

# Haemolytic Anemia due to Paravalvular Leak Following Mitral and Aortic Valves Replacement

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## Abstract

**Background:** Paravalvular leak (PVL) can complicate mitral and aortic valves replacement. Most PVLs are often clinically insignificant. However, large leaks can lead to heart failure and infective endocarditis. Intravascular hemolytic anemia is common in small PVLs. Reoperation for closure of PVL is associated with high mortality. Transcatheter closure is less invasive and can be used in high-risk patients.

**Case summary:** We present a case of a 38-year-old man with a history of Aortic Valve replacement (AVR) and Mitral valve replacement (MVR) who developed hemolytic anemia and haemoglobinuria. The patient was managed initially conservatively but later underwent redo valve surgery after exclusion of other causes of hemolytic anemia. Postoperatively, haemoglobinuria disappeared dramatically whereas anemia resolved gradually after surgery.

**Discussion:** Significant intravascular hemolysis is a rare but serious complication of PVL that poses diagnostic problem to cardiac surgeons, but also for cardiologists and internal medicine professionals especially when the prosthetic valve function is considered adequate. PVL is the flow of blood through a track between the native cardiac tissue and the implanted valve due to any compromise in closure between the two. PVL is also more frequently seen after mitral (up to 20%) valve replacement than aortic prosthetic valves. PVLs are more frequently diagnosed by Transesophageal echocardiography (TEE) than Transthoracic echocardiography (TTE) due to its ability to detect minute jets of regurgitated blood.

**Conclusion:** Either repair or re-replacement of prosthetic valves with PVLs is needed in about 1% to 5% of patients. The case study is presented to highlight PVL as a rare cause of haemoglobinuria and hemolytic anemia.

**Keywords:** Paravalvular leak; Hemolytic anemia; Haemoglobinuria; Aortic valve replacement; Mitral valve repair; Regurgitated jet; Heart failure

## Introduction

Paravalvular leak (PVL) is an alarming complication after placement of cardiac valves. PVL is seen in 2% to 17% following mitral and aortic valves replacement [1-3]. It can lead to haemolysis or heart failure or both and 3% of such patients have to be reoperated to close PVL [4-6]. Hemolytic anemia is exceedingly rare complication after aortic valve replacement (AVR) and is often underestimated. Regurgitated blood flow or jet from the paravalvular leak or subvalvular stenosis is the underlying mechanism responsible for hemolysis. Intravascular hemolysis appears to be independent of the severity of PVL as assessed by echocardiography [7]. The standard therapy for these PVL is its surgical closure or valve re-replacement. However, there is high morbidity and mortality rates after redo surgery with high risk of leak recurrence [1-6,8].

## Case Presentation

A young watchman of 35-year-old of poor socioeconomic class presented with two weeks history of shortness of breath, palpitations and fatigue in emergency department of a tertiary care cardiac hospital in Rawalpindi, Pakistan on April 4, 2017.

He had past history of heart murmur detected in 1999 during medical examination for recruitment as a soldier in Army. He also had Percutaneous Transcatheter Mitral Commissurotomy (PTMC) performed in 2011 in a tertiary care hospital in Peshawar, Pakistan. He was diagnosed last year with Pulmonary tuberculosis for which he had completed 6 months triple drug Antituberculosis treatment.

His echocardiography on admission in RIC confirmed severe mitral and severe aortic regurgitation. He was operated for Double

Valve Replacement (DVR) with bileaflet St Jude mechanical aortic and mitral valves on April 14<sup>th</sup>, 2017 in RIC by open heart surgery. He was discharged from hospital on April 21<sup>st</sup>, 2017. He presented again on August 1<sup>st</sup>, 2017 and was readmitted for haematuria and anemia (Hb of 4.4 g/dl). The case was discussed with cardiac surgeon who suggested to exclude other etiologies that might explain the patient's condition. He was managed conservatively and transfused three pints of blood. He was investigated for anemia and red discoloration of urine. His peripheral blood film showed normochromic normocytic blood picture with red cell fragmentation. Erythrocytic sedimentation rate (ESR) was 10 mm fall/hour. Complement reactive protein (CRP) was 3 mg/l. Serum Prothrombin, Activated Partial Thromboplastin Time (APTT) and International normalized ratios (INR) were 12.0, 25.7 and 2.31 respectively. Serum cholesterol and triglycerides were 159 mg/dl and 271 mg/dl respectively. His liver function tests showed serum Bilirubin 1.3 mg/dl. Alanine Aminotransferase (ALT) 35 U/l and serum Alkaline Phosphatase 140 U/l. His Lactic dehydrogenase was 2662 U/l. He was investigated for hemolytic anemia due to presence of schistocytes in peripheral blood smear. Serum haptoglobin levels of less than 0.5 g/l (normal 0.5-3.2.) Antineutrophil Antibody (ANA) and

