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CASE REPORTS

Necrotizing Fasciitis Due to Penicillin-resistant *Streptococcus pneumoniae*: Case Report and Review of the Literature

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Necrotizing fasciitis (NF) is a life-threatening infection involving rapid necrosis of subcutaneous and fascial tissues. *Streptococcus pneumoniae* (SPN) soft tissue infection is exceedingly uncommon, reported primarily in patients with immunosuppression or other underlying conditions. We report a case of NF and septic shock in a healthy 32-year-old man, whose only predisposing factor was antecedent blunt trauma. Pathological examination and culture of the extensive tissue debridement were positive only for SPN. The serotype 9V isolate was penicillin (PCN)-resistant (MIC = 2.0), and closely-related by pulse field gel electrophoresis and multilocus fingerprinting to clone France 9V-3, an important genetic reservoir for increasing PCN-resistance worldwide. This unique case has implications for our pathogenic understanding and empiric management of NF.

Introduction

Streptococcus pneumoniae (SPN) is a major human pathogen that produces pneumonia, sepsis and meningitis.[1] Increasing prevalence of acquired resistance to penicillin (PCN) and other antimicrobial agents is an important problem in the management of serious SPN infections.[2,3] Necrotizing fasciitis (NF) is a potentially life-threatening condition involving rapid necrosis of subcutaneous and fascial tissues, often accompanied by septic shock.[4] The most widely recognized single causative agent of NF is group A *Streptococcus* (GAS); mixed aerobic/anaerobic aetiologies are also well-documented.[5,6] In contrast to GAS, necrotizing fascial and soft tissue infections produced by SPN are exceedingly uncommon, reported previously only in patients with immunosuppression or other significant underlying conditions.[7]

We report a case of extensive NF and septic shock in a healthy 32-year-old man, whose only predisposing factor was antecedent blunt trauma. Pathological examination was characteristic for NF, and Gram stain and culture of the extensive tissue debridement were positive only for SPN. The serotype 9V isolate was PCN-resistant (MIC = 2.0) and genetically related to the well-described clone France 9V-3. The potential implications of this case for our pathogenic understanding and empiric management of NF are discussed.

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Case Report

A previously healthy 32-year-old Hispanic male presented to the emergency department with left flank and rib cage pain and overlying erythema. Five days earlier he had been in a fistfight with his brother. As he ran away he collided with a fence and injured his left side. Pain initially subsided in the 2 days after the incident, but then worsened again, preventing him from sleep. At presentation he was afebrile but tachycardic (pulse = 110 beats/min). He had no additional complaints, but was noted to desaturate with exertion. The patient was not known to abuse alcohol or illegal drugs and denied such activity. Physical examination was remarkable for localized erythema and ecchymosis of the left flank with pain in the inferiolateral aspect. There were no rales heard and no cough. Complete blood count showed a marked leukocytosis (41 000 cells/mm^3). A computed tomogram revealed a slightly displaced left lateral tenth rib fracture and soft-tissue haematoma, associated with adjacent pulmonary atelectasis but without infiltrate to suggest pneumonia. He was admitted for treatment of the presumed cellulitis and observation. Meropenam, levofloxacin and metronidazole were begun empirically.

On the second hospital day pain increased, erythema and ecchymosis spread across his flank and upper abdomen (Fig. 1a). The patient was febrile and the peripheral leukocyte count rose to 51 000 cells/mm^3 with many immature neutrophils. He was taken to surgery with intraoperative diagnosis of NF; extensive debridement of left flank and abdominal wall subcutaneous tissues was performed (Fig. 1b). Aerobic and anaerobic bacterial cultures were obtained in appropriate transport media. The patient developed hypotension requiring pressor support, acute renal insufficiency (serum creatinine 265.2 μmol/l: 3 mg/dl

