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Case Report

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Fatal necrotizing fasciitis due to *Streptococcus pneumoniae* after renal transplantation

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Introduction

Necrotizing fasciitis is an uncommon, devastating soft-tissue infection primarily involving superficial fascia, subcutaneous fat and deep fascia that relatively spares skin and underlying muscle [1]. It most frequently occurs in the abdominal wall, extremities and perineum, where the pathogen may be introduced in the subcutaneous space via disruptions of overlying skin. Besides direct inoculation, haematogenous spread from a distant site may probably occur. The disease predominantly develops in diabetics, alcoholics, immunosuppressed patients, illicit drug users and patients with peripheral atherosclerotic vascular disease. Despite rapid diagnosis and treatment, case fatality rate is high and any delay may correlate with worse outcome [1].

A wide variety of organisms have been implicated in necrotizing fasciitis and are causative for monomicrobial (most often due to β-haemolytic streptococci group A) and polymicrobial (most often due to non-group A streptococci plus anaerobes and/or facultative anaerobes and often Enterobacteriaceae) infections. Necrotizing fasciitis due to *Streptococcus pneumoniae*, however, is exceedingly rare. Here we report a case of pneumococcal fasciitis in a patient after renal transplantation and present a concise mini-review of the literature.

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Case

A 64-year-old white male without prior splenectomy underwent living related renal transplantation for autosomal-dominant polycystic kidney disease on 27 November 2001. His initial immunosuppressive treatment (body weight 85 kg) consisted of prednisone (50 mg/day), mycophenolate (1 g twice daily) and cyclosporin (375 mg twice daily); no anti-lymphocyte antibodies were necessary to prevent/treat graft rejection. The patient felt well with stable renal function until 29 December, when he slipped on ice and fell on his left elbow. Six days later, the elbow became exquisitely tender, but on physical examination no abnormal finding was noted and the skin was intact. On 1 January 2002, the patient was symptomatically treated for coughing and a sore throat; no diagnostic procedure was undertaken. During an outpatient visit on Friday 4 January, conventional radiographies were repeated because of persistent pain in the left elbow and now revealed an intra-articular fracture of the olecranon. The limb was subsequently immobilized with a half-open splint. On the same occasion, a rise in serum creatinine (from 142 to 242 µmol/l; normal range 70–105 µmol/l), a reduction in urine volume and an elevated C-reactive protein (358 mg/l; normal range < 5 mg/l) was found. Since an acute transplant rejection was suspected, the patient was scheduled for renal biopsy on the following Monday, but was not hospitalized over the weekend because of the apparently good general clinical condition. On 6 January, the patient noticed exaggerated pain in the left elbow and sudden onset of dyspnoea and anuria for which he presented in the emergency room. At this time, regular medications included mycophenolate (1 g twice daily), cyclosporin (175 mg twice daily), prednisone (30 mg/day), atenolol (25 mg/day) and dalteparin (5000 IE subcutaneously/day). On physical examination, the patient appeared severely ill with cool and mottled extremities. Blood pressure

was 70/50 mmHg, his heart rate was 120 beats per min, respiratory rate was 40 per min and body temperature was 35.7°C. Soon after arrival, the patient had to be intubated because of respiratory failure. On mechanical ventilation, bronchial breath sounds and occasional rales were heard over the base of the right lung. A chest radiograph showed left-sided pleural effusion and atelectasis as well as an opacification of the lower right lung. Laboratory examinations revealed a normal leukocyte count with 47% band forms and a normal platelet count; C-reactive protein was 283 mg/l, serum creatinine 312 µmol/l, creatine kinase 7561 (<270) U/l, aspartate aminotransferase (ASAT) 434 (<50) U/l and potassium 7.5 mmol/l. In addition, severe metabolic acidosis was noted (pH 6.88, lactate 12.8 (0.6–2.4) mmol/l; bicarbonate 10.1 mmol/l, base excess −22.9 mmol/l). Continuous veno-venous haemodiafiltration was started for acute anuric renal failure with haemodynamic instability and maintained during the entire hospitalization. After removal of the splint, a pasty swelling around the elbow with large erythematous changes of the skin of the upper arm was found. A presumptive diagnosis of septic shock due to soft-tissue infection was made and antibiotic therapy with adjusted doses of clindamycin, piperacillin/tazobactam and netilmicin was started. Treatment with cyclosporin and mycophenolate was discontinued. The serum concentration of cyclosporin was 273 µmol/l 12 h after admission. A local aspirate of the elbow revealed Gram-positive diplococci. Subsequently, repeated blood cultures and local aspirates yielded *S.pneumoniae* serogroup 9 with susceptibility against penicillin. Despite haemodynamic instability requiring large doses of vasoactive drugs, surgical exploration and extensive debridement was performed immediately. The intra-operative site showed vast necrosis of skin, subcutaneous tissue and muscle fascia. Notwithstanding, haemodynamic status remained unstable, severe lactic acidosis persisted (minimal lactate 8.4 mmol/l) and clinical conditions further deteriorated with developing neutropenia (nadir 0.64 $\times 10^9$/l), thrombocytopenia (55×10^{12}/l), liver failure (ASAT 23936 U/l, alanine aminotransferase 8593 (<50) U/l, alkaline phosphatase 302 (30–115) U/l, ammonia 268 (9–33) µmol/l), rhabdomyolysis (creatine kinase 9137 U/l, myoglobin 41654 (23–72) µg/l, LDH 24519 (150–420) U/l) and coagulopathy, resulting in severe wound bleeding that could not be controlled by repeated transfusions of fresh frozen plasma, platelets and red blood cell units. On 7 January, 35 g of human immunoglobulins were transfused for uncontrolled septic shock and assumed β-haemolytic streptococcal fasciitis. Despite a second surgical debridement and continued antibiotic coverage, soft-tissue necrosis spread involving the lower abdominal wall and left leg within one day. The patient died of multiorgan failure 44 h after admission. A necropsy was not permitted.

