CASE REPORT

Persistent bacteraemia caused by *Staphylococcus aureus* in the gall bladder

Alexander Tin Han Yu,¹ Tony Cun,² Esther Benamu,¹ Cybele Renault^{1,3}

¹Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University, Stanford, California, USA

²Department of Medicine, Stanford University, Stanford, California, USA

³Division of Infectious Diseases, Department of Medicine, Veterans Affairs Health Care System, Palo Alto, California, USA

Correspondence to

Dr Alexander Tin Han Yu, atyu@stanford.edu

Accepted 20 October 2017

SUMMARY

Staphylococcus aureus bacteraemia (SAB) remains a complex disease with a high associated morbidity and mortality, especially when it is able to establish an occult nidus safe from antimicrobial eradication. Without rapid identification and intervention, the nidus can cause persistent relapse of disease, morbidity and mortality. Having a high clinical suspicion for the foci of occult *S. aureus* is important, and awareness of potential sites of infection is critical and can be life-saving. We present a unique case of a 65-year-old man with end-stage renal disease receiving haemodialysis who developed septic shock from SAB. Despite 18 days of appropriate antibiotics, the patient had persistent high-grade bacteraemia until his gall bladder was ultimately percutaneously drained. The day after drainage, he cleared his blood cultures, although he ultimately passed away as he decided to transition his care to focus on comfort measures.

BACKGROUND

Staphylococcus aureus is a major cause of morbidity and mortality, with *S. aureus* bacteraemia (SAB) 30-day mortality rates estimated to be 20%.¹ This is due to the increasing prevalence of methicillin-resistant *S. aureus* (MRSA), as well as the organism's ability to cause aggressive, invasive and, at times, occult disease. The identification of potential sites of metastatic infection is paramount, as it not only affects the choice and duration of antibiotic but also reveals areas that can cause significant morbidity (eg, epidural abscesses), or act as sources of persistent bacteraemia and relapsed infection despite appropriate therapy. Paulsen *et al*² highlighted the complexity of SAB and its management in their 2016 meta-analysis, where they demonstrated an all-cause mortality benefit from infectious disease consultation due to increased detection of complications such as endocarditis and otherwise occult metastatic infection.

The ability of *S. aureus* to infect the gall bladder is not well recognised, and has not previously been reported in the literature as a potential source of persistent SAB. We present a case of MRSA bacteraemia leading to gall bladder seeding, which was undrained and led to persistent bacteraemia despite 18 days of appropriate antibiotic therapy. We then review previously described cases of *S. aureus* in the gall bladder.

CASE PRESENTATION

A 65-year-old man with end-stage renal disease (ESRD) requiring haemodialysis presented to our academically affiliated Veteran's hospital in the Spring of 2016. He was referred from his dialysis centre with fever, altered mental status and hypotension. Past medical history included coronary artery disease and severe peripheral arterial disease resulting in a left femoral–popliteal bypass graft and long-standing dry gangrene of the right first and fourth toes.

The patient was started on empiric intravenous vancomycin and piperacillin–tazobactam. Admission blood cultures returned positive for MRSA (four of four bottles), with a vancomycin minimum inhibitory concentration (MIC) of 1. Despite therapeutic vancomycin levels (trough >15 µg/mL), he required transfer to the intensive care unit for haemodynamic support 48 hours after admission. His tunnelled dialysis catheter (TDC) was removed and confirmed to be the source by culture of the catheter tip. On physical examination, he had no other identifiable sources. Notably, despite long-standing dry gangrene of the right toes, there was no erythema, warmth or purulence concerning for acute soft tissue infection.

Despite removal of the TDC and treatment with vancomycin, the patient continued to have persistent high-grade bacteraemia (all bottles growing MRSA and cultures positive <24 hours after collection). He continued to have no focal symptoms or signs to reveal a persistent focus of infection. Thus, a multitude of diagnostic studies were obtained in the pursuit of an asymptomatic source.

