NECROTIZING FASCIITIS AND FLESH-EATING BACTERIA

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Abstract

Necrotizing fasciitis is one of the most serious diseases that doctors face in their practice. It is defined as a rare, life-threatening, rapidly spreading soft tissue infection resulting from a polymicrobial origin, with a predominance of anaerobic organisms (flesh-eating bacteria). The disease is manifested by necrosis of muscles, fascia and surrounding soft tissues. Diagnosing necrotizing fasciitis is one of the biggest challenges for clinicians. The accuracy of the diagnosis increases with good knowledge of the clinical finding, laboratory parameters, imaging and macroscopic and microscopic findings. Despite the advanced medical technology and modern intensive care, this disease still leads to high mortality. The purpose of this review is to present up-to-date information on necrotizing fasciitis - microbial etiology, clinical characteristics, early diagnosis and effective treatment strategies. Materials and methods: review of scientific literature, research and international experience related to the disease. Conclusion: Due to the insignificance of skin findings at the beginning of the disease, the diagnosis of necrotizing fasciitis is often extremely difficult. Knowledge of the disease, early diagnosis, prompt surgical treatment and adequate antibiotic therapy lead to a reduction in mortality.

Key words: *necrotizing fasciitis, flesh-eating bacteria.*

Introduction

Necrotizing fasciitis is one of the most serious and challenging infections that doctors face in their practice. It is defined as a rare, life-threatening, rapidly progressive soft tissue infection resulting from a polymicrobial origin, with a predominance of anaerobic organisms (flesh-eating bacteria). The disease is manifested by necrosis of muscles, fascia and surrounding soft tissues. According to the Centers for Disease Control and Prevention (CDC), there are about 700 to 1,200 new cases of the disease in the United States each year [1]. Despite advanced medical technology and modern intensive care, this disease is still associated with a high mortality rate (25-30%) [2].

The purpose of this review is to present up-to-date information on necrotizing fasciitis - microbial etiology, clinical characteristics, early diagnosis and effective treatment strategies.

Materials and methods: review of scientific literature, research and international experience related to the disease.

History - In the fifth century BC, Hippocrates described a necrotizing soft tissue infection resulting from a complication of streptococcal infection – "erysipeloids all over the body, while the cause is only a trivial incident. Bones, flesh and tendons or nerves "drip" from the body and have many deaths" [3]. The first description of a necrotizing soft tissue infection in England was made by the surgeon Leonard Gillespie and physicians Gilbert Blaine and Thomas Trotter in the 18th century. At that time, necrotizing soft tissue infection was known by various names - spreading and destroying the surrounding tissue ulcer, gangrenous ulcer, malignant ulcer, putrefactive ulcer, infection with flesh-feeding bacteria, progressive bacterial synergistic gangrene, and hospital gangrene. Later, the term "hospital gangrene" began to be used more often.

In 1871, during the American Civil War, military surgeon Joseph Jones reported 2,642 cases of hospital gangrene with a mortality rate of 46% [3]. In 1883, Dr Jean-Alfred Fournier described the necrotizing infection of the perineum and scrotum, now called Fournier's gangrene. The term "necrotizing fasciitis" was first introduced by Wilson in 1952. The definition has become more comprehensive, including not only fascial infection but also other soft tissue infections [4].

Epidemiology - The incidence of necrotizing fasciitis is three per 100,000 with 10,000 new cases per year in the United States [5]. Although unusual (0.24 per million per year) [6], due to a good blood supply, periorbital necrotizing fasciitis has a reported mortality of 8-15% and a degree of vision loss of 13.8% [7]. There is no age predilection for necrotizing fasciitis. However, middle-aged and elderly patients (over 50 years of age) are more likely to be infected [8]. In Fournier's gangrene, the incidence was reported to be 10 times higher in men than in women (frequency of 1.6 men per 100,000) [9]. Some authors report a predominance of necrotizing fasciitis among women (54%), other report almost equal prevalence between both sexes [7, 10]. Necrotizing fasciitis is relatively uncommon in children. Such cases have been reported in poor countries where poor hygiene predominates and other associated risk factors are malnutrition and immunosuppression [11].

