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Life-threatening necrotizing fasciitis

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Abstract Necrotizing fasciitis is characterized by a rapidly progressing necrosis of subcutaneous fat and fascia, which can be life-threatening without prompt recognition, surgical intervention, and immediate antibiotic therapy. Necrotizing fasciitis has been subdivided into type 1, or polymicrobial necrotizing fasciitis, and type 2, or group A streptococcal necrotizing fasciitis.[13,40] In addition, synonyms, such as streptococcal gangrene and "flesh-eating bacteria syndrome," have been used in the literature.[13,39]

Introduction

Necrotizing fasciitis appears to have been in existence, at least since the days of Hippocrates. In the fifth century BCE, he wrote, "... many were attacked by the erysipelas all over the body ... the erysipelas would quickly spread in all directions. Flesh, sinews, and bones fell away in large quantities. ..."[1] Although there has been a substantial decrease in the morbidity and mortality from streptococcal and staphylococcal infections, such as necrotizing fasciitis, in the mid 20th century, there has been a reemergence of these organisms as major pathogens during the last 2 decades.[2,38] The prominent media coverage of the "outbreak of flesh-eating bacteria" in 1994 again raised public awareness of the potential seriousness of infection with invasive group A streptococcus.[39] Today, approximately 500 to 1500 cases of necrotizing fasciitis are reported in the United States per year.[2]

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Pathogenesis

Approximately 10% of cases of necrotizing fasciitis are caused by group A streptococcus alone. Most cases are a result of mixed infection with anaerobic and aerobic bacteria, including streptococci, *Staphylococcus aureus*, *Escherichia coli*, *Bacteroides*, and *Clostridium* species. Rare pathogens include *Pseudomonas aeruginosa*, *Haemophilus influenzae* type b, *Aeromonas hydrophila*, and *Vibrio vulnificus*.[3] Polymicrobial infection often reflects organisms introduced at sites of trauma or surgery.

Several factors such as surface proteins, host factors, and toxin production have all been implicated in the renewed virulence of streptococci in many settings, including necrotizing fasciitis. Surface proteins on group A β-hemolytic streptococci are associated with the invasiveness of a given strain. Dozens of M surface proteins exist, forming the basis for the Lancefield classification system.[4] The M1 and M3 surface proteins in particular have been shown to facilitate bacterial adherence to infected tissue and to possess antiphagocytic properties directed against polymorphonuclear leukocytes.[5] Epidemiologic data have revealed a strong correlation between a decreased preva-

lence of the M1 and M3 surface proteins during the middle part of the century and a decreased seriousness of group A β-hemolytic streptococci infections.[6] Conversely, the apparent reemergence of invasive group A β-hemolytic streptococci infection has been closely linked with the renewed prevalence of group A streptococci bearing M1 and M3 surface proteins.[7,8,38]

Recently, nonsteroidal anti-inflammatory drug use has been potentially implicated in the progression to necrotizing fasciitis.[9,10] Depression of lymphocyte function, attenuation of the signs and symptoms of inflammation, and delay in diagnosis until shock or tissue gangrene were apparent are all proposed mechanisms.

Underlying comorbidities that may predispose to necrotizing fasciitis include diabetes mellitus, alcohol abuse, peripheral vascular disease, renal failure, odontogenic infection, and malignancy.[11,12] Group A streptococcal necrotizing fasciitis, however, often occurs in young, previously healthy patients. This is postulated to be due to the absence of previous exposure to these more virulent strains of bacteria, as an absence of protective antibody appears to predispose persons to infection. In a recent report reviewing pediatric cases of necrotizing fasciitis, the most frequent initiating factor was varicella and the most frequently isolated bacterium was *P aeruginosa*.[42]

Mortality rates range from 20% to 40%. Higher mortality rates are found in people with diabetes, malnutrition, obesity, arteriosclerosis, and advancing age.[14,15] In addition, delay in diagnosis and treatment and infections with invasive group A streptococcus are associated with higher mortality rates.[3,16] Prompt intervention lowers the mortality rate to 12%.[16]

Clinical features

Necrotizing fasciitis often begins with pain deceptively out of proportion to any skin findings.[13,17,18] Soon, however, the clinical presentation changes to an exquisitely tender, swollen area of extensive soft tissue erythema that does not respond to antibiotics, heat application, or elevation.[9,11,19] The disease progresses at an alarming rate, with skin changing from a shiny red-purple to a pathognomonic gray-blue with ill-defined patches often within 36 hours after onset. Violaceous bullae may develop.[13] Necrosis of the superficial fascia and fat produces a thin, watery, malodorous fluid. The area may later become anesthetic as cutaneous nerves are destroyed. A hard, wooden feel of the subcutaneous tissues may be present.[3,11] Crepitance has been noted in approximately 30% and is associated with polymicrobial infections, including Enterobacteriaceae and *Clostridium*.[22] Patients can become extremely toxic, with high fever, anxiety, altered mental status, leukocytosis, shock, and tachycardia.[11,20,37] The most common primary site is an extremity, although necrotizing fasciitis can affect any body part.[12] When present in the perineum and genitalia, it is known as Fournier's gangrene, which is due to infection with group A streptococci or mixed infection with enteric bacilli and anaerobes.[41] This entity originates from the scrotum and rapidly progresses to the perineum and anterior abdominal wall. The testes are spared from necrosis because of their separate blood supply. Urethral obstruction can occur from excessive penile edema. Fournier's gangrene may be overlooked initially in the work-up of fever in an elderly demented man.[13,21]

