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CONCISE ARTICLE

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Four cases of necrotizing fasciitis caused by *Klebsiella* species

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Abstract Presented here are four cases of necrotizing fasciitis caused by *Klebsiella* spp. that were treated at one hospital over a 2-year period. *Klebsiella* necrotizing fasciitis can occur via direct inoculation, local trauma or, more commonly, hematogenous spread from other septic foci. Early, aggressive, surgical debridement and appropriate antimicrobial treatment are the cornerstones of treatment for this condition. Necrotizing fasciitis due to *Klebsiella* spp. is unique in that it is commonly associated with multiple septic foci. While liver abscesses and endogenous endophthalmitis are better-known associations of disseminated *Klebsiella* infection, necrotizing fasciitis is increasingly recognized as one of the manifestations of this syndrome. When treating *Klebsiella* necrotizing fasciitis, awareness of the potential for multiorgan involvement should prompt a thorough search for associated foci of infection.

Introduction

Necrotizing fasciitis is a life-threatening and limb-threatening soft tissue infection associated with rapidly progressive necrosis of the subcutaneous tissue and superficial fascia [1–3]. Single-organism necrotizing fasciitis is usually caused by invasive *Streptococcus* spp., most commonly group-A streptococci [1–3]. However, the incidence of single-organism necrotizing fasciitis caused by other organisms has recently been increasing [3–5]. Single-organism necrotizing fasciitis due to *Klebsiella* spp. is unique, since it is strongly associated with predisposing conditions, such as diabetes mellitus, and has a propensity for metastatic dissemination resulting in multiple sites of infection. Necrotizing fasciitis is increasingly recognized as a potential manifestation of disseminated *Klebsiella* infections [6, 7]. Awareness of the potential for multiorgan involvement should prompt a thorough search for these associated foci of infection. Described here are the cases of four patients treated at our institution between 2000 and 2002 for necrotizing fasciitis caused by *Klebsiella* spp. To our knowledge, only seven similar cases have been reported in the literature thus far [6–11].

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Case reports

Case 1 involved a 43-year-old man with a history of diabetes mellitus who presented with left-sided swelling of the neck associated with erythema, neck tenderness and fever. Subcutaneous crepitus was noted on the left side of his neck. Chest radiograph demonstrated subcutaneous emphysema with pneumomediastinum in the left neck and chest wall. An urgent computed tomography (CT) scan confirmed subcutaneous emphysema of his neck, chest wall and superior mediastinum. Nasolaryngoscope examination was normal. A presumptive diagnosis of gas gangrene was made and the patient was started on parenteral ceftriaxone and metronidazole.

Laboratory findings were as follows: total leukocyte count, 25.6 per mm^3; hemoglobin, 15.7 g/dl; platelet count, 183 per mm^3; serum creatinine, 132 μmol/l; and glucose, 23.8 mmol/l. Emergency wound debridement was performed, and necrotizing fasciitis of the left neck, extending from the middle-third of the sternocleidomastoid muscle to the clavicle, was noted intraoperatively. A

pure growth of a *Klebsiella* strain susceptible to ceftriaxone, cephalexin and gentamicin was isolated from blood, tissue and fluid cultures.

The erythema on the left side of the patient's neck gradually progressed to his chest wall and crepitus was again noted. Twenty days after the initial debridement, repeat CT scan demonstrated progression of the necrotizing soft tissue infection into the anterior chest wall and superior mediastinum. No other septic foci were noted in the chest or the abdomen. Repeat surgical debridement noted progression of the necrotizing infection superior to the angle of the jaw and inferior to the chest wall. Tissue cultures again grew a *Klebsiella* strain (with an antimicrobial susceptibility pattern identical to the first isolate) and methicillin-resistant *Staphylococcus aureus* (MRSA). A *Klebsiella* strain was also cultured from blood and urine. Intravenous vancomycin was added to the parenteral ceftriaxone and metronidazole regimen. The patient's condition improved after the second debridement, and he was discharged after 64 days of hospitalization. Antimicrobial therapy was continued orally for an additional 2 weeks after discharge.

Case 2 involved a 40-year-old diabetic man who was admitted with swelling of the left buttock associated with tenderness and fever. On examination, tenderness was elicited over the left gluteal region associated with minimal surrounding erythema and induration. A provisional diagnosis of cellulitis was made. Laboratory findings on admission were as follows: total leukocyte count, 10.8 per mm^3; hemoglobin, 12.8 g/dl; platelet count, 154 per mm^3; and serum creatinine, 132 mmol/l. He was started on parenteral cloxacillin and penicillin.

