Case Report

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Fatal necrotizing fasciitis caused by *Haemophilus influenzae* serotype f

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We describe a case of fatal lower limb necrotizing fasciitis in a 65-year-old man who was treated with broad-spectrum antibiotics, limb amputation and tissue debridement. The causative organism was identified by PCR as *Haemophilus influenzae* serotype f, which is a highly unusual cause of necrotizing fasciitis.

Case report

A 65-year-old man with a history of hypertension, gout and excess alcohol consumption (70 units per week) presented to the Accident and Emergency (A&E) Department in May 2007 with a swollen, painful left leg. He reported lower leg swelling that had started 36 h previously, progressive bruising and erythema of his thigh and intermittent rigors. There was no preceding trauma.

On examination, he was noted to be jaundiced with a palpable liver. He was haemodynamically unstable with hypotension and oligouria. There were haemorrhagic blisters and surrounding erythema over the medial aspect of his left thigh. Arterial blood gases revealed a metabolic acidosis and routine blood tests demonstrated Hb 13.7 g dl⁻¹, white cell count 4.8×10^9 l⁻¹, platelets 82×10^9 l⁻¹ and creatinine 300 µmol l⁻¹. The provisional working diagnosis was of necrotizing fasciitis, and broad-spectrum antibiotic therapy was commenced, as per the hospital empirical antibiotic treatment guidelines, with benzylpenicillin 2.4 g four hourly, clindamycin 600 mg q.d.s. and metronidazole 500 mg t.d.s. A single dose of cefuroxime 1.5 g was administered to provide Gram-negative cover pending tissue microscopy and culture results. He was transferred to the intensive care unit and a skin biopsy was performed for frozen section histology. The skin sample (Fig. 1) showed complete loss of the epidermal surface with underlying dermal and subcuticular oedema and patchy inflammation. The inflammatory response was mainly centred on vascular structures with evidence of fibrinoid necrosis, vascular lumen obliteration and local apoptotic cell debris. Some rather granular matter was present, suggestive of bacterial debris, although the Gram stain did not reliably confirm organisms by light microscopy.

Following a period of stabilization on the intensive care unit, and 6 h after his initial presentation, he underwent a left above knee amputation and extensive debridement of necrotic tissue. Post-operatively he remained septic with increasing inotropic requirements. His renal function

deteriorated further requiring continuous veno-venous filtration and he developed multi-organ failure with worsening metabolic acidosis. In light of his deteriorating condition, meropenem was added to his antibiotic regime and he underwent further debridement of the left leg stump. Unfortunately, his condition continued to deteriorate despite intensive therapy and he died within 14 h of admission.

Blood cultures had been taken in A&E prior to the administration of antibiotics and further specimens received for culture included swabs of the blisters and surgically debrided deep tissue. *Haemophilus influenzae* was isolated from all of these specimens with no other organisms being detected. The organism did not possess a β -lactamase enzyme and was found to be susceptible to amoxicillin and cefuroxime. The reference laboratory (Colindale, UK) subsequently confirmed it to be serotype f using PCR. Following 5 days prolonged incubation, the tissue cultures and skin swabs remained negative for other organisms, including anaerobes.

Discussion

Necrotizing soft tissue infections are rare infections that are associated with a high mortality and can affect any of the layers within the soft tissue compartment (dermis, subcutaneous tissue, superficial fascia, deep fascia or muscle). They were first described by Jones (1871) as 'hospital gangrene' and Wilson (1952) subsequently used the term necrotizing fasciitis, which is now recognized to describe rapidly progressive infection of the fascia and subcutaneous tissue, with thrombosis of the microcirculation.

Using bacteriological differentiation, two types of necrotizing fasciitis are described (Morton & Pasternack, 2005). In Type I, at least one anaerobic species is isolated in combination with other facultative anaerobes, including streptococci (other than group A) and members of the *Enterobacteriaceae*. In Type II, group A streptococci are

Fig. 1. Frozen section of a skin biopsy. The skin sample showed complete loss of the epidermal surface (E) with underlying dermal and subcuticular oedema with patchy inflammation. The inflammatory response was mainly centred on vascular structures (arrowed) with evidence of fibrinoid necrosis, vascular lumen obliteration and local apoptotic cell debris. Some rather granular matter was present, suggestive of bacterial debris, although Gram stain did not reliably confirm organisms by light microscopy (haematoxylin and eosin stain, original magnification $\times 200$).

isolated either alone or in combination with other species. However, no combination of bacterial species is either diagnostic or found in all cases (Anaya & Dellinger, 2007).