INVESTIGATIONS

A transoesophageal echocardiogram (TOE) revealed a small vegetation on the aortic valve without other valvular abnormalities. All indwelling lines were removed, with a catheter placed and removed on dialysis days. MRI of the gangrenous toes did not show a fluid collection or abscess. Spine MRI showed possible discitis but no epidural abscesses. After 11 days of persistently MRSA-positive blood cultures (all bottles drawn positive), ceftaroline was added to vancomycin for salvage therapy. A CT angiogram of the chest revealed a non-occlusive clot in the right internal jugular vein, which was radiographically felt to be a chronic clot associated with his prior TDCs rather than an acute process. The patient was not felt to be safe to undergo a TOE, and thus a transthoracic echocardiogram was

CrossMark

To cite: Yu ATH, Cun T, Benamu E, *et al*. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220656

Figure 1 CT of the abdomen with intravenous contrast. Arrow: Gall bladder with circumferential wall thickening.

ordered for follow-up and did not show changes in the previously seen vegetation or valves.

Despite a lack of focal findings on an abdominal examination, CT of the abdomen and pelvis was obtained, which showed circumferential gall bladder wall thickening and bowel oedema, initially attributed to volume overload from ESRD and fluid resuscitation (figure 1). However, a subsequent indium-111-labelled white blood cell (WBC) scan showed abnormal focal uptake in the gall bladder (figure 2), and notably no activity in his foot, graft or vasculature. Liver function tests (LFTs) at the time showed a minimally elevated aspartate aminotransferase of 50 IU/L and alkaline phosphatase of 161 IU/L, with normal alanine aminotransferase and bilirubin levels. His gall bladder was percutaneously aspirated, revealing 15 cc of serosanguinous drainage that later grew MRSA (vancomycin MIC 1) and vancomycin-resistant *Enterococcus faecium*.

OUTCOME AND FOLLOW-UP

Unfortunately, the patient's condition failed to improve, and he was transitioned to comfort care, per his wish. Blood cultures obtained 1 day after the gall bladder was drained were negative for MRSA. These were the first negative blood cultures during the course of his 19-day hospitalisation.

DISCUSSION

We present a unique case of a patient with TDC-associated MRSA bacteraemia seeding the gall bladder. The gall bladder then served as a persistent source of bacteraemia until drained, all without overt symptoms of gall bladder pathology. We extensively investigated other possible nidi of infection. The initial source was confirmed to be the TDC with >15 colonies of MRSA growth on the TDC tip and was removed. Tagged WBC scan and other imaging were not consistent with an infected clot, graft or toes, and the size and stability of our patient's small aortic vegetation seems unlikely to have been his reason for continued high-grade bacteraemia. Additionally, after 18 days of positive blood cultures, our patient cleared his blood less than 24 hours after gall bladder drainage. While previous case reports have noted the possibility of *S. aureus* bacteraemia leading to gall bladder pathology, this is the first reported case to our knowledge where after seeding, the gall bladder acted as a nidus for persistent SAB.

Biliary tract and gall bladder infections most frequently involve enteric Gram-negative organisms, with the majority of infections being polymicrobial. These infections are most commonly associated with obstructive physiology, classically due to gallstones or strictures.^{3 4} It has been estimated that the incidence of *S. aureus* causing biliary tract infections ranges anywhere from

Figure 2 Indium-111-labelled white blood cell scan. Physiological uptake occurs in the nasal bone, sternum and spleen. Arrow: Gall bladder with focal uptake.

0.5% to 7%.^{3–6} We found 18 reported cases of *S. aureus* infection associated with gall bladder or biliary tract disease in adults reported in the English-language literature.^{5–20}

Of these 18 previously reported cases (table 1), half presented initially with right-sided abdominal pain that suggested underlying gall bladder pathology. Of the remaining nine cases, two cases were too altered at the time of presentation to provide a reliable history or examination, and four cases did not comment explicitly on abdominal symptomatology.^{11 17} Thirteen of 18 patients were bacteraemic at the time of discovery of gall bladder infection, with blood culture results either not reported or not collected in three of the remaining five cases. Interestingly, the

Table 1 Summary of reported cases of gall bladder and biliary tract infections associated with *Staphylococcus aureus*

