Postirradiation *Klebsiella pneumoniae*-Associated Necrotizing Fasciitis in the Western Hemisphere: A Rare but Life-Threatening Clinical Entity

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Abstract: Necrotizing fasciitis (NF) caused by *Klebsiella* spp. is a unique entity, particularly, in Asia, where virulent strains of *Klebsiella* predominate. It is now clear that *Klebsiella* spp. are capable of causing NF either isolated or in the context of disseminated disease. We present a unique case of NF caused by *Klebsiella pneumoniae* in the Western hemisphere after radiotherapy in a hospitalized patient with significant comorbidities. Physicians should be aware of nosocomially acquired *K. pneumoniae* fasciitis after radiotherapy in the setting of chronic comorbidities, such as diabetes and malignancy. Early diagnosis, surgical intervention, and appropriate empirical antibiotics are essential for a favorable outcome in such rare but life-threatening cases of NF.

Key Indexing Terms: Necrotizing fasciitis; *Klebsiella pneumoniae*; Radiotherapy; Soft tissue infection; Gram negative bacteria. **[Am J Med Sci 2009;338(3):217–224.]**

Necrotizing fasciitis (NF) is a life-threatening soft tissue infection.[1–3] Although single-organism NF is usually caused by invasive streptococci,[1–3] other organisms have been implicated in the pathogenesis of this entity,[3,4] including *Klebsiella* spp. NF is increasingly recognized as a potential manifestation of disseminated *Klebsiella* infections and is strongly associated with predisposing conditions, such as diabetes mellitus.[5,6] Awareness of the potential for multiorgan involvement should prompt a thorough investigation of patients for metastatic foci of infection. We describe a unique case of NF caused by *Klebsiella* spp. in a patient who had recently received radiotherapy and we summarize the available literature.

CASE REPORT

We describe the case of a 77-year-old man with a medical history significant for adult onset diabetes mellitus for 30 years, metastatic follicular thyroid cancer with metastasis to the spine, and a pathologic fracture of the left hip necessitating a total hip replacement 1 year ago. He had received treatment with radioactive iodine 4 months before admission. He was a native American who lived in Massachusetts and had never traveled outside the United States. Because of worsening back and left hip pain, he was admitted to the hospital, and on the eighth day of hospitalization he was initiated on radiation therapy targeting the left hip and lumbar spine with significant improvement of his pain. On the 15th day of hospitalization, he developed hypotension, fever, and signs of septic shock and was transferred to the intensive care unit. He required inotropic support with vasopressors and was initially administered intravenous vancomycin and levofloxacin. The following day he was noted to have erythema and increased warmth of both thighs. At that time, his temperature was 38°C and there was erythema and tenderness over the left inner thigh and right lateral thigh. Pertinent laboratory data included a white cell count of 2.8×10^9/L, lactic acid of 5.4 mg/dL, and a serum creatinine of 1.6 mg/dL. His antimicrobials were changed to clindamycin, vancomycin, and cefepime for rapidly progressive cellulitis and concern for NF. He was taken to the operating room for fasciotomy that revealed NF and wide debridement of both thighs was performed. *Klebsiella pneumoniae* sensitive to all antimicrobials tested was isolated from blood, urine, and tissue cultures from the left thigh. The patient continued to deteriorate, but the family decided not to proceed with another surgery and to keep the patient comfortable. He died on the 18th day of hospitalization.

DISCUSSION

Necrotizing Fasciitis

NF is a life-threatening soft tissue infection that involves subcutaneous tissue, superficial fascia and results in rapidly spreading necrosis of the skin and underlying structures.[7] Despite advances in the management of this entity, mortality remains high.[8] In most NF cases, the causative organism cannot be isolated and, although polymicrobial infection is more common, single bacterial species can be isolated in up to 29% of culture-positive wounds.[9] Gram-negative enteric bacilli and Gram-positive cocci have been identified in the majority of patients.[9–12]

