Rapidly fatal necrotizing fasciitis: report of three cases

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Abstract: Necrotizing fasciitis is a rare but life-threatening soft tissue infection characterized by necrotizing process of the subcutaneous tissues and fascial planes, with resulting skin gangrene and systemic toxicity. We describe three fatal cases of clinically undiagnosed necrotizing fasciitis caused by Streptococcus pyogenes. In all cases, the evolution of disease was fulminant, and all patients were treated with non-steroidal anti-inflammatory drugs. Recently have been reported an association between using of this drugs with an increased incidence of fulminant evolution of necrotizing fasciitis. The paper also highlighted the correlation between the histopathologic features of infected tissue with poor acute inflammatory response, and a high concentration of bacteria in infected tissue, which have been confirmed using Gram staining modified by Brown&Bremm. These presented cases emphasize the need for early diagnosis, because prompt clinically recognition prevents unnecessary morbidity and mortality.

Key Words: Necrotizing fasciitis, Streptococcus pyogenes, Forensic

Necrotizing fasciitis (NF) is aggressive and destructive infection of the subcutaneous tissues, associated with substantial mortality and long-term morbidity. It was actually first described by Hippocrates in the 5th century BC as a complication of erysipelas [1]. NF caused by beta-hemolytic streptococci was first described by Meleney in 1924. It has been described under various synonyms, including hospital gangrene, hemolytic or acute streptococcal gangrene, Meleney’s gangrene and Fournier’s gangrene. Wilson first coined the term “necrotizing fasciitis” in 1952. It has been considered as a severe but relatively rare disease [1-3]. In recent years, there has been reported a dramatic increase in the number of NF caused by Streptococcus pyogenes (S. pyogenes) associated with toxic shock syndrome (TSS) [2, 3].

According to medical data from Forensic institute in Nis - Serbia, for 20 years there was no recorded cases of NF, and then in less than a year, we recorded three cases. To the best of our knowledge, there are no previous reported similar cases from Serbia.

Case report

In the three cases presented the diagnosis of S. pyogenes NF was based on the antemortem medical data, apperances at postmortem examination, histopathological findings together with definitive bacteriological identification from postmortem cultures from the infected site and blood. Histopathological examination of affected soft tissues and parenchymal organs were conducted using clasic Hematoxilin&Eosin (HE) staining, and histochemistry

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methods: Van-Gieson for elastic tissue and Gram staining modified by Brown&Bremm, for gram positive bacteria identification in the deparafinized tissue sections. This research on the human cadavers was approved by the Internal Ethic Committee of the Medical Faculty University of Nis (Serbia), and conducted at the Institute of Forensic Medicine of this Faculty.

**Case 1.** A 48-year-old previously healthy woman was admitted to hospital, confused, non-febrile, hypotensive and dyspnoeic, five days after pectoral muscle injury, with gross edema of the arm and chest wall on the right side. The patient was treated with naproxen during 5 days. The initial diagnosis was partial rupture of pectoral major muscle.

The physical examination showed a diffuse, erythematous, tender, and nonfluctuant swelling of the arm and chest on the right side with multiple blisters and bullae filled with serosanguinous fluid. Radiologic examination showed no signs of fractures and no gas in the soft tissues, and the needle aspiration of the chest swelling gave about 15 ml of brownish offensive-smelling liquid. The patient was immediately given antibiotics and other supportive treatment, but her general condition rapidly deteriorates and she died soon after admittance.

Postmortem examination showed haemorrhagic gangrena of the skin and necrotizing fasciitis of the arm, neck, hip, and most of the chest and abdominal wall on the right side (Figure 1 and 2). An underlying extensive myositis was present also (Figure 3B). The pericardial, pleural and peritoneal cavity contained bloodstained fluid, and pleura, epicard and peritoneum showed evidence of marked petechial haemorrhage. Congestion and diffuse pulmonary tissue bleeding (Figure 3A), and extensive haemorrhage in the adrenal glands was present.

**Case 2.** A 56 year old insulin non-dependent diabetic female patient presented to the hospital with two days history of a tender left-sided chest pain, associated with a swelling of left upper arm. The past medical history wasn’t significant for injuries. The patient was treated with ibuprofen during

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**Figure 1.** The right side of the body of a 48-year-old woman, showing a signs typical of necrotizing fasciitis: diffuse skin haemorrhage with multiple blisters and bullae filled with serosanguinous fluid (case 1).

**Figure 2.** Extensive necrotic, haemorrhagic and bullous skin changes: necrotizing fasciitis of the right arm (case 1).