Case report	Age sex	Comorbidities	RUO pain	Fever	LFTs	GB inflammation on US/CT	Bacteraemia	Metastatic foci	Presumed source of bacteraemia	Management	Outcome
Diener <i>et al</i> ¹⁴	78 M	Ampulla of Vater CA	Not reported	Yes	Tbi/ALP elevated	Not reported	Not reported	Not reported	Stent placement	Intravenous antibiotics	Survival
Hemmer <i>et al</i> ¹⁶	74 F	GB CA	Yes	Yes	Normal	Yes	Not reported	No	N/A	PO antibiotics+cholecystectomy	Death
Ishak <i>et al</i> ⁹	18 M	None	Not reported	Yes	Tbi/AST/ALT elevated	Imaging not done	No	Not reported	N/A	Not reported	Death
Ishak <i>et al</i> ⁹	19 F	None	Not reported	Yes	Not reported	Imaging not done	No	Not reported	N/A	Not reported	Death
Ito <i>et al</i> ¹⁸	71 M	RCC, DM	No	No	AST/ALT 3x ULN	Yes	Yes	Yes	Unknown	Intravenous antibiotics+percutaneous GB drainage	Survival
Kim <i>et al</i> ¹⁰	36 F	AIDS, HCV	Yes	Yes	Normal	Yes	Yes	Yes	Unknown	Intravenous and PO antibiotics+percutaneous GB drainage	Survival
Lindberg <i>et al</i> ²⁰	23 M	Abdominal trauma	Not reported	Not reported	Not reported	Imaging not done	Yes	Not reported	Wound	Cholecystectomy	Death
Martin <i>et al</i> ¹³	67 F	ESRD, DM, prior MRSA bacteraemia	Yes	Yes	Normal	Yes	Yes	No	Biliary	Intravenous antibiotics+cholecystectomy	Death
Merchant <i>et al</i> (2002)	64 F	Prior cholelithiasis	Yes	Yes	Normal	Yes	Yes	No	Biliary	Intravenous antibiotics+cholecystectomy	Survival
Merchant <i>et al</i> (2002)	73 F	DM, CVD, AVR	Yes	No	ALP mildly elevated	Yes	Yes	No	CVC	Intravenous antibiotics+percutaneous GB drainage	Death
Merchant <i>et al</i> (2002)	48 M	HCV, cirrhosis, DM	Yes	No	AST 2x ULN	Yes	Yes	No	Unknown	Intravenous antibiotics+percutaneous GB drainage then cholecystectomy	Survival
Nepal <i>et al</i> ¹¹	50 F	DM	No	Yes	Mild AST/ALT elevation and ALP 2x ULN	Yes	Yes	No	Biliary	Intravenous antibiotics+cholecystectomy	Survival
Nguyen and Ramus ⁸	75 M	CVD	Yes	No	Mild ALP elevation	No	Yes	No	Wound	Intravenous antibiotics+cholecystectomy	Death
Segireddy <i>et al</i> ⁷	85 M	CVD, TAA, COPD, lung CA	Yes	Yes	Normal	Yes	Yes	No	N/A	Intravenous antibiotics+cholecystectomy	Survival
Segireddy <i>et al</i> ⁷	50 M	CKD, laryngeal CA	Yes	No	Normal	Yes	Blood cultures not done	No	N/A	Intravenous antibiotics+cholecystectomy	Survival
Tascini <i>et al</i> ¹²	72 M	COPD	No	No	Not reported	Not reported	Yes	Not reported	CVC	Intravenous antibiotics+percutaneous GB drainage	Survival
Thomas <i>et al</i> (1981)	19 M	None	No	Yes	Not reported	Not reported	Yes	Yes	Biliary	Intravenous antibiotics+cholecystectomy	Survival
Yao and Scialdone ¹⁷	35 M	AIDS, IVDU	No	Yes	ALP 4x ULN	No	Yes	No	Biliary	Intravenous antibiotics+percutaneous GB drainage then cholecystectomy	Survival
<i>Our patient</i>	65 M	ESRD, CVD, prior MRSA	No	Yes	Mild AST, ALP elevation	Yes	Yes	No	Gall bladder	Intravenous antibiotics+percutaneous GB drainage	Death

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVR, aortic valve replacement; CA, cancer; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; GB, gall bladder; HCV, hepatitis C virus; IVDU, intravenous drug use; LFT, liver function test; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; N/A, not applicable; PO, per os; RCC, renal cell carcinoma; RUQ, right upper quadrant; TAA, thoracic aortic aneurysm; Tbi, total bilirubin; ULN, upper limit of normal; US, ultrasound.

majority of patients described, in addition to our case, were found to have either normal or only mildly elevated LFTs.

