Case Report

Community-Acquired Monomicrobial *Pseudomonas aeruginosa* Necrotizing Fasciitis: A Case Report

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Background: Community-acquired monomicrobial *Pseudomonas* necrotizing fasciitis [NF] is a rare and unclassified type of NF. Late recognition and using non-antipseudomonal antibiotics may lead to poor outcomes. This report describes the clinical features and management of *Pseudomonas aeruginosa* NF in a cancer patient.

Case Report: A 68-year-old Thai man with poorly controlled diabetes and advanced lung cancer, who was taking docetaxel for 12 days, was admitted to Chulabhorn Cancer Center. His medical history suggested a prior minor injury to his left thigh. He presented with fever and an erythematous lesion in his left thigh and developed changes in consciousness and respiratory failure. Clinical features showed septic shock with diabetic ketoacidosis [DKA], a hyperosmolar hyperglycemic state [HHS], multiple foci of ecthyma gangrenosum, and soft tissue infection. He was then empirically treated with meropenem, had resuscitation of hemodynamics, and DKA/HHS corrected. Central necrosis later developed with blebs on his left thigh. NF was diagnosed and necrotic tissue resection was immediately performed. *P. aeruginosa* was isolated from hemocultures and tissue culture. A 2-week course of antibiotics with adequate tissue debridement improved clinical and microbiological outcomes.

Conclusion: A case of monomicrobial *P. aeruginosa* NF was diagnosed after minor trauma in a severely immunocompromised host. The patient's excellent outcome was achieved by a high index of suspicion by physicians in host factors, prompt diagnosis, early anti-pseudomonal antibiotic treatment, good hemodynamic resuscitation, immune reversal therapy, and immediate surgical debridement.

Keywords: *Pseudomonas* necrotizing fasciitis, Soft tissue infection, Hemodynamics, *P. aeruginosa*, Immunocompromised host

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Pseudomonas aeruginosa necrotizing fasciitis [NF], a flesh-eating infection, is a rare, life-threatening, rapidly progressive skin and soft tissue infection, which has been known since the time of Hippocrates[1]. Late recognition of *Pseudomonas* NF causes more than 21 to 28% of mortality and exceeds 60% mortality in bloodstream infection[2-6]. *Pseudomonas* NF has been described in the literature for more than 30 years. The incidence of NF in Northern Thailand is 7.45 cases per 100,000 in the general population, which is higher than that in developed countries[7]. A previous study showed that almost all *P.aeruginosa* NF cases are commonly related to polymicrobial and hospital-acquired infection, such as post-surgical wound infection, periorbital infection, and Fournier's gangrene[3,8-14]. Community-acquired monomicrobial *P. aeruginosa* NF is an unclassified type of NF. There are many risk factors of hosts who are prone to developing *Pseudomonas* NF, especially in immunocompromised conditions. However, almost all of the guidelines for management of skin and soft tissue infections do not have recommendations for treatment of *P. aeruginosa* NF. Although surgical

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necrotic resection is still the cornerstone of successful treatment, empirical therapy with non-antipseudomonal antibiotics may lead to poor outcomes.

Materials and Methods

The medical records of the patient with *Pseudomonas aeruginosa* NF who was hospitalized at Chulabhorn Hospital, a specialized cancer center was permitted by the hospital director and retrospectively analyzed. This study was approved by the Ethics Committee for Human Research, Chulabhorn Research Institute (EC No. 035/2560).

Case Report

A 68-year-old Thai man had poorly controlled diabetes and advanced lung cancer with a past history of multiple episodes of chemotherapy and corticosteroids. Twelve days after docetaxel in the last cycle, he visited the emergency department at Chulabhorn Hospital (a specialized cancer center) with acute febrile illness and alteration of consciousness. His medical history was reviewed and he had a previous minor traumatic injury by applying a wooden massage roller to his left thigh, but he denied any prioropening wounds. His history showed fever with minimal pain and an erythematous lesion that had been on his left thigh for 2 days. He became drowsy and developed progressive dyspnea at rest. A physical examination showed a temperature of 37.8°C, blood pressure of 90/60 mmHg, pulse rate of 120 beats per minute that was irregular and respiratory rate of 30 breaths per minute. He had drowsiness with multiple purplish patches at the tip of the nose, neck, and legs. With regard to the cardiovascular system, he had an irregular heart rate and no signs of valvular heart disease. A pulmonary examination showed tachypnea, but no adventitious sounds. An abdominal examination was unremarkable. The left inner thigh showed erythematous, warm, mild swelling of the skin. The quick sequential organ failure assessment [qSOFA] score was 3. Clinical features were septic shock with respiratory failure. Multiple foci of ecthyma gangrenosum and soft tissue infection in the left thigh resulted in emergency doctors starting empirical anti-pseudomonal antibiotic treatment (meropenem) to cover the severe *Pseudomonas* skin and soft tissue infections.