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Coomb's tests were negative. Serum complement levels were normal. Glucose 6 phosphate dehydrogenase (G6PD) and Paroxysmal Nocturnal Haemoglobinuria (PNH) work up were negative. Folic acid and vitamin B12 were within normal limits. Ultrasound abdomen showed grade I renal parenchymal changes. His urine Routine Examination (RE) showed protienurea, 8-10 pus cells and RBC casts. Urine culture did not yield any growth. Cystoscopy was normal. Urologist consultation ruled out any urological pathology. Mantoux test was positive with 15 mm induration. Urine and Sputum microscopy for acid fast bacilli were negative. Gene Xpert MTB/Rif Assay for *Mycobacterium tuberculosis* were negative. Ultrasound abdomen revealed congested liver with multiple gall stones, grade I renal parenchymal changes. Computed Tomography (CT) chest and abdomen were unremarkable. He had to be transfused once a week with 1-2 pints/week. Repeat Transthoracic Echocardiography and Transoesophageal Echocardiography showed normal functioning mechanical mitral and aortic valves with normal disc excursions. Mean pressure gradient (MPG) at mitral and aortic valves were 5 mmHg and 18 mm Hg respectively. There was a mild leak at mitral valve and moderate paraprosthetic leak from aortic valve. There was no clot or pericardial effusion (Videos 1 and 2) (Table 1). His Aortography revealed normal coronaries and aorta with mild to moderate paravalvular leaks. It was planned to redo surgery with new bioprosthetic mitral and Aortic valves. Post operatively his urine routine examination was normal. Echocardiography showed intact prosthetic mitral and aortic valves with no perivalvular leak (Video 3). Transthoracic echocardiography did not reveal any abnormality except for the replaced prosthetic mitral and aortic valves in place. Informed consent was taken from patient for case presentation.

Discussion


Haematuria is a common symptom with several differentials in its diagnosis. Often it is difficult to diagnose its exact etiology and needs detailed work up [9]. Red discolouration of urine and haematuria are

Time	Events
Past History 1999 and 2011	Patient had past history of heart murmur detected in 1999 during medical examination for recruitment as a soldier in Army. He also had Percutaneous Transmitral commissurotomy (PTMC) performed in 2011 in a tertiary care hospital in Peshawar, Pakistan.
Present presentation (Day 1)	Shortness of breath, palpitations and fatigue for 2 wk in emergency department of a tertiary care cardiac hospital in Rawalpindi Institute of Cardiology, Rawalpindi, Pakistan on April 4 <sup>th</sup> 2017. His Echocardiography on admission in RIC confirmed severe Mitral and severe Aortic regurgitation
14 <sup>th</sup> day of admission	He was operated for Double Valve Replacement (DVR) with bileaflet St Jude mechanical prosthetic valve on April 20 <sup>th</sup> , 2017 in RIC by open heart surgery
27 <sup>th</sup> day (3 <sup>rd</sup> wk) of admission	He was discharged from hospital on April 31 <sup>st</sup> , 2017.
102 <sup>nd</sup> post op day/ 12 <sup>th</sup> post op wk	Readmitted with haematuria and anaemia (Hb of 4.4g/ dl). Cardiac surgeon advised conservative management and work up to exclude other causes of haematuria as an outpatient.
Follow-up in OPD in next 2 wk	Investigated for anaemia and red discolouration of urine. His peripheral blood film showed normocytic normochromic blood picture with red cell fragmentation. Ultrasound abdomen showed grade I renal parenchymal changes. His urine Routine Examination (RE) showed protienurea, 8-10 pus cells and RBC casts. Urine culture did not yield any growth. Cystoscopy was normal. Urologist consultation ruled out any urological pathology. Ultrasound abdomen revealed congested liver with multiple gall stones, grade I renal parenchymal changes. Computed Tomography (CT) chest and abdomen were unremarkable.
Outpatient clinic (16 <sup>th</sup> post op wk)	Transthoracic echocardiography, transoesophageal echocardiography and aortogram confirmed a mild leak at mitral valve and moderate paraprosthetic leak from mechanical aortic valve.
17 <sup>th</sup> wk	Redo surgery with replacement of mechanical mitral and aortic valves with bioprosthetic prosthetic valves. Post operatively, his urine routine examination was normal. Transthoracic Echocardiography showed intact prosthetic mitral and aortic valves with no perivalvular leak.