Risk factors - More than 70% of necrotizing fasciitis cases have been reported in people with at least one of the following conditions: immunosuppression, diabetes, obesity, malnutrition, alcoholism, drug abuse, smoking, nonsteroidal anti-inflammatory drugs, kidney disease, peripheral vascular disease, chronic systemic diseases and skin injuries, including insect bites, trauma and surgical wounds. Hematogenous spread of infection has also been reported, for example in people with streptococcal pharyngitis [12]. Other potential sources include intramuscular injections, insulin injections, a fistula that connects the skin to the body's internal organs, odontogenic infections, varicella lesions [13, 14, 15]. For unknown reasons, the disease sometimes occurs in people with an apparently normal general condition [16]. Necrotizing fasciitis can occur in any part of the body, but is more common in the limbs, perineum, and genitals. Isolated cases occur on the chest and abdomen. Common causes of necrotizing fasciitis of the perineum and genitals (Fournier's gangrene) are trauma, surgery, urinary tract infections, stones and abscesses of the Bartholin's glands [4].

Classification - There are different classifications of necrotizing fasciitis, based on the affected anatomical site, surgical management, and the etiological causative agent. The classification system based on the causative organisms, according to which necrotizing soft tissue infections are divided into four types, was first described by Giuliano and his colleagues in 1977 [4, 17].

The most common (70 to 80% of cases) is Type I infection [18]. It is a polymicrobial infection caused by aerobic, anaerobic and facultative anaerobic Gram-positive and Gram-negative bacteria. Most of the pathogens originate from the intestinal flora or the abdomen and groin areas - enterococci, *Escherichia coli, Pseudomonas spp., Bacteroides, Clostridium* [17]. Elderly people with comorbidities such as diabetes, obesity, immunodeficiency or recent surgery are mainly affected [17]. The cause of the infection is not usually a trauma, but there is a previous history of abscess or intestine perforation. Clostridial infection represents 10% of type I infection. Associated bacterial species (*Clostridium perfringens, Clostridium septicum* etc.) usually cause gas gangrene, also known as myonecrosis and produce strong toxins that can lead to vital organ dysfunction and death. Clostridial myonecrosis is common with heroin injections.

Type II infection involve mainly the limbs and accounts for 20 to 30% of cases [17, 18]. The causative agent is usually *Streptococcus pyogenes*, alone or with co-infection with *Staphylococcus aureus* (including methicillin-resistant strains). It affects more often young, healthy adults with a history of injury causing a violation of the dermis - ruptures, burns, recent surgery, childbirth, venous drug use [4].

Mortality in type 1 and type 2 infections is 20% and 30-35%, respectively [19]. The percentage increases when it affects the lower part of the face, the neck area and the areas near the mediastinum, which can lead to lung complications.

Type III infection is caused by the marine V*ibrio vulnificus* and *Aeromonas hydrophila* species. They inhabit salt water and usually cause infection when there is damaged skin integrity, even with barely visible skin changes [4].

Type IV infection is very rare and is caused by bacteria of the genera Candida and Zygomecetes [20].

Signs and symptoms - The superficial fascia is the main site of the pathological process. Bacteria inoculate this usually sterile site either by penetrating injury or by hematogenous spread. They multiply rapidly, synthesizing enzymes and toxins that facilitate their further spread across the fascial plane. Rapid microbial proliferation leads to thrombosis in blood vessels and necrosis of the superficial fascia. The destruction of the superficial fascial layer together with the adjacent blood vessels to the skin leads to progressive skin ischemia and ultimately deep skin loss.

