BRIEF REPORT

Necrotizing Fasciitis Due to *Streptococcus pneumoniae* after Intramuscular Injection of Nonsteroidal Anti-Inflammatory Drugs: Report of 2 Cases and Review

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Two cases of pneumococcal necrotizing fasciitis (NF) occurred after intramuscular injections of nonsteroidal anti-inflammatory drugs; another 5 cases reported in the literature fulfilled the criteria for NF involving *Streptococcus pneumoniae*. Conditions associated with alterations of immune function could be identified in 6 of the 7 cases; 2 patients died despite surgical and antimicrobial treatment.

"Necrotizing fasciitis" (NF), a term introduced by Wilson [1], was first described as "hospital gangrene" in the American Civil War era [2]. It is a life-threatening infection of the superficial muscle fascia and the adjacent deep layer of the subcutaneous tissue. Progression to septic shock can occur within hours; the mortality rate ranges from 20% to 60% [3]. It is usually caused by β-hemolytic streptococci or a polymicrobial infection of both anaerobic and aerobic flora. Initially, local pain seems out of proportion to physical findings. Later, discoloration of the skin and development of bullae are signs of progressive necrosis and microthrombosis, thus leading to impaired cutaneous nerve function. These characteristics can help to differentiate NF from cellulitis with only superficial involvement of the skin [4]. Predisposing factors are diabetes mellitus, injection drug abuse, age of >50 years, arterial hypertension, vascular diseases, and obesity or malnutrition. When $\geq$3 of these factors are present, the mortality rate seems to reach 50% [5].

NF due to *Streptococcus pneumoniae* is rare. We report 2 cases of pneumococcal fasciitis and review the literature. Our patients had been treated with im injections of nonsteroidal anti-inflammatory drugs (NSAIDs) before infection.

Methods. Our case definition of pneumococcal NF required the presence of an infection, found by means of direct visualization or imaging technique, that involved the superficial muscular fascia and the surrounding deep layer of the subcutaneous tissue (involvement of the muscle or the skin was optional or secondary); pneumococci isolated from culture of blood and/or local aspirates; and incipient or evident septic shock (e.g., hypotonia, tachycardia, dependence on supportive measures for circulation, multiorgan failure, or death).

We searched the literature through MEDLINE (1966–1999), Serline (unlimited), and Science Citation Index of the Web of Science (1983–1999) for the following terms: "pneumococcal soft tissue infection"; "pneumococcal necrotizing fasciitis"; "soft tissue infection/microbiology" and "etiology"; "soft tissue infection" and "intramuscular injections"; "necrotizing fasciitis" and "intramuscular injections"; "intramuscular injections/complications of"; "necrotizing fasciitis" and "nonsteroidal anti-inflammatory drugs"; and "intramuscular injections" and "nonsteroidal anti-inflammatory drugs." The reference lists of the chosen articles served as additional sources.

Case reports. The first patient was a 68-year-old man with known arterial hypertension. Eight years prior to presentation, an infrarenal aortic aneurysm was treated with a composite graft. Four years prior to presentation, he had had an aortic dissection type B, which was treated conservatively.

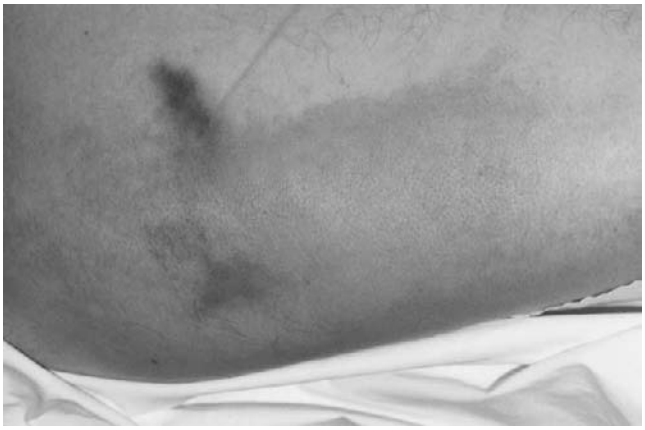

Figure 1. Necrotizing fasciitis due to *Streptococcus pneumoniae* after im injection of nonsteroidal anti-inflammatory drugs in a 68-year-old man (left thigh with site of injection on admission). Note minimal erythema of clearly demarcated area.