Despite intravenous antimicrobial therapy, the patient became progressively more septic and hypotensive with progressive swelling and tenderness of his buttock. CT scan of the pelvis demonstrated gas within the fascial planes and myositis of the gluteus maximus. No septic foci were noted in the abdomen or in the pelvic organs. Emergency wound debridement was performed 4 days after admission. Intraoperatively, extensive necrotizing fasciitis of the left buttock with an intramuscular abscess in the left gluteus was noted. Cultures of blood taken on admission and tissue taken during surgery grew a *Klebsiella* strain susceptible to ceftriaxone, cephalexin and gentamicin. The antibiotic regimen was consequently converted to ceftriaxone and gentamicin.

Repeat surgical debridement was performed 48 h later. A second set of tissue cultures using samples from this operation again produced a *Klebsiella* strain with the same antimicrobial susceptibility pattern. Urine culture performed to investigate frequency and dysuria resulted in the isolation of a *Klebsiella* strain with an identical antibiogram. The patient's condition improved after the second debridement and a secondary closure of his wounds was performed. He was discharged after 20 days of hospitalization. The parenteral ceftriaxone and metronidazole was administered for 16 days followed by oral cefuroxime. The total duration of antimicrobial therapy was 52 days.

Case 3 involved a 56-year-old man with a medical history of diabetes mellitus and chronic liver disease who was admitted with pain and swelling of his right knee and calf for the previous 2 days. He was a hepatitis B carrier. On examination, a mild effusion of the right knee associated with erythema and tenderness over the right calf was noted. His range of motion in the right knee was complete. He was also noted to have a non-tender hepatomegaly. Laboratory findings on admission were as follows: total leukocyte count, 21.48 per mm^3, hemoglobin, 11.3 g/dl; platelet count, 307 per mm^3; serum creatinine, 97 μmol/l; total bilirubin, 19 g/l; alkaline phosphatase, 162 U/l; alanine transaminase, 33 U/l; and aspartate transaminase, 57 U/l. Aspiration of the right knee was attempted, but no fluid was yielded. He was started empirically on intravenous penicillin and cloxacillin.

A CT scan of the patient's abdomen demonstrated an abscess (7.2×4.8 cm) in the right lobe of the liver and abscesses in his right kidney. Blood cultures taken on admission isolated a *Klebsiella* strain susceptible to ceftriaxone, cephalexin and gentamicin. A diagnosis of disseminated sepsis due to a *Klebsiella* sp. was made. Two-dimensional echocardiography and funduscopic examinations showed no evidence of infective endocarditis or endogenous endophthalmitis. Intravenous antibiotic therapy was changed to ceftriaxone, gentamicin and metronidazole. Human immunodeficiency virus serology was negative.

Erythema and pain of the patient's right lower limb progressed despite the antimicrobial treatment and were accompanied by ascending erythema, increasing skin induration and hemorrhagic bulla formation. Emergency wound debridement was performed 5 days after admission. Intraoperatively, necrotizing fasciitis of the lateral and posterior compartments of his right lower limb and popliteal fossa was noted. This was later confirmed on histological examination of the resected tissue specimen. Tissue culture resulted in pure growth of a *Klebsiella* strain.

The patient's recovery was complicated by disseminated intravascular coagulation and decompensation of chronic liver disease. He underwent five further surgical debridement procedures to control the infection and for wound closure. Repeat CT scan of the abdomen demonstrated progressive reduction in the size of the liver and renal abscesses, and these were therefore treated conservatively. The patient was discharged after 93 days in our hospital. Antimicrobial treatment was administered for a total duration of 125 days.

Case 4 involved a 76-year-old diabetic female who was admitted with right posterior thigh pain associated with fever and shortness of breath of 2 days duration. There was no history of injury or antecedent trauma. On examination she was febrile and hypotensive, and her right posterior thigh was swollen, tender and erythematous with small bulla formation. Laboratory studies showed the following values: leukocyte count, 12.4 per mm^3; hemoglobin, 17.2 g/dl; platelet count, 109 per mm^3; glucose, 28.2 mmol/l; serum creatinine, 256 μmol/l; alkaline