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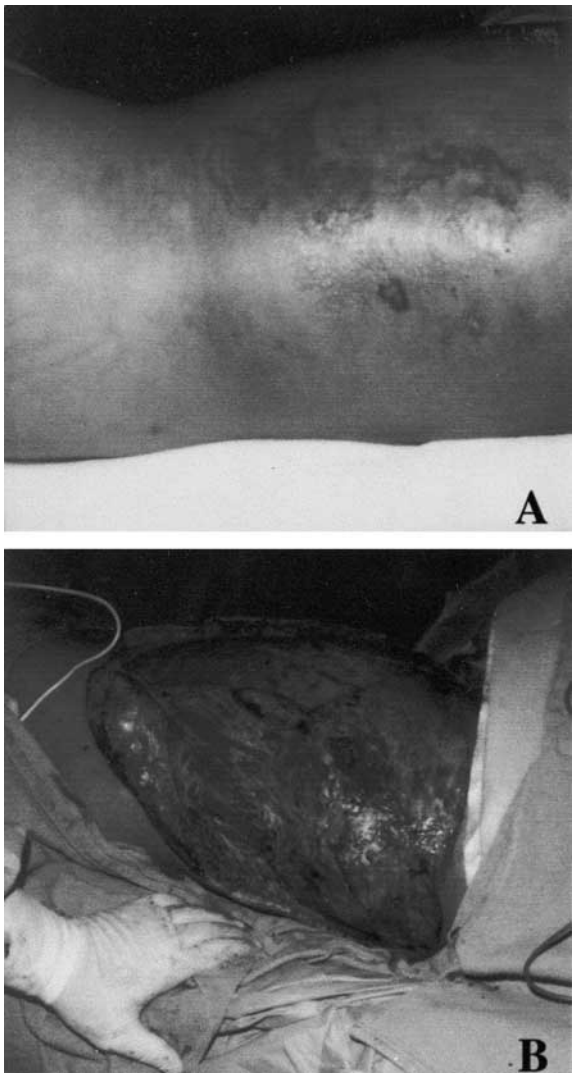

Figure 1. Thirty-two-year-old male patient, lying prone, with necrotizing fasciitis due to *Streptococcus pneumoniae*. (A) Preoperatively, extensive erythema, induration and tenderness of right flank was noted. (B) Intraoperatively, extensive necrotic fascial tissue was identified and debrided.

hyponatremia (serum sodium = 112 mEq/l), acidosis (serum bicarbonate = 16 mEq/l), and evidence of moderate disseminated intravascular coagulation. He returned to surgery on the following day, at which time further debridement was performed until healthy tissue was reached, the wounds ultimately extending throughout the entire left flank, left chest and left abdominal wall. Antibiotics were changed to vancomycin and clindamycin.

Microscopic histopathology of the necrotic tissue is shown in Figure 2. Gross necrosis was observed throughout the subcutaneous tissue fascia, with some areas of muscle involvement. There was acute dermatitis and panniculitis with fibrin thrombi in the small vessels. Abundant perivascular infiltrates of neutrophils were seen within oedematous dermal collagen, and vesicle formation in the overlying skin. Brown and Brehm stain revealed abundant bacteria of a single staining pattern and morphology, namely Gram-positive lancet-shaped diplococci. Blood cultures were negative, but surgical wounds yielded a pure growth of SPN. Antibiotic sensitivity testing of the isolate revealed MICs to PCN of 2.0 μg/ml, cefotaxime 0.75 μg/ml, ceftriaxone 0.50 μg/ml, cefuroxime 2.00 μg/ml, erythromycin 0.125 μg/ml, and vancomycin 0.50 μg/ml, plus disk sensitivity to clindamycin.

The patient completed a treatment course with ceftriaxone and clindamycin. He underwent extensive allografting to close his wound, but ultimately experienced a complete recovery and was discharged from the hospital 30 days after admission. At follow-up 1 month and 6 months later he remained well, but was subsequently lost to follow-up Screening immunological studies revealed normal quantitative immunoglobulins and CH_{50}; HIV serology testing was declined.

