CASE REPORT

Systemic thrombolysis: cure for prosthetic mitral valve thrombosis in the comorbid, non-surgical candidate

Brian Beckord,¹ Robert Berkowitz,² Cholene Espinoza,¹ Neil Anand²

¹Hackensack University Medical Center, Hackensack, New Jersey, USA

²Department of Cardiology, Hackensack University Medical Center, Hackensack, New Jersey, USA

Correspondence to
Brian Beckord,
brianbeckord@gmail.com

Accepted 9 May 2014

SUMMARY

Severe haemolytic anaemia is a rare complication of prosthetic valve thrombosis (PVT). Emergent surgical replacement of the affected valve is normally the treatment of choice unless contraindicated, such as in high surgical risk patients. Systemic thrombolysis is the alternative to surgical valve replacement. The purpose of this report is to highlight the unique case of an elderly man with New York Heart Association class IV heart failure, history of extensive cardiopulmonary surgeries and haemorrhagic stroke, who presented with severe haemolytic anaemia secondary to prosthetic mitral valve thrombosis. After weighing the risks and benefits, our decision was to use systemic thrombolytic therapy, even in light of the patient's previous intracranial haemorrhage. Pretreatment and post-treatment Doppler echocardiography showed markedly reduced regurgitant jetting that ultimately resolved completely, thereby eliminating the underlying cause of haemolysis and achieving symptom resolution.

BACKGROUND

Prosthetic valve thrombosis (PVT) is a relatively common complication of mitral valve replacement with studies reporting postoperative rates as high as 24% for mild non-obstructive type PVT and 0.3–1.3% for more severe obstructive type PVT.^{1 2} Haemolysis resulting from mechanical valve replacement has been well documented, but few studies have addressed the relationship between PVT and acute onset severe haemolytic anaemia.

Our objective is to present a unique case of acute onset severe haemolytic anaemia resulting from PVT, and describe the successful administration of systemic thrombolysis in a high-risk patient who was not a candidate for surgical replacement.

CASE PRESENTATION

An elderly man with an extensive medical history significant for coronary artery disease, severe persistent asthma, New York Heart Association (NYHA) functional class IV diastolic heart failure, spontaneous intracranial haemorrhage (2012) secondary to warfarin-induced supra-therapeutic International Normalised Ratio (INR), status post mitral/aortic valve replacement for mitral and aortic regurgitation (2002), left internal mammary vessel to left anterior descending-coronary artery bypass grafting (2005) and right middle lobe lobectomy (2010), with subsequent empyema requiring

right-sided decortication, who was admitted for grossly bloody urine of unknown aetiology.

At presentation, the patient's only complaint was blood tinged urine. Physical examination revealed jaundice and a new grade III/VI mitral regurgitation murmur. Initial blood work revealed unconjugated hyperbilirubinaemia, elevated lactate dehydrogenase (LDH), decreased haptoglobin and moderate schistocytes on peripheral blood smear. Urinalysis was positive for blood, which upon further investigation was found to be lysed red blood cells that had passed through the kidneys. The results indicated that intravascular haemolysis was taking place and, due to the acute onset of symptoms, without other systemic signs, thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome (TTP-HUS) or mechanical mitral valve-induced haemolysis was suspected. Urgent plasmapheresis and echocardiography were ordered to address both differentials. Plasmapheresis had no effect on the patient's haemodynamic or renal status which was reflected by the haemoglobin (Hgb) continuing to decrease while LDH and creatinine (Cr) continued to increase (figure 1). Echocardiography revealed high pressure regurgitant jetting across the prosthetic mitral valve, a consequence of acute onset mitral valve thrombosis secondary to inadequate anticoagulation. Of note, the patient's anticoagulation therapy had been discontinued because of a haemorrhagic stroke due to warfarin-induced supratherapeutic INR 1 year prior to this admission. Four days after admission the patient's Hgb had dropped from 11.4 to 6.4 g/dL, with a corresponding rise in both LDH (10 562 U/L) and Cr (2.4 mg/dL) (figure 1).

