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**Case Report**

# Recurrent Prosthetic Paravalvular Leakage in Culture-negative Endocarditis Caused by *mycoplasma hominis*: A Case Report

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**Abstract:** Background: Culture-negative endocarditis in patients with previous prosthetic valve replacement is a challenging disease with high mortality and poor outcomes. Recurrent paravalvular leakage is a common complication in patients with prosthetic valve but is rarely realized to endocarditis. Objectives: To report a diagnostic strategy for culture-negative endocarditis caused by atypical pathogen in patients with previous prosthetic valve replacement. Patients and Methods: We present a case report about recurrent prosthetic valvular leakage with preoperatively unknown cause. Traditional clinical laboratory for pathogen detection and echocardiography were routinely performed. The patient received aortic and mitral valve replacement and tricuspid annuloplasty. Metagenomic next-generation sequence tests on removal tissue and blood are performed. Results: Preoperative imaging finding of vegetation and blood culture was negative. Metagenomic next-generation sequence tests on resected valve tissue and blood specimens revealed 236 and 154 unique read-pairs aligning to *mycoplasma hominis*, respectively. Retrospective serological immunofluorescence assay revealed cross-reaction to *mycoplasma pneumonia*. Haematoxylin-eosin-stained histological section of the mobile vegetation attached to the mitral mechanism prosthesis demonstrated hyalinization in intercellular substance and infiltration of neutrophils, lymphocytes, and plasmocytes, which indicated chronic infective endocarditis. Culture-negative endocarditis were diagnosed by multidisciplinary team. Azithromycin was selected for anti-*mycoplasma hominis*. The patient made an excellent recovery and repeat transthoracic echocardiography performed at discharge demonstrated a good prosthetic valve function. Conclusion: Culture-negative endocarditis may be a criminal in cryptogenic paravalvular leakage. A multiple-image-technique strategy combined with metagenomic next-generation sequence to patients with recurrent paravalvular leakage are recommended for early diagnosis ant timely antibiotic administration for potential endocarditis.

**Keywords:** Culture-negative Endocarditis, Recurrent Prosthetic Paravalvular Leakage, *mycoplasma hominis*

# 1. Introduction

### *1.1. Learning Points*

Endocarditis is a potential etiology in patients with recurrent prosthetic paravalvular leakage even if the blood culture and imageological examination is negative.

While echocardiography is the main examination for endocarditis, multiple imageological techniques should be considered for further endocarditis identification if the patients are still high suspicious of endocarditis.

Metagenomic next-generation sequencing test should be considered for endocarditis diagnosis and etiological identification, especially performed on the removal prosthetic valve tissue.

### *1.2. Introduction of Prosthetic Valve Replacement*

Prosthetic valve replacement has a long history for valve disease treatment and is increasing in recent years with low morbidity and mortality [1, 2]. Nevertheless, the advanced technique has been in dilemma due to a few but severe complications, particularly the prosthetic valve endocarditis (PVE) with increasing frequency and poor outcome [3, 4]. PVE is the most severe complication of cardiac valve replacement, with a reported incidence of 0.3-1.2% per patient-year, corresponding to 3-6% of all patients receiving a prosthetic valve with 5 years of implantation [5]. Acute prosthetic material decline and paravalvular leakage are common in PVE. Culture-negative endocarditis accounting for about 41% of PVE [3], especially after 1 year of surgery, not only presents a challenging diagnosis of endocarditis [6], but also worsens the prognosis due to absent or delayed sensitive antibiotics therapy.

# 2. Case Description

### *2.1. Timeline*

Initial presentation Complaint for 3-year history of cardiopalmus and presented abdominal distension and hematuresis for 10 days.

Day 4 Transthoracic echocardiography (TTE) demonstrated severe paravalvular regurgitation without sign of vegetation or abscess. Left ventricular ejection fraction was 60%.

Day 5 Enhance-contrast thoracic computed tomography revealed left pneumonia and mediastinal lymphadenectasis.

Day 6 Three sets of blood culture were performed.

Day 8 Started on intravenous Levofloxacin 500 mg qd for suspicion of urinary tract infection.

