Severe necrotizing soft tissue disease

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Abstract · We present three patients, two men (aged 30 and 75 years), and one woman (aged 22 years), who were treated in our hospital for severe necrotizing soft tissue disease. One patient died within the first hour of reaching the hospital. The other two patients underwent emergency surgical resection of affected tissue, of which one died of septic shock with multi-organ failure. Severe necrotizing soft tissue disease is a rare group of infections characterized by extensive fulminant necrosis of soft tissue, severe systemic toxicity, and a high mortality rate. A key clinical feature is a marked discrepancy between the severity of pain perception and local findings. Treatment consists of extensive, often-repeated surgical debridement, antimicrobial therapy, fluid resuscitation, and cardiopulmonary support. Early diagnosis and surgical treatment are essential for survival.

Keywords · Severe necrotizing soft tissue disease, fasciitis necroticans, clostridial myonecrosis

Introduction
Severe necrotizing soft tissue disease (SNSTD) is a term that is applied to a group of infections of the soft tissue compartment. The absence of a clear definition has led to several classification systems. Some authors recommend that a distinction be made between superficial and deep soft tissue infections [1]. The group of superficial infections includes necrotizing cellulitis, and Melaney's gangrene [2]. These infections are limited to the cutis and subcutis. The group of deep infections consists of necrotizing fasciitis and myonecrosis. These infections develop in the subcutis or muscle and from there spread throughout the body, with fast and widespread necrosis of soft tissue and severe systemic toxicity. The mortality rate varies from 6% to 76% [1,3-8].

The incidence of SNSTD in the Netherlands is unknown, the yearly estimated rate in the United States is 500 to 1500 cases [1,9]. SNSTD can occur in every anatomic area, but the abdomen, perineum, and lower extremities are most frequently affected. It is often secondary to trauma, surgery, peri-anal and urogenital abscesses, and decubitus ulcers, but the portal of entry remains unclear in a large proportion of patients. SNSTD of the perineum, often secondary to anorectal or urogenital infections, is called Fournier's gangrene. SNSTD is more likely to develop in patients with pre-existing conditions, such as diabetes mellitus, cardiovascular disease, congestive heart failure, innate or acquired immunodeficiency, chronic renal failure, or chronic hepatic disease. Other risk factors include immunosuppressive medication, intravenous drug abuse, smoking, and alcoholism. SNSTD in patients with rheumatic disease has rarely been described. We describe the clinical records of three patients diagnosed in our hospital with SNSTD and discuss the clinical presentation and treatment of deep SNSTD.

Case reports
Patient A, a 22-year-old female kick-boxing professional, was referred to our hospital because of a painful left upper leg that she had had for three days. She had recently been diagnosed with systemic lupus erythematosus/rheumatoid arthritis overlap syndrome, for which she was being treated with prednisone, paracetamol, and tramadol. On presentation, she appeared ill but alert. She had a blood pressure of 88/56 mmHg, a heart rate of 120 bpm and her temperature was 36.8 ºC. Her urinary output was <0.5 ml/kg per hour for at least 4 hours. Physical examination of the legs revealed a painful, oedematous left leg with a haematoma present on the dorsal side of the upper leg. Besides the haematoma no apparent skin changes were observed. She did not appear to have respiratory or cardiac problems. However, an arterial blood gas sample and ECG were not performed. Laboratory studies included leucopenia of 1.8×10⁹/L, thrombocopenia of 64×10⁹/L, and an elevated creatinine phosphokinase (CK) plasma level of 7499 U/I. Renal function and lactate were not determined at that time.