The patient was hydrated and remained haemodynamically unstable, requiring daily transfusions of packed red blood cells (PRBCs) to maintain Hgb above 7.0 g/dL. Repeat transesophageal echocardiogram confirmed mitral valve thrombosis with 2+ regurgitant jetting. HUS-TTP was ruled out as a differential and the patient's acute renal failure was attributed to haemoglobinuria-induced acute tubular necrosis and clogging of renal glomeruli by haemolytic debris. Haemodynamic collapse and/or irreversible renal failure were imminent without expeditious resolution of the patient's haemolytic anaemia.

The patient was an incredibly high-risk cardiac surgical candidate with NYHA functional class IV diastolic heart failure and three previous intrathoracic surgeries, including two open heart surgeries

To cite: Beckord B, Berkowitz R, Espinoza C, et al. *BMJ Case Rep*. Published online: [please include Day Month Year] doi:10.1136/bcr-2013-203071

Figure 1 Lactate dehydrogenase (LDH), haemoglobin (Hgb) and serum creatinine (Cr) values during the patient's hospital course.

and middle lobe lobectomy, with subsequent empyema requiring decortication. It was understood that if open valve replacement was attempted, severe adhesions would be encountered, making a redo mitral valve replacement nearly impossible, a formidable procedure for a patient with such severe comorbidities. Thus, systemic thrombolysis was considered as an alternative to surgery. Important to remember, systemic thrombolysis was also contraindicated in this patient due to a history of anticoagulant-induced haemorrhagic stroke 1 year prior. Substantial time and consideration was spent weighing the risks and benefits of both treatment modalities, including the utilisation of multiple transthoracic and trans-esophageal echocardiograms, as well as percutaneous coronary catheterisation, to better estimate the patient's surgical risk. It was decided that the patient's three previous intrathoracic surgeries, pulmonary compromise, along with NYHA class IV heart failure, posed an unacceptable surgical risk, and despite the traditional contraindication, systemic thrombolysis appeared to be the safer option.

Twenty-eight days after admission the patient was transferred to the cardiac-surgical intensive care unit and transfused with PRBCs to a Hgb of 10.0 gm/dL, a precaution for unexpected bleeding secondary to the procedure. Systemic thrombolysis was administered as a 10 mg bolus of recombinant tissue plasminogen activator (rtPA) followed by 1 mg/min for 90 min. The patient was monitored closely with neurological testing every 15 min and observed for other signs of acute bleeding. Aminocaproic acid was available as an antidote to tPA in the event that uncontrolled spontaneous bleeding took place.

Sixty minutes into the procedure the murmur of mitral regurgitation was no longer audible. Repeat transthoracic and transesophageal echocardiograms, as well as fluoroscopy, revealed disappearance of thrombus and significantly reduced mitral regurgitant jetting with normalisation of the transmitral gradient. A profound improvement in the patient's Cr and LDH was also observed (figure 1).

Shortly after completing the procedure, a large painless haematoma was noted in the right groin and proximal right lower extremity. Vascular consult was called and arterial duplex of the right lower extremity revealed a pseudoaneurysm of the femoral artery, site of a previous percutaneous catheterisation. The pseudoaneurysm was successfully treated with local injection of Thrombin. Haemodynamic stabilisation was initially

delayed secondary to a tPA-induced pseudoaneurysm leading to blood loss into the retroperitoneal space and upper thigh. Haemodynamic stability was achieved within 4 days of the procedure, at which point an intravenous heparin drip was re-started and the patient was transitioned back onto a therapeutic dose of warfarin. The remainder of his postoperative course was uneventful. The patient was successfully discharged to a rehabilitation centre, and eventually home.

