CASE REPORT

Tricuspid and mitral endocarditis due to methicillin-resistant *Staphylococcus aureus* exhibiting vancomycin-creep phenomenon

Pranathi Rao Sundaragiri,¹ Saraschandra Vallabhajosyula,² Toufik Mahfood Haddad,³ Dennis J Esterbrooks⁴

¹Division of Hospital Internal Medicine, Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

²Division of Critical Care Medicine, Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

³Department of Internal Medicine, Creighton University School of Medicine, Omaha, Nebraska, USA

⁴Division of Cardiovascular Diseases, Department of Internal Medicine, Creighton University School of Medicine, Omaha, Nebraska, USA

Correspondence to

Dr Saraschandra Vallabhajosyula, Vallabhajosyula.Saraschandra@mayo.edu

Accepted 15 October 2015

SUMMARY

Right-sided infective endocarditis (RIE) is commonly due to *Staphylococcus aureus* and often involves the tricuspid valve (TV). A 31-year-old man with prior intravenous drug use presented with substernal pain, cough, dyspnoea and fever. Examination revealed a febrile, tachycardic male with peripheral infective endocarditis stigmata and right-heart failure. Laboratory parameters demonstrated leucocytosis, lactic acidosis and methicillin-resistant *S. aureus* (MRSA) bacteraemia.

Echocardiography demonstrated multiple TV echodensities and chest imaging confirmed septic emboli. The MRSA species demonstrated 'vancomycin-creep', necessitating therapy with daptomycin and ceftaroline. Owing to persistent bacteraemia and septic shock, the patient underwent TV surgery, but continued to have a poor postoperative course with subsequent death. Indications for surgical therapy of RIE are limited to the European guidelines and most data are extrapolated from left-heart disease. MRSA exhibiting vancomycin-creep portends a poorer prognosis and requires aggressive therapy. We advocate the use of ceftaroline salvage therapy with daptomycin, pending further trials.

BACKGROUND

Infective endocarditis (IE) is a common cardiac condition and carries a high mortality rate of 30%, but has seen rapid decline in incidence, severity and mortality, with the advent of effective antimicrobial therapy since the mid-1940s.^{1–3} Right-sided IE (RIE) commonly affects the tricuspid valve (TV) and constitutes 5–10% of all cases of IE.⁴ Intravenous drug use (IVDU) is a common risk factor for IE, with poor hygiene and unsafe injection practices especially increasing the risk.^{4–5} Multiple organisms have been reported to cause IE, however, in the early 21st century, a high rate of *Staphylococcus aureus* infections have been noted.^{5–6} We report a case of a young patient who developed concomitant TVIE and mitral valve (MV) IE with *S. aureus*. Additionally, we highlight the phenomenon of 'vancomycin-creep', which is becoming a significant confounder in effective management of methicillin-resistant *S. aureus* (MRSA) infections.^{7–9}

CASE PRESENTATION

A 31-year-old Caucasian man presented to our tertiary care academic medical centre reporting

constant, severe, sharp substernal chest pain for 10 days. This was associated with exertional dyspnoea, non-productive cough, bilateral lower extremity swelling, fevers and chills. He also reported a poor appetite, vague left upper quadrant abdominal discomfort, worsening fatigue and myalgia. The medical history was significant for recurrent IVDU and a recent episode of IE 3 months prior. At that time, the patient was admitted to an outside medical centre, where he was noted to have a small vegetation involving the TV on transesophageal echocardiogram (TEE). Blood cultures were positive for methicillin-sensitive *S. aureus* (MSSA), and the patient received intravenous daptomycin therapy for a period of 6 weeks. Subsequent blood cultures remained negative. He reported worsening symptoms 10–12 days after discontinuation of the antimicrobial therapy.

On the current visit, his examination revealed an elevated temperature (103°F) with tachycardia (130/min) and tachypnoea (37/min). Cardiac examination demonstrated elevated jugular venous pulsation at 15 cm, widely split S₂ with loud P₂ component and grade III/VI non-radiating pansystolic murmur at the lower left sternal border. Other significant findings included bilateral scattered expiratory wheezes, tender splenomegaly (2 cm), bilateral pitting pedal oedema, fingernail splinter haemorrhages, Osler's nodes and absence of Roth spots.

INVESTIGATIONS

Laboratory parameters were significant for normocytic normochromic anaemia (haemoglobin 7.9 g/dL), leucocytosis (19 600/mm³) with immature and band forms, lactic acidosis (2.6 mmol/L), elevated cardiac biomarkers (B-type natriuretic peptide 3499 pg/mL and troponin-I 3.66 ng/mL) and elevated inflammatory markers (erythrocyte sedimentation rate 86 mm/h, C reactive protein 205 mg/L). Preliminary blood cultures demonstrated Gram-positive cocci in clusters, later confirmed as MRSA. Acute kidney injury (AKI) (serum creatinine 3.5 mg/dL with fractional excretion of sodium 0.3%) and urinary tract infection (UTI) with positive MRSA urine cultures were noted.

