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CASE REPORT

Synchronous multifocal necrotizing soft tissue infections: a case report and literature review

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Abstract

Necrotizing soft tissue infections are a group of conditions with a common pathophysiological basis, affecting any or all layers of the soft tissue compartment. They are rare, life-threatening diseases that require a high index of suspicion for early detection as well as urgent surgical debridement. Rarely, they can occur in more than one non-contiguous site of the body ('multifocal' disease), and this is associated with a much higher mortality than monofocal disease. Here, we present the case of a 46-year-old male with bilateral upper limb necrotizing soft tissue infection following an unclear history of trauma. The patient developed septic shock necessitating transfer to the intensive care unit following emergency surgery. Microbiological tests yielded *Streptococcus pyogenes*, *Staphylococcus aureus* and opportunistic *Candida spp.* and *Actinomyces* infections. A total of seven surgical debridements were performed; fortunately, the patient survived. We discuss the presentation, diagnosis and management of this case including primary reconstruction of the soft tissue defects, and review the literature on necrotizing soft tissue infections as a clinical entity, incorporating clinical updates from the latest guidelines worldwide.

Level of Evidence: Level V, therapeutic study.

Keywords Human · Soft tissue infections · Upper extremity · Septic shock · Debridement

Introduction

Necrotizing soft tissue infections (NSTIs) encompass all infections with a necrotizing component involving any or all layers of the soft tissue compartment, from the superficial dermis and subcutaneous tissue to the deeper fascia and muscle [1]. They are relatively rare clinical entities; however, their incidence has been rising over the years [2]. Of the various forms of NSTIs, necrotizing fasciitis is the most well known in the literature and in the media (popularised as the 'flesh-eating disease'). These conditions in fact share a similar pathophysiological basis, involving a rapid horizontal spread of bacteria along tissue planes facilitated by bacterial enzymes and toxins [3]. Consequently, the true involved area often extends well beyond clinically identifiable boundaries and can only be delineated upon surgical exploration [3].

NSTIs affect males more than females but respect no age limits [2]. They are life-threatening diseases with mortality rates ranging between 20 and 76% even with early surgical intervention [2]. Most patients who develop NSTIs have one or more predisposing factors such as trauma/surgery, diabetes mellitus and immunocompromised states [2]. Notably, in patients with upper limb NSTI, the predominant risk factor appears to be intravenous drug use (IVDU) [4].

Rarely, NSTIs can occur in multiple non-contiguous areas of the body—multifocal disease [5–9]. This is not well reported in the literature. Here, we present a case of bilateral upper limb NSTI followed by a review of the literature on this extreme disease.

Case report

A 46-year-old male with a history of IVDU presented to the Emergency Department with extensive wounds on both upper limbs. The mechanism of injury was unclear and was reported

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to have been caused either by a dog bite or IVDU. The patient was alert and afebrile but was tachypnoeic, tachycardic and hypotensive. On examination (Fig. 1a, b), his upper limbs were erythematous, oedematous and covered with moderately exudative wounds, some of which were reported to be chronic non-healing since 2013 from IVDU. The dorsum of his right hand showed signs of desquamation, and there were multiple confluent areas of purpura bilaterally, particularly over the extensor surfaces. Capillary refill time was > 3 s distally, but sensation was intact. Joint movements at the elbow, wrist and fingers were limited by severe pain (numerical rating scale 7/10).

A bedside ultrasound scan revealed extensive subcutaneous oedema in both upper limbs with no focal collection. Similarly, plain radiographs demonstrated soft tissue swelling with no obvious subcutaneous gas. Blood tests showed anaemia (Hb 87 g/L), metabolic acidosis (pH 7.23, bicarbonate 12 mmol/L, lactate 6.4 mmol/L), acute kidney injury (eGFR 10 mL/min/1.73 m^2, urea 31.3 mmol/L, creatinine 567 μmol/L), coagulopathy (prothrombin time 17.4 s, INR 1.5), hypoalbuminaemia (22 g/L), elevated C-reactive protein (286 mg/L) and raised creatine kinase (1009 U/L). Taken together, the working diagnosis was NSTI associated with septic shock. The patient was commenced on the 'sepsis 6' pathway and was booked for urgent surgical debridement. While awaiting transfer to theatre, he was managed with aggressive resuscitation measures and started on empirical triple antibiotic therapy consisting of intravenous vancomycin, clindamycin and meropenem.

