

Case report

Haemolytic anaemia after mitral valve repair due to recurrent mild to moderate mitral regurgitation

Anna Björkenheim,¹ Soon-Ok Cha,² Irina Dioubanova³¹Department of Cardiology, School of Medical Sciences Campus USÖ, Örebro, Sweden²Department of Cardiothoracic and Vascular Surgery, School of Medical Sciences Campus USÖ, Örebro, Sweden³Department of Clinical Physiology, School of Medical Sciences Campus USÖ, Örebro, Sweden**Correspondence to**Dr Anna Björkenheim, anna.bjorkenheim@regionorebrolan.se

Accepted 4 August 2019

SUMMARY

A 52-year-old man underwent mitral valve repair for mitral regurgitation. Four months postoperatively, the patient developed dyspnoea, fatigue and dark urine. He presented to his primary care physician 6 months postoperatively, where an evaluation revealed anaemia and mild renal failure. The haemoglobinuria was misdiagnosed as gross haematuria and the patient consequently underwent several unnecessary invasive urological exams. A transthoracic echocardiogram showed a recurrent mitral regurgitation that was considered non-significant, before performing additional laboratory testing and a renewed echocardiogram. The above results showed evidence of haemolysis and a mild to moderate mitral regurgitation, although with a high velocity jet. The patient was diagnosed with haemolytic anaemia that necessitated blood transfusions and a reoperation with a mechanical valve, after which the patient made a full recovery. Importantly, it was mainly the velocity of the jet and not the severity of the mitral regurgitation that caused the mechanical trauma to red blood cells.

BACKGROUND

Subclinical haemolysis is common in patients with prosthetic heart valves.^{1 2} Haemolysis leading to anaemia is considerably less prevalent (less than 1%), especially in patients with modern valves, and is more frequently seen in patients with mechanical valves than in those with bioprosthetic valves.^{1 2} Although rare, haemolytic anaemia can occur even after mitral valve repair.³ Haemolytic anaemia after mitral valve repair is a serious complication that is difficult to manage medically and therefore usually requires mitral valve replacement.¹ However, as haemolytic anaemia is associated mainly with prosthetic valves, the diagnosis can be overlooked in patients who have undergone mitral valve repair, especially in patients in whom the recurrent mitral regurgitation is mild.

Here we describe a patient with previous mitral valve repair, in whom haemoglobinuria was misdiagnosed as gross haematuria. This then subjected the patient to unnecessary invasive urological exams; further, the recurrent mitral regurgitation was considered not significant. Both delayed the correct diagnosis of haemolytic anaemia.

CASE PRESENTATION

A previously healthy, fit 52-year-old man presented to the emergency department in Örebro University

Hospital in October 2017 with a 3-week history of dyspnoea on exertion and chest tightness. An evaluation revealed a holosystolic murmur, best heard over the apex, which radiated to the axilla. Transthoracic and transoesophageal echocardiograms showed a severe mitral regurgitation due to prolapse of the A2 segment of the anterior leaflet and chordal rupture (videos 1 and 2). The patient underwent mitral valve repair with a 40 mm Carpentier-Edwards physio II annuloplasty ring (Edwards Lifesciences Corporation, Irvine, California, USA) and four artificial chordae. On direct inspection during surgery, the valve was perceived as abnormally large and the leaflets myxomatous, and the patient was considered to have Barlow's mitral valve disease. A post-extracorporeal circulation transoesophageal echocardiogram showed no mitral regurgitation nor was there any postoperative mitral regurgitation. At a follow-up visit 2 months postoperatively, the patient had fully recovered and there was no murmur on physical examination. However, no blood samples were obtained at this visit.