Symptoms may include fever (above 38°C), swelling of the affected region, and severe localized pain disproportionate to appearance as the infection spreads subcutaneously along the fascial plane [10]. Initial signs in the skin are similar to erysipelas, cellulite or abscess, thus complicating the diagnosis in the early stages. Spots of discoloration of the skin usually occur with pain and swelling, but without a definite margin or lymphangitis [19]. Skin and soft tissues hardening and swelling outside the area of skin changes are common in patients with early necrotizing changes [4]. Normal tissues usually surround the redness and swelling. Overlying skin may look shiny, radiant and taut. Progression of necrotizing fasciitis includes: bulging, bleeding from the skin that occurs before necrosis (due to thrombosis of blood vessels, the skin changes color from red to purple and black), the presence of gas in the tissues (crepitation) and reduced or absent sensation on the skin (due to necrosis of the underlying nerves) [4, 19, 20]. Due to the rich blood supply of the orbit, the thin eyelids skin, and the lack of subcutaneous adipose tissue between the skin and muscle, necrosis of the eyelids proceeds rapidly, although periorbital necrotizing fasciitis becomes noticeable earlier [21]. Systemic findings in patients with necrotizing fasciitis include tachycardia, tachypnea, low blood pressure, profuse sweating, and even an altered mental state or diabetic ketoacidosis. Rapid progression to shock, despite antibiotic therapy, is another indicator of the disease. However, in immunocompromised patients (malignancy, corticosteroid or chemotherapy, HIV/AIDS or before organ or bone marrow transplantation), there may be no typical clinical findings. In addition, they are twice as likely to die of necrotizing fasciitis, therefore great care should be taken in this group of patients [4].

Diagnosis - The diagnosis is still predominantly clinical based on the clinical symptoms and disease progression. Early diagnosis is difficult because at first the disease often resembles an ordinary superficial skin infection [17]. The gold standard for diagnosis is surgical examination and high index of disease suspicion. If in doubt, a small incision may be made in the affected tissue, and if the tissue along the fascial plane is easily removed with a finger, the diagnosis is confirmed [4].

Imaging studies - Imaging has a limited role in the diagnosis of necrotizing fasciitis. Ordinary radiography may help to identify subcutaneous emphysema (the presence of gas in the subcutaneous tissue), which strongly suggests necrotizing changes, but the absence of gas does not exclude the disease. Because necrotizing skin infections caused by bacteria other than *Clostridium* spp. usually do not show subcutaneous emphysema, radiography is an insufficiently sensitive method to detect all cases. Computed tomography and magnetic resonance imaging are much more sensitive and can be carried out in patients with equivocal clinical findings and when the diagnosis is in doubt. Computed tomography can show the initial site of infection, extent of the disease, asymmetric fascia thickening, fat accumulation, gas presence along the fascial plane and fluid-filled bullae can be located quickly and easily [4, 10]. Ultrasonography is also a possible option, providing useful information concerning the nature and extent of infection, mainly in cases of gas gangrene and especially when the diagnosis is unclear [22].

Laboratory diagnosis - Several laboratory-based scoring systems have been proposed for establishing early diagnosis of necrotizing fasciitis [23]. Laboratory indicators that most commonly suggest necrotizing fasciitis include increased white blood cell count, azotemia, elevated blood glucose levels, abnormal coagulation profile and decreased platelet and fibrinogen levels. However, the values of these indicators should be interpreted with caution, as they would be false positives if other inflammatory conditions were present [4], although leukocytosis and hyponatremia have been found to predict necrotizing infection.

Microbiological diagnostics - Wound secretions, tissue samples and blood for blood culture in case of suspicion of bacterial penetration into the blood are examined. The materials are plated on appropriate liquid and solid culture media and cultivated in aerobic and anaerobic atmosphere. In the presence of bacterial growth, Gram-stained microscopic slides are observed and tests are performed to detect the relevant bacterial species.

Evaluation of a frozen section incisional biopsy specimen from the compromised site that includes deep fascia and possibly muscle has also been recommended as a means to achieve earlier diagnosis of necrotizing fasciitis in patients [24].