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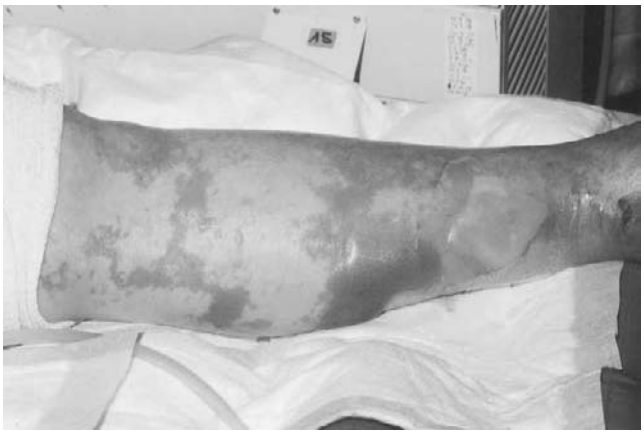

Figure 2. Necrotizing fasciitis due to *Streptococcus pneumoniae* after im injection of nonsteroidal anti-inflammatory drugs in a 68-year-old man (terminal presentation of patient's left leg, with extensive necrosis).

Three days after onset of an upper respiratory tract infection with cough and sore throat, he presented to his physician with pain in his right big toe. The diagnosis of acute gout arthritis was made, and the patient was treated with an im injection of diclofenac, 75 mg, in his left thigh. Two days later, he complained of severe pain at the injection site. He collapsed and was admitted to our hospital the same day with refractory hypotension.

Physical examination revealed that the patient was severely ill, hoarse, and had a temperature of 35.7°C and cold skin with signs of impaired perfusion. His blood pressure was 70/50 mm Hg, and his pulse was 110 beats/min. The site of the injection was exquisitely tender, but it showed only minimal erythema and a slight rise in temperature (figure 1). The remaining findings of the physical examination were unremarkable. Laboratory studies showed a normal leukocyte count, with 69% band forms, and thrombocytopenia (platelet count, $66{,}000 \times 10^9$ cells/L). There were signs of impaired coagulation, such as prolonged partial thromboplastin time of 42 s (normal maximum, 36 s) and an elevated fibrinogen level of 6.6 g/L (normal maximum, 3 g/L). The following values were also noted: creatine kinase level, 1099 U/L (normal range, 85–350 U/L); creatinine level, 309 μmol/L (normal range, 59–116 μmol/L); and serum aspartate aminotransferase level, 206 U/L (normal range, 10–41 U/L). Blood gas analysis revealed severe metabolic acidosis (pH, 7.1; bicarbonate, 7.7 mmol/L [normal range, 18–29 mmol/L]) with a normal lactate level at that time. An initial normal leukocyte count, normal lymphocyte count, and normal levels of complement factors showed no evidence of a compromised immunologic status; further tests (e.g., for HIV) were not done.

Ultrasonography of the left thigh revealed no signs of abscess, blood, or air pocket formation. Nevertheless, septic shock, probably due to NF, was strongly suspected, and the patient underwent surgical exploration 48 h after the injection. Intraoperative findings showed large patchy areas of necrotic subcutaneous tissue but no abscess formation. Extensive debridement was done. Antibiotic therapy with ceftriaxone, gentamicin, and clindamycin was administered perioperatively. Two days later, cultures of blood and wound aspirates yielded penicillin-sensitive *S. pneumoniae*.

Despite daily extensive surgical debridements, the local and systemic inflammatory reactions were never under control. Necrosis continued to extend, involving the hip joint and lower abdominal wall within days. Dialysis was begun on day 2. On day 3, arterial circulation of the lower left extremity became marginal (figure 2). On hospital day 6, the patient died of septic shock and multiorgan failure.

The second patient was an 83-year-old woman. A mediastinal mass had first been detected 14 years prior to presentation. A needle aspiration was performed, but definitive diagnosis could not be made. Because the patient remained asymptomatic, no further diagnostic tests were done. On review, 4 years prior to presentation, the mass had diminished in size. Laboratory tests revealed a slight deficiency of IgA, IgG1, and IgG2. Therefore, an adult teratoma or a thymoma was suspected.

The patient first presented to her physician with pains in the right hip joint region. Degenerative arthritis was suspected, and she was treated with an im injection of denoxicam in the right thigh. Two days later, the pain had substantially increased. The patient was now unable to walk; she seemed progressively ill, and she was admitted the next day.