Serological analysis revealed the SPN isolate to belong to serotype 9V. The isolate was further studied by pulsed-field gel electrophoresis (PFGE) together with genetic fingerprinting for three PCN-binding proteins (*pbp1a-pbp2b-pbp2x*), dihydrofolate reductase (*dhf*), and pneumococcal surface protein A (*psp*A).[8,9] As shown in Figure 3, these data revealed nearly identical restriction enzyme digest patterns to the well characterized SPN clone France 9V-3 that is commonly associated with PCN resistance worldwide.

Discussion

SPN is a formidable human pathogen and the most common cause of community-acquired bacterial pneumonia in adults. Infection of the soft tissues, however, has not been recognized as an important component of the pneumococcal clinical spectrum. Reports of simple cellulitis due to SPN are infrequent,[10,11] and cases of deeper or necrotizing soft tissue infections exceedingly rare. Table I summarizes the 11 confirmed cases of SPN deep or necrotizing soft-tissue infection that we could identify upon review of the medical literature. The majority of these patients possessed significant underlying medical conditions known to be associated with increased susceptibility to invasive bacterial disease. In contrast, our patient was a previously healthy 32-year-old male free of underlying medical conditions except for recent blunt trauma to the affected area. Although antibiotic pretreatment precludes a categorical assertion that SPN alone produced NF in our patient, the tissue Gram stain and culture findings from extensive devascularized tissue debridement indicate a primary role. The development in such a patient of severe and extensive pneumococcal NF warrants a brief reexamination of the virulence properties of the organism as well as the pathogenic mechanisms by which bacterial infection produces soft tissue necrosis.

Invasive SPN infections typically occur at the extremes of age and in patients with a number of well-recognized medical risk factors.[7,12] These risk factors include splenectomy,[13] HIV infection,[12] sickle cell disease,[15] diabetes mellitus,[16] rheumatological disorders,[17] myeloma,[18] alcoholism,[12] intravenous drug abuse[19] and intercurrent influenza infection.[20] This broad host susceptibility pattern reflects the importance of multiple immune system components in defence against SPN. *In vitro* and laboratory animal studies confirm: (1) the opsonizing activities of type-specific anticapsular antibody and complement; (2) efficient neutrophil phagocytosis and killing; and (3) hepatosplenic clearance as critical defences against invasive SPN infection.[21]