Duplex ultrasound imaging ruled out a deep venous thrombosis. A supplementary computed tomography (CT) scan showed diffuse intramuscular and perimuscular effusion suggesting a myositis (Figure 1). The differential diagnosis included a spontaneous haematoma and/or exacerbation of a chronic myositis often seen with systemic lupus erythematosus. An investigatory policy was maintained. On the second day of admission, the patient developed a septic shock. She had an altered state of mind and appeared to be agitated as well. Her blood pressure was 80/40 mmHg with a heart rate of 140 bpm and despite intravenous fluid resuscitation of 125 ml/hour during...
the previous 24 hours, the patient was anuric. Blood tests showed elevated C-reactive protein (CRP) of 70 mg/l, a leucopenia of 3.2×10^9/L, a thrombopenia of 53×10^9/L, renal failure (blood urea nitrogen 16.4 mmol/l, creatinine level of 350umol/L), signs of muscle tissue destruction (LDH of 2132 U/L and CK plasma level of 43501U/L, potassium level 8.3 mmol/L). Arterial blood gas analysis revealed a pH of 7.2, bicarb 8.7 and a base excess of -17. Amoxicillin/clavulanic acid 1200mg and gentamycin 160mg was started and the patient was transferred to the intensive care unit (ICU), where she developed a cardiac arrest and was successfully resuscitated.

On the ICU an exploration of the left upper leg was performed. The subcutis was oedematous and the fascia had a firm appearance but did not bleed when it was incised. Superficial muscle tissue had a normal colour. A Gram stain of the excised tissue revealed streptococci, confirming the diagnosis of necrotizing fasciitis. The patient was treated with amoxicillin 4×1000mg, clindamycin 4×600mg and a total dosage of intravenous immunoglobulins (IVIG) 3 g/kg was given over three days. Further exploration showed necrosis of fascia and muscle with thrombosis of multiple branches of the profundal femoral artery. Therefore, immediate additional extensive necrosectomy of skin, fascia, and muscle tissue from the upper left leg up to the skin in the groin area was performed. The next day a transfemoral amputation was performed.

Blood and tissue cultures revealed *Streptococcus pneumoniae*, and amoxicillin was switched to benzylpenicillin 12×10^6 U while clindamycin was continued. Progression of the sepsis with increasing indicators of infection (CRP, 227 mg/ml; leukocytes, 15.9×10^9/L) made amputation at the level of the hip joint necessary on day six. Histopathology of the acquired tissue revealed *Enterococcus faecium*, and blood cultures revealed *Pseudomonas aeruginosa*. Despite numerous additional necrosectomies, the patient’s condition deteriorated and she died of multiple organ failure on the ninth day of admittance.

Patient B, a previously healthy 36-year-old man, was referred with severe pain in his right leg after lifting bricks the previous day. He was moderately ill at presentation, with a temperature of 37.7ºC and no further physical abnormality of the right leg. Within three hours of admission, the patient developed a septic shock. His blood pressure decreased to 90/50 mm Hg with a heart rate of 132 beats/min and he was anuric. Laboratory abnormalities included elevated CRP of 159 mg/l, leucopenia of 1.9×10^9/L, thrombopenia of 86×10^9/L, an elevated CK and LDH plasma level of 32072 U/l and 1600 U/l respectively. Creatinine and lactate plasma levels were 234 umol/l and 3.3 mmol/l respectively.

A CT scan showed an aberrant aspect of the right upper leg with a vastly infiltrated aspect of the fasciae, which confirmed

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**Figure 1.** A transverse computed tomography scan of patient A’s upper legs shows extensive subcutaneous oedema and perimuscular and intramuscular effusions.
the diagnosis of necrotizing fasciitis (Figure 2). The patient was transferred to the ICU for cardiac, pulmonary and inotropic resuscitation. Awaiting Gram stain, cefuroxim 750mg and gentamycine 320 mg was administered. Exploration of the upper leg revealed thrombosed veins in the skin and subcutis. The vastus lateralis and medialis were decompressed, and tissue for cultures and histopathology were obtained. Fascia and muscle appeared to be avital. No pus or evident necrosis was seen. A second inspection was performed a few hours later. Owing to progression of the necrotizing fasciitis, an exarticulation in the hip joint was deemed necessary. Gram stain showed Gram-positive cocci in chains. Histopathology showed necrotizing fasciitis with bacterial overgrowth in all resection planes and extensive necrosis of fascia of the muscles. Cefuroxim and gentamycin were switched to clindamycin 4×600 mg and benzylpenicillin 18×10^6 U and a total dosage of IVIG 3g/kg over three days was given. During the next few days, necrosectomy was performed twice more.