The patient arrived in theatre within 4 h from initial presentation. On skin incision, a characteristic greyish 'dishwater' exudate was observed, and the finger test was positive. Wide exploration and debridement were undertaken, with necrotic deep fascia debrided from the right upper limb extending from the dorsum of the hand to the mid-forearm. Furthermore, the belly of the abductor pollicis longus muscle was non-viable and was debrided until tissue with good capillary refill remained. On the left upper limb, all necrotic tissue in the epidermis and dermis was debrided but the fascia and muscles were found to be well vascularised and viable. Both

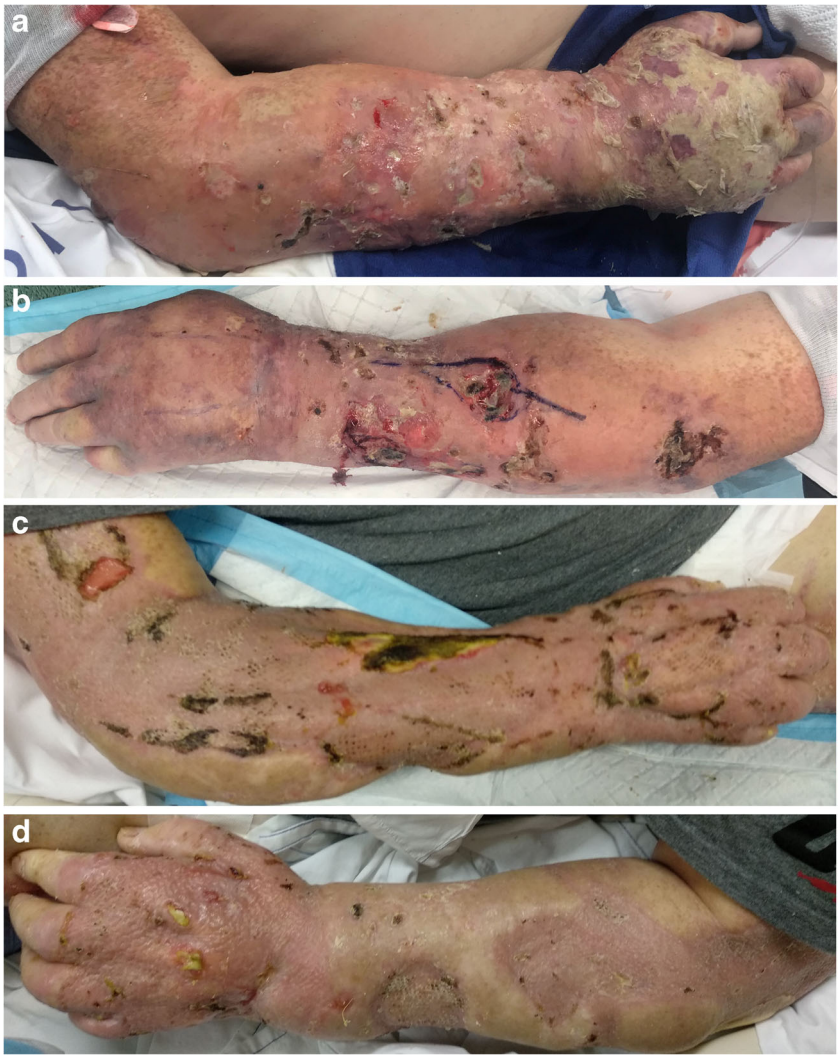

Fig. 1 **a**, **b** Pre-operative views of the right and left arms, respectively. **c**, **d** Appearances of the right and left arm, respectively, at outpatient clinic (day 32 since skin graft application). Small areas of open wound remain on the right forearm, which may need further skin grafting in the future

upper limbs were washed with copious amounts of hydrogen peroxide and normal saline and dressed in betadine gauze and crepe bandages. The patient was admitted to the Intensive Care Unit (ICU) post-operatively for close monitoring and life support (including continuous renal replacement therapy), and intravenous immunoglobulin was administered.

Histological analysis of the right upper limb specimens showed extensive necrosis of the fascia and muscle tissue with diffuse cocci-like bacterial colonies and neutrophil infiltration, consistent with a diagnosis of necrotizing fasciitis with myonecrosis. The left upper limb was diagnosed clinically as necrotizing cellulitis given the sparing of fascia and muscles on surgical exploration. Gram stain and culture of wound swabs demonstrated the presence of *Streptococcus pyogenes*, *Staphylococcus aureus* and *Candida spp*. Blood cultures from the time of presentation yielded *S. pyogenes*, *S. aureus* and *Actinomyces odontolyticus*.

The patient remained in the ICU for a total of 15 days, over the course of which he underwent six further debridements, although by the second re-look procedure, there was minimal necrotic tissue on either limb. Seven days after the initial operation, negative pressure wound therapy with VAC® dressing was applied to the skin defects; the dressings were changed at least once a week in theatre. Transthoracic and transoesophageal echocardiograms were also performed to rule out infective endocarditis as a potential source of the multifocal distribution of NSTI—these investigations were negative.