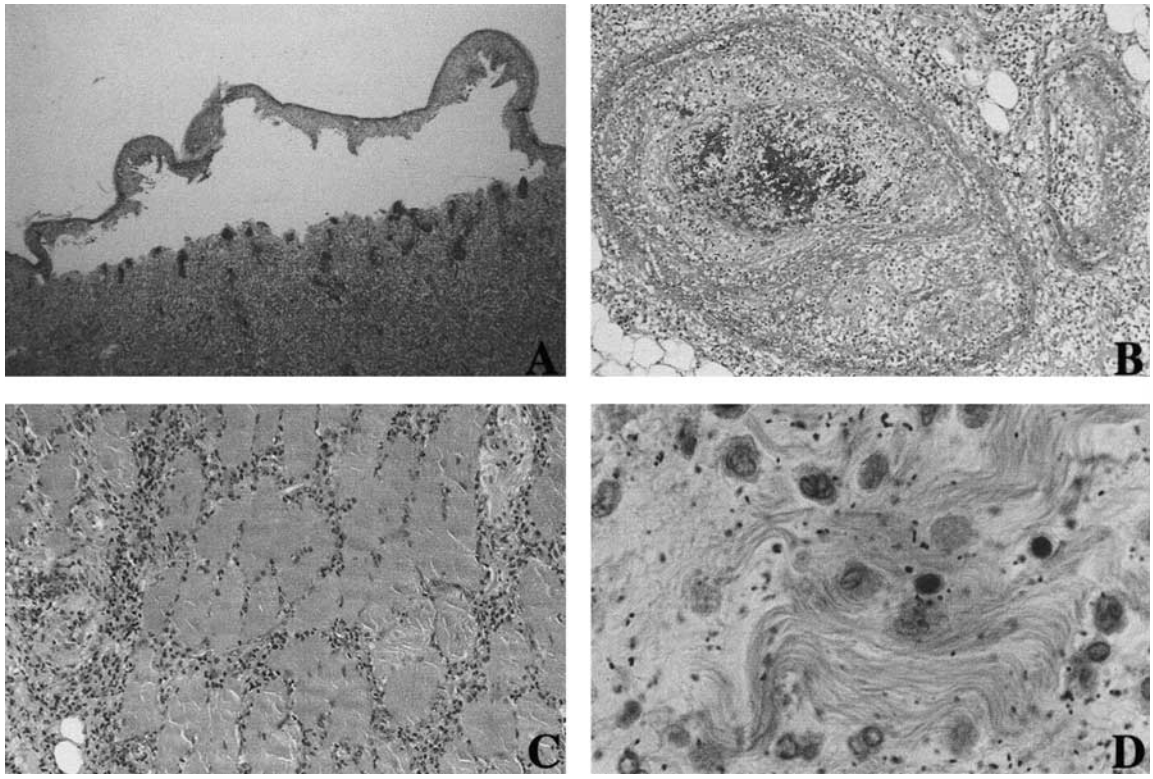

Figure 2. Histopathological examination of debrided tissue. (A) Fasciitis and deep dermatitis with necrosis, neutrophilic infiltrate and overlying vesicle formation; (B) fibrinous thrombosis of a fascial blood vessel; (C) focus of necrotizing myositis; (D) Brown & Brehm stain revealing abundant Gram-positive lancet-shaped diplococci.

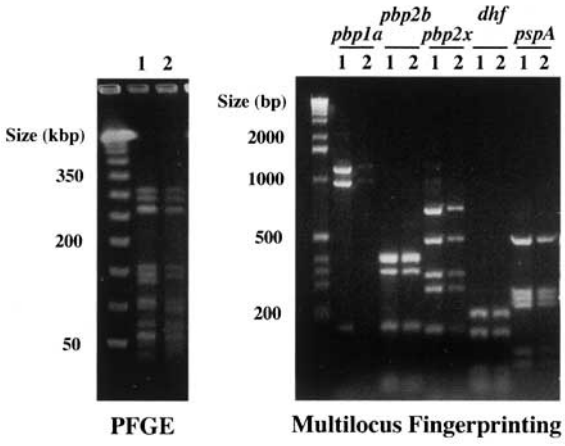

Figure 3. Genetic comparison of *Streptococcus pneumoniae* necrotizing fasciitis clinical isolate (1) with clone France 9V-3 (2). Pulsed-field gel electrophoresis (PFGE) was performed with *Sma*I-digested total chromosomal DNA. Multilocus fingerprinting employed restriction enzyme analysis of PCR amplicons for the penicillin-binding protein genes *pbp1a*, *pbp2b*, and *pbp2x* (*Hae*I + *Rsa*I digest), together with the dihydrofolate reductase gene *dhf* and the pneumococcal surface protein A gene *pspA* (*Hae*III + *Rsa*I + *Hinf*I digest).

Screening immunological studies in our patient were negative for complement deficiency or hypogammaglobulinaemia, and he had not suffered from frequent infections during his lifetime. Blunt trauma leading to rib fracture and flank haematoma undoubtedly provided a nidus for the localization of SPN infection; however, the route of inoculation of this nidus is uncertain. Haematogenous spread, as in patients with distant SPN cellulitis complicating pneumonia,[22] or direct inoculation through a small break in the skin, as in IV drug abusers with localized SPN cellulitis,[23] are possibilities.