Pathology

The histological hallmark is extensive inflammation and necrosis of the subcutaneous fat, fascia, and muscle. Angiitis and focal dermal necrosis are prominent with spread along fascial planes. Fibrinoid necrosis is present in the media of vessels passing through the destroyed fascia. Fibrin thrombi are present. The epidermis, dermis, and skin appendages in the area of gangrene undergo coagulation necrosis. Numerous polymorphonuclear leukocytes and mononuclear cells and large numbers of bacteria are present in the upper layers of the dermis.[23-25] The classic histopathology of necrotizing fasciitis can be seen most often when a deep incisional biopsy specimen is obtained from the central area of an ecchymotic necrotic plaque.[43]

Differential diagnosis

Initially, it is often difficult to differentiate cellulitis from necrotizing fasciitis. Clues that suggest necrotizing fasciitis rather than cellulitis include severe pain out of proportion to skin findings, rapidly spreading edema, bullae formation, mental status changes, concurrent signs of streptococcal toxic shock syndrome (if streptococcus is the pathogen), marked leukocytosis,[37] or elevated creatinine kinase level.[17,26] Anesthesia of overlying skin can provide a clue that the process is necrotizing fasciitis rather than a simple cellulitis, as local skin anesthesia may antedate the appearance of skin necrosis.[9] Other conditions that may mimic early necrotizing fasciitis are trauma with hematoma, arthritis, bursitis, phlebitis, and deep vein thrombosis.[9] In one study of group A streptococcal necrotizing fasciitis, 35% of the patients initially had other diagnoses, including sciatica, viral illness, cellulitis, traumatic knee effusion, and bursitis.[20] Although diagnosis is primarily clinical, aspirating for Gram's staining and culturing, frozen tissue sections demonstrating a massive polymorphonuclear fascial infiltrate, and radiographic studies showing gas or extensive fluid along soft-tissue planes may be helpful in some cases.[16,28] Since subcutaneous air is not present in pure group A streptococcal necrotizing fasciitis, but rather is seen when mixed aerobic-anaerobic or clostridial infection is the cause, the findings of imaging studies are often nonspecific. When necrotizing fasciitis is suspected, radiographic studies

should not delay surgical evaluation, but rather be used to expedite surgical intervention.

Treatment

Extensive surgical debridement (fasciotomy) is the mainstay of effective treatment. The goal of surgical intervention is to remove all necrotic tissues, including muscle, fascia, and skin, to preserve viable skin, and to achieve hemostasis. On occasion, amputation is necessary.[27] A series of debridements with surgical reexploration may be necessary to ensure complete removal of all necrotic tissues. Antimicrobial therapy is directed toward the results of the initial Gram's staining and culturing of aspirate. Initial broad-spectrum therapy with a β-lactam/β-lactamase inhibitor and clindamycin is suggested until the etiology is known. There is evidence to suggest that clindamycin, a protein synthesis inhibitor, suppresses toxin production by streptococci, making it a necessary component of initial antibiotic therapy, until cultures and sensitivities are available.[11,29] In nosocomial infections where methicillin-resistant *S aureus* is prevalent or in cases with serious penicillin allergy, empiric therapy with vancomycin and clindamycin would be considered. In immunocompromised patients, especially neutropenic children, an aminoglycoside is routinely added to provide adequate coverage for *Pseudomonas*.[3] Hyperbaric oxygen therapy remains controversial[32]; however, if available, it may be a beneficial adjunct for a subset of patients with anaerobic gram-negative necrotizing fasciitis.[30,31] Surgery and antimicrobial therapy should never be postponed if considering hyperbaric oxygen. Intravenous immunoglobulin (IvIG) has been useful in uncontrolled reports for patients with severe group A streptococcal necrotizing fasciitis.[33] Early anecdotal reports suggest potential improvement of outcome in patients with concurrent streptococcal toxic shock syndrome treated with IvIG, by decreasing the superantigen activity of the bacteria on cytokine release by T cells.[34,35,44] There are limited data that IvIG may be used in selected patients to delay debridement until they are stabilized for surgery.[45] Nutritional support is crucial for enhancing wound healing postoperatively.[3,36] In addition, supportive medical therapy consists of management of fluid and electrolyte disturbances and anemia.[3,15] Extensive reconstructive surgery is often necessary.

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