A case series of 89 patients with a diagnosis of necrotizing fasciitis reported that 54 % of cases were polymicrobial, with streptococcal species, staphylococcal species, enterococci and members of the *Enterobacteriaceae* being common isolates. Of the remaining cases, 28 % were monomicrobial and in 18 %, no organism was isolated (Wong *et al.*, 2003). More recently, a published series of 87 patients with necrotizing fasciitis reported monomicrobial infection in 59 patients (67.8 %). *Staphylococcus aureus* and members of the *Enterobacteriaceae* accounted for approximately half of these cases with other organisms causing monomicrobial infection including β -haemolytic streptococci (primarily group A), *Aeromonas* species, *Pseudomonas aeruginosa*, *Vibrio vulnificus* and *Acinetobacter baumannii*. Mixed infection was documented in 17 patients and there was no organism identified in 11 patients (Liu *et al.*, 2005). Both groups found that *Bacteroides* were the most commonly detected anaerobes.

Of note, *H. influenzae* was not isolated in any of the cases included in the studies described above and is rarely reported as a cause of necrotizing fasciitis. On review of the literature, there is one case report of an adult, who had insulin-dependent diabetes mellitus, who developed necrotizing fasciitis due to unencapsulated *H. influenzae* (Stumvoll & Fritsche, 1997). There are three reports of necrotizing fasciitis caused by haemophili in infants, with two of these occurring in association with evidence of pharyngeal infection and affecting the cervical region. In one of these cases, *H. influenzae* was isolated in association with three other pathogens, including two anaerobic species (Bush *et al.*, 1984). The second case of cervical

necrotizing fasciitis was caused by *Haemophilus* species other than *H. influenzae* and occurred in association with bacteraemia, pneumonia and meningitis in a 5-month-old infant (Cordeiro *et al.*, 1997). The third reported case was of lower limb necrotizing fasciitis caused by monoinfection with *H. influenzae* serotype b (Collette *et al.*, 1987).

There are six capsular types of *H. influenzae*, referred to as serotypes a–f, distinguishable from non-typable strains by the presence of one of six structurally and serologically distinct polysaccharide capsules. Prior to the introduction of the Hib vaccine, most invasive disease occurring as a consequence of *H. influenzae* was due to serotype b, affecting primarily children less than 2 years. In the post-vaccination era, there has been concern about the development of serotype replacement (Kapogiannis *et al.*, 2005), with a simultaneous increase in the number of non-serotype b capsulate *H. influenzae* being reported in Brazil, Portugal, Canada and Denmark (Tsang *et al.*, 2006; Bruun *et al.*, 2004). Tsang *et al.* (2006) examined 52 *H. influenzae* isolates from patients with invasive disease and found 26 of the isolates to be serotype a, 20 to be non-typable, three to be serotype b and one isolate each of serotypes c, d and f.

H. influenzae serotype f is an uncommon cause of invasive infection in adults. Slater *et al.* (1990) report five cases of adults with bacteraemia due to *H. influenzae* serotype f. Four of these cases occurred secondary to respiratory tract infections (three cases of pneumonia and one of epiglottitis) and the fifth, a patient with dysgammaglobulinaemia, had no obvious infective focus. Bruun *et al.* (2004) report 13 cases of invasive *H. influenzae* serotype f infection in adults, with eight of these occurring as a consequence of pneumonia or infective exacerbation of chronic obstructive pulmonary disease and one case each of meningitis,

epiglottitis, osteomyelitis, cholangitis and neutropenic bacteraemia with no clinical focus.

In conclusion, this case highlights a number of notable and unusual features. *H. influenzae* is an unusual cause of necrotizing fasciitis, and as far as we are aware, this is the first time that *H. influenzae* serotype f has been implicated in this clinical presentation. When invasive disease does occur as a consequence of *H. influenzae* infection, it predominantly affects children and is more frequently due to serotypes other than f. The background of excess alcohol consumption may have contributed to the severe infection that developed in this patient. He was jaundiced with hepatomegaly on admission and chronic liver disease is associated with an increased mortality due to necrotizing fasciitis. International epidemiological surveillance of encapsulated *H. influenzae* isolates would provide useful information with regard to Hib serotype replacement and would also reveal whether *H. influenzae* contributes to necrotizing soft tissue infections more frequently than has been previously recognized.

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