

Teaching Point
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Sepsis and a painful shoulder in a haemodialysis patient

Roshni Rathore¹, John Cheesbrough², Monika Pasztor³ and Alex Woywodt¹

¹Department of Nephrology, Lancashire Teaching Hospitals NHS Foundation Trust, Lancashire, UK, ²Department of Microbiology, Lancashire Teaching Hospitals NHS Foundation Trust, Lancashire, UK and ³Department of Microbiology, University Hospitals of Morecambe Bay NHS Foundation Trust, Lancashire, UK

Correspondence and offprint requests to: Alexander Woywodt; E-mail: Alex.Woywodt@lthtr.nhs.uk

Introduction

Soft tissue infections are common in patients with end-stage renal failure, particularly those with concomitant diabetes and peripheral vascular disease. They usually affect the lower extremities and their microbiology is dominated by gram-positive organisms. Empirical antibiotic treatment is usually straightforward, and success or failure is heavily influenced by the degree of underlying vascular disease. We present an unusual case of treatment-resistant and eventually fatal soft tissue infection of the shoulder in a maintenance haemodialysis patient with known chronic lymphocytic leukaemia (CLL). We discuss the case with emphasis on the differential diagnosis of unusual soft tissue infections in a dialysis patient. We review possible causes of treatment failure, unusual organisms and implications for treatment.

Case

A 59-year-old male patient on haemodialysis presented feeling unwell and with fever of 2 days duration.

The patient had a complex previous medical history and had been chronically ill for quite some time. He had complications of diabetes in the form of peripheral neuropathy and diabetic retinopathy. Furthermore, he had been diagnosed with CLL in July 2003, for which he had initially received chemotherapy with fludarabine and cyclophosphamide. As of now, he was deemed stable in this regard and had not received any chemotherapy whatsoever for several years. However, on the background of diabetic nephropathy, he had started haemodialysis in 2006. Four weeks prior to the current admission, he had been hospitalized with urinary tract infection and prostatic abscess. Cultures had been negative. He had received a prolonged course of ciprofloxacin and had made an uneventful recovery.

On presentation to our unit, he was febrile and appeared acutely unwell, although he was still haemodynamically stable. Clinical examination showed extensive soft tissue swelling with erythema on his left shoulder and a 4-mm

central necrotic lesion (Figure 1) as well as enlarged cervical lymph nodes bilaterally. On closer questioning, the patient recalled some minor trauma to the shoulder a few days previously. This minor trauma involved grazing his left shoulder along the door edge. The injury was so trivial that he had not taken any notice of it. The remainder of the clinical examination was unremarkable and no other focus of infection was apparent. Specifically, the chest was clear and the abdomen entirely soft. There was no evidence of diabetic foot infection. There was no suggestion of prostatic infection on clinical examination. His native forearm fistula looked unremarkable as well. C-reactive protein was 271 mg/L and plasma lactate was 4.6 mmol/L/(normal, 0.5–2.2 mmol/L). Blood cultures were obtained and intravenous co-amoxiclav was begun. However, the next day the patient was unchanged clinically and remained pyrexial while the soft tissue swelling had increased in size and also became very tender. The clinical impression was now clearly that of spreading cellulitis. Serum immunoglobulin levels came back as normal. Unusual organisms were considered as well as necrotizing fasciitis and a retained foreign body. Blood cultures were now reported as growing a gram-negative organism. Co-amoxiclav was replaced with Meropenem. Another detailed history was obtained; the patient lived in a rural location in

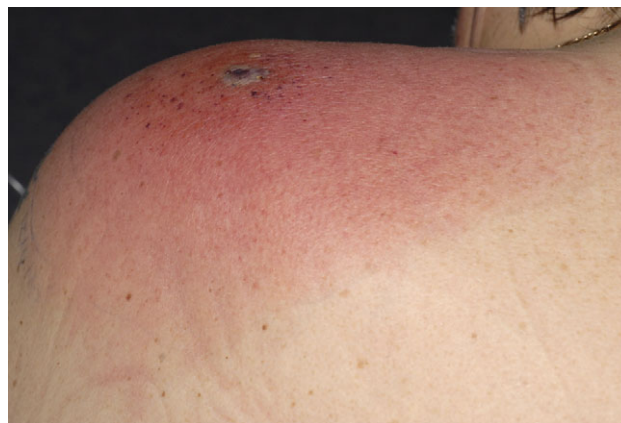


Fig. 1. The patient's left shoulder on Day 3.