On admission, the patient was awake but disoriented. Her temperature was 38.8°C, her blood pressure was 100/60 mm Hg, and her pulse was 100 beats/min and regular. The findings of the physical examination were unremarkable except for a very painful, dark-reddish defined area at the site of injection, and both of her wrists were very tender. Laboratory studies

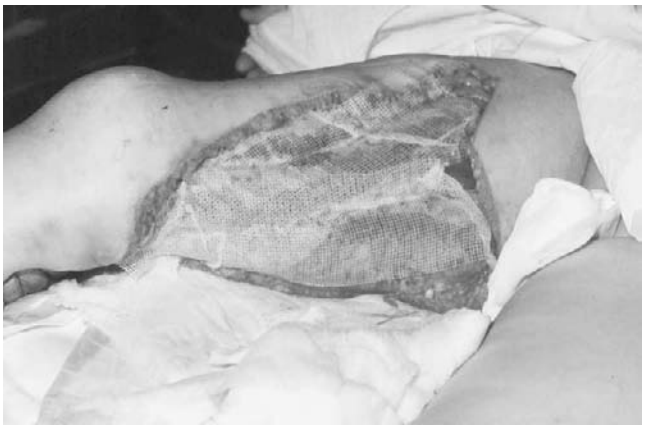

Figure 3. Necrotizing fasciitis due to *Streptococcus pneumoniae* after im injection of nonsteroidal anti-inflammatory drugs in an 83-year-old woman (inner right thigh after extensive surgical debridement). Note necessity for ablation of all infected tissue unto healthy muscular layer.

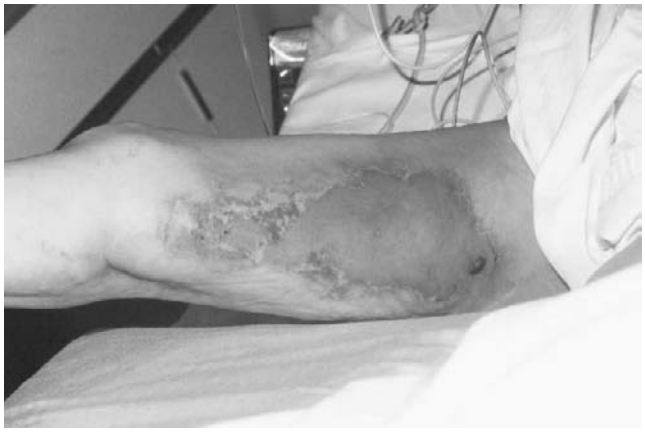

Figure 4. Necrotizing fasciitis due to *Streptococcus pneumoniae* after im injection of nonsteroidal anti-inflammatory drugs in an 83-year-old woman (inner right thigh after complete wound healing by total skin transplantation at end of hospital stay).

revealed a normal leukocyte count, with elevated band forms, and thrombocytopenia (platelet count, $59{,}000 \times 10^9$ cells/L). Her creatinine level was 309 U/L and her creatine kinase level was normal. The diagnosis of an incipient septic shock due to an infection of the right thigh was made. Surgical exploration was done immediately. The intraoperative site showed vast necrosis of skin, subcutaneous tissue, and muscle fascia. On the next day, purulent discharge was surgically removed from both wrists. Culture of blood and local aspirates yielded *S. pneumoniae.* Therefore, the diagnosis was pneumococcal NF with septic arthritis of both wrists. Daily surgical debridements (figure 3) and antibiotic therapy with ceftriaxone showed good results, and the patient recovered gradually. Values for IgA, IgG1, and IgG2 were consistently ~20% below normal levels. She was discharged 6 months later, after a prolonged convalescence due to arthrosis and chronic diarrhea (figure 4).

Literature review and discussion. NF due to *S. pneumoniae* is rare. It is not even mentioned in systematic reviews about soft tissue infections, such as that of Lewis [6]. Literature review yielded 4 case reports [7–10]. One additional case report classified as cellulitis met our criteria for NF [11] (table 1). Pneumococci were isolated from cultures of blood and site aspirates, in 3 cases, and cultures of either wound aspirates or blood, in 1 case each. Besides the clinical findings, the diagnosis of NF was confirmed by CT in 2 cases [7, 10]; by ultrasound, in 1 case [9]; and by description of the intraoperative presentation, in 2 cases [8, 11]. No trauma or skin laceration as a concomitant factor is described, but all patients had some immunocompromising condition, such as injection drug abuse, diabetes mellitus, chronic renal failure, or systemic lupus erythematosus. In the patient with systemic lupus erythematosus, concomitant hypocomplementemia and immunosuppressive drugs were considered additive risk factors for this disease [7, 10, 12]. Two of 7 patients with pneumococcal NF died (mortality rate, 29%), despite combined surgical and antimicrobial treatment.