Blood and tissue cultures revealed *Streptococcus pyogenes* (group A Streptococcus). The chosen antimicrobial treatment was maintained.

One week after admission, reconstructive surgery was performed to cover skin defects in the groin area. With the application of a vacuum-assisted wound closure, the wounds healed. Transfer to a nursing department occurred 23 days after admission. The patient was transferred to a rehabilitation centre on day 65.

**Figure 2.** A transverse computed tomography scan of patient B’s upper legs shows a swollen aspect of the muscles of the right leg, with highly infiltrated fascias.

Patient C, a 76-year-old man, was referred to our emergency room (ER) with a painful arm that he had had for 12 hours; he had a two hour history of a sensibility disorder and paresis of his left arm. During transportation to the ER, the paramedics noticed formation of bullae and copper-like discolorations on his left arm (Figure 3). The patient was already in septic shock when he arrived at the ER. His blood pressure was 95/57 mm Hg and his heart rate was 146 beats/min. On physical examination, the patient had asymmetrical pupils, a reduced corneal reflex, and a paralysis of the left arm. The haemorrhagic bullae on his left arm and thorax had increased in size and number.

Laboratory findings revealed an elevated CRP of 180 mg/l, leukocytosis of 10.4 x 10⁹/L, and a highly elevated CK of 11,500 U/l. Arterial blood gas analysis showed a severe metabolic acidosis, with a pH of 6.78, a HCO₃⁻ of 11.3 mmol/l, and a base excess of –22. Extensive subcutaneous myonecrosis, emphysema, and gas embolisms in the bone marrow were seen on the CT scan (Figure 4). Within 45 minutes of arrival, the patient sustained a cardiac arrest and died despite cardiopulmonary resuscitation. The post mortem examination revealed gas gangrene of left arm and left flank, mediastinal emphysema, pneumatosisis coli, and widespread gas embolisms in the systemic circulation and multiple organs. The focus of infection appeared to be a tumour of the caecum with a covered perforation. Gram stain of the affected tissue revealed Gram-positive rods and a marked absence of leukocytes. Blood and tissue cultures revealed *Clostridium septicum* in abundance.

**Discussion**

The three patients described here all developed SNSTD, with fatal outcome in two cases. The causative agents in all three cases were different. In the section below we will discuss the different types of (deep) SNSTD, the clinical presentation, diagnosis and treatment.

Necrotizing fasciitis (NF) is a rare bacterial infection that is caused by proliferation and spreading of pathogens from subcutaneous tissue alongside superficial and deep fascial planes. The fascia are therefore more the route through which the infection spreads than the true source of the infection. The following two types can be distinguished clinically.

Type 1 occurs in 80% of cases and usually affects immuno-compromised patients. It is a polymicrobial infection of aerobic and anaerobic bacteria that act synergistically to create a favourable environment for the proliferation of pathogenic and non-pathogenic microorganisms. Bacteria commonly identified are aerobic and anaerobic non-group A streptococci, coagulase-positive and coagulase-negative *Staphylococcus*, *Bacteroides*, *Enterococcus*, *Enterobacteriaceae*, and *Vibrio* strains. The mortality rate of type 1 is approximately 21% [7].

Type 2, also known as (haemolytic)-streptococcal gangrene, is caused by Lancefield Group A β-haemolytic *Streptococcus pyogenes* (GAS, S. pyogenes), alone or combination with *Staphylococcus*...
The course of the disease is usually faster than in type 1 infections. In contrast to type 1 infections, half of type 2 infections occur in young and previously healthy people. Type 2 infection is usually preceded by (blunt) trauma or surgery; however, in 50% of cases, there is no visible portal of entry. In Patient B the cause of NF was probably blunt or excoriating trauma after heavy labour. As stated previously, patient B developed a septic profile a matter of hours, probably due to streptococcal toxic shock syndrome. Type 2 necrotizing fasciitis is notorious for the occurrence of streptococcal toxic shock syndrome (STSS), which is attended by high fever, an early onset of shock, multiple organ failure, and a high mortality rate. The mortality rate of severe invasive GAS infections is 14% to 34%, but can increase further when STSS develops [12-15].