North Lancashire. He had not travelled abroad and denied any recent contact with animals. A plain X-ray of the shoulder showed no evidence of a foreign body. Soft tissue ultrasound showed no collection. Magnetic resonance imaging (MRI) of the shoulder showed soft tissue swelling without evidence of joint involvement and no necrotizing fasciitis (Figure 2). The organism grown from peripheral blood was subsequently identified as *Serratia marcescens*, sensitive to Meropenem, but resistant to co-amoxiclav. A diagnosis of cellulitis and sepsis due to *S. marcescens* was made. We decided against trying to isolate the organism from a swab from the central necrotic lesion or from a punch biopsy, as we did not think this would be successful after several days of antibiotic treatment. However, the patient deteriorated further clinically. A decision was made against transfer to an intensive care unit, in line with the patient's previous wishes and substantial co-morbidity. He passed away on Day 11 of his hospital stay. An autopsy was not performed.

Discussion

Soft tissue infections are common in patients with end-stage renal failure. In a large study from the USA covering 424 700 days of dialysis experience, soft tissue infections (excluding post-operative cases) accounted for as many as 28.3% of all infectious episodes [1]. The majority of those (19.3% of all infections) occurred below the knee [1]. The microbiology of those infections is not well characterized and large studies are lacking. A small Turkish study in diabetic patients on dialysis suggested that the majority (59%) of soft tissue infections of the foot are caused by gram-positive organisms with *Staphylococcus aureus* in the lead [2]. In comparison, soft tissue infections that do not affect the lower extremities and are not connected to vascular access are less common and also less well charac-

terized. In the large American study cited above [1], such infections accounted for only 9% of all episodes (again excluding post-operative infections); the majority were community acquired [1].

Empirical therapy for moderate to severe cellulitis must include an agent that covers *Streptococcus pyogenes* and *S. aureus*, which are culprits in the majority of cases. Factors, such as immunosuppression, previous methicillin-resistant *Staphylococcus aureus* (MRSA) infection, previous antibiotic therapy and duration need to be considered as well. Failure to respond to standard treatment within 24 h or rapidly progressing area of cellulitis should prompt a thorough re-evaluation. The differential diagnosis of soft tissue infections not responding to standard treatment is extensive. Unusual pathogens (Table 1) or resistance patterns need to be considered as well as underlying structural causes and disorders that may mimic soft tissue infection (Table 2). In this case, calciphylaxis seemed unlikely as calcium, phosphate and parathyroid hormone were well controlled. The rapid onset of symptoms and quick deterioration argued against neutrophilic dermatosis, cutaneous metastasis and diabetic muscle infarction. We felt that clostridial infection was also very unlikely, as there was no evidence of gas clinically or on imaging. Infection due to *Pasteurella* sp. and *Capnocytophaga* sp. were also quickly excluded from our differential diagnosis, as the patient denied any contact with pets whatsoever. *Vibrio* and *Aeromonas* are rare but feared causes of severe soft tissue infection, which are usually acquired from contaminated brackish water or shellfish. Such exposure was also denied by the patient. Cutaneous anthrax was also briefly considered, not least due to the central necrotic lesion seen in this case. The disease is caused when spores of *Bacillus anthracis* are introduced subcutaneously, usually after contact with animals or their products, such as hides. Occasional cases have been seen in the USA in mail handlers during the 2001 bioterrorism attacks. Extensive oedema out of proportion to the size of the lesion and lymphadenopathy are also typical of cutaneous anthrax. Fever and malaise are also seen. However, there was no history of contact with animals or their products or mail effectively excluding this possibility. A retained foreign body was excluded with plain X-ray, although this, too, seemed unlikely based on the history. In summary, we felt necrotizing fasciitis or cellulitis due to an unusual organism were the most likely diagnoses.