Treatment - Treatment of necrotizing fasciitis consists of early and aggressive removal of necrotic tissue, administration of broad-spectrum antibiotics, and hemodynamic supporting [25]. Early detection of the disease and initiation of timely treatment help reduce morbidity and mortality. Treatment should be performed by a multidisciplinary team of internists, microbiologists and surgeons.

Nutritional support is required from the first day of the patient's hospital admission (preferably in the intensive care unit), to replace lost proteins and fluid from large wounds and/or the resulting toxic shock.

Empirical antibiotic therapy should be started as soon as this condition is suspected and the antibiotics may be corrected after the culture and antibiogram results are known. High doses of intravenous broad-spectrum antibiotics are used, covering Gram-positive, Gram-negative and anaerobic bacteria - Penicillin, Vancomycin, Clindamycin, Meropenem, 3rd generation cephalosporins, Linezolid, Tetracyclines, Quinolones.

The basis of the treatment of necrotizing fasciitis - surgical debridement is associated with a lower mortality when performed within 24 hours [26]. It consists in the most complete possible removal of necrotic and poorly supplied blood tissue until healthy, viable (bleeding) tissue is reached. In some cases, more than one surgery or an amputation of an affected limb may be needed to effectively stop the spread of the infection. However, limb amputations generally do not

significantly affect the mortality rate [27]. After surgery, management in an intensive care unit is recommended and adequate measures are needed to protect tissues, bones, tendons and cartilage (especially in Fournier's gangrene) and to promote faster wound healing [4]. Survivors of necrotizing fasciitis can have significant cosmetic and functional defects.

Hyperbaric oxygen therapy - It is generally considered to be an important factor in the treatment of clostridial myonecrosis or gas gangrene. Increased oxygen partial pressure can enhance the antibacterial activity of leukocytes, inhibit bacterial growth, enhance the effect of antibiotic treatment, and improve tissue repair. However, various studies have failed to show statistically significant outcome differences in terms of mortality and length of hospitalization [28]. As a result, the hyperbaric oxygen therapy is not a mandatory component of necrotizing fasciitis therapy.

Vacuum assisted closure (VAC) therapy - In recent years, there has been worldwide increase in the use of VAC therapy for fast and effective wound closure [29, 30]. The use of VAC devices is supporting by several studies in the general surgery, orthopedic, and gynecological literature. Several randomized studies have demonstrated improved wound healing and a significant reduction of wound surface area in full-thickness wounds treated with VAC devices as compared to conventional gauze therapy [31]. The advantages of VAC therapy in wound management that make it a promising adjuvant therapy for wound closure are noticeable reduction of the wound area and the formation of granulation tissue, effective wound cleansing and the ability to remove exudate.

Supporting therapy includes intravenous hydration, wound care, anticoagulants to prevent thromboembolic episodes, pain control, etc.

Intravenous immunoglobulin - According to some studies intravenous immunoglobulin has also been used in the treatment of necrotizing fasciitis, particularly if it is associated with group A streptococcal infection. However, due to the small number of patients given and the different methodologies used they are controversial and difficult to compare.

AB103 - The efficacy of a new type of treatment that affects the immune response, called AB103 was assessed by one study. It showed no difference in mortality with use of this therapy, but it is difficult to draw definitive conclusions due to low-quality evidence [32].

Prevention - Most people are in good health before they show signs of necrotizing fasciitis. Basic hygiene practices such as hand washing, wound care, monitoring for signs of infection (increased pain, swelling, purulent discharge, fever) would reduce the likelihood of developing necrotizing fasciitis.

Conclusion

Necrotizing fasciitis is a rare but potentially fatal disease - without treatment, the mortality rate reaches 100% [30]. Immunodeficiency conditions, multiple medical comorbidities, and intravenous drug abuse are among the major risk factors. Initially, the patient's good clinical condition can deteriorate rapidly with the development of sepsis, multiorgan failure and death, so good knowledge and high index of suspicion of the disease in patients is of great importance. Early diagnosis, combined with timely surgical debridement, appropriate antibiotic treatment, management of postoperative complications and a multidisciplinary team approach are essential for successful treatment.

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