Four months postoperatively, the patient developed dyspnoea, fatigue and dark urine after an upper respiratory tract infection. He presented to his primary care physician with persisting symptoms 6 months postoperatively. An evaluation revealed a haemoglobin level of 122 g/L, creatinine of 140 µmol/L, an estimated glomerular filtration rate of 47 mL/min/1.73 m² and a urine dipstick greatly positive for blood. There were no visible blood clots in the patient's urine, however. No centrifugation of the urine specimen, testing of the supernatant for haeme or further urinalysis were performed. The patient was referred to the urology department because of gross haematuria. The patient also contacted the cardiology department and was referred for a subacute echocardiogram that showed a well-functioning mitral valve with a non-significant regurgitation. However, no physical examination was performed. No laboratory tests were obtained between 1 month follow-up and 6 months postoperatively when the patient presented to his primary care physician.

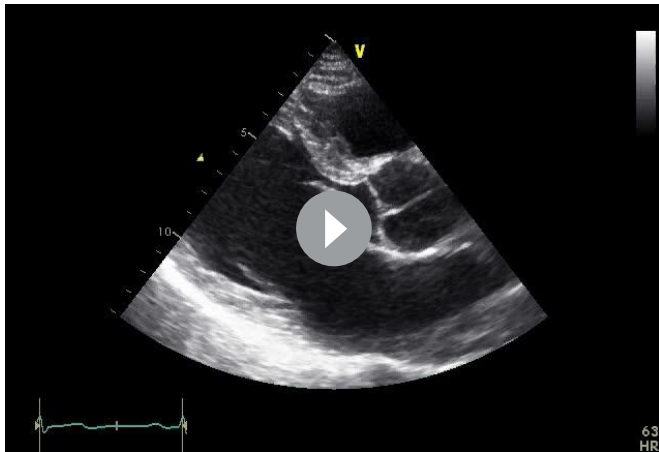
INVESTIGATIONS

A CT scan of the urinary tract, a cystoscopy and ureteropyeloscopy bilaterally showed no pathology. The haemoglobin level decreased further to 94 g/L and the patient received two blood transfusions. The patient also experienced intermittent bilateral flank pain.



© BMJ Publishing Group Limited 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Björkenheim A, Cha S-O, Dioubanova I. *BMJ Case Rep* 2019;**12**:e230280. doi:10.1136/bcr-2019-230280

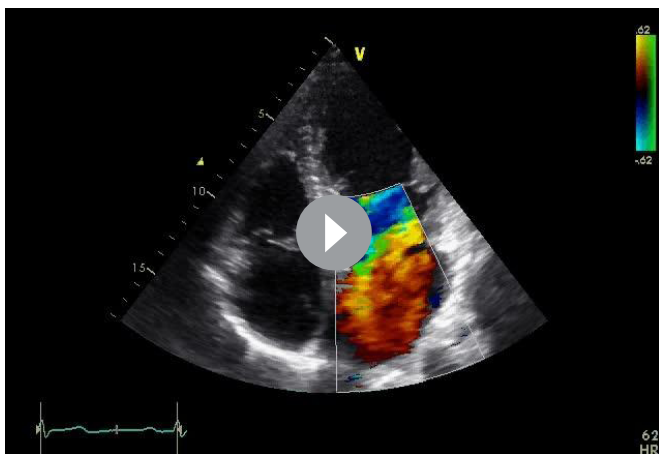


Video 1 Transthoracic echocardiogram showing a severe mitral regurgitation due to prolapse of the A2 segment of the anterior leaflet and chordal rupture in the parasternal long axis view.