Generally, NF is a synergistic polymicrobial infection.[3] Although most reported cases of NF occur in a community-acquired setting,[13] NF can result from nosocomial infection and can be a devastating complication for patients who have undergone invasive procedures or recent surgery, especially in patients with morbid obesity or who have undergone chemotherapy. Postprocedural NF tends to be polymicrobial, and the diversity of organisms is probably the result of manipulation of areas that are contaminated (eg, gastrointestinal tract).[14] However, the epidemiology of NF varies according to geographical settings and the affected host. In 2 studies of NF in cirrhotic patients in Taiwan, NF was mainly monomicrobial, often caused by Gram-negative bacilli,[15,16] which is probably related to the variable distribution of these Gram-negative pathogens in aquatic environments in Taiwan and also to the predisposition of this subgroup of patients to infections associated with these pathogens.

Predisposing factors for the development of NF caused by *Streptocccus pyogenes* include penetrating injuries, blunt trauma, minor cuts, burns, surgical procedures, varicella infection, and muscle strain.[17,18] NF may also occur as a nosocomial

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Submitted February 2, 2009; accepted in revised form March 3, 2009.

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or postoperative infection.[19] It may also occur spontaneously in immunocompromised patients[7] and can also affect previously healthy and young persons. Primary or idiopathic NF is a different clinical entity characterized by the absence of an external port of entry of bacteria. This type of infection occurs in patients with chronic debilitating diseases and has been postulated to be the result of either hematogenous spread of bacteria or bacterial invasion through small unrecognized breaks in the epidermis.[20] Diabetes mellitus is the most common underlying disease[7,21] associated with the development of NF, whereas other systemic host debilitating disorders include advanced age, peripheral vascular disease, cancer, human immunodeficiency virus, malnutrition, alcohol abuse, or obesity.[7,11,21–23] NF has also been reported in renal transplant patients who receive immunosuppressive agents.[24] Patients with cirrhosis are more susceptible to necrotizing soft tissue infections caused by Gram-negative pathogens.[15] Mortality seems to be higher with comorbidities. In 1 study, mortality was significantly increased in patients with 2 or more comorbidities, such as diabetes mellitus combined with liver cirrhosis.[25]

Radiotherapy as a Risk Factor for NF

Acute infections secondary to mucositis during concurrent chemotherapy and radiation are common.[26] Potential causes for the increased incidence of infectious complications are related to alterations on the mucosa and soft tissue, lymphatic vascular injury leading to lymphedema, vascular damage caused by radiation with impairment of oxygen delivery, and immunologic function. Thus, the inflammatory response and the reparative process of local tissues are impaired after radiotherapy.[27] Thus, bacteria introduced into these tissues may lead to an aggressive soft tissue infection.

Daly et al[28] reported 5 patients with slightly progressive mixed polymicrobial necrotic wound infections of the subcutaneous tissue and skin around surgical incisions that traversed fields of pelvic irradiation. The authors concluded that the local obliterative endarteritis and poor collagen formation caused by radiation favor the development and spread of necrotizing infection.[28] Only 8 cases reports of NF have described the association of this infection with NF (Table 1).[29–34] Maluf et al[29] were the first to report the potential association between chemoradiation therapy and NF caused by *S. pyogenes.* Most authors suggested that radiation therapy could be a risk factor for NF in combination with other risk factors, such as diabetes,[31] chemotherapy,[30] advanced age, vascular disease, and malignancy[31] and that the cumulative effects of these risk factors could favor the development, progression, and persistence of NF.[31] Radiation-induced noninfectious myo-fasciitis has also been described in the literature.[35,36] Our patient is the ninth case described and also had advanced age and significant comorbidities, such as diabetes mellitus, vascular disease, and malignancy, as risk factors. Although more data is necessary, radiotherapy seems to be a risk factor for the development of NF.