Necrotizing fasciitis is a rare but feared subtype of severe soft tissue infection. One clinical hallmark of the disorder is an acutely unwell patient with pain that is out of proportion to the local findings on examination. The disease is characterized by the presence of liquefied, necrotic tissue and inflammation resulting from bacterial exotoxins released in the fascial layers. Early definitive imaging is crucial as surgical debridement of necrotic tissue is the mainstay of treatment of necrotizing fasciitis. A typical finding on imaging is thickening and enhancement of one or both of the superficial and deep fascial layers. Magnetic resonance imaging is often regarded as the investigation of choice in diagnosing necrotizing fasciitis. Perifascial fluid is detected with MRI as abnormally increased signal intensity on T2-weighted images along thickened deep fascial planes. Gas bubbles, if present, appear as focal signal voids on both

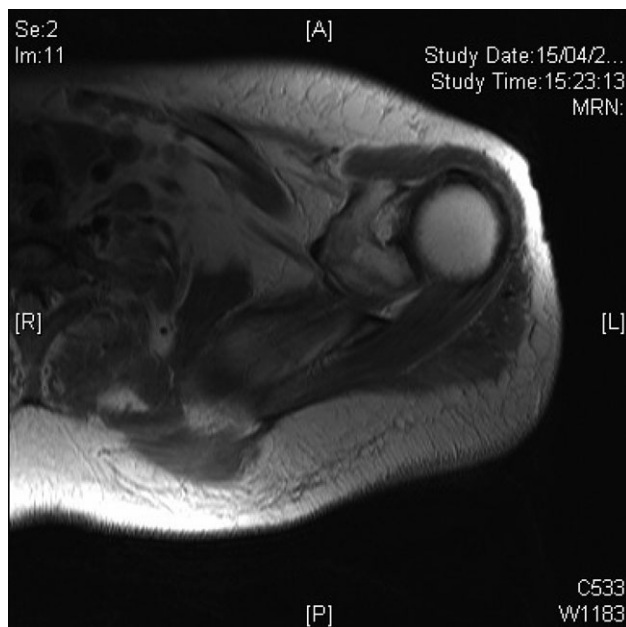


Fig. 2. MRI of the patient's shoulder. Note extensive soft tissue swelling. There is no evidence of necrotizing fasciitis or abscess.

Table 1. Soft tissue infections that do not respond to standard therapy

Organism	Comment
<i>Capnocytophaga</i> infection	Usually acquired through dog bite, systemic infection more common in asplenia
Clostridial infection	Contamination by <i>Clostridia</i> spores (spectrum of wound contamination, anaerobic cellulitis and gas gangrene)
Cutaneous anthrax	Contact with animal hide, wool or hair (sheep, goat, cattle) or contaminated heroin in intravenous drug abuse
<i>Eikenella corrodens</i>	Human bites. Organism is usually resistant to macrolide antibiotics.
Necrotizing fasciitis	Pain out of proportion of clinical findings. Group A <i>Streptococci</i> leading cause in absence of co-morbidity. Other microbes including <i>Staphylococci</i> , <i>Escherichia coli</i> and other aerobes and anaerobes more common if underlying disease present; MRI diagnostic.
<i>Pasteurella</i> infection	Acquired from cat or dog bites
<i>Pseudomonas</i> spp.	Typically causes ecthyma gangrenosum, often in patients with underlying neutropenia
<i>Pyomyositis</i>	Often <i>Staphylococcus aureus</i>
<i>Vibrio/Aeromonas</i>	Contact with brackish salt water or shellfish

T1- and T2-weighted images. In our case, these findings were all absent. This gave us confidence to exclude necrotizing fasciitis in our patient.