**Figure 3.** Internal postmortem examination findings (case 1): Petechial haemorrhage of the pericardium with marked pleural and pulmonal haemorrhage (3A); an extensive haemorrhagic myositis of the chest wall muscles (3B).
3 days. The initial diagnosis was stabil pectoral angina. At the admission, except of the slight edema of left side of the chest wall, there were no other skin changes. Over the next few hours, the patient became hypotensive and dyspnoeic, the skin of the trunk on the left side became red and swollen with haemorrhagic bullae. The body temperature was normal, and the parenteral supportive therapy was applied. The patient became restless and looked severely ill, and despite all efforts of treatment she died 10 hours after admission.

Postmortem examination showed similar features to those in case 1. Necrotizing fasciitis and myositis affected the upper arm, chest wall and lumbar region on the left side (Figure 4). There was haemorrhage of the pleura, pericardium, peritoneum, as well as the pulmonal, renal and adrenal tissue.

**Case 3.** A 57 years old man was admitted to hospital in very hard condition, and febrile for 24 h, five days after injury from a fall. Before admission, the patient was treated with aspirin and diclofenac.

The physical examination showed a few abrasions on the head and right arm, as well as severe edema and confluent bruising of the arm, shoulder, and upper third of the trunk on the right side. These were to be result of the fall before admission. Radiologic examination revealed no fracture. The patient was febrile, tachicardic and hypotensive. The only treatment given was intravenous saline and symptomatic therapy. There was a rapid decline in his clinical condition and death ensued 3 hours after admission.

Postmortem examination showed right-sided necrotizing fasciitis affecting the arm and chest on the right side. The underlying muscles was necrotic, swollen, with large amount of foul-smelling fluid. The myocardium was pale and flabby and the other internal organs were congested with various degree of hemorrhage.

Etiological examination. Sterile specimens, smears and tissue cuts, taken from skin, subcutaneous and muscle tissue, and blood, were cultured for both anaerobic and aerobic organisms. Bacteriological identification confirmed pathogen Streptococcus pyogenes in all cases. Unfortunately, there were no technical requirements for determining the serotypes of these bacteria.

**Histopathology.** In all cases histopathological examination confirmed the diagnosis of necrotizing fasciitis: necrosis of the superficial fascia and blood vessels thrombosis. Other consistent features include the following: severe subcutaneous fat necrosis and overlying dermis with slight to moderate inflammatory cells infiltration, and myonecrosis of underlying skeletal muscle (Figure 5). Van-Gieson stained preparations confirmed “melting” of fibrous connective tissue (Figure 6). Using Gram staining modified by Brown&Bremm, a massive invasion of gram positive bacteria were seen in necrotic areas of the skin, subcutaneal tissue, between fat lobules, and in muscle tissue (Figure 7). The internal organs findings include the following: pulmonal microthrombosis and variable degrees of hemorrhage from case to case; myocardial fragmentation and degeneration with some neutrofiles and a variable number of red blood cells in the intestinal tissue; focal and spotty necrosis of liver; extensive haemorrhaging in the renal and adrenal glands tissue.

**Discussion**

Streptococcus pyogenes (group A, beta-haemolytic streptococcus in the Lancefield classification) is one of the most common human pathogens. Invasive group A streptococcal infections can cause a variety of skin, soft tissue infections and TSS by the action of streptococcal pyrogenic exotoxins [4]. The mortality and morbidity of group A streptococcal necrotizing fasciitis has evolved differently.
In the pre-antibiotic era this infection carried a mortality rate of about 25% when treated with surgery (such as “bear claw” fasciotomies) alone. Mortality due to group A streptococcal NF has not decreased and continued to range from 30% to 70% despite antibiotics, appropriate surgical debridement, and intensive supportive care. This suggests that strains that are more virulent must be responsible [4, 5].

NF has been divided into distinct groups based on bacterial culture results. Type I comprise polymicrobial infection (but not including S. pyogenes) that typically involves the trunk and generally results from surgical wound complications. Type II involves group A streptococci, with or without staphylococci. This type of infection more typically affects the extremities. A third type of necrotizing infection is caused by marine vibrios (gram-negative rods such as Vibrio vulnificus), and the typical portal of entry is a puncture wound or skin abrasion exposed to seawater [3 - 5]. NF may affect patients of all ages, without sex or race predilection. It usually occurs in the perineum, extremities, or abdominal wall, but it can affect any part of the body [4, 6]. Predisposing factors include a history of penetrating or blunt trauma [6], muscle strain [7], burns, childbirth, chickenpox [8], non-steroidal anti-inflammatory drugs (NSAIDs) [9], etc. Most patients who develop NF have pre-existing conditions that result in immunosuppression, such as advanced age [1], diabetes mellitus, chronic renal failure, peripheral vascular disease [1, 4]. However, NF also occurs in young, previously healthy individuals who sustained minor trauma to an extremity. In this population, the pathogenic organism is commonly a virulent strain of Streptococcus pyogenes, with the clinical presentation of streptococcal TSS [7].