Cultures obtained from the blood and tissue of patient A showed *Streptococcus pneumoniae*, which is a very rare causal pathogen of SNSTD. Only a few cases have been reported in the literature. It is known that patients with SLE are specifically prone to infections caused by *S. pneumoniae* [10,16,17]. This is thought to be because of the diminished phagocytosis capacity of neutrophils and macrophages, immunoglobulin- and complement dysfunctions and functional asplenia witnessed in SLE patients [18].

Clostridial myonecrosis (CM), is a rare, rapidly progressive necrotizing infection of skeletal muscle and possibly the most severe necrotizing soft tissue infection known to mankind. CM is caused by different types of anaerobic, but often aerotolerant, *Clostridium* bacteria, with *C. perfringens* responsible for most infections [19-21]. These bacteria can be found in soil, but also colonize the gastrointestinal tract of humans and animals. CM is posttraumatic in 50% and postsurgical in 35%. After surgery and trauma, the culprit pathogen is usually *C. perfringens*. In ideal circumstances it has a generation time of 8-10 minutes and its destruction of muscle tissue can progress by several inches per hour [22]. Its growth is accompanied by gas production; therefore it is sometimes referred to as *gas gangrene*. In 10% of patients, however, CM occurs spontaneously, most often caused by *C. septicum*, as was the case in patient C [19-21]. Haematogenic spreading from a mucosal defect of the gastrointestinal tract is typical for this type of infection. Colonic cancer especially is a well known cause of *C. septicum* infections. Other predisposing factors are other malignancies, diverticulitis, leukaemia, and a poor general condition. Mortality of *C. septicum* infections reaches 70%, most likely due to unclear presentation, as in patient C [3].

The pathophysiology of NF and CM is based on the production of bacterial pyrogenic endotoxins and exotoxins. These toxins trigger an acute systemic inflammatory response syndrome, with release of pro-inflammatory cytokines and interleukins, which leads to tissue necrosis. Subsequent activation of the clotting cascade causes thrombosis of blood vessels, infarction, and further progression of necrosis. Systemic release of cytokines, tissue necrosis, and extensive thrombosis leads to septic shock and multi-organ failure. In GAS infections, the occurrence of STSS can cause or aggravate multi-organ failure due to the production of highly aggressive toxins [5,12,23].

In contrast to NF, the (cyto)toxins and proteases in CM induce direct local and systemic vascular dysfunction and suppression of acute inflammatory response [22]. This explains the fulminant course of this infection and rapid progression of tissue necrosis.

Clinical presentation. A rapid diagnosis and treatment of SNSTD is of utmost importance. Even though it is common for SNSTD to occur after trauma or surgery, no portal of entry is evident in 10% to 50% of patients [3,7,11,24]. Clinical presentation of CM is similar to that of NF. Patients frequently present with pain, fever, erythema, swelling, and in case of gas production, subcutaneous emphysema. Early on in cases of CM, fever may be absent for a prolonged period [3]. For NF as well as CM the most important symptom of beginning SNSTD is a discrepancy between the excruciating pain and the noticeable skin changes [1,3-6]. In NF the infection first goes through a 'horizontal-phase' where it spreads alongside the fascial planes and through muscle tissue before ‘surfacing’. In CM the infection spreads through the muscle tissue first before becoming apparent at skin level. As the infection progresses, the skin may become warm, erythematous, and swollen. Vesicles and bullae appear in about 30% to 40% of patients [7,11]. Tissue crepitation is a classic and pathognomonic sign, but is very often absent [1,3-6,9]. When bullae and/or crepitation start to appear, the damage to the subcutaneous and muscle tissue is vast and usually requires extensive debridement or amputation. At an even later stage, painless ulcers and black necrotic plaques may occur, and septic shock then develops, manifested by high fever, hypotension, tachycardia, and multi-organ failure, including respiratory insufficiency, renal and liver failure, diffuse intravascular coagulation, and loss of consciousness or coma.