ECG demonstrated sinus tachycardia, normal atrioventricular and intra-ventricular conduction intervals without repolarisation changes. The patient's chest X-ray demonstrated multiple patchy ill-defined airspace opacities that were noted on a

CrossMark

To cite: Sundaragiri PR, Vallabhajosyula S, Mahfood Haddad T, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211974

subsequent CT scan to be bilateral thick-walled angiocentric cavitory lesions suspicious for septic pulmonary emboli (figures 1 and 2). Additionally, left lung upper lobe consolidation, small pericardial effusion and splenic infarction were noted. Transthoracic echocardiogram (TTE) demonstrated multiple mobile vegetations on the anterior and septal leaflets of the TV and adjacent chordae tendinae, severe tricuspid regurgitation (TR), mild pulmonic regurgitation and right ventricular systolic pressure of 66 mm Hg. Left ventricular (LV) function was hyperdynamic with LV ejection fraction (LVEF) of 65–70% without any wall motion abnormalities. Subsequent TEE demonstrated two mobile tricuspid echo densities on the anterior and septal leaflets of the TV with the largest 3.1×2.5 cm, severe TR, trace mitral, aortic and pulmonic regurgitation, hyperdynamic LV (LVEF 65–70%) (figures 3–5 and video 1). Renal ultrasound was unrevealing for acute pathology.

TREATMENT

The patient was admitted to the intensive care unit for management of definite IE (2 major modified Duke criteria) and administered intravenous hydration and intravenous vancomycin therapy. He had evidence of septic emboli in the pulmonary vasculature and systemic vasculature as evidenced by splenic infarction, Janeway lesions, UTI and splinter haemorrhages. This was hypothesised to be due either to left-sided emboli owing to occult right-to-left cardiac shunt (not demonstrated on TEE), presence of intrapulmonary shunting due to septic emboli with necrosis, or IE of the aortic or MV with embolisation.

Owing to continued positivity of blood cultures, worsening AKI and MRSA demonstrating vancomycin minimum inhibitory concentration (MIC)-creep of 2 µg/mL, the patient was transitioned to daptomycin and ceftaroline. The patient continued to have severe sepsis, bacteraemia and AKI. Subsequently, on post-hospitalisation day 9, the patient underwent TV exploration with intraoperative findings demonstrating posterior leaflet involvement with 2×3 cm vegetation, destruction of anterior and septal leaflets, annular destruction and patchy RV free wall necrosis. Additionally, vegetations were noted on the chordae tendinae of the MV extending into the LV. The patient underwent partial resection of the anterior and posterior TV leaflets with annular resection and irrigation of the right atrium and LV.

OUTCOME AND FOLLOW-UP

Postsurgically, the patient continued to deteriorate despite intravenous hydration, renal replacement therapy and antimicrobials.

Figure 1 Chest roentgenogram on admission, demonstrating multiple patchy ill-defined opacities.

Figure 2 CT of the chest and abdomen demonstrating multiple diffuse thick-walled angiocentric cavitory lesions highly suspicious for septic emboli and left upper lobe consolidation.

The patient remained haemodynamically unstable requiring high doses of vasopressor and inotropic support, eventually decompensating into multiorgan dysfunction. He progressed to pulseless electrical activity and, despite three consecutive returns of spontaneous circulation, the patient continued to have incessant cardiorespiratory compromise. After detailed discussions with the patient's family, aggressive cardiorespiratory manoeuvres were stopped leading to the patient's demise.

DISCUSSION

RIE constitute 5–10% of all IE cases, with 90% of the lesions involving the TV.^{7–10} *S. aureus* is the most common bacteria, with 5% and 20% mortality in RIE and left-sided IE, respectively.¹¹ Common complications of RIE are pulmonary emboli, pulmonary infarction, pulmonary abscesses, pneumothoraces and purulent pulmonary effusions. Rarely, pulmonary hypertension, right heart failure (RHF), severe TR and obstruction of pulmonary circulation due to multiple pulmonary emboli, can occur.⁵ Concurrent left-sided IE is seen in about 13% of

Figure 3 Transesophageal echocardiogram demonstrating multiple mobile echo densities (red arrows) over tricuspid valve.