Day 11 Transesophageal echocardiography revealed severe paravalvular regurgitation. Sign of vegetation or abscess were still absent. Erythrocyte osmotic fragility test direct and indirect Coombs' tests were negative. Levels of erythrocyte CD 55 and CD 59 had no significant decrease.

Day 12 Negative blood cultures were reported.

Day 13 Levofloxacin therapy end.

Day 21 Attempt to transcatheter closure for paravalvular leakage failed.

Day 22 Coronary angiography demonstrated no coronary stenosis.

Day 28 Referred for surgical intervention. Started on combination of intravenous Vancomycin 500 mg q8h, and intravenous Imipenem and cilastatin sodium 500 mg q6h.

Day 29 Metagenomic next-generation sequence tests on excised valve tissue and blood specimens revealed *mycoplasma hominis* infection.

Day 33 Started on intravenous Azithromycin 500 mg qd.

Day 47 Discharged from tertiary hospital and transferred to local hospital for antibiotic administration.

One-month Postoperative TTE showed a well-seated prosthetic tissue valve.

### *2.2. Case Description*

In June 2021, a 53-year-old male complained a 3-year history of cardiopalmus and presented abdominal distension and hematuresis for 10 days. The patient was a non-smoker without history of drug abuse, previous fever, recent invasive procedure or dental intervention. Additional medical histories included aortic and mitral mechanism valve replacement in 2010 and mitral repair for paravalvular leakage in 2014. Physical examination only revealed cardiac murmurs. Suspicious of urinary tract infection, levofloxacin therapy started following blood culture.

Laboratory tests revealed slightly elevated inflammation markers (procalcitonin 0.41ng/mL). Three sets of blood cultures were negative. Urinalysis revealed elevated both red blood cells and white blood cells, especially for the fragmented red blood cells. Direct and indirect Coombs' tests were negative as well as erythrocyte osmotic fragility test. Levels of erythrocyte CD 55 and CD 59 had no significant decrease. Peripheral blood smear revealed both increasing in neutrophilic myelocytes and metamyelocytes. Estimated glomerular filtration rate was 35%. The ambulatory electrocardiogram demonstrated atrial fibrillation complicated with long ventricular interval. Enhance-contrast thoracic computed tomography revealed left pneumonia and mediastinal lymphadenectasis. Preoperative TTE and repeat transeophageal echocardiography (TEE) both revealed severe mitral paravalvular regurgitation. Color doppler flow imaging demonstrated 14.5 $cm^2$ regurgitation on mitral valve. No imaging finding of vegetation or abscess were detected. Coronary angiography found no stenosis on coronary.

Attempt to transcatheter closure for paravalvular leakage failed. In view of progressive heart failure and persistent hematuresis, the patient received aortic and mitral valve replacement with mechanism valve and tricuspid annuloplasty. Macroscopic signs of vegetation on mitral mechanism valve and mass of pannus on aortic valve were detected during the surgery. Metagenomic next-generation sequence tests on resected valve tissue and blood specimens revealed 236 and 154 unique read-pairs aligning to *mycoplasma hominis*, respectively. Retrospective serological immunofluorescence assay revealed cross-reaction to *mycoplasma pneumonia*. Haematoxylin-eosin-stained histological section of the mobile vegetation attached to the mitral mechanism prosthesis

demonstrated hyalinization in intercellular substance and infiltration of neutrophils, lymphocytes, and plasmocytes, which indicated chronic infective endocarditis. (Figure 1).

Agnogenic recurrent prosthetic paravalvular leakage is a diagnostic challenging disease. Endocarditis should raise physicians and cardiovascular surgeons' caution even if the blood culture and echocardiography examination are negative. Metagenomic next-generation sequencing is a sensitive technique for etiological identification in endocarditis, especially in culture-negative form. Besides, mycoplasma hominis is a rare pathogen in endocarditis and is worth case report.

Intravenous antibiotic combination of vancomycin and imipenem and cilastatin sodium was selected as postoperative antibiotic prophylaxis at first. And azithromycin was selected for anti-*mycoplasma hominis*. The patient made an excellent recovery and repeat TTE performed at discharge demonstrated a good prosthetic valve function. Azithromycin continued for 6 months at least.