**Figure 3.** Patient C. Purplish skin discolorations and haemorrhagic bullae.
Diagnosis. SNSTDs are mainly diagnosed by deep tissue biopsy, with cultures for aerobic and anaerobic microorganisms. The clinical presentation can be hard to distinguish from a cellulitis. Special attention must be given to signs of SIRS. Laboratory tests will reveal an elevated CRP and leukocytosis. Leucopenia can also be present, as was the case in two of our patients. Disseminated intravascular coagulation and haemolysis can cause thrombopoenia and anaemia. A metabolic (lactate) acidosis can occur due to ischaemia and necrosis. Elevated LDH and CK indicate tissue destruction. Elevated creatinurine and blood urea nitrogen levels are indicative of renal failure. Hyperglycaemia can occur due to a decreased sensitivity of the peripheral tissue for insulin.

The “finger-test” consists of making a 2-cm incision down to the deep fascia. Ominous signs are the lack of bleeding, appearance of “murky dishwater fluid” [5,24]. If gently probing a finger dissects the subcutaneous tissue without resistance, SNSTD must be suspected.

Imaging studies can be helpful in assessing the source and the extent of the infection and possible gas production. For this purpose, CT and magnetic resonance imaging are the preferred techniques [9,24]. These entities have high sensitivity, but low specificity and performing imaging studies is only advised if it will not gravely delay surgical treatment.

Treatment. Treatment of necrotizing fasciitis and myonecrosis consists of surgical resection of necrotic tissue, administration of systemic antibiotics (after obtaining cultures), and if necessary, fluid resuscitation and cardiopulmonary support. Surgical treatment is of the utmost importance, extensive and aggressive debridement must be performed until healthy tissue is reached. The affected area must be inspected frequently – several times a day – and renewed resection performed if necessary. In anticipation of the cultures, patients should be treated with broad-spectrum antibiotics as soon as possible covering Streptococcus and Clostridium spp., gram-negative, and (other) anaerobic microorganisms. If there a GAS infection is suspected, it is recommended that clindamycin is added for its inhibitive effect on bacterial superantigen synthesis [5,12,14]. If clostridial myonecrosis is suspected, the combination of penicillin and metronidazole, or piperacillin-tazobactam is advised [1,4,9]. If there is still no reason to suspect a causative agent, we would advise giving a combination of antimicrobial agents covering streptococci, Gram-negatives as well as anaerobic microorganisms. A combination of penicillin, gentamycin and clindamycin or amoxicillin/ clavulanic acid and gentamycin is therefore a rational empirical regimen in a patient with severe necrotizing soft tissue disease of unknown cause.

The use of IVIG is still a matter of debate for there is no high level of evidence. However, it is recommended in severe streptococcal infections [1,6,9,25]. Studies show an increased survival in patients treated with IVIG. If patients are not suitable for operation IVIG should surely be considered to increase patients’ chance of survival [15,25-27]. Hyperbaric oxygen therapy is advised in clostridial myonecrosis but may be a logistic problem for some facilities.

Conclusion
Severe necrotizing soft tissue disease is a rapidly progressive infectious disease associated with a high morbidity and mortality rate, even in young, healthy individuals. An early diagnosis, extensive surgical resection of necrotic tissue, and rapid initiation of well-targeted antibiotic treatment are pivotal in its treatment.

Figure 4. A transverse computed tomography scan of the left hemithorax and left arm of patient C shows subcutaneous emphysema and extensive muscular necrosis. Gas effusion into the bone marrow of left humeral head is also visible. Previously published in “Janssen et al. Gas gangrene spreading to the bone marrow. The Netherlands Journal of Medicine. 2006 Jul-Aug;64(7):256-7.”
References