditis, positive blood cultures are crucial; demonstrating the presence of bacteria [2]. At least two positive blood cultures are mandatory; they must be taken within at least 12-hour interval. Furthermore, the microorganisms identified in the culture must be typically known to cause infective endocarditis. Infective endocarditis is an infection of the cardiac native or prosthetic valves commonly caused by *Staphylococcus aureus*, viridans streptococci group, and coagulase-negative staphylococci [3,4]. In this patient, blood culture done outside hospital on Day '0' showed *Acinetobacter* spp and sensitive to Ceftazidime, Cotrimazole, Piperacillin/ Tazobactam. Therefore, he was treated with Ceftazidime, and Piperacillin/ Tazobactam. This patient had serial blood culture; they did not grow common organism. In this patient, *Acinetobacter* spp was grown in Day '0'; *Enterococcus* spp was detected in Day '57'; and, *Burkholderia cepacia* was demonstrated in Day '46'. Infective endocarditis is typically caused by *Staphylococcus aureus*, viridans streptococci group, and coagulase-negative staphylococci. Staphylococci, streptococci, and enterococci bacterial species are estimated to account for ~80% of all cases [5]. It is another reason for case reporting a case of IE with unusual organism.

Risk factors for IE include congenital heart disease, structural and valvular heart disease, implantation of prosthetic heart valves, and intravenous drug abuse [6]. This patient had open cardiac surgery at 3 areas of heart 5 years ago: repair of ventricular septal defect, mitral valvuloplasty for rheumatic mitral regurgitation and aortic prosthetic valve replacement for severe aortic regurgitation. He recovered well in previous surgery; he only had fever 2 months prior to admission to hospital. There was limited report on patient who developed IE several years after repair for both congenital and acquired (valvular) heart disease. He had clinical evidence as well as echocardiographic evidence of IE. This is another reason for sharing experience.

The blood culture was sterile on two different timing in this patient; Day '6' and Day '24'. According to Brouqui & Raoult, the chances of false negative blood culture results ranges from 2.5 to 31% [7]. False negative test results may be due to the followings: (1) use of antibiotic therapy prior to blood sample collection; (2) bacteria that are difficult to culture like *Coxiella Burnetii*; (3) fungal infective endocarditis [8]. Negative blood cultures are found

in approximately 24% of all cases of infective endocarditis; that of prosthetic valve endocarditis is 23% [9,10]. Therefore, having negative blood culture in this patient in Day '6' and Day '24' may be due to the use of antibiotic therapy prior to blood sample collection. We should have done serological testing [2] and tissue cultures during cardiac surgery in this case.

Clinically the patient was having fever, undue tachycardia, unexplained anemia and rising creatinine although his blood culture was sterile. Then, the treating team decided to remove and replace poorly functioning prosthetic valve with vegetation. Therefore, clinical parameters are paramount important in assessing the response to treatment in infective endocarditis. This is the lesson we would like to share.

In this patient, blood culture was done 5 times within hospital stay (62 days). Among them, blood culture was positive in 3 different sets done at Day'0', Day'46' and Day'57'. The organisms were as follows: *Acinetobacter* spp in Day '0'; *Enterococcus* spp in Day '57'; and, *Burkholderia cepacia* in Day '46'. *Burkholderia cepacia* is known to be multi-drug resistant bugs; and, is rarely found in infective endocarditis. However, *Burkholderia cepacia* prosthetic valve endocarditis in a 38-year-old man with poor dentition and a history of intravenous drug use and mitral valve replacement was reported [11,12]. Moreover, *Burkholderia cepacia*-induced native valve endocarditis in patient without any predisposing factors was mentioned in rare reports [13,14]. In addition, Falcão Pedrosa Costa et al described *Burkholderia cepacia*-induced infective endocarditis in a renal transplant patient; it was associated with an intracardiac fragment of a catheter inserted 16 years before [15]. This patient had IE due to multi-drug resistant *Burkholderia cepacia* [16-19]; anti-microbial resistant lead to fatal sequelae. It was reported that endocarditis due to *Burkholderia cepacia* was rare but serious, leading to valve dysfunction and heart failure [19].

Another point to discussed is that 'Is Redo prosthetic aortic valve indicated?'. Early surgical intervention for PVE is indicated if the patient develops heart failure due to valve dehiscence, the development of intracardiac fistula, or the presence of severe prosthetic valve dysfunction. Therefore, 'Redo' prosthetic aortic valve was not wrong. The patient's hemodynamic status was stable during and immediately after cardiac surgery.

Two sets of blood cultures on different days, Day '6' and Day '24', at two different laboratories were sterile. Nonetheless, the patient was not responding clinically; fever was swinging; undue tachycardia persisted; anemia increasing. Therefore, the prosthetic aortic valve was replaced again with mono-leaflet mechanical valve on Day '42'. The blood culture on Day '46' showed *Burkholderia cepacia*; it was resistance to all antibiotics (quinolone, cephalosporin, aminoglycosides, trimethoprim- sulfamethoxazole, tigecycline and colistin). Although blood cultures on Day '48' & Day '54' were sterile, the clinical condition was deteriorating. Day '57' blood culture result was *Enterococcus* spp and sensitive to Ampicillin and Levofloxacin; they had been given previously. It can be concluded that this patient had unusual microorganisms like

Acinetobacter spp, Burkholderia cepacia and Enterococcus spp; Burkholderia cepacia was multi-drug resistant.

Conclusion

Prosthetic valve endocarditis is a catastrophic complication of cardiac valve replacement and is associated with high mortality rates. It is important to achieve an early diagnosis and initiate the treatment as early as possible. Early referral to tertiary center is important. Blood culture as well as serological testing for PCR should be encouraged. Infective endocarditis caused by multidrug resistant organism like Burkholderia cepacia is potentially fatal.

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Declaration of conflict of interest

The authors declared no potential conflicts of interests with respect to authorship and publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting cases.

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