The pathogenesis of severe NF in nonimmunocompromised patients is incompletely understood. The rapid clinical course, associated systemic toxicity, and histopathological findings in our patient were characteristic of those observed in NF produced by GAS or polymicrobial flora.[24] A consistent histopathological feature of NF appears to be intravascular thrombosis of vessels at all levels of infected tissue, though invasion of the vessels themselves with bacteria or inflammatory cells is typically absent.[25] Such thrombosis results in devascularized and ultimately necrotic tissue, a favourable environment for bacterial replication while an unfavourable condition for host cellular clearance mechanisms or antibiotic penetration. In our patient a dense neutrophilic inflammatory infiltrate was also present along with SPN in the oedematous reticular dermis, fascia, subcutaneous fat, and foci of muscle. These infiltrating neutrophils, if activated to degranulate, would release hydrolytic enzymes (e.g. elastase) and reactive oxygen species that could exacerbate

Table I. Severe deep or necrotizing soft-tissue infections produced by *Streptococcus pneumoniae.*

Age and sex of patient	Description of lesion	Anatomic location	Underlying illnesses	Medications or risk factors	*S. pneumoniae* identification	Therapy	Outcome	Reference
14 yr, F	Faciitis	Neck	SLE	Prednisone, azothiaprine	Blood cx	PCN	Recovery	49
18 yr, F	Necrotizing fasciitis	Neck, tongue	SLE, renal insufficiency	Prednisone	Blood + tissue cx	PCN, debridement	Recovery	50
21 yr, M	Fasciitis, pyomyositis	Calf	None	Intravenous drug abuse	Blood + tissue cx	Clindamycin, gentamycin	Septic shock, death	23
22 yr, F	Fasciitis	Neck, pharynx	SLE	Prednisone, cyclophosphamide	Blood cx	PCN	Septic shock, recovery	17
37 yr, F	Pyomyositis	Buttocks	None	IM injection at site	Tissue cx	PCN, drainage	Recovery	51
44 yr, F	Necrotizing fasciitis	Calf	DM, foot ulcers, nephropathy	Tuberculosis, hypothyroidism	Tissue cx	Imipenam, amputation	Recovery	52
53 yr, M	Pyomyositis	Shoulder, biceps	none	None	Blood + tissue cx	PCN	Recovery	53
56 yr, M	Necrotic cellulitis	Leg	Chronic stasis dermatitis	ETOH abuse	Blood + tissue cx	Antibiotics, debridement	Recovery	10
60 yr, F	Fasciitis	Leg	ESRD	not described	Blood + tissue cx	VAN, PCN depridement	Recovery	49
68 yr, F	Necrotic cellulitis	Multifocal	Rheumatoid arthritis	Indomethacin	Blood cx	PCN	Recovery	54
69 yr, M	Necrotic cellulitis	Foot	Type II DM, CLL	Hypo-IgG cyclophosphamide	Blood + tissue cx	PCN, tobramycin	Gangrene, death	55

local tissue injury.[26] In NF produced by *Clostridium perfringens*, neutrophils may accumulate in the feeding blood vessels, injuring the endothelium and contributing to progressive vascular insufficiency and ischemic necrosis.[27]

Specific bacterial factors and toxins contribute to the pathogenesis of NF by preventing phagocytic clearance and by direct damage to fascial cellular and extracellular matrix components. For example, studies of isogenic factor-deficient mutants of GAS in the murine subcutaneous infection model have implicated the β-haemolysin streptolysin S, the surface M protein, the hyaluronic acid capsule, and an extracellular cysteine protease as critical to establishment of NF.[28–30] Likewise, SPN possesses a number of virulence determinants that could have contributed to the development of NF in our patient. The polysaccharide capsule interferes with opsonophagocytosis by preventing either the Fc region of immunoglobulins or complement component iC3b fixed to deeper SPN cell surface structures from interacting with neutrophil receptors[31,32] SPN produces a hyaluronidase and several neuraminidases which recognize substrates associated with mammalian connective tissue and extracellular matrix; these factors could play a role in the migration of the organism through fascial tissues.[33] Pneumolysin is a thiol-activated SPN cytotoxin that forms oligomers resulting in transmembrane pores in a wide range of eukaryotic target cells.[34]

In addition to direct cytotoxicity, pneumolysin can strongly induce the production of nitric oxide, an important vasoactive mediator operative in septic shock.[35] Finally, peptidoglycan and teichoic acid are solubilized from the SPN cell wall by the activity of an autolysin released during stationary growth phase.[36] The cell wall components are potent activators for release of tumour necrosis factor, IL-1, IL-6 and IL-8 resulting in altered vascular permeability, neutrophilic activation and attendant inflammatory tissue damage.[37] SPN techoic acid and peptidoglycan also activate the alternative pathway of complement, hastening the accumulation of leukocytes, and inducing a procoagulant activity on the surface of endothelial cells.[38,39] These factors could contribute to the neutrophilic infiltrate and vascular thrombosis observed histopathologically in our patient.