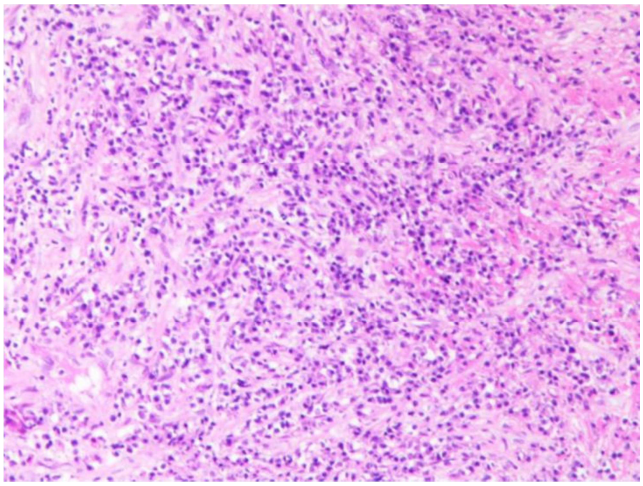

***Figure 1.*** *Haematoxylin-eosin-stained histological section of the mobile vegetation attached to the mitral mechanism prosthesis demonstrated hyalinization in intercellular substance and infiltration of neutrophils, lymphocytes, and plasmocytes.*

# 3. Discussion

PVE, a predisposing condition in the increasing numbers of patients with valve replacement, is the most severe form of infective endocarditis [7]. The incidence of PVE is 6.0/1000 per patient-years in patients prior to prosthetic valve replacement [8]. PVE, especially for culture-negative form, is a significantly potential cause for recurrent paravalvular leakage, frequently resulting in acute prosthetic material decline and worsen outcome due to absent or delayed effective antibiotics [9].

Acute heart failure, acute renal failure, arrhythmias and conduction disturbances are the common symptoms of PVE [10] which are all reflected on this reported case. Hospital mortality of PVE is reported at 19.2%, of which cardiac cause, sepsis, multi-organ failure are the common death causes [11]. Identified risk factors for early PVE are mechanism valve and active phase of disease such as previous endocarditis without antibiotics treatment. Late PVE is lower in mechanism valve but higher in bioprostheses. Indeed, the time from valve replacement surgery to PVE and prosthetic material is not important, but the mode of acquisition and microorganism involved [10]. A greater exposure to healthcare contact and lack of complete endothelization are easier to cause early prosthetic material infection. Late PVE is commonly caused by the prosthesis seeding during a transient bacteremia originating at a distant infected focus [11]. Negative blood cultures are more frequent in late PVE due to previous antibiotics therapy or fastidious bacteria such as *Coxiella burnetii*, *Bartonella* and *mycoplasma* [12]. Hence, serial cardiac examinations should be taken in patients suspicious of PVE and further pathogen identification should be performed if the cultures are negative.

Diagnosing PVE can be challenging due to the prosthetic valve impeding identification of vegetations and abscesses [6]. Repeat TTE/TEE and multiple imagine techniques should be performed in patients suspected with PVE. Even in the absence of echocardiographic findings of vegetation or abscess, PVE must be always considered in patients with new periprosthetic regurgitation, particularly the recurrent condition. Coronary angiography and intracranial arterial angiography help detect endocarditis and intracranial complication. Given the diagnostic difficulties in TEEs in PVE, especially transcatheter aortic valve replacement, $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) has been utilized as a diagnostic examination for PVE [6, 13, 14]. The European Society of Cardiology recommend “routine” $^{18}$FDG-PET-CT in patients highly suspected of PVE in view of its potential for identification [15]. Here, we present a figure demonstrating different degrees of focal $^{18}$FDG uptake around the aortic prosthetic valves in another patient with culture-negative PVE caused by *Enterococcus faecalis,* which was detected by metagenomic next-genneration sequence. (Figure 2).