Following step-down of the patient's care from the ICU to the ward, split-thickness skin grafts were harvested from the patient's thighs for soft tissue reconstruction in both upper limbs. The patient has been recuperating since, with close input from physiotherapy to minimise muscle deconditioning, and on the 43rd day from admission, he was transferred to an inpatient rehabilitation unit to further support his convalescence. At his first outpatient clinic review (day 32 since skin graft application), the grafts appeared to be healing well (Fig. 1c, d).

Discussion

Necrotizing soft tissue infections (NSTIs) are limb- and life-threatening conditions. They can affect any part of the body, with the extremities (lower limbs > upper limbs), perineum and abdominal wall being the most common sites [2]. Rarely, more than one area of the body can be affected ('multifocal' disease), either simultaneously ('synchronous') or sequentially ('metachronous') [5]. Multifocal involvement, as well as head and neck or truncal involvement, is associated with a worse prognosis [6]. Although various classifications have been used to describe NSTIs (e.g. anatomical/microbiological) [3], they share the same principles for diagnosis and treatment, and there is now increasing acceptance of the term 'NSTI' as a catch-all phrase to describe these pathophysiologically similar entities.

Diagnosis

The most common findings of NSTI on clinical examination are the triad of erythema, pain and oedema [2, 3]—non-specific, cardinal signs of acute inflammation resembling uncomplicated cellulitis. Nevertheless, pain out of proportion to signs of soft tissue infection is thought to be pathognomonic of necrotizing disease. As vessel thrombosis occurs in advanced stages, the consequent skin ischaemia manifests as purpuric skin discoloration, haemorrhagic bullae and ulceration [3]. Fever may not always be present even in advanced disease, and some studies report that this is especially true for upper limb NSTIs [3, 4]. However, this may be influenced by the time to presentation and the patient's immunological status. In this case, our patient was apyrexial on presentation, but this was on a background of an immunocompromised state, as evidenced by opportunistic infections by *Candida spp.* and *Actinomyces*. Conversely, there may be constitutional symptoms but no pathognomonic signs [10].

Wong and colleagues [11] developed a scoring system known as the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC), designed to distinguish NSTIs from other non-necrotizing soft tissue infections (Table 1). According to the authors, a cut-off score of ≥ 6 (out of 13) has a positive predictive value of 92%, and a score of ≥ 8 has a positive predictive value of 93.4%. However, other groups have failed to replicate the high diagnostic sensitivity of the original study [12, 13]. Borschitz and colleagues proposed a modification to the LRINEC scoring system by substituting erythrocyte count and fibrinogen levels for serum sodium and glucose levels, and introducing the clinical variables of pain, temperature, heart rate and renal function [14]. Using this modified system, the authors showed that the test had better sensitivity as well as positive and negative predictive values than the original LRINEC. Our patient scored 10 on the LRINEC, appearing to support the clinical relevance of this scoring system. In practice, however, the inconsistent performance of the scoring system means that it will likely serve only as an adjunct to clinical assessment.

Radiological investigations may also aid the diagnosis of NSTI. The presence of subcutaneous gas is a characteristic feature on plain x-ray radiographs, computed tomography (CT) or magnetic resonance imaging (MRI) [1, 15]. It is important to note, however, that the absence of soft tissue gas does not exclude NSTI; for example, gas may be absent in pure aerobic infections caused by *S. pyogenes* [1, 15]. Ultrasound has the advantage of being rapidly performed at bedside but is less sensitive than CT or MRI [1]. Ultimately, the diagnosis of NSTI is primarily clinical, and surgical

Table 1 Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) [11] and scores for our patient

Variable (units)	Score	Laboratory values for index patient	Patient score
Haemoglobin (g/dL)		8.7	2
> 13.5	0		
11–13.5	1		
< 11	2		
White cell count ($\times 10^3/mm^3$)		3	0
< 15	0		
15–25	1		
> 25	2		
C-reactive protein (mg/L)		286	4
< 150	0		
≥ 150	4		
Sodium (mmol/L)		130	2
≥ 135	0		
< 135	2		
Creatinine (μmol/L)		567	2
≤ 141	0		
> 141	2		
Glucose (mmol/L)		3.7	0
≤ 10	0		
> 10	1		
Total score			10

debridement should not be delayed by scoring systems or radiological investigations once the clinical suspicion arises. On the operating table, the findings of necrotic tissue, murky and greyish ('dishwater') fluid and minimal tissue resistance to finger dissection (positive finger test) are all supportive of the diagnosis of NSTI.