Antibiotic testing found our isolate to be PCN resistant (MIC = 2.0) but susceptible to cephalosporins. Recent data from the Emerging Infections Program/Active Bacterial Core Surveillance (ABCS) indicates that in the United States 25% of invasive SPN isolates are no longer susceptible to PCN (CDC, 1998 Notifiable Diseases Summary/MMWR). Importantly, PCN-resistance may be associated with an increased risk of adverse outcome in patients with invasive SPN infections.[40,41] Using a methodology detecting variation in unlinked, variable chromosomal loci in combination with overall genetic similarity (by PFGE), we determined unambiguously the relatedness of our patient isolate to isolates belonging to SPN clone France 9V-3.[8,9] France 9V-3 is one of two pandemic clones hypothesized to be largely responsible for the worldwide increase in PCN-resistance, since it appears to serve as a genetic reservoir for susceptible SPN to acquire PCN resistance via horizontal genetic transfer.[42]

This report of PCN-resistant SPN producing severe NF and septic shock in a previously healthy young adult further emphasizes the need for caution in the antibiotic management of this disorder. The clinical presentation and tempo of illness were indistinguishable from the more common GAS aetiology, where aggressive surgical intervention remains the cornerstone of therapy and intensive supportive care measures are a critical component of successful management. Although GAS remain highly sensitive to PCN *in vitro*, treatment failures of high-dose PCN in invasive soft-tissue infection have been reported clinically[43] and

demonstrated in animal models.[44] Clindamycin, acting ribosomally and free from inoculum effect, has shown better efficacy in animal models of GAS myositis[45] and was associated with improved outcome when present as a component of the antibiotic regimen in pediatric patients with invasive GAS infection.[46] The observation that NF can be produced by SPN and other species such as *Staphylococcus aureus*[47] or *Enterococcus faecalis*[48] commonly resistant to PCN amplifies this point. Broader spectrum antibiotic coverage of patients with NF is warranted pending definitive culture results and sensitivity testing, even following visualization of Gram-positive cocci on stain of infected tissue.

It is unknown whether additional cases of NF due to SPN may arise in other patients following this report. Nevertheless, we anticipate that consideration and study of our SPN isolate in comparison to the more common GAS isolates may benefit our understanding of the basic pathogenesis of bacterial necrotizing soft tissue infection.

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Cutaneous and Mediastinal Lymphadenitis due to *Mycobacterium kansasii*

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***Mycobacterium kansasii* most commonly causes a slowly progressive pulmonary disease. Skin and disseminated infections are seen less frequently and only in immunocompromised hosts. To our knowledge, no case of *Mycobacterium kansasii* infection or skin infection associated with additional organ involvement in an immunocompetent patient has been reported.**

Case Report

A 79-year-old previously healthy female patient presented with a 2-month history of low-grade fever, a non-productive cough, itching and night sweats. Empirical amoxycillin followed by erythromycin were ineffective. She had lost 3 kg of weight in 2 months. Physical examination revealed a febrile patient with bilateral (mainly right-sided) scattered pulmonary crepitations, and disseminated papulonodular skin lesions over the face, scalp, back, chest, right breast, abdomen, arms and buttocks. Lesions ranged from 0.5 to 2 cm in diameter and two of the scalp lesions were ulcerated and crusting. The patient had no lymph adenopathy and no further outstanding features were noted. Her full blood count was normal outside of a haemoglobin 11 g/dl.

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