K. pneumoniae Fasciitis

Klebsiella spp. are opportunistic human pathogens that cause severe diseases, such as septicemia, pneumonia, urinary tract infection, and soft tissue infection.[37] Although *K. pneumoniae* is a common co-pathogen in patients with polymicrobial NF,[38–40] monomicrobial NF caused by *Klebsiella* spp. is very rare. All previous cases included in our literature review were found using a Pubmed search (1980 to November, 2008) of the English-language medical literature applying the term "*Klebsiella* fasciitis." The references cited in these articles were examined to identify additional reports. We identified 38 cases of *K. pneumoniae* fasciitis in the literature.[5,6,25,39,41–52] One case of fasciitis caused by *K. oxytoca*[53] and 1 case of NF caused by *K. aeruginosa*[52] have also been reported. In a large series in China, *K. pneumoniae* was the most common pathogen isolated,[25] unlike the previous series, in which *Streptococcus* was the prevalent pathogen.[11] *K. pneumoniae* was the most common Gram-negative pathogen identified as cause of monomicrobial NF with 13 of 59 cases (22%).[25] In another study of patients with NF, *K. pneumoniae* (16%; 4 of 25 patients) and Group A streptococci (16%) were the most common microorganisms identified in microbiologic cultures.[46]

Most of the 38 cases occurred in Asian countries, with 14 (36.8%) cases being reported in China,[25,44] 8 cases (21%) in Taiwan,[5,39,42,49] 5 (13.2%) cases in Turkey,[43,46] 4 cases (10.5%) in Singapore,[51] 2 cases in Malaysia,[47,50] 1 case in Saudi Arabia,[52] 1 case in Hong Kong,[41] and 1 case in Japan.[45] One case in Canada occurred in a native of India who had recently traveled to Singapore.[6] Only 1 case has been reported in the United States of 1 native of Cambodia who had recently traveled to Cambodia.[48] We report the first case, to our knowledge, of *K. pneumoniae* causing NF in a native American who did not have any travel history.

In Table 2, we present data on 15 cases of monomicrobial NF caused by *Klebsiella* spp., in which the organism was cultured from tissue specimens taken during surgical debridement and in which details on clinical presentation and the treatment administered were available.[5,6,41–43,47–52]

With the exception of a 10-day-old neonatal infant in Turkey,[43] the age of 15 patients with NF caused by *K. pneumoniae*, where data were available, varied from 7 to 76 years with a median age of 52 years.[5,6,42–44,47–52] Eleven of 15 (73.3%) of these patients[6,41–44,47–49,52] were men with 4 of 15 (26.6%) being women.[5,45,50,51]

Significant comorbidities were present in these patients with *K. pneumoniae* fasciitis. Twelve (80%) of these patients had diabetes,[5,6,41,42,44,49–52] 3 patients (20%) had cirrhosis,[41,48,51] 1 had chronic renal failure,[52] 1 had malignancy,[47] and 1 had no identified comorbidity,[43] whereas 2 comorbidities were noticed in 3 patients.[41,51,52] In the large series of *K. pneumoniae* fasciitis from China, all patients had underlying disease, including diabetes mellitus in 13 patients and both diabetes and cirrhosis in 3 patients.[25] NF was not the initial presentation in 2 of these diabetic patients who had metastatic infection with *K. pneumoniae* bacteremia.[25] One of the patients had in addition acute pyelonephritis and the other had a liver abscess. Data from the small number of reported cases, thus, suggest that monomicrobial *K. pneumoniae* is strongly associated with diabetes mellitus and chronic liver disease. Most of the previously reported cases of *Klebsiella* NF were associated with other septic foci of infection, commonly liver abscesses, urinary tract infections, and endogenous endophthalmitis.[5,6,41] When *K. pneumoniae* bacteremia occurs in these patients, clinicians should be vigilant about metastatic soft tissue infections. In 10 cases,[5,6,41,44,48,51] at least one other organ was involved, ie, liver,[5,6,44,51] eyes,[5] urinary tract,[49,51] kidneys,[5,51] pancreas,[5] peritoneum,[41] and knee.[48] Consistent with the literature, the commonest site of associated pathology was the liver (5 cases, 50%) followed by the urinary tract in 4 cases (40%).[49,51]

In our review of 15 cases of *K. pneumoniae* with available data, risk factors that could be related with the development of NF caused by this pathogen were identified in 9 patients (60%). These included recent travel to Asia,[6,48] previous infectious process due to *K. pneumoniae*, such as emphysematous cystitis,[49] spontaneous bacterial peritonitis,[41] and