Table 1 Summary of cases of necrotizing fasciitis caused by *Klebsiella* species

Ref.	Patient age/sex	Underlying comorbidity/ predisposing condition(s)	Site(s) affected	Site of isolation of *Klebsiella* spp.	Type and duration of antimicrobial therapy	Outcome
PR	43/M	Diabetes mellitus	Left neck, chest wall and urinary tract	Tissue, blood and urine cultures	Parenteral ceftriaxone, metronidazole and vancomycin followed by oral cefuroxime (74 days)	Survived, 2 debridements
PR	40/M	Diabetes mellitus	Left buttock and thigh and urinary tract	Tissue, blood and urine cultures	Parenteral ceftriaxone and gentamicin followed by oral cefuroxime (52 days)	Survived, 2 debridements and secondary wound closure
PR	56/M	Diabetes mellitus, chronic liver disease, hepatitis B carrier	Right popliteal fossa and right lower limb, right lobe of liver and right kidney	Tissue, blood and urine cultures	Parenteral ceftriaxone, gentamicin and metronidazole followed by oral cefuroxime (125 days)	Survived, 6 debridements and skin graft cover; developed DIVC and decompensation of chronic liver disease
PR	76/F	Diabetes mellitus	Right posterior thigh	Tissue and blood cultures	Parenteral penicillin, cloxacillin and gentamicin (patient succumbed within 48 h)	Died, toxic shock syndrome: developed septic shock, ARF and DIC
[6]	71/F	Diabetes mellitus	Left leg, left eye, abscesses in the liver, both kidneys and pancreas	Tissue culture from the lower limb and pus from the liver abscess	Ceftriaxone	Survived, multiple debridements of the lower limb and evisceration of the left eye
[6]	40/M	Diabetes mellitus	Left lower limb, liver abscesses	Tissue cultures of the left lower limb and blood cultures	Cefazolin and gentamicin (37 days)	Survived
[7]	47/M	Diabetes mellitus	Both lower limbs and liver abscess	Tissue cultures from the left and right lower limb, pus from liver abscess and blood cultures	Ceftriaxone	Survived with 2 surgical debridements
[8]	52/M	Diabetes mellitus, liver cirrhosis	Both lower limbs, spontaneous bacterial peritonitis of ascitic fluid	Blood cultures, tissue cultures from the lower limb	Amoxicillin/clavunate and ofloxacin	Died
[10]	10 days/ M	None	Perianal region	Tissue culture from perianal wound		Survived

PR, present report; M, male; F, female; DIC, disseminated intravascular coagulation; ARF, acute renal failure; CSF, cerebrospinal fluid.

phosphatase, 66 U/l; total bilirubin, 71 μmol/l; and serum albumin 28 g/l. She was admitted with a presumptive diagnosis of cellulitis. Empirical parenteral penicillin, cloxacillin and gentamicin were administered.

A few hours later, the patient developed septic shock requiring inotropic support and was admitted to the intensive care unit. An emergency debridement was performed, and necrotizing fasciitis of the posterior thigh was noted intraoperatively. After the operation, the patient developed acute renal failure and disseminated intravascular coagulation to which she succumbed 30 h after admission. Tissue cultures taken at operation and blood culture taken on admission both grew a *Klebsiella* strain that was susceptible to ceftriaxone, cephalexin and gentamicin.

Discussion

Monomicrobial necrotizing fasciitis caused by *Klebsiella* spp. is a relatively new phenomenon, with the earliest case being reported in 1996 [11]. All four of the patients reported here were treated between 2000 and 2002. Although the *Klebsiella* isolates obtained from these patients were not speciated, they were most probably *Klebsiella pneumoniae*, since this is by far the most common species isolated from humans. Necrotizing fasciitis due to this organism is rare and, to our knowledge, only 11 cases (including the four presented here) have been reported in the literature. Most of the cases occurred in Asian countries, with nine cases being reported from Singapore and Taiwan, one occurring in a native of India who had recently traveled to Singapore, and one case occurring in Turkey [6–11].

All previous cases included in our literature review were found using a PUBMED search of the English-language medical literature with the following keywords: necrotizing fasciitis, *Klebsiella*, and liver abscess. All articles in which the term "*Klebsiella* necrotizing fasciitis" appeared in the abstract were retrieved. The references cited in these articles were examined to identify additional reports. For the purpose of our review, we selected only those cases of monomicrobial necrotizing fasciitis due to *Klebsiella* strains in which the organism was cultured from tissue specimens taken during surgical debridement. Only seven cases met this criteria [6–11]. Details of clinical presentation and the treatment administered were available for five of these patients. Thus, along with the four cases reported here, a total of nine cases were analyzed (Table 1).

Seven of the patients were male and two were female. Their ages ranged between 10 days and 76 years (median age, 47 years). Eight patients were diabetic and two had chronic liver disease. In seven cases at least one other organ was involved, i.e., liver, eyes, urinary tract, kidneys, pancreas, and peritoneum. Consistent with the literature, the commonest site of associated pathology was the liver. Bacteremia was documented in seven cases.

Genomic DNA typing using pulsed-field gel electrophoresis (PFGE) and capsular serotyping was not performed in our four cases. Capsular serotyping was performed in only one of the previously reported cases and in that case the capsular serotype was K1 [6].

The clinical features of necrotizing fasciitis caused by *Klebsiella* spp. are similar to those of necrotizing fasciitis caused by other organisms, i.e., severe sepsis, a propensity for multiorgan failure and high mortality [1–3]. Extensive fascia and subcutaneous tissue necrosis with overlying skin necrosis have been noted intraoperatively (see Table 1). However, the potential for multifocal infection is unique to necrotizing fasciitis caused by *Klebsiella* spp., and awareness of this feature is of paramount importance.