**Table 1:** Paravalvular leak (PVL) as a rare cause of mitral and aortic valves replacement and is associated with high mortality.



**Video 1:** Transthoracic Echo apical 5 chamber view showing aortic & mitral bileaflet type mechanical valve in situ with a significant paravalvular leak from aorta to left ventricle through aortic prosthesis sewing ring.



**Video 2:** Trans esophageal Echo at mid Esophageal level showing Aortic prosthesis in short axis which shows clearly abnormal flow outside the sewing ring causing regurgitation from aorta to left ventricle evident from one to 3 O Clock position.



**Video 3:** Apical 5 chamber view showing normal leaflet excursion and no paravalvular leak.

alarming not only for patients but also concerning for the physician to carry out thorough investigation. The most common cause of haematuria is urinary tract infection [10]. Our patient developed red discolouration of urine postoperatively in a week. Microscopic examination showed granular casts, 6-8 pus cells/HPF and occasional red cell. Routine urine culture and for *Mycobacterium tuberculosis* did not yield any growth. Urine for *Mycobacterium tuberculosis* PCR was also negative.

Ureteric and renal stones often present with pain and microscopic haematuria [9]. Ultrasound abdomen of our patient did not show any abnormality except for grade I renal parenchymal changes. CT chest and abdomen was unremarkable. The prevalence of haematuria in

anticoagulated patients within the therapeutic range is similar to those without anticoagulants [11,12]. Serum Prothrombin (PT), Activated Partial Thromboplastin Time (APTT) and International normalized ratio (INR) in our patient were 12.0, 25.7 and 2.31 respectively.

The prevalence of urinary tract carcinomas among patients with macroscopic haematuria usually ranges from 3% to 6%. Ultrasound abdomen, Computed Tomography (CT) abdomen and Cystoscopy were unremarkable in our patient. Despite extensive investigation, no cause can be identified in up to 50% of patients with macroscopic haematuria and 70% with microscopic haematuria [13].

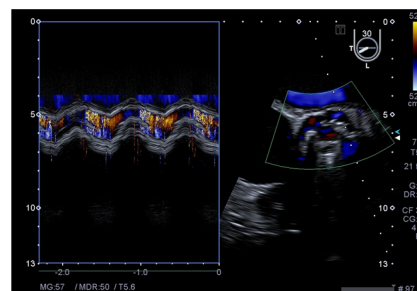
With a rare number of complicated with PVL, significant intravascular hemolysis is a cause of major concern, not only for cardiac surgeons, but also for cardiologists, haematologists and internal medicine professionals, even when the prosthetic valve function is considered adequate [7].

Replacement of native valves with prosthetic heart valve either surgically or by transcatheter (TAVI) approach can be complicated by paravalvular or paraprosthetic leak (PVL) [14]. PVL is the flow of blood through a track between the native cardiac tissue and the implanted valve due to any compromise in closure between the two. PVL can vary in shape, size and tract. It can be crescentic, oval or round shaped and can have parallel, perpendicular or serpiginous track. It is more commonly seen in mechanical valves than in bioprosthetic valves. Our patient developed PVL after placement of aortic and mitral mechanical valves. PVL has been reported including small non-significant jets to 20% of regurgitated blood. PVL is also more frequently seen after mitral (up to 20%) valve replacement than aortic prosthetic valves. There was a mild leak at mitral valve and moderate paraprosthetic leak from mechanical aortic valve in our patient. Transthoracic Echo apical 5 chamber view showed aortic and mitral bileaflet type mechanical valve *in situ* with a significant paravalvular leak from aorta to left ventricle through aortic prosthesis sewing ring (Video 1).