Figure 4 Transesophageal echocardiogram with three-dimensional reconstruction of tricuspid valve demonstrating multiple mobile echo densities (blue arrows).

patients and portends a poorer prognosis.⁷ In a retrospective study by Baraki *et al.*,⁴ involving 33 patients with isolated TV IE (TVIE), it was found that about 88% had normal LVEF but only 48% had normal RV function. Evidence of clinical RHF was noted in only about 33% of the patients. The sensitivity and specificity of the Duke criteria have not been thoroughly studied in RIE and may not be applicable.⁷ Diagnosis is challenging due to predominant pulmonary symptoms and absence of peripheral manifestations. TTE is a good screening modality (sensitivity 40–63%) due to the anterior location of the TV as well as the large vegetations associated with RIE. TEE is a more sensitive (sensitivity 90–100%) imaging tool, especially for endocarditis-related abscesses as well as associated left-sided involvement.^{5 12}

Surgical therapy in these patients is frequently life-saving and is required in 25–50% of cases.^{5 13 14} European Society of Cardiology guidelines generally recommend avoiding surgery for RIE, except in the following situations: (1) RHF secondary to severe TR with poor response to diuretic therapy; (2) IE caused by organisms that are difficult to eradicate (eg, fungi), or bacteraemia for at least 7 days (eg, *S. aureus*, *Pseudomonas aeruginosa*) despite adequate antimicrobial therapy; and (3) TV vegetations >20 mm that persist after recurrent pulmonary emboli with or without concomitant RHF. Current suggested surgical approaches for RIE are (1) radical excision of infected regions;

Video 1 Transesophageal echocardiogram with colour Doppler four-chamber view demonstrating severe tricuspid regurgitation.

(2) valve repair when feasible and (3) excision of valve followed by prosthetic valve replacement.⁵ A conservative approach is preferred for patients with IVDU since they have a much higher incidence of recurrent IE, usually due to continued drug abuse.^{4 15} A retrospective study of 33 patients noted significant improvement in the New York Heart Association class in patients following surgical therapy for isolated TVIE. The 1-year, 5-year and 10-year mortalities were reported to be 88%, 73% and 73%, respectively.⁴ Overall surgical outcome of isolated TVIE is reported to be better than left-sided IE.⁴ Assessment of the impact of surgery on outcomes in IE is difficult, because most patients who need surgery are frequently those with severe complications related to virulent organisms. Older age, infection with *S. aureus* (especially MRSA), renal failure, high EuroSCORE and reduced LVEF or RVEF, were associated with higher postoperative mortality.⁴ In general, prognosis is better if surgery is undertaken early, before cardiac tissue destruction, heart failure or deterioration in the clinical status, which increase the complications of surgery.^{4 16}

S. aureus is the most common pathogen causing IE and is considered to be an independent risk factor for higher morbidity and mortality, with an even higher mortality rate of 30–37% with MRSA.^{5 10} The management of MRSA RIE has been extrapolated from trials on left-sided IE due to the lack of controlled trials on treatment of RIE. Vancomycin has high failure rates in MRSA IE due to poor penetration of valvular tissue and weak bactericidal action.⁷ Teicoplanin requires high serum levels for effective therapy and has higher failure rates compared to vancomycin.⁷ Furthermore, as in our patient, some MRSA strains, although susceptible to vancomycin, have a higher MIC >2 µg/mL but <4 µg/mL, a phenomenon termed ‘vancomycin MIC-creep’, suggestive of greater virulence.^{8 9} These strains of MRSA have been associated with poorer prognosis, greater treatment failure and higher mortality, especially with bacteraemia, compared to non-bacteraemic patients.^{7–9} Daptomycin is considered first-line therapy for MRSA with higher vancomycin MICs, and is as efficacious as vancomycin or vancomycin/gentamicin combination therapy for treatment of MRSA RIE.¹⁷ However, since daptomycin is inactivated by alveolar surfactant, its efficacy in the treatment of RIE complicated by septic pulmonary emboli and/or pneumonia is unclear.¹⁷ A combination of daptomycin and ceftaroline (salvage therapy) is highly bactericidal against MRSA strains with reduced susceptibility to glycopeptides, lipopeptides or even daptomycin itself.^{18 19} Proposed mechanisms for this superior activity are β-lactam-daptomycin synergy via the ‘see-saw effect’, intrinsic activity of ceftaroline against MRSA and observed decrease in

Figure 5 Transesophageal echocardiogram with colour Doppler demonstrating severe tricuspid regurgitation.