Eventually, in our patient, blood cultures grew *Serratia* and the diagnosis became clear. *Serratia marcescens* is facultative anaerobic, gram-negative bacillus, belonging to the family Enterobacteriaceae (Figure 3). Due to its ubiquitous presence in the environment and its preference for damp conditions, *S. marcescens* is also commonly found growing on bathroom tiles where it manifests as a pink discoloration and slimy film feeding off phosphorus-containing materials such as soap and shampoo residue. *Serratia marcescens* was discovered in 1819 by Venetian pharmacist Bartolomeo Bizio, as the cause of blood-red discoloration of Polenta [3]. Bizio named the organism 4 years later in honour of physicist Serafino Serrati; the epithet *marcescens* (Latin for 'decaying') was chosen as Bizio believed that the organism decayed into a mucilage-like substance upon reaching maturity. *Serratia marcescens* has been evoked as a naturalistic explanation of medieval accounts of the miraculous appearance of blood on the Eucharist. One example, the miracle of the mass at Bolsena in 1263, is commemorated in Raphael's famous fresco in the Vatican's Apostolic Palace [4].

An increased prevalence of infections caused by *Serratia* species in intensive care units has been reported. Infections include bacterial meningitis, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Soft tissue infection due to *Serratia* is uncommon [5, 6]. It has also been reported as a sequel to Iguana bites [7] and we excluded this cause of the infection in our patient. More recently, *Serratia* infections due to contaminated Propofol ampoules have been described [8]. Other nosocomial outbreaks have been reported as well. It has been found that *Serratia* is resistant to chlorhexidine [9], which is a commonly used disinfectant in hospitals. We were unable to ascertain the source of infection in our patient but we speculate he may have acquired it in the shower following his minor trauma to the shoulder. Similar cases of severe and even fatal *Serratia* soft tissue infection in dialysis patients have been described previously [10]. Pascual *et al.* [11] reported a fatal case of *Serratia* tissue and muscle infection in a renal transplant recipient [11]. Fatal cases of *Serratia* infection have also been described previously in leukaemia [12]. We also considered acquired immunoglobulin deficiency due to CLL in our differential diagnosis. Up to a quarter of

Table 2. Disorders that can mimic soft tissue infections^a

Calciophylaxis	Vascular calcification and skin necrosis in end-stage renal failure; deep biopsy required
Cutaneous metastases	Biopsy is crucial to diagnosis
Diabetic muscle infarction	Sterile cultures unless superimposed infection in poorly controlled diabetes
Pyoderma gangrenosum	Underlying IBD or malignancy, often refractory to treatment
Foreign body	History and imaging (plain X-ray) will often yield the correct diagnosis, surgical exploration required.

^aIBD, inflammatory bowel disease.