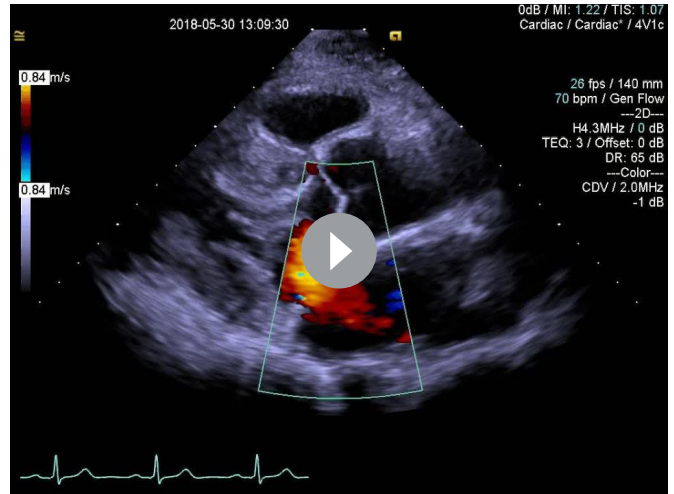
Renewed evaluation revealed a new holosystolic murmur over the apex, radiating to the back, and a renewed transthoracic echocardiogram showed a mild to moderate mitral regurgitation with a high velocity jet of just over 6 m/s directed posterolaterally (video 3). There was no echocardiographic evidence of significant mitral stenosis. Additional blood samples showed an increased lactate dehydrogenase of 49 μ kat/L, an undetectable haptoglobin level, an increased bilirubin of 30 μ mol/L, an increased reticulocyte count of 5% and a negative direct antiglobulin test. Furthermore, a peripheral blood smear showed the presence of schistocytes.

DIFFERENTIAL DIAGNOSIS

The fact that the patient presented with anaemia and gross haematuria without visible blood clots speaks against pathology in the urinary tract, including malignancy, even though it could not be excluded at this stage of the investigation. The previous recent upper respiratory infection and signs of mild renal failure raise the possibility of post-infectious haemolysis or infection-related glomerular disease as differential diagnoses. Additional laboratory testing, however, revealed increased levels of reticulocytes, lactate dehydrogenase and bilirubin, as well as



Video 2 Transthoracic echocardiogram showing a severe mitral regurgitation due to prolapse of the A2 segment of the anterior leaflet and chordal rupture in the apical four-chamber view with colour flow Doppler.



Video 3 Transthoracic echocardiogram showing a mild to moderate mitral regurgitation with a high velocity jet directed posterolaterally in the parasternal long axis view.

reduced haptoglobin, all of which suggest intravascular haemolytic anaemia. A negative direct antiglobulin test speaks against immune haemolysis. Furthermore, the presence of fragmented red blood cells, schistocytes, on a peripheral blood smear suggests mechanical trauma as the cause of the haemolysis. A comprehensive evaluation of the laboratory findings, and the patient's history of recent mitral valve repair, a new murmur and a regurgitant high velocity jet through the mitral valve, made the diagnosis of intravascular haemolytic anaemia due to mitral regurgitation very likely.

TREATMENT

The patient was administered beta blockers, iron and vitamins B₁₂ and folate. He was also administered the xanthine derivative pentoxifylline to improve the flexibility of red blood cells, as he was reluctant to the warfarin treatment necessary after a reoperation with a mechanical valve. The haemoglobin level was thereafter stable at around 100 g/L and no additional blood transfusions were needed. However, 2 months later, a transthoracic echocardiogram, including a stress test, was performed that showed progressing moderate mitral regurgitation. At perioperative inspection, the annuloplasty ring and all artificial chordae remained in place. The patient underwent a mitral valve replacement with an On-X mechanical valve (On-X Life Technologies, Austin, Texas, USA) 11 months after the mitral valve repair and was administered warfarin.

OUTCOME AND FOLLOW-UP

The patient was highly symptomatic due to the moderate haemolytic anaemia and was therefore on sick leave for the better part of the year 2018. After the mitral valve replacement, the patient made a full recovery, and his haemoglobin and creatinine levels and the estimated glomerular filtration rate swiftly normalised and the haemolysis ceased. The patient is continuously followed in the cardiology outpatient clinic with the last follow-up in June 2019, has a haemoglobin level of 158 g/L and is now working full time.