DISCUSSION

Independent of treatment, mortality rates associated with severe PVT are approximately 10%.³ Thus, it is imperative that a rapid and accurate diagnosis is made, allowing for immediate implementation of therapeutic intervention to prevent haemodynamic collapse and irreversible renal failure. PVT typically presents as a subacute onset of valvular dysfunction and rarely as the acute onset of severe symptoms, as was seen in our patient. Thrombi that form on mechanical valves are a result of endothelial, coagulative and haemodynamic influences, as dictated by Virchow's triad.⁴ The immediate thrombogenicity of a new valve results from the interaction between platelets and coagulation factors with injured endocardium. Late valve thrombosis, months to years after valve replacement, results from inadequate anticoagulation producing platelet and coagulation factor deposition on the mechanical valve.⁵⁻⁷ Our patient's anticoagulation therapy was discontinued by his primary care physician after he developed an acute intracerebral haemorrhage secondary to a supra-therapeutic INR. Unfortunately, his anticoagulation regimen was never resumed, likely leading to the development of his PVT.

Diagnosis of PVT is based upon clinical and laboratory data, supported by the imaging modalities of fluoroscopy, transthoracic echocardiography and transesophageal echocardiography. Management of PVT depends on thrombus size, right versus left-sided thrombus and the patient's specific comorbidities leading to unique surgical or systemic thrombolytic risks.⁸ As was the case in our patient, symptomatic left-sided PVT is traditionally addressed with surgery, reserving systemic thrombolysis for patients that are critical ill with acute PVT when immediate surgery is not possible, or a contraindication to surgery such as low cardiac output, respiratory insufficiency or repeat cardiac surgeries.⁹ Introduced in the 1970s, systemic thrombolysis was

developed as a therapeutic alternative for patients considered to be poor surgical candidates. A review by Lengyel *et al*¹⁰ found that systemic thrombolysis was effective in 82% of cases, but was associated with mortality rates as high as 10%, relegating it to second-line therapy. However, a more recent review by Bonou *et al*³ reminds us that the Society for Heart Valve Disease recommends that thrombolysis is the first-line therapy in all patients with left-sided PVT, with thrombus burden <0.8 cm² regardless of NYHA functional class. Furthermore, if the left-sided PVT thrombus burden is more significant (>0.8 cm²), the American College of Chest Physicians still recommends systemic thrombolysis as the first-line therapy in patients deemed high risk for surgery.¹¹ Surgical valve replacement mortality rates have been reported as high as 17.5% for patients with NYHA functional class IV heart failure, one of the many comorbidities afflicting the patient in this case report.⁸ Thus, it is obvious that while systemic thrombolysis posed a significant risk to our patient, it appeared to be the safer option with potentially curative results.

In patients with haemodynamic instability, 'rescue' thrombolysis is accomplished using either: rtPA (10 mg bolus+90 mg in 90 min) followed by intravenous heparin drip or streptokinase (1 500 000 U in 60 min) without heparin.⁸ Absolute contraindications to systemic thrombolysis include a history of haemorrhagic stroke, active internal bleeding, recent cranial trauma or neoplasm, blood pressure >200/120 mm Hg and diabetic haemorrhagic retinopathy.¹⁰ As such, treatment options available to our patient were considered contraindicated. The complexity of this case required significant collaboration among cardiothoracic surgery, cardiology, renal and haematology specialists. After exhaustive review of the patient's medical history, current

clinical status and recent literature, it was decided that the patient was not a candidate for surgery, due to an unacceptable surgical risk imposed by multiple previous cardiac surgeries, pulmonary compromise, as well as his NYHA class IV heart failure. Although considered a contraindication, we felt that systemic thrombolysis represented less risk in this extremely complex patient and had the novel potential to remove haemolytic debris from his renal glomeruli leading to improved renal function.