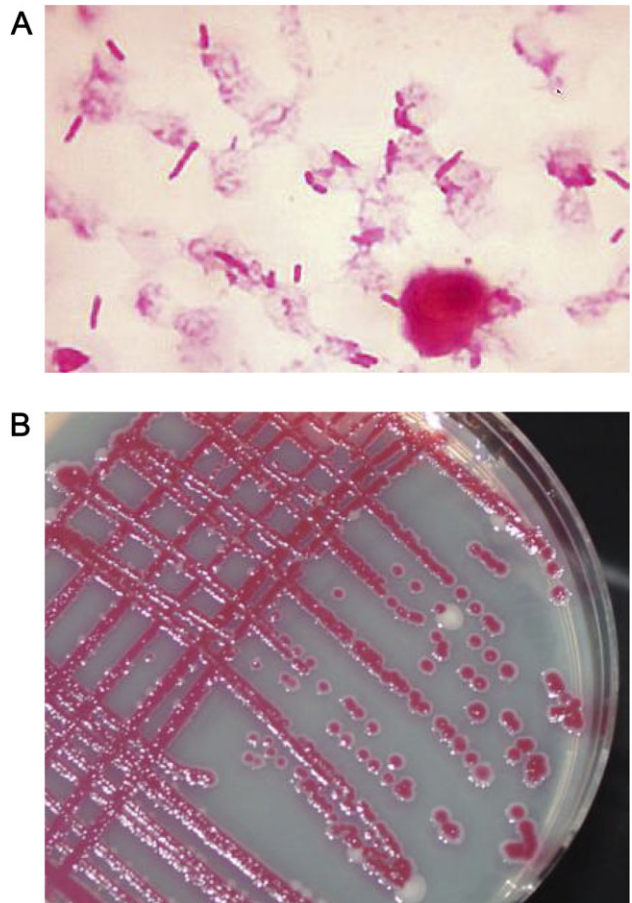


Fig. 3. Panel (A) Peripheral blood with gram-negative rods. Panel (B) *Serratia marcescens* (pink) on Muller-Hinton agar.

patients with CLL may have hypogammaglobulinaemia. However, this was not the case in our patient. Interestingly, *Serratia* can rarely cause necrotizing fasciitis as well [13], although this diagnosis was excluded by imaging as detailed above.

Generally, the organism is usually also susceptible to third generation cephalosporins, although these may be unreliable due to induced AmpC enzyme with resistance emerging [14]. The organism in our case was sensitive to Meropenem and treated accordingly. However, in hindsight, one wonders whether another antimicrobial agent, such as ciprofloxacin or gentamicin, could have been added to the regime. Quinolone resistance has been reported due to outer membrane protein alterations that result in diminished antibiotic permeability and mutations in the genes controlling DNA supercoiling although the isolate in this case was sensitive to the drug. All *S. marcescens* produce aminoglycoside-destroying enzymes that may affect the activity of tobramycin and amikacin but not gentamicin¹⁶. Unfortunately, aminoglycosides could not be administered in our case due to a previous history of severe ototoxicity, with persistent hearing impairment, as a sequel to Gentamicin treatment. It is worthwhile to note that strains of Meropenem-resistant *Serratia* sp. carry an inducible AmpC beta-lactamase which can be selected out by exposure to some beta-lactam antibiotics. Initial isolates can appear sensitive but resistance can emerge on treatment with cephalosporins as well as outbreaks due to multiresistant strains [15]. Despite the unfortunate outcome, the case provided an opportunity to reiterate the differential diagnosis and management of soft tissue infection, including unusual causes and organisms.

Conclusions

Our patient presented with progressive *Serratia* cellulitis that did not respond to initial antibiotic treatment with intravenous co-amoxiclav. A broad variety of uncommon organisms were considered as well as disorders that mimic soft tissue infections. Once *S. marcescens* was isolated from the bloodstream and sensitivities became available, the treatment was switched to Meropenem, which also penetrates extremely well into soft tissues. We therefore feel that the failure of treatment was due to the concomitant disease and immunosuppression in the context of chronic lymphatic leukaemia, rather than the choice of the antibiotic regime.

Teaching points

- (1) While the differential diagnosis of soft tissue infection not responding to standard treatment is extensive, it is important to bear in mind that the area of cellulitis can extend over the first 48 h of treatment even when a fully sensitive typical organism is the cause. Providing the patient is systemically improved, this should not be regarded as evidence of treatment failure
- (2) Causes of genuine failure of the antibiotic treatment include MRSA infection necrotizing fasciitis, clostridial infection, retained foreign body and unusual bacteria associated with contact to animals or contaminated water.
- (3) *Serratia marcescens* is a gram-negative rod that often colonises chronic cutaneous ulcers or wounds and may be implicated in hospital-acquired soft tissue infections. It is an infrequent cause of cellulitis acquired in the community but severe and fatal infections can occur in the immunocompromised host.
- (4) Infections due to gram-negative bacilli, such as *S. marcescens*, should be considered as a cause of cellulitis in immunocompromised patients.

Conflict of interest statement. None declared.

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