Management

The gold standard management of NSTI remains prompt surgical debridement with aggressive resuscitation and broad-spectrum intravenous antibiotics [1, 16–18]. A systematic review showed that surgical debridement within 12 h of suspected diagnosis is associated with a lower mortality rate (14%) compared with surgery after 12 h (25.8%) [19]. In terms of antibiotics, latest guidelines worldwide recommend broad coverage of aerobic and anaerobic bacteria as well as methicillin-resistant *S. aureus* (MRSA), for instance, a combination of vancomycin and piperacillin-tazobactam [1, 16–18]. In addition, for confirmed group A streptococcal infections, a combination of penicillin and clindamycin is particularly effective [18]. All patients should return to the operating theatre for a second look within 24 h of the first debridement, and further debridements should be repeated until the infection is controlled [16].

Two recent Cochrane guidelines reviewed the evidence for hyperbaric oxygen therapy (HBOT) and intravenous immunoglobulin (IVIG) as adjunctive therapies for NSTI. These are controversial treatments with wide variations in local practices. The aim of HBOT is to increase the oxygen supply to the infected site, thereby improving the effectiveness of antibiotics and improving healing, while killing the offending bacteria by oxygen toxicity [20]. IVIG, on the other hand, is thought to benefit NSTI patients with associated severe sepsis or septic shock by providing antibodies that neutralise circulating exotoxins produced by gram-positive organisms [1]. The Cochrane reviews however found that there was insufficient high-quality evidence for either therapy, and given that they are not without risks, the authors concluded that they should not be routinely recommended in NSTI [16]. Moving forward, a prospective cohort study (PROTREAT) is ongoing that evaluates the effects of HBOT on markers of endothelial damage in NSTI [21]; the results of this study may provide indirect evidence for the utility of HBOT in NSTI.

Negative pressure wound therapy (NPWT) is an increasingly common part of wound management especially with large skin defects as those seen after radical debridement of NSTI. The advantages of NPWT include isolation of the wound, increased tissue perfusion, decreased wound oedema, decreased bacterial load and facilitation of subsequent reconstructive surgery [22]. NPWT should however only be applied after all necrotic and infected tissue has been debrided [1], and regular dressing changes are needed which, depending on wound size, can cause severe pain requiring general anaesthesia. In a small retrospective study, there is evidence to suggest that leaving the wound open to air in the immediate postoperative period (first 7 days after debridement) is as safe as NPWT without the pain associated with dressing changes and

with the added advantage of allowing quick wound inspection at the bedside [23]. NPWT with intermittent or continuous irrigation using a range of fluids is also applicable in this setting.

Multifocal disease

Multifocal NSTIs are poorly reported in the literature. The monofocality of most cases of NSTI may be explained by the angiothrombotic nature of the disease, whereby the invasion of causative organisms into deeper layers of soft tissue induces widespread thrombosis of dermal capillary beds [3]. Capillary thrombosis acts as a physical barrier to immune cells and administered drugs but also to the spread of offending pathogens [5]. A number of cases of multifocal NSTI have been recently documented [5–9, 24]. Yoshii and colleagues [9] reported a case of bilateral upper limb necrotizing fasciitis in an otherwise healthy 31-year-old male following intentional injection of narcotic drugs, whereas Tocco and colleagues [5] described a 44-year-old diabetic male with no history of trauma who was diagnosed with necrotizing fasciitis in the left arm and right gluteus, eventually ending up in coma. In three further case reports [6–8], patients had two- or four-limb necrotizing fasciitis; all three developed septic shock and two died. From these and other case studies, it seems that multifocal NSTI is associated with an increased mortality by up to sixfold compared with monofocal disease [24, 25]. Interestingly, some evidence suggests that bilateral upper limb involvement is associated with a better survival rate than bilateral lower limb involvement [24]; the mechanism for this remains unclear.

Conclusions

This case of synchronous multifocal NSTI in the upper limbs of an immunocompromised host adds to the growing number of reports on multifocal NSTIs, which will hopefully shed light on the true incidence of this unique clinical entity. Fortunately, our patient survived in spite of the high mortality rate associated with multifocal NSTIs. A high index of suspicion and a low threshold for surgery must be maintained, with the use of scoring systems such as the LRINEC and radiological investigations only as an adjunct to clinical assessment. Aggressive resuscitation, broad-spectrum intravenous antibiotics and early surgical debridement remain the cornerstone of effective management of NSTIs. There is currently insufficient evidence to support the routine use of hyperbaric oxygen therapy or IVIG, with future research hopefully providing clearer answers to these questions.

Compliance with ethical standards

Conflict of interest KS Tong, DC Williams, MA Seifman, DJ Hunter-Smith and WM Rozen declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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