PVLs are more frequently reported in studies using TEE than Transthoracic echocardiography (TTE) due to its ability to detect minute jets of regurgitated blood. Preoperatively, TEE at mid Esophageal level of our patient shows aortic prosthesis in short axis with clearly abnormal flow outside the sewing ring causing regurgitation from aorta to left ventricle evident from one to 3 O Clock position (Video 2) Transesophageal Echo at mid oesophageal level along with M mode showing aortic mechanical valve *in situ* with significant leak above the mechanical valve disc clearly shown in M mode and 2 D mode from 1 to 3 o'clock position (Figure 1).

Either repair or re-replacement of prosthetic valves with PVLs is needed in about 1% to 5% of patients [15-18]. Chronic paravalvular mitral and aortic regurgitation if untreated can lead to heart failure due to left ventricular (LV), left atrial (LA) volume and pressure overload. Secondary elevation in pulmonary arterial pressure may result in right-sided heart failure. Paravalvular regurgitation causes turbulent flow through the valvular defect and mechanical trauma increases red blood cell steering stress. Red cell fragmentation often leads to hemolytic anemia in patients with prosthetic heart valves. Clinically significant intravascular hemolysis is more common in high-velocity jets through smaller PVL especially in iron and folate deficient patients [19,20].

A detailed transesophageal echocardiogram (TEE) is often necessary for a definitive diagnosis, to exclude LA thrombus, evaluate prosthetic function, characterize the severity of regurgitation, and to accurately localize the defect Aortic paravalvular defects are often best visualized using transthoracic echocardiography or intracardiac



**Figure 1:** Transesophageal Echo at mid oesophageal level along with M mode showing aortic mechanical valve *in situ* with significant leak above the mechanical valve disc clearly shown in M mode and 2 D mode from 1 to 3 O'clock position.



**Video 4:** Parasternal long axis view showing biprosthetic mitral valve with normal leaflet excursion.

echocardiography given the more anterior location of the aortic valve. In contrast, TEE is especially useful for evaluation of mitral paravalvular defects and their closure and in posterior aortic defects. Strong Doppler color flow signals in relatively small LV outflow tract that may lead to overestimation whereas acoustic shadowing may lead to underestimation of paravalvular aortic regurgitation [21].

Transthoracic echocardiography and transesophageal echocardiography of our patient showed mild leak at mitral valve and moderate paraprosthetic leak from mechanical aortic valve. There was no clot or pericardial effusion. Aortography revealed normal coronaries and aorta with mild to moderate paravalvular leaks.

Although medical therapy can improve symptoms, heart failure due to volume and pressure overload and need for repeated blood transfusions requires closure of the defect [21]. Our patient had to be transfused several times during the course of investigations and conservative management. Postoperatively, there was no regurgitation/perivalvular leak. Apical 5 chamber view shows normal leaflet excursion and no paravalvular leak (Video 3). Parasternal long axis view shows biprosthetic mitral valve with normal leaflet excursion (Video 4).

His urine became clear dramatically and hemoglobin maintained without transfusions. PVLs that cannot be managed conservatively can be treated either surgically or using the transcatheter deployment of the occluder devices (plugs) [14]. Moderate to severe paravalvular leak (PVL) after both surgical and transcatheter aortic valve replacement is associated with increased mortality [19,20]. Reoperation is first-choice procedure when PVL when there is significant dysfunction, mechanical instability of the prosthetic valve and growth of large vegetation that may need redo surgery. Registries showed that surgery reduced mortality from 12% to 26% in comparison to conservative management [22]. However, the operative risk is quite high and long-term follow-up in these patients is often complicated by recurrent leak and increased mortality [15-17].

Recently, transcatheter closure of PVL has emerged as a new treatment strategy that can be offered to patients with isolated PVL or to those with a very high risk of repeat surgery [23]. Transcatheter approach involves deployment of occluder devices or coils and adopting either a percutaneous or a transapical approach.

## Conclusion

PVL is a significant cause of intravascular hemolysis leading to hemolytic anemia. The condition can lead to diagnostic problem and requires a multidisciplinary approach for its diagnosis and treatment. PVL closure is standard of treatment and requires team work. Successful PVL closure not only corrects valvular regurgitation but also intravascular hemolysis.

## Author Contributions

Ali AM was involved as the main author with actively engaged in laboratory work up of patient and in compilation of data and writing of this piece. Ali M and Kiyani AM were lead consultants of the patient involved in the management of the case. Hussain B reviewed the write up.

## Conflict of Interest

None declared.

## Competing Interest

Nil

## Funding

Nil

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