The clinical signs and symptoms of NF are nonspecific. Most commonly, infection developed within 24 to 72 hours at a site of minor local trauma. Excruciating pain with usually involves extremities, with or
without cutaneous findings, may be the only clue of infection and it is the most common reason for patients
to seek medical care [2 - 6]. In the beginning, the skin is red-hot, smooth, tense and tender, without sharp
demarcation between the involved and normal skin. Early in the course of disease, patients may have an
influenza-like syndrome characterized by chills, fever, myalgia, nausea, vomiting, and diarrhoea. As the
disease progresses, the skin become dusky, covered with bullae filled with serosanguinous fluid. When the
bullous stage is observed, there is already extensive necrotizing fasciitis and myositis and patients usually
exhibit haemodynamic disturbances caused by systemic toxicity with evidence of multiorgan failure such
as disseminated intravascular coagulation, respiratory failure and septic shock [3-5, 9].

All the cases of NF in this report had a fulminating course with fatal outcome. The cause of death
is toxic shock with a generalized severe multisystem disorder. There was evidence of trauma in two cases
(cases 1 and 3) with spreading of infection away from the primary site and systemic toxic effects. In one
case (case 2), subcutaneous and deep muscle tissue was affected without defined bacterial portal of entry.
The portal of entry of streptococci cannot be proven in at least half of the cases. Among this patients,
hematogenous spread of group A streptococci from a distant site of infection (asymptomatic or symptomatic
pharyngitis) probably occurs. The other possibility, which is of course highly conjectural, is that group A
streptococci reside in a dormant state in the deep tissue and trauma of various types reactivates their growth
[4, 6, 7].

The major autopsy findings of reported cases are extensive subcutaneous and muscle tissue
destruction. The extent of fascial necrosis was more widespread than changes in the overlying skin. The
precise mechanism that resulting in liquefactive necrosis of the superficial fascia and fat is not known.
Some investigators believe it is caused by bacterial enzymes, including hyaluronidase and lipases, which
degrade fascia and fat, respectively [3, 4].

The common histopathologic features of this cases are severe subcutaneous fat necrosis, myonecrosis,
thrombosis of blood vessels, abundant bacteria spreading along fascial planes, and relatively few acute
inflammatory cells. Pathogenic mechanisms that account for the lack of acute inflammatory response in
infected tissue remain to be elucidated. These mechanisms may involve both host and pathogen factors.
Infection, local ischemia, and reduced host defense mechanisms combine to form a vicious cycle, which is
responsible for the initiation and spread of the lesion [4, 10].

Bakleh M. et al. emphasized correlation between the histopathologic features of resected tissue in
patients with NF and clinical outcome [11]. According to this research, the mortality rate was higher in
cases with poor acute inflammatory response and a high concentration of bacteria in infected tissue. Our
conclusion was the same, because histopathological examination showed poor neutrophil response (HE
method) and severe presence of bacteria (Gram staining modified by Brown&Bremm) in infected tissue of
all three cases.

One of the possible reasons for poor inflammatory response is using NSAIDs drugs for pain and
inflammation. As stated above, all three patients in this report were treated with NSAIDa, which has recently
been reported to be associated with an increased incidence of fulminant evolution of NF. Impairment of
the host immune response has been proposed as an explanation for this association by augmentation of
cytokine production, inhibition of granulocyte adherence, cell activation, and phagocytosis by NSAIDs [3,
9, 10]. We suspect that administration of NSAIDs in patients with skin and soft tissue infections, particularly
those caused by Streptococcus pyogenes, delays diagnosis by masking symptoms and signs, allowing a
minor infection to develop into a fulminant one.

Conclusion

The cases we have described of fulminant streptococcal necrotizing fasciitis reinforce the message
that Streptococcus pyogenes can be fatal in a very short period. Diagnosis is often missed because of
paucity of symptoms and the unfamiliarity of this pathological entity, not only among clinicians but also for pathologists. For the pathologist is important to be aware of existence of this condition and to perform appropriate dissection with retention of materials for microbiological and histological examination.
References