Previous antibiotics treatment and increasing numbers of unusual and fastidious pathogens, such as *C. burnetii*, *Bartonella* and *mycobacterium chimaera* have result in an increasing frequency of culture-negative endocarditis in PVE (27-41%) [8]. Limitation of conventional pathogenic examination may miss diagnosis in patients with agnogenic recurrent paravalvular leakage, resulting in absent or delayed effective antibiotics therapy and acute prosthetic dehiscence with native annulus. Serological examination using immunofluorescence assays titer of $\geq$ 1:800 for *C. burnetii* anti-phase I and *Bartonella* are recommended. However, cross-reaction between *C. burnetii*, *Bartonella* and *Chlamydia* may provide miss etiological information to clinicians [16]. Of note, serological tests may be false negative in patients with impaired immunity, which is a high risk for endocarditis. Thus, we performed mNGS test on this patient for broad-range bacteria identification and unique read-pairs aligning to *mycobacterium chimaera* was detected both on resected valve tissue and blood specimen. In view of sample contamination and long-term persistence of past bacterial DNA, caution

should be exercised when interpreting mNGS result with the full clinical context and correlated with all other laboratory.

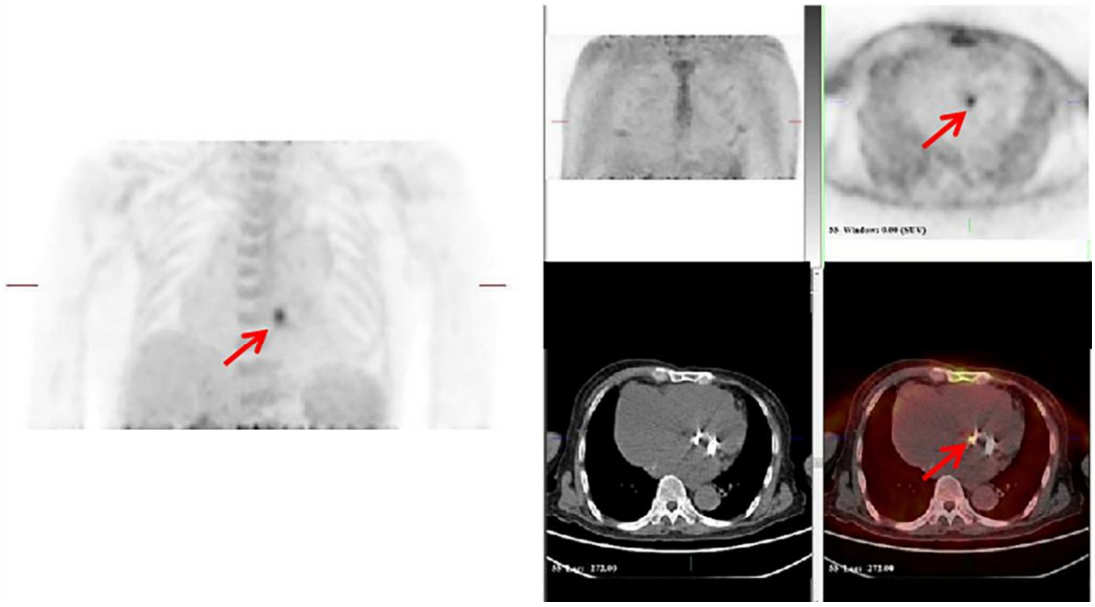

***Figure 2.*** *Different degrees of focal $^{18}$FDG uptake around the aortic prosthetic valves in another patient with culture-negative PVE caused by Enterococcus faecalis, which was detected by metagenomic next-genneration sequence.*

## 4. Conclusion

Here, we describe a PVE case with recurrent prosthetic leakage caused by *mycoplasma hominis*, a rare and fastidious microorganism for which conventional examination cannot diagnose and identify. While TTE or TEE are negtive for endocarditis detection, multiple imageological techniques should be considered for further endocarditis identification if the patients are still high suspicious of endocarditis. Metagenomic next-generation sequence performed on blood and specially directly on vegetation or removal valve tissue is recommended in these patients to identify or exclude endocarditis.

## Conflict of Interest Statement

All the authors do not have any possible conflicts of interest.

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