Our cases resemble those found in the literature. The first patient was known to have generalized arteriosclerosis due to longstanding arterial hypertension, which has also been listed as a risk factor [13]. Moreover, he had had an infection of the upper respiratory tract 3 days before injection, which is known to favor infection with *S. pneumoniae.* The second patient had a persistent immunoglobulin deficiency, probably due to the mediastinal tumor, which made her more susceptible to pneumococcal infection. Levels of complement factors were normal at the time. The 2 cases suggest a relationship between im injections of NSAIDs and pneumococcal NF. Conditions associated with alterations of immune function can be identified in 6 out of 7 cases. This observation is in contrast to that of patients presenting with group A streptococcal NF, who typically lack recognizable immune dysfunction [4].

Lethal outcomes in patients with NF who undergo therapy with NSAIDs are reported, and the impact of these drugs on the severity of the disease is controversial [14–16]. Their wide-

Table 1. Pneumococcal necrotizing fasciitis: literature review.

Author [reference]	Year	Age, years	Sex	Comorbidity	Site	Cultures positive for pneumococci	Therapy	Outcome
Present report	2001	68	M	im NSAIDs	Leg	Local/blood	Ctri, Gm, Cm, surg	Died
Present report	2001	83	F	im NSAIDs, thymoma	Leg	Local/blood	Ctri, surg	Survived
Lewis et al. [11]	1975	21	M	Injection drug abuse	Leg	Local/blood	Cm, Gm, surg	Died
Hill and Karsh [10]	1997	30	F	Systemic lupus erythematosus	Neck	Blood	Pen, surg	Survived
Patel et al. [8]	1994	60	F	Renal failure	Leg	Local/blood	Pen, surg	Survived
Di Nubile et al. [7]	1991	18	F	Systemic lupus erythematosus	Neck	Local/blood	Pen, surg	Survived
Choudri et al. [9]	1995	44	F	Insulin-dependent diabetes mellitus	Thigh	Local	Pen, surg	Survived

NOTE. Cm, clindamycin; Ctri, ceftriaxone; F, female; Gm, gentamicin; M, male; Pen, penicillin; surg, surgical intervention.

spread use makes it difficult to define their causal contribution to the evolution of severe infection. Nevertheless, NSAIDs enhance the production of TNF-α in the presence of endotoxins [17] by impairing the normal feedback loop during the production of TNF and other cytokines, and, therefore, acting as an additional stimulus to the proinflammatory cascade. In addition, they are potent inhibitors of neutrophil granulocyte chemotaxis and phagocytosis by inhibiting the lipoxygenase pathway, which is specially true for diclofenac and indomethacin. In the same way, they also decrease leukotriene production by leukocytes, which are compounds known to play a role in the inflammatory response [18]. Finally, they confound the progression of disease by suppressing fever and pain through inhibition of prostaglandin synthesis, thus blurring the signs of onset of serious infection [19].

Considering the aforementioned pathophysiological impact of NSAIDs, treatment with NSAIDs may well have been an accelerating factor in the evolution of NF. Intramuscular injections per se can provoke severe tissue trauma, representing a local portal of entry for infection, even when correctly administered [20–23]. Necrosis at the infection site appears to be independent of the drug given, and it is a strong additional risk factor for soft tissue infection. The combination of im injection with NSAIDs seems to multiply the risk of serious infective complications.

Not much is known about the interaction of pneumococcal fasciitis, im injections, and NSAIDs. In a review of the literature (table 1), none of the other patients were described as having received im injections or NSAIDs. An extended search for pneumococcal soft tissue infections and im injections revealed 1 case of pneumococcal cellulitis after injection of steroids [24]; 1 case each of abscess formation after injection of NSAIDs [25], steroids, or contraceptive drugs [26]; and 1 case of pyomyositis after injection of a drug that most probably was an NSAID or a local anesthetic [27]. Two additional cases of pneumococcal cellulitis after oral application of NSAIDs were reported [28, 29].

Both of our patients were treated with im injection of NSAIDs before admission, and both of them developed severe NF at the injection site. The indications for the injection were pain due to suspected gout arthritis in 1 patient and arthrosis in the other. Considering today's large arsenal of oral and rectal drugs with adequate bioavailability, im applications of NSAIDs should be used with utmost care, and, wherever possible, the means of treatment should be changed to another application form.

In summary, we describe 2 cases of NF due to *S. pneumoniae.* Our cases differ from the 5 cases we identified in the literature by the fact that they occurred after im administration of NSAIDs. Less severe skin infections due to *S. pneumoniae* that have involved im injections have also been described. Most likely, host factors, including immunodeficiency or pharmacological skewing of host defense mechanisms, may contribute to progression of the infection and extensive tissue damage. First-line therapy still consists of immediate, extensive surgical debridement of necrotic areas combined with antibiotic therapy.

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