In necrotizing fasciitis caused by other organisms, the initiating event is usually direct inoculation from a superficial site (e.g., trauma, operative incision, preexisting ulcer or injection sites) [1–3]. In contrast, *Klebsiella* spp. may cause necrotizing fasciitis by two mechanisms, either direct entry from undetected trauma of the affected site or, more commonly, from hematogenous spread from other septic foci. Hematogenous spread from another site is supported by (i) the temporal sequence of infection (i.e., necrotizing fasciitis developing shortly after *Klebsiella* infection at other sites) [7, 8], (ii) simultaneous multifocal necrotizing fasciitis (e.g., both lower limbs) [7, 8] and (iii) the presence of a separate septic focus (usually with the primary source being liver abscesses). Regardless of the mode of entry, once established, necrotizing fasciitis due to *Klebsiella* spp. has a propensity to spread and to involve other organ systems. All four of our patients had bacteremia and two developed urinary tract infections with a *Klebsiella* strain after the onset of fasciitis. This underscores the invasive character of virulent strains of *Klebsiella* and the propensity for multiorgan involvement once a septic site has developed.

This infection is strongly associated with diabetes mellitus and chronic liver disease. The majority of previously reported cases of *Klebsiella* necrotizing fasciitis were associated with other septic foci of infection, commonly liver abscesses, urinary tract infections and endogenous endophthalmitis [6–8]. Therefore, in patients with *Klebsiella* sepsis associated with soft tissue infections, *Klebsiella* necrotizing fasciitis should be actively excluded. A high index of suspicion and awareness are important, since early diagnosis and surgical debridement have been shown to improve survival [3].

The antimicrobial susceptibility patterns of the *Klebsiella* strains causing necrotizing fasciitis in all four of our cases were identical, showing resistance to ampicillin but susceptibility to other antibiotics, including all cephalosporins and aminoglycosides tested. Multiple antimicrobial resistance was not detected. This antibiogram is characteristic of invasive strains of *K. pneumoniae* in the Orient (Singapore, Taiwan, China and Japan) [9]. The antimicrobial regimen chosen to treat our patients therefore included parenteral cephalosporin (ceftriaxone) in combination with an aminoglycoside (gentamicin). The parenteral antimicrobial agents were discontinued after 2 or 3 weeks,

depending on clinical response. At this juncture, the aminoglycoside was stopped to avoid nephrotoxicity and an oral cephalosporin was administered for an additional 1–2 months to prevent a relapse.

Geographical variation in the virulence of *K. pneumoniae* strains has recently been recognized [12], and the polysaccharide capsule envelope is considered a major pathogenic factor for the organism. K1 and K2 are the most virulent serotypes [13]. The K1 serotype has been found to be rare in North America and Europe in seroepidemiology surveys, but it is the predominant serotype in the Orient [12–16]. This may explain why the most common etiologic agent of pyogenic liver abscess in the West is *Escherichia coli* while in the Orient, *Klebsiella* spp. comprise the most common causative organism [13, 16]. Furthermore, the syndrome of disseminated *Klebsiella* infection seems to occur exclusively in cases of infection with serotypes K1 and K2 [13].

The syndrome of disseminated *Klebsiella* infection with multiple metastatic septic foci is an emerging clinical syndrome seen predominantly in the East, where virulent strains of *K. pneumoniae* (K1 and K2 serotype) appear to be predominant. It is important to recognize that necrotizing fasciitis can be part of this syndrome. Necrotizing fasciitis is a surgical emergency, and early debridement is life saving. Patients with liver abscesses due to *Klebsiella* spp. who develop cutaneous signs of soft tissue infections, such as erythema, swelling and tenderness, should be treated with caution and a high index of suspicion. When monomicrobial necrotizing fasciitis is due to a *Klebsiella* sp., the clinician should also be aware of this syndrome, since the associated conditions may require urgent treatment for optimal outcome. Endogenous endophthalmitis, for example, is a sight-threatening condition with a poor prognosis if not treated early.

In summary, necrotizing fasciitis due to *Klebsiella* spp. is a unique entity, particularly in the Orient where virulent strains of *Klebsiella* predominate. It is now clear that *Klebsiella* spp. are capable of causing necrotizing fasciitis either as an isolated phenomenon or in association with a disseminated syndrome. The condition is frequently associated with other septic foci of infection and multi-organ involvement. Disseminated infection with *Klebsiella* spp. should be borne in mind when a *Klebsiella* strain is isolated from any source such as liver abscess, tissue from sites of necrotizing soft tissue infections, peritoneal fluid or any normally sterile site.

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