In the cases previously described in the literature, it is challenging to determine if the gall bladder was the primary source of infection or if the gall bladder became secondarily seeded haematogenously. In four cases, there were no symptoms to suggest preceding bacteraemia, and there was no obvious alternative source of bacteraemia, making a primary gall bladder or biliary source possible. In one case, the original source of gall bladder infection was thought to be iatrogenic from biliary stent placement.¹⁴ However, in at least five cases, it appears that the gall bladder was likely seeded following the onset of bacteraemia. These patients had evidence of widely disseminated MRSA infection or had an obvious alternative primary source. None of the above cases had persistent SAB, although all had surgical resection or drainage of the gall bladder shortly after discovery.

Identification of metastatic infectious foci in the setting of SAB is crucial, as highlighted in recent studies.^{21 22} In a 2012 study, Vos *et al*²¹ examined the outcomes of patients undergoing aggressive, early search for metastatic foci of infection with ¹⁸F-fluorodeoxyglucose-positron emission tomography combined with low-dose CT (¹⁸F-FDG PET/CT) within 2 weeks of detection of Gram-positive bacteraemia. Compared with matched historical controls for whom no ¹⁸F-FDG-PET/CT was performed, a significantly higher number of metastatic infectious foci were diagnosed in the study group (67.8% vs 35.7%, $P < 0.01$), and the mortality rate at 6 months was lower (19.1% vs 32.2%, $P = 0.014$).²¹ A 2017 study from the Netherlands found that ¹⁸F-FDG PET/CT detected metastatic infectious foci in 73 of 99 patients with high-risk SAB, 71.2% of which were asymptomatic.²² ¹⁸F-FDG PET/CT led to treatment modifications in 74 of the 99 high-risk patients and 3-month mortality was lower compared with those who did not undergo ¹⁸F-FDG PET/CT (12.4% vs 32.7%, $P = 0.003$).²² Although we considered PET/CT and tagged WBC imaging modalities, we chose tagged WBC based on our desire to maximise test specificity in the setting of a high pretest probability of an undrained source of infection, particularly in a patient with concern for osteomyelitis (in the setting of toe dry gangrene) and presence of a vascular graft—two clinical scenarios where tagged WBC imaging is thought to be useful.^{23 24}

The preponderance of normal or only mildly elevated LFTs and the lack of symptoms in our patient and in prior reports highlight the importance for considering the gall bladder as a potential source in cases of refractory SAB despite appropriate antimicrobial therapy.

Learning points

- The gall bladder has the potential to act as a source of persistent SAB despite appropriate antimicrobial therapy.
- It is likely that *Staphylococcus aureus* infection of the gall bladder is under-recognised.
- The gall bladder should remain on the differential diagnosis as a potential nidus of *S. aureus* disease even in the absence of physical examination or laboratory abnormalities suggesting gall bladder pathology.

Contributors ATHY's contributions included drafting of the article, literature review and critical revisions of the article. TC's contributions included drafting of the article,

literature review and critical revisions of the article. EB's contributions included drafting of the article and literature review of the article. CR's contributions included critical revisions of the article and approval of article. All authors read and approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- van Hal SJ, Jensen SO, Vaska VL, *et al*. Predictors of mortality in *Staphylococcus aureus* Bacteremia. *Clin Microbiol Rev* 2012;25:362–86.
- Paulsen J, Solligård E, Damås JK, *et al*. The Impact of Infectious Disease Specialist Consultation for *Staphylococcus aureus* Bloodstream Infections: A Systematic Review. *Open Forum Infect Dis* 2016;3:ofw048.
- Brook I. Aerobic and anaerobic microbiology of biliary tract disease. *J Clin Microbiol* 1989;27:2373–5.
- Westphal JF, Brogard JM. Biliary tract infections: a guide to drug treatment. *Drugs* 1999;57:81–91.
- Merchant SS, Falsey AR. *Staphylococcus aureus* cholecystitis: a report of three cases with review of the literature. *Yale J Biol Med* 2002;75:285–91.
- Takara D, Sugawara G, Ebata T, *et al*. Preoperative biliary MRSA infection in patients undergoing hepatobiliary resection with cholangiojejunostomy: incidence, antibiotic treatment, and surgical outcome. *World J Surg* 2011;35:850–7.
- Segireddy M, Riederer K, Johnson LB. Molecular analysis of 2 cases of methicillin-resistant *Staphylococcus aureus* cholecystitis and a review of the literature. *Diagn Microbiol Infect Dis* 2010;68:304–6.
- Nguyen DQ, Ramus NI. A fatal case of MRSA septicaemia and gallbladder empyema. *Int J Surg* 2004;2:120–1.
- Ishak KG, Rogers WA. Cryptogenic acute cholangitis—association with toxic shock syndrome. *Am J Clin Pathol* 1981;76:619–26.
- Kim J, Gregson DB, Church DL. A case of acute cholecystitis caused by methicillin-resistant *Staphylococcus aureus* in an immunocompromised patient. *Can J Infect Dis Med Microbiol* 2011;22:e7–9.
- Nepal SK, Giri S, Panday K. Successful treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia and cholecystitis. *BMJ Case Rep* 2012;2012:bcr2012007281.
- Tascini C, Di Paolo A, Polillo M, *et al*. Case report of a successful treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and MRSA/vancomycin-resistant *Enterococcus faecium* cholecystitis by daptomycin. *Antimicrob Agents Chemother* 2011;55:2458–9.
- Martin J, Miller D, Ménard GE. Treatment considerations for recurrent MRSA bacteremia leading to cholecystitis. *J Gen Intern Med* 2011;26:669–72.
- Diener MK, Ulrich A, Weber T, *et al*. A case of methicillin-resistant *Staphylococcus aureus* infection following bile duct stenting. *World J Gastroenterol* 2005;11:1396–8.
- Thomas WEG, Thornton JR, Thompson MH. Staphylococcal acalculous cholecystitis. *Br J Surg* 1981;68:136.
- Hemmer PH, Zeebregts CJ, Roelofs E, *et al*. Gallbladder carcinoma presenting as an empyema with *Staphylococcus aureus*. *ANZ J Surg* 2004;74:289–90.
- Yao L, Scialdone C. Empyema of the gallbladder in a patient with AIDS-related complex. *Clin Imaging* 1990;14:157–8.
- Ito Y, Funabashi Yoh M, Toda K, *et al*. Staphylococcal scalded-skin syndrome in an adult due to methicillin-resistant *Staphylococcus aureus*. *J Infect Chemother* 2002;8:256–61.
- Nguyen DB, See I, Gualandi N, *et al*. Completeness of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection Reporting From Outpatient Hemodialysis Facilities to the National Healthcare Safety Network, 2013. *Infect Control Hosp Epidemiol* 2016;37:205–7.
- Lindberg EF, Grinnan GL, Smith L, *et al*. Acalculous cholecystitis in Viet Nam casualties. *Ann Surg* 1970;171:152–7.
- Vos FJ, Kullberg BJ, Sturm PD, *et al*. Metastatic infectious disease and clinical outcome in *Staphylococcus aureus* and *Streptococcus* species bacteremia. *Medicine* 2012;91:86–94.
- Berrevoets MAH, Kouijzer JJE, Aarntzen E, *et al*. (18)F-FDG PET/CT Optimizes Treatment in *Staphylococcus aureus* Bacteremia and Is Associated with Reduced Mortality. *J Nucl Med* 2017;58:1504–10.
- Glaudemans AW, Signore A. FDG-PET/CT in infections: the imaging method of choice? *Eur J Nucl Med Mol Imaging* 2010;37:1986–91.
- Lewis SS, Cox GM, Stout JE. Clinical utility of indium 111-labeled white blood cell scintigraphy for evaluation of suspected infection. *Open Forum Infect Dis* 2014;1:ofu089–8.

Copyright 2017 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