DISCUSSION

According to recent ESC/EACTS guidelines, mitral valve repair should be the preferred technique when the results are expected

to be durable in patients with primary mitral regurgitation (class I recommendation, level of evidence C).⁴ Haemolytic anaemia after mitral valve repair has been previously described in few case reports and in a small study.^{3 5 6} In 32 patients, Lam *et al* found that the median time from surgery to diagnosis of haemolytic anaemia was 3 months, that most patients had severe mitral

regurgitation and that the majority of patients consequently underwent mitral valve replacement with favourable outcomes.³ However, neither European nor American cardiology societies have guidelines for management of haemolytic anaemia after mitral valve repair.^{4 7}

In the current case, the correct diagnosis of haemolytic anaemia due to mitral regurgitation was delayed for two main reasons. First, the haemoglobinuria was misdiagnosed as gross haematuria and the patient was subjected to several invasive urological exams. Second, a renewed transthoracic echocardiogram was performed but the recurrent mitral regurgitation was considered non-significant. However, neither the primary physician nor the cardiologist did a proper physical exam, and the anaemia was not properly investigated. Had additional laboratory testing, including further urinalysis, been performed, the haemolysis would probably have been diagnosed earlier with considerably less discomfort for the patient. In a similar case report, a 43-year-old patient with a mechanical valve presented with what appeared to be gross haematuria but turned out to be haemoglobinuria due to a paravalvular leak. Before the correct diagnosis was established, that patient, as well as the patient in our case, underwent extensive urological investigations.⁸ In the present case, the laboratory results also revealed mild renal failure, most likely secondary to iron deposits following intravascular haemolysis, which has previously been described.⁹ The renal impairment promptly resolved after the haemolysis ceased.

Mitral valve replacement is generally effective in eliminating severe haemolysis in patients with prosthetic valves.¹ In patients who are at high surgical risk, treatment with pentoxifylline is an option to improve red blood cell deformability and reduce blood viscosity.^{1 10} In a study of 20 patients with prosthetic valves treated with pentoxifylline, the authors reported a reduction in haemolysis in 60% of patients compared with 5% in the placebo group.¹¹ However, to our knowledge, pentoxifylline has not been used previously in patients with haemolytic anaemia after mitral valve repair. In the present case, the haemoglobin level was stabilised and the patient needed no additional blood transfusions on treatment with pentoxifylline; however, the patient was also administered beta blockers and oral iron, vitamin B₁₂ and folate replacement, which makes the effect of pentoxifylline difficult to evaluate. The stabilisation could just as easily be the beta blockers' reduction of the shearing forces acting on the red blood cells.

Our recommendation is that the evaluation of patients who have undergone valve surgery, as well as valve repair, should include a history, physical examination and laboratory tests including haemoglobin, creatinine and lactate dehydrogenase. Furthermore, the clinician should liberally refer patients for renewed transthoracic echocardiograms, especially in patients where new symptoms and anaemia have occurred. Importantly,

Patient's perspective

I felt suddenly tired and experienced chest tightness on a Saturday morning in the beginning of October 2017. The symptoms persisted and worsened a week later with shortness of breath on exertion and fatigue. I was admitted to the cardiology department and diagnosed with mitral regurgitation that required surgery. In all dialogues with cardiologists and surgeons, both diagnosis and actions were clear and my opinion was well respected when it came to the choice between mitral valve repair and valve replacement with a mechanical valve. I preferred the valve repair to avoid lifelong anticoagulation.

The surgery was performed. I had some side effects of the medications and the anaesthesia but the recovery went well, and just over 2 months postoperatively I worked and lived as usual. Three months postoperatively, I considered my fitness and strength levels on a par with preoperation.

In the middle of February 2018, I suffered a severe cold. I also noticed blood in the urine, at first only a little but it quickly increased and I never fully recovered from the cold. I contacted the cardiology department in April 2018 and was referred to an echocardiogram where a minimal regurgitation was seen which was considered not to be the cause of my symptoms. Despite repeated attempts, it took until the end of April 2018 until the primary care unit accepted me for examination. I was then referred to the urology department who examined the urethra, bladder, ureters and kidneys without finding the cause for the blood in my urine. At this point I was feeling really ill and could not understand how I could be so tired and infirm without it being possible to find a cause. Additionally, I got very painful kidney stone like attacks regularly.