The only complication experienced by the patient was a pseudoaneurysm of the right femoral artery. Doppler analysis revealed that the pseudoaneurysm was a result of tPA acting at the site of a percutaneous catheterisation which had taken place 1 week prior in an attempt to better estimate the patient's cardiac surgical risk. Figure 1 portrays the patient's hospital course in relation to haemoglobin, lactate dehydrogenase and creatinine. It is dramatically clear that the patient's haemoglobin stabilised in sync with the return of renal function and decrease in LDH, indicating that a significant reduction in haemolysis was successfully accomplished.

Contributors BB conducted analysis of data, wrote the first draft of the manuscript and rewrote new drafts based upon input from coauthors. RB initiated the conception of the case report, planned the analyses and interpretation of data and gave feedback on the first draft of the manuscript. CE critically revised the manuscript and interpretation of data. NA critically revised the manuscript. All authors read and approved the final manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Deviri E, Sareli P, Wisenbaugh T, *et al*. Obstruction of mechanical heart valve prostheses: clinical aspects and surgical management. *J Am Coll Cardiol* 1991;17:646–50.
- Gohlke-Bärwolf C, Acar J, Oakley C, *et al*. Guidelines for prevention of thromboembolic events in valvular heart disease. *Eur Heart J* 1995;16:1320–30.
- Bonou M, Lampropoulos K, Barbetseas J. Prosthetic heart valve obstruction: thrombolysis or surgical treatment? *Eur Heart J Acute Cardiovasc Care* 2012;1:122–7.
- Gencbay M, Turan F, Degertekin M, *et al*. High prevalence of hypercoagulable states in patient with recurrent thrombosis of mechanical heart valves. *J Heart Valve Dis* 1998;7:601–9.
- Yin W, Alemu Y, Affeld K, *et al*. Flow-induced platelet activation in bileaflet and monoleaflet mechanical heart valves. *Ann Biomed Eng* 2004;32:1058–66.
- Leguyader A, Watanabe R, Berbé J, *et al*. Platelet activation after aortic prosthetic valve surgery. *Interact Cardiovasc Thorac Surg* 2006;5:60–4.
- Barbetseas J, Nagueh SF, Pitsavos C, *et al*. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. *J Am Coll Cardiol* 1998;32:1410–17.
- Roudau R, Serri K, Lafitte S. Thrombosis of prosthetic heart valves: diagnosis and therapeutic considerations. *Heart* 2007;93:137–42.
- Roudaut R, Lafitte S, Roudaut MF, *et al*. Fibrinolysis of mechanical prosthetic valve thrombosis: a single-center study of 127 cases. *J Am Coll Cardiol* 2003; 41:653–8. This single centre series underlines the risk of embolism during fibrinolysis, with possible permanent damage.
- Lengyel M, Fuster V, Keltai M, *et al*. Guidelines for management of left sided prosthetic valve thrombosis: a role for thrombolytic therapy. *J Am Coll Cardiol* 1997; 30:1521–6. This international conference led to the development of guidelines for the management of left-sided PVT.
- Salem D, O'Gara T, Madias C, *et al*. Valvular and Structural Heart Disease American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST J* 2008;133(6_Suppl):593S–629S.

Learning points

- ▶ Prosthetic valve thrombosis (PVT) is a relatively common complication of mitral valve replacement with studies reporting postoperative rates as high as 24% for mild non-obstructive type PVT and 0.3–1.3% for more severe obstructive type PVT.^{1 2}
- ▶ Severe haemolytic anaemia is a rare complication of PVT which requires prompt diagnosis and aggressive treatment to prevent haemodynamic collapse and irreversible renal failure.
- ▶ Although surgical replacement has been classically considered first-line treatment in left-sided PVT, use of systemic thrombolysis, despite contraindications, should be considered and its risks evaluated in reference to the comorbidities of individual patient.
- ▶ It should also be recognised that systemic thrombolysis may, in fact, have the added benefit of reclaiming renal function by removing haemolytic debris, allowing the kidney to more efficiently repair itself. Further research is necessary to elucidate the mechanism of this added benefit.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-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

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

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