S. aureus ceftaroline MIC even on loss of daptomycin susceptibility.^{8 18} Limited clinical trials have demonstrated that the synergistic combination of ceftaroline and daptomycin can decrease resistance to daptomycin, and can be de-escalated to a single agent therapy without loss of efficacy.¹⁹ Combination therapy therefore seemed reasonable in our case and may be indicated in patients with a clinical presentation similar to our patient. However, combination (salvage therapy) requires further randomised trials to evaluate the added efficacy of this regimen for the management of patients with complicated TVIE.

Learning points

- ▶ Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most common organism in right-sided infective endocarditis (RIE), especially among intravenous drug users.
- ▶ Early surgical therapy is not indicated for RIE, except in patients with severe right heart failure, persistent bacteraemia and IE vegetations >20 mm.
- ▶ MRSA with 'vancomycin-creep' portend a worse prognosis, greater virulence and higher mortality.
- ▶ Daptomycin is advocated as first-line therapy for MRSA organisms exhibiting vancomycin-creep phenomenon.
- ▶ Ceftaroline salvage therapy enhances daptomycin efficacy by increased synergy, inhibition of cationic innate immunity proteins and 'see-saw effect' on the bacterial cell wall.

Acknowledgements The authors would like to thank Renuga Vivekanandan, MD, from the Division of Infectious Diseases, Department of Internal Medicine, Creighton University School of Medicine, Omaha NE, for her guidance on the Infectious Diseases and antimicrobial therapy discussion.

Contributors PRS was responsible for patient evaluation, clinical management, literature review, and drafting and finalising the manuscript. SV was responsible for literature review and finalising the manuscript. TMH was responsible for patient evaluation, clinical management, literature review and drafting the manuscript. DJE was responsible for critical review and finalising the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Cabell CH, Jollis JG, Peterson GE, *et al.* Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med* 2002;162:90–4.
- 2 Prendergast BD. The changing face of infective endocarditis. *Heart* 2006;92:879–85.
- 3 Dawson MH, Hunter TH. The treatment of subacute bacterial endocarditis with penicillin. Results in twenty cases. *JAMA* 1945;127:129–37.
- 4 Baraki H, Saito S, Al Ahmad A, *et al.* Surgical treatment for isolated tricuspid valve endocarditis—long-term follow-up at a single institution. *Circ J* 2013;77:2032–7.
- 5 Weymann A, Schmack B, Rosendal C, *et al.* Tricuspid valve endocarditis with septic pulmonary emboli in a drug addict. *Ann Thorac Cardiovasc Surg* 2012;18:481–4.
- 6 Murdoch DR, Corey GR, Hoen B, *et al.* Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med* 2009;169:463.
- 7 Akinosoglou K, Apostolakis E, Marangos M, *et al.* Native valve right-sided infective endocarditis. *Eur J Intern Med* 2013;24:510–19.
- 8 Holmes NE, Howden BP. What's new in the treatment of serious MRSA infection? *Curr Opin Infect Dis* 2014;27:471–8.
- 9 Brink AJ. Does resistance in severe infections caused by methicillin-resistant *Staphylococcus aureus* give you the 'creeps'? *Curr Opin Crit Care* 2012;18:451–9.
- 10 Miró JM, del Río A, Mestres CA. Infective endocarditis in intravenous drug abusers and HIV-1 infected patients. *Infect Dis Clin North Am* 2002;16:273–95.
- 11 Nishimura RA, Otto CM, Bonow RO, *et al.* 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 Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57–185.
- 12 Evangelista A, Gonzalez-Alujas MT. Echocardiography in infective endocarditis. *Heart* 2004;90:614–17.
- 13 Olaison L, Pettersson G. Current best practices and guidelines: indications for surgical intervention in infective endocarditis. *Infect Dis Clin North Am* 2002;16:453–75.
- 14 Jault F, Gandjbakhch I, Rama A, *et al.* Active native valve endocarditis: determinants of operative death and late mortality. *Ann Thorac Surg* 1997;63:1737–41.
- 15 Habib G, Hoen B, Tornos P, *et al.*, ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009;30:2369–413.
- 16 Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? *Circulation* 2010;121:1141–52.
- 17 Zainah H, Zervos M, Stephane W, *et al.* Daptomycin failure for treatment of pulmonary septic emboli in native tricuspid and mitral valve methicillin-resistant *Staphylococcus aureus* endocarditis. *Case Rep Infect Dis* 2013;2013:653582.
- 18 Sakoulas G, Moise PA, Casapao AM, *et al.* Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. *Clin Ther* 2014;36:1317–33.
- 19 Barber KE, Werth BJ, Rybak MJ. The combination of ceftaroline plus daptomycin allows for therapeutic de-escalation and daptomycin sparing against MRSA. *J Antimicrob Chemother* 2015;70:505–9.

Copyright 2015 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