Finally, during the time I was admitted to the urology department in May 2018, urologists, nephrologists, cardiologists and cardiac physiologists collaborated and the correct diagnosis was quickly made. I was given the choice between a reoperation with a mechanical valve or treatment with a medication that would make the blood cells more resistant to the mechanical force they are exposed to as they pass through the leaking valve. I decided to try the medication, again arguing, although it may seem inconsequent, against anticoagulation, but mainly to postpone a still likely operation. Unfortunately, the medication did not work as well as I had hoped and surgery became necessary.

During the recovery after the reoperation I experienced a better dialogue about medications and follow-up, which meant that I experienced this recovery as smoother than the first. I also approached the rehabilitation training with a calmer pace this time. I now, 3 months later, feel recovered, but I also have some thoughts left.

The mechanical valve is only 25 mm in diameter, theoretically making the area through which the blood passes strongly restricting my cardiac output—how will this affect me?

My maximum heart rate is still considerably lower than before the two operations although I am now only medicating with warfarin, why?

Learning points

- ▶ Haemolytic anaemia may occur even after mitral valve repair.
- ▶ Even a mild to moderate regurgitation can cause mechanical trauma to the red blood cells, secondary to high velocity jets.
- ▶ The haemolytic anaemia usually ceases after a reoperation with mitral valve replacement.
- ▶ Free haemoglobin in the circulation can cause significant damage to the kidneys.
- ▶ Haemoglobinuria can easily be misdiagnosed as haematuria, resulting in extensive invasive urological investigation.

all patients with haemolytic anaemia have recurrent mitral regurgitation, although it is not the severity of the mitral regurgitation but rather the leaking site, dispersion and velocity of regurgitant jets that cause the clinically important haemolysis.

Contributors The patient is currently under the care of AB. S-OC performed both the mitral valve repair and the mitral valve replacement. ID performed one of the echocardiograms. AB came up with the idea of the case report. All authors discussed the results and contributed substantially to the manuscript and approved the final version. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Shapira Y, Vaturi M, Sagie A. Hemolysis associated with prosthetic heart valves: a review. *Cardiol Rev* 2009;17:121–4.
- 2 Skoularigis J, Essop MR, Skudicky D, *et al*. Frequency and severity of intravascular hemolysis after left-sided cardiac valve replacement with Medtronic Hall and St. Jude Medical prostheses, and influence of prosthetic type, position, size and number. *Am J Cardiol* 1993;71:587–91.
- 3 Lam BK, Cosgrove DM, Bhudia SK, *et al*. Hemolysis after mitral valve repair: mechanisms and treatment. *Ann Thorac Surg* 2004;77:191–5.
- 4 Baumgartner H, Falk V, Bax JJ, *et al*. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–91.
- 5 Zhu X, Hu Z, Fang L, *et al*. Hemolysis combined with renal injury after mitral valve repair. *Heart Surg Forum* 2018;21:187–e9.
- 6 Naik AV, Bhalgat PS, Bhadane NS, *et al*. Very early onset traumatic hemolysis following mitral valve repair in a pediatric patient. *Indian Heart J* 2016;68(Suppl 2):S237–40.
- 7 Nishimura RA, Otto CM, Bonow RO, *et al*. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;70:252–89.
- 8 Meadows S, Gordon P, Inman R. Mistaken identity: haemoglobinuria secondary to paravalvular leak masking as haematuria. *BMJ Case Rep* 2017;2017:bcr-2016-218066.
- 9 Latham W. The renal excretion of hemoglobin: regulatory mechanisms and the differential excretion of free and protein-bound hemoglobin. *J Clin Invest* 1959;38:652–8.
- 10 Disegna E, De Caro A, Nori N, *et al*. Pentoxifylline in prosthetic valve: a case report. *Aging Clin Exp Res* 2019;31:431–4.
- 11 Golbasi I, Turkay C, Timuragaoglu A, *et al*. The effect of pentoxifylline on haemolysis in patients with double cardiac prosthetic valves. *Acta Cardiol* 2003;58:379–83.

Copyright 2019 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow