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CASE REPORT
Other

Purpura fulminans manifesting with *Staphylococcus aureus* endocarditis: a case report

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Background Purpura fulminans (PF) is a haematologic emergency that can occur in the setting of severe septic shock. Its pathophysiology is not well-understood; however, some evidence suggests it may be mediated by excessive protein C consumption.

Case summary In this case report, we describe a patient with PF secondary to methicillin-resistant *Staphylococcus aureus* endocarditis. She presented with severe septic shock and, despite haemodynamic improvement, developed a significant purpuric rash. Diagnostic work-up was notable for severely decreased serum levels of protein C. This patient was successfully treated with protein C concentrate and surgical valve replacement.

Discussion While PF is rarely associated with *S. aureus* infection, this presentation may be more frequently encountered among clinicians in the current opioid epidemic. Quick recognition is crucial and a multidisciplinary approach, including intravenous infusion of protein C, may be considered.

Keywords Purpura fulminans • Septic shock • Methicillin-resistant *Staphylococcus aureus* • Endocarditis • Protein C concentrate • Case report

Learning points

- Purpura fulminans is a rare but deadly complication of sepsis. It is associated with an acquired depletion of protein C.
- Quick recognition is crucial. Seek multidisciplinary consultation as indicated.
- Protein C repletion may be considered.

Introduction

Purpura fulminans (PF) is a life-threatening emergency with extensive tissue thrombosis and haemorrhagic skin necrosis. Classically, PF presents as the result of congenital or acquired protein C or S deficiency or in the setting of septic shock secondary to *Neisseria meningitidis*.[1] We describe the first reported case of endocarditis secondary to methicillin-resistant *Staphylococcus aureus* (MRSA) that was complicated by PF.

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Timeline

Sixteen months prior to presentation	Diagnosed with methicillin-resistant *Staphylococcus aureus* endocarditis; status post-bioprosthetic aortic valve replacement
Ten months prior to presentation	Heroin relapse complicated by recurrent endocarditis; medically managed with intravenous antibiotics
Upon presentation to the emergency room	Presented with severe septic shock
Hospital day 6	Diagnosed with purpura fulminans
Hospital day 7	Treatment with intravenous protein C initiated
Hospital day 19	Underwent bioprosthetic tricuspid valve replacement
Post-operative day 42	Completed 6 weeks of intravenous antibiotics and discharged to skilled nursing facility for further rehabilitation
Fifteen months after discharge	Seen in follow-up and doing well

Case presentation

A 30-year-old female was admitted for nausea, vomiting, and altered mental status. The patient had a past medical history of treatment-naïve Hepatitis C and remote intravenous drug abuse that was complicated by MRSA tricuspid valve (TV) endocarditis. She underwent a bioprosthetic TV replacement 16 months previously, however, suffered a heroin relapse 6 months later that was complicated by recurrent endocarditis; she was medically managed with 6 weeks of intravenous gentamycin, cefazolin, and rifampin. She was doing well until this presentation and taking no medications.

Her vital signs upon presentation were significant for fever of 40.5°C, blood pressure 70/30 mmHg, heart rate 134 b.p.m., and respiratory rate of 34 breaths per minute with appropriate oxygen saturation. Physical exam was remarkable for jugular venous distention of 10 cm and grade II/VI holosystolic and diastolic murmurs at the left lower sternal border. Skin had a livedo reticularis appearance with numerous tattoos. Electrocardiogram revealed sinus tachycardia with rightward axis deviation and right atrial enlargement. Admission labs were significant for white blood cell count of 23.4 $\times$ 10^9/L (3.7–11.0 $\times$ 10^9/L), platelet count of 37 000/μL (150–400 $\times$ 10^3/μL), lactic acidosis of 6.9 mmol/L (0.5–2.2 mmol/L), PT INR of 1.8 (0.9–1.3), D-dimer >35 200 ng/mL (<500 ng/mL), and fibrinogen 234 mg/dL (200–400 mg/dL). The patient was empirically started on vancomycin and piperacillin-tazobactam due to concern for septic shock; blood cultures subsequently grew MRSA and piperacillin-tazobactam was discontinued. Transthoracic and transoesophageal echocardiograms demonstrated thickened bioprosthetic TV leaflets with severe stenosis (peak/mean gradient 20/14 mmHg) and regurgitation and a large mobile echodensity consistent with vegetation (*Figure 1*). Chest computed tomography demonstrated numerous subpleural nodules concerning for embolic phenomena.

She was supported with aggressive volume resuscitation, maximal doses of three vasopressors (norepinephrine 50 mcg/min, epinephrine 50 mcg/kg/min, and vasopressin 0.04 units/min), and continuous venovenous haemodialysis due to acute renal failure with haemodynamic improvement by hospital day 3. However, her skin lesions progressively worsened and, by hospital day 5, included (i) violaceous discolouration of distal nose and ears, (ii) large purpuric plaques on arms and legs, most severe distally and of all digits, and (iii) haemorrhagic bullae scattered within purpuric plaques with large areas of grey discolouration suggestive of necrosis (*Figure 2*). Our leading differential diagnosis was vasopressor-induced skin necrosis given her significant exposure to vasopressors. However, the exposure was

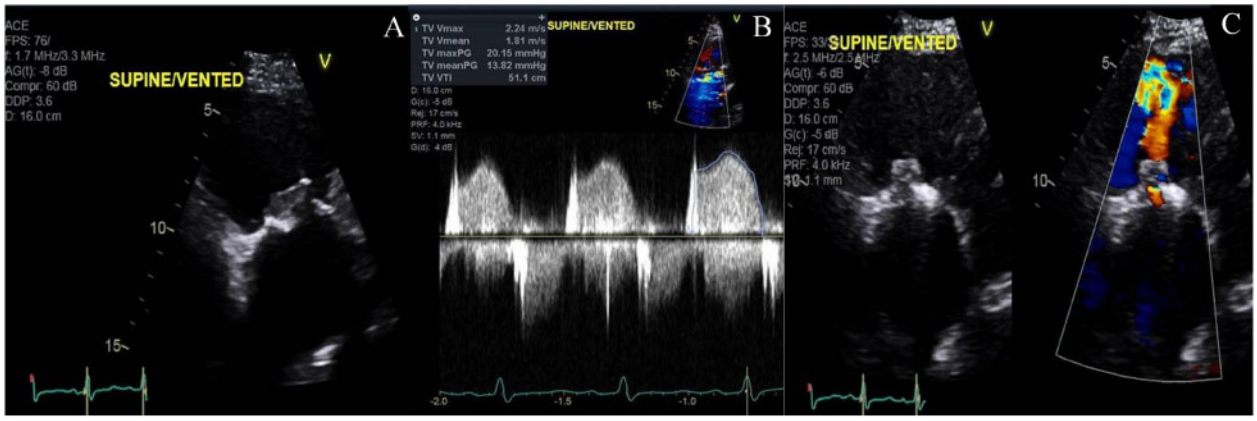

Figure 1 Transthoracic echocardiogram demonstrating a severely thickened bioprosthetic tricuspid valve with a large mobile echodensity consistent with vegetation. (*A*) Right ventricular inflow view in the parasternal long axis with (*B*) continuous wave Doppler and (*C*) apical four-chamber view with colour flow Doppler.

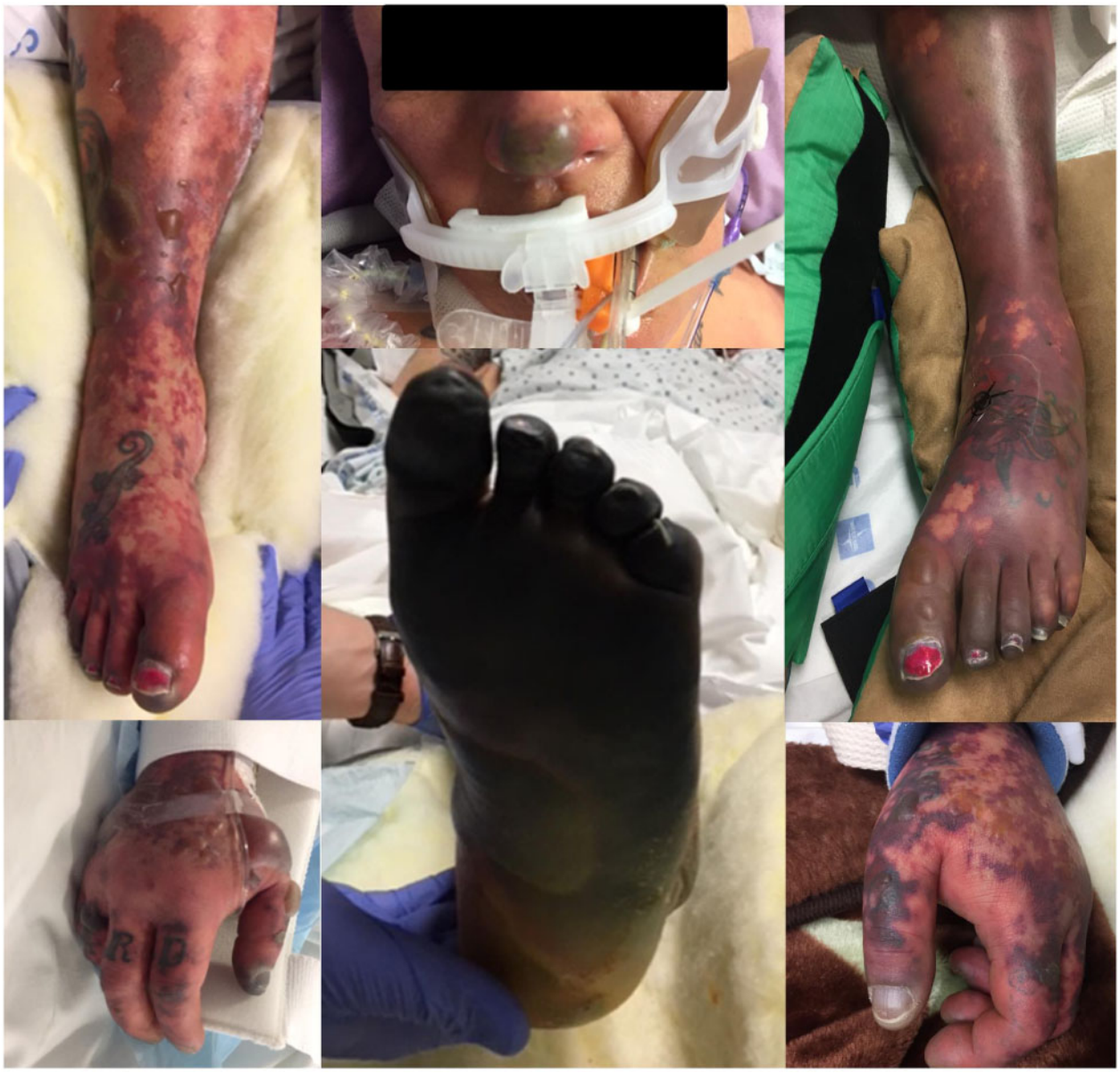

Figure 2 Purpuric plaques and scattered haemorrhagic bullae noted on face and distal extremities with large areas of necrosis.

not prolonged and the appearance of the rash was atypical. The haemorrhagic appearance of the rash raised a concern for a vasculitic process such as catastrophic anti-phospholipid syndrome, levamisole-mediated vasculitis given a history of substance abuse, or antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis in light of significant renal dysfunction. The differential also included cryoglobulinaemia or a viral-mediated process such as Hepatitis B or human immunodeficiency virus (HIV) given a history of untreated Hepatitis C and previous intravenous drug abuse. Finally, our differential included PF given a severe septic state with profound coagulopathy and thrombocytopenia despite no evidence of underlying liver dysfunction at baseline. Further work-up noted: C3 86 mg/dL (86–166 mg/dL), C4 14 mg/dL (13–46 mg/dL), negative lupus anticoagulant, serum levamisole, cryoglobulins, and negative serologic testing for active Hepatitis B, HIV, and anti-neutrophilic cytoplasmic antibodies. Function of protein C was 45% (76–147%), protein S 31% (59–131%), and antithrombin 54% (84–138%). Factor VIII: C of 441 suggested appropriate liver synthetic function. This constellation of findings was consistent with PF with secondary bullae formation and skin necrosis.

On hospital day 7, intravenous human protein C concentrate (Ceprotin) was initiated with 100 units/kg bolus followed by 50 units/kg infusion every 6 h. With this, skin lesions rapidly improved and thrombocytopenia resolved (*Figure 3*). Blood cultures remained positive on repeated cultures and ultimately cleared following transition

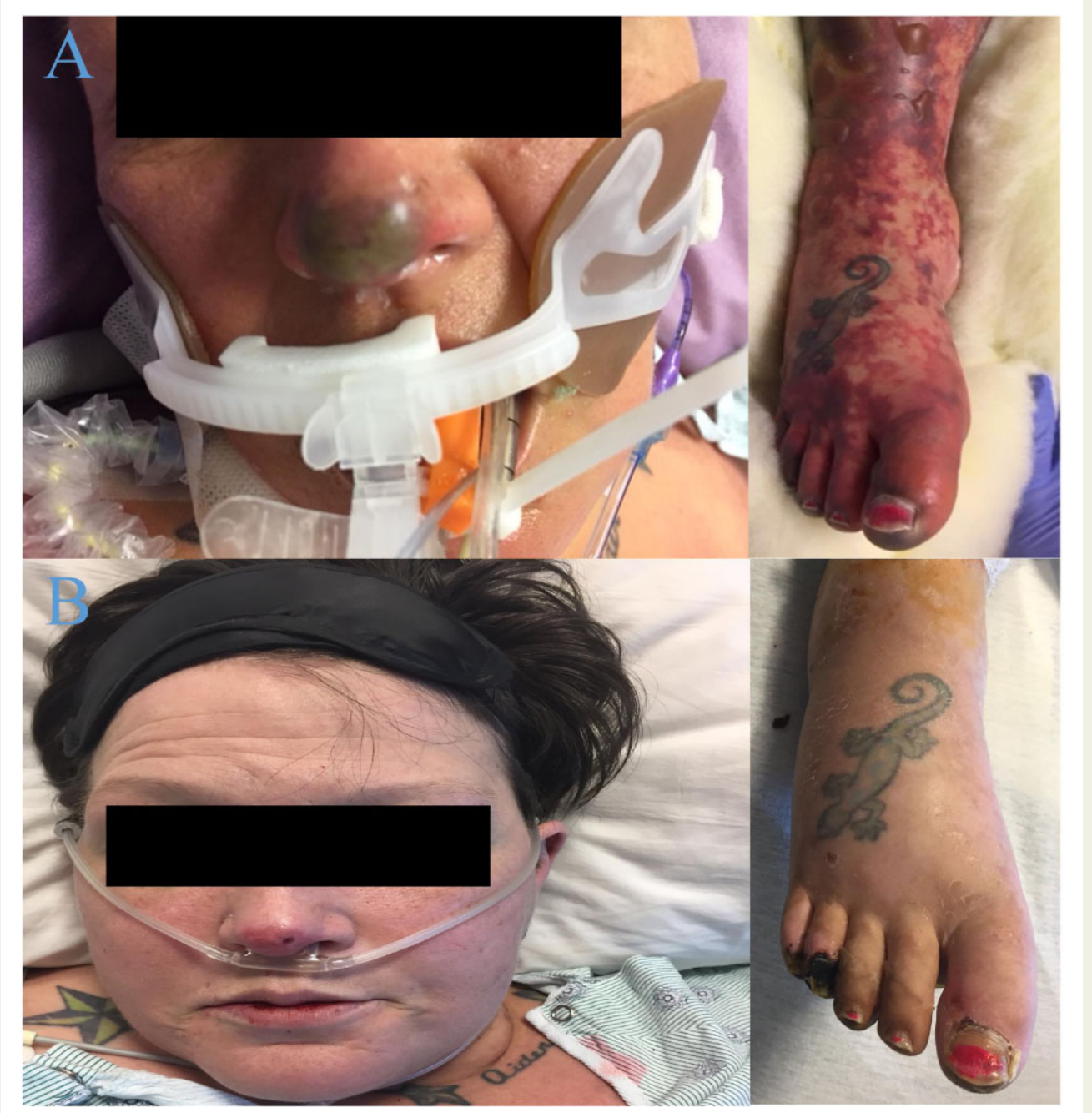

Figure 3 Skin lesions (*A*) before and (*B*) after receipt of protein C concentrate.

from vancomycin to ceftaroline on hospital day 16. She was taken to the operating room on hospital day 19 with findings notable for obstructive vegetation involving all three TV leaflets, abscess cavity around the annulus, and vegetations extending into the right ventricle and subvalvular space. She underwent debridement and removal of the infected valve (*Figure 4A*) followed by bioprosthetic TV replacement. Movat staining showed a pericardial tissue valve with marked acute inflammation and fibrinous vegetation (*Figure 4B*). Gomori methenamine silver stain showed bacterial cocci which on Gram stain revealed Gram-positive cocci in clusters.

Post-operatively she did well though remained dialysis dependent. Dry gangrene of her left foot and several right toes persisted. For this, she has followed with Vascular Surgery. She was ultimately discharged to a skilled nursing facility after completion of ceftaroline for 6 weeks for rehabilitation given a prolonged hospital stay. She has been seen in follow-up and is doing well.

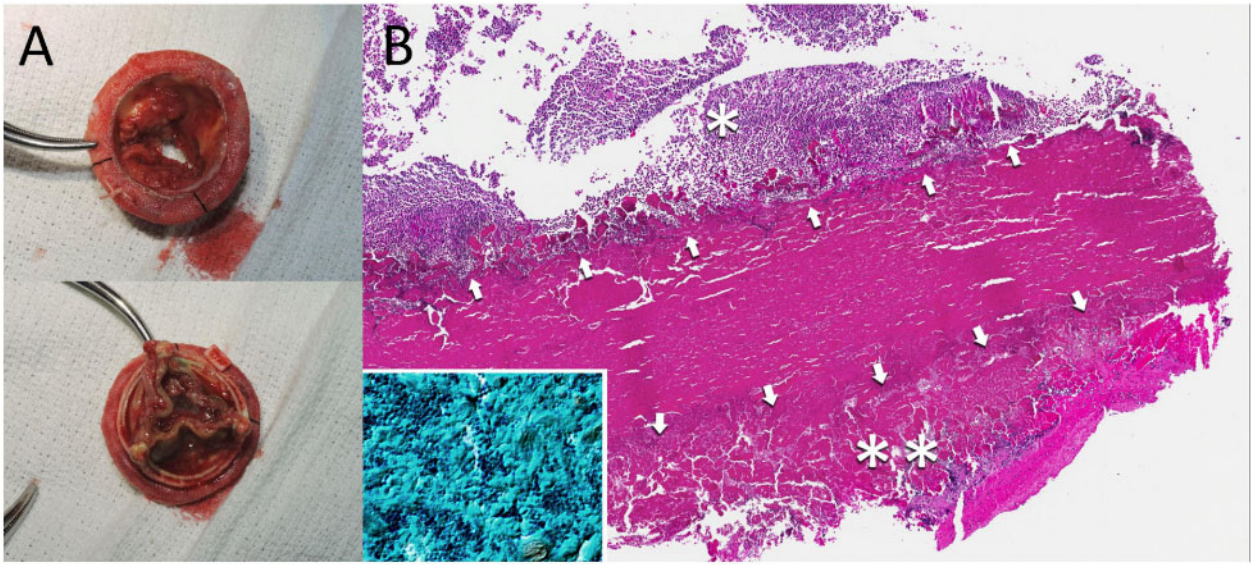

Figure 4 (*A*) Atrial and ventricular aspects of the infected bioprosthetic tricuspid valve. (*B*) Histologic examination shows a bovine pericardial tissue valve delineated by the arrows with acute inflammatory exudate (asterisk) and fibrinous vegetation (double asterisk). The diagnosis of bacterial endocarditis is confirmed by demonstrating the presence of bacterial cocci on the Gomori methenamine silver stain (inset).

Discussion

Sepsis-associated PF has a high mortality rate and includes four primary features: purpuric skin lesions, fever, hypotension, and disseminated intravascular coagulation. Meningococcemia is, by far, the pathogen most commonly attributed to PF, followed by streptococcal infection.[1] Despite 35 million estimated hospital discharges annually in the USA related to *S. aureus* bacteraemia,[2] there is a scant association between this organism and PF.[3–6] In the current opioid epidemic, this presentation may become more commonly encountered in clinical medicine.

Protein C is activated in the microcirculation by the binding of thrombin to the endothelial surface glycoprotein, thrombomodulin.[1] Activated protein C inactivates coagulation factors Va and VIIa, promotes fibrinolysis by inhibition of plasminogen activator inhibitor and reduction of thrombin activatable fibrinolysis inhibitor, and may decrease endothelial cell apoptosis in response to inflammatory cytokines. During an acute inflammatory response, an acquired deficiency of endogenous anticoagulants, including protein C, protein S, and antithrombin, develops.[7] Protein C is disparately reduced during this process which may in part be explained by a reduction in vessel wall expression of thrombomodulin and the endothelial cell protein C receptor. A rapid and prolonged depletion of protein C occurs in septic shock, presumably due to increased consumption, degradation, or decreased hepatic synthesis, causing widespread microvascular thrombosis with tissue toxicity and injury from an overall procoagulant effect and the production of proinflammatory cytokines. There is a strong correlation between the severity of protein C deficiency and the extent of thrombotic skin lesions and adverse clinical outcomes.[8]

In experimental models, use of activated protein C has been shown to decrease hypercoagulability, block tumour necrosis factor production, inhibit neutrophil attachment to selectins, and improve outcomes with meningococcal shock.[9]

Although the therapeutic use of activated protein C in severe septic states has been entertained since 1990 with several large randomized controlled trials demonstrating lack of efficacy,[10,11] limited data exists regarding its use in patients with PF with most published experience in the form of isolated case reports or retrospective case series.[5,12–14] In a randomized study investigating the use of protein C concentrate in children with severe meningococcal sepsis and PF, treatment was noted to be safe and led to dose-dependent increases of plasma activated protein C levels and resolution of coagulation imbalances.[15] Although there was no significant observed mortality benefit, this study did demonstrate that lower baseline levels of activated protein C was a significant predictor for mortality.

Conclusions

In this case report, we describe the first patient with PF secondary to MRSA endocarditis who was successfully treated with protein C concentrate and surgical valve replacement. Although there is scant association between PF and MRSA, this presentation may become more commonly encountered in the current opioid epidemic. Future studies with larger number of patients are indicated to determine whether administration of protein C concentrate can reduce mortality or amputation rates, thereby improving outcomes in these critically ill patients.

Lead author biography

Dr Anirudh Kumar is a general cardiology fellow at the Cleveland Clinic Foundation. He performed his undergraduate studies at Rice University, medical school at Baylor College of Medicine, and internal medicine training at Duke University Medical Center. He plans to pursue a fellowship in interventional and structural cardiology.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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