Prior to the present illness, the patient had been successfully vaccinated for hepatitis B, but he never received vaccination for pneumococci. Serologies were negative for HIV-1 and -2, HTLV-1 and -2, and hepatitis C.

Discussion

Streptococcus pneumoniae is an important bacterial pathogen and major cause of pneumonia, meningitis, sinusitis and otitis media in humans. It may less frequently cause endocarditis, arthritis, peritonitis and, uncommonly, a variety of other infectious diseases. Skin and soft tissue manifestations of invasive pneumococcal disease are extremely diverse in presentation and include cellulitis, subcutaneous and muscle abscesses, wound infections, mastitis and inguinal adenitis [2]. Nevertheless, necrotizing fasciitis due to *S.pneumoniae* is rare and only a few cases [3,4] have been reported to date. In general, primary or secondary defects in antibody formation and complement, insufficient or poorly functioning polymorphonuclear cells, and defective clearance of pneumococcal bacteraemia have an important impact on the immunologic capacity of the host and predispose to pneumococcal infections. In cases of necrotizing fasciitis due to *S.pneumoniae*, one patient had antecedent blunt trauma but was otherwise healthy [3], whereas risk factors in others included illicit drug abuse, systemic lupus erythematodes, diabetes mellitus, renal insufficiency, tumour necrosis factor antagonist or other immunosuppressive therapy and possibly intramuscular injection of nonsteroidal anti-inflammatory drugs. To our knowledge, this is the first report of a patient who developed rapidly fatal necrotizing fasciitis due to *S.pneumoniae* shortly after renal transplantation. Besides immunosuppressive drugs, no other risk factor could be identified; the patient was not splenectomized and did not suffer from frequent infections during his lifetime. Blunt trauma leading to local haematoma may have provided a nidus for localization of infection, as suggested previously [3]. However, the route of infection in our case remains uncertain, with both haematogenous spread from an assumed pulmonary infection or direct inoculation through a small wound in the skin being valuable possibilities. As evidenced in this case, the diagnosis may be difficult early in the course of illness because of the paucity of skin findings, with cellulitis accompanied by local pain and fever being commonly the first signs; indeed, pain out of proportion to physical findings in a patient with evidence of a systemically toxic condition should raise the clinical suspicion of necrotizing fasciitis [1]. Treatment modalities comprise early aggressive surgery with frequent wound debridements, broad-spectrum antibiotic coverage, hyperbaric oxygen, and supportive care [1].

The frequency and seriousness of pneumococcal infections in renal transplant recipients has been recognized for over 20 years and immunization of these

patients has been suggested [5]. Although current guidelines recommend the use of pneumococcal vaccine for all adults aged $\geqslant 65$ years and for selected people aged <65 years, including those taking immunosuppressive therapy and those who had undergone organ transplantation [6], practices of immunization vary considerably in the latter situation even today. This controversy may be mainly due to studies suggesting suboptimal vaccine coverage since a diminished immune response with loss of protective antibodies has been observed [7]. However, a recent study concluded that polyvalent polysaccharide pneumococcal vaccination is safe and effective in patients with well-functioning renal allografts in the short term [8]. It is of note that the subtype of the *S.pneumoniae* isolated in our case is covered by the actual polyvalent pneumoccocal vaccine. One may only speculate that a prior vaccination would have reduced the severity and ultimately the fatality of pneumococcal disease in this patient. Importantly, further well-designed long-term controlled studies are needed to elucidate the efficiency of a pneumococcal vaccination in the renal transplant population.

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