A complete blood count showed marked leukocytosis with neutrophil predominance and mild thrombocytopenia. Cell counts were as follows: white blood cells, 22,410 cells/mm^3; neutrophils, 84%; lymphocytes, 4%; hemoglobin level, 9.6 g/dL and platelet count,128,000/mm^3. His blood chemistry profile showed a blood urea nitrogen level of 87 mg/dL, serum creatinine level of 3.86 mg/dL, serum sodium level of 129 mmol/L, and serum bicarbonate level of 10 mmol/L. Arterial blood gas analysis showed metabolic acidosis with a pH of 7.25. A liver function test showed a serum albumin level of 1.9 g/dL, total bilirubin level of 0.77 mg/dL, alanine aminotransferase level of 11 U/L, prothrombin time of 16.8 s, INR of 1.35, and aPTT of 30.6 s. The serum cortisol level was 10.23 U/L and creatine phosphokinase level was 22 U/L. Anti-HIV was non-reactive. Urinalysis showed a white blood cell count of 5-10/LPF and a urine Gram stain showed Gram-negative bacilli. An electrocardiogram and chest x-ray were unremarkable.

The patient's blood sugar level was 1,012 mg/dL, the serum ketone level was positive, and serum osmolarity was 353 mOsm/mL. Diabetic ketoacidosis [DKA] and a hyperosmolar hyperglycemic state [HHS] were diagnosed. All clinical and laboratory data showed a sequential organ failure assessment [SOFA] score of 8. Aggressive fluid resuscitation and vasopressor therapy were performed until hemodynamics were stable. Insulin therapy was started for correction of DKA and HHS, and the patient was admitted to the intensive care unit. In a next day, central necrosis developed and blebs formed on the medial side of his left thigh (Figure 1A). The laboratory risk indicator for the NF [LRINEC] score was 8. NF was diagnosed and emergency debridement was performed by a surgeon. Intraoperative findings showed necrotic tissue with pus along the distal half of the antero-medial fascia and excisional debridement was performed. Pus and tissue from necrotic tissue showed a few small, slender-shaped, Gram-negative bacilli (Figure 1B). Finally, *P. aeruginosa* was isolated from hemocultures, urine culture, pus, and tissue culture. Antimicrobial susceptibility testing [AST] of *P. aeruginosa* by the

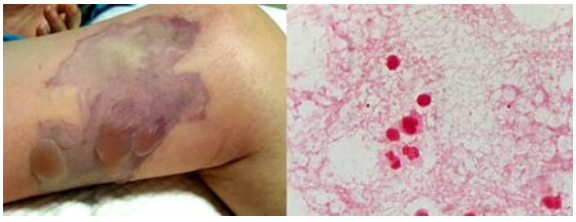

Figure 1. (A) *P. aeruginosa* necrotizing fasciitis in the left thigh; (B) Gram stain from necrotic tissue shows a few small, slender-shaped, Gram-negative bacilli.

Clinical & Laboratory Standards Institute criteria for AST 2017 showed sensitivity to ceftazidime, cefepime, piperacillin-tazobactam, meropenem, ciprofloxacin, levofloxacin, aztreonam, colistin, gentamicin, and amikacin. Hemocultures were negative 2 days later. A physician specializing in infectious diseases was consulted and antibiotics were deescalated from meropenem to ceftazidime. A 2-week course of ceftazidime and adequate tissue debridement showed improved clinical and microbiological outcomes.

Unfortunately, the patient developed hospital-acquired pneumonia after 2 weeks of remission of infection and 1 month of hospitalization. A family conference decided not to proceed with any invasive procedure because of the advanced cancer and the patient finally died.

Discussion

NF is a severe skin and soft tissue infection and is related to a poor outcome. Many experts and guidelines suggest clinical and laboratory criteria for diagnosing NF. However, misdiagnosis of NF still occurs in 41 to 80% of patients[15]. NF is classified into three types by pathogens. Type 1 NF, which has less systemic complications, is affected by polymicrobial organisms, including anaerobes. Type 1 NF usually occurs adjacent to oral areas, the perineum, and genitalia, and is related to surgical procedures involving the bowel or penetrating trauma, sites of injection in drug users, and spreading from vulvovaginal infection[16-18]. Type 1 NF occurs in patients with diabetes, alcoholism, malignancy, myelotoxic chemotherapy, and malnutrition[6,8,19,20]. Type 2 NF, which is more severe than type 1, commonly affects the extremities in immune competent hosts, and is associated with multiorgan failure. Type 2 NF is from monomicrobial organisms, especially *Streptococcus pyogenes*[21], and a few reported cases of *Staphylococcus aureus*. Moreover, some authors have described type 3 NF, which is commonly caused by marine organisms (*Vibriovulnificus aeromonas* spp)[18].

P. aeruginosa is an aerobic Gram-negative bacillus, which is awell-known etiology of infection in immune compromised hosts and related to a fatal outcome. This report highlights a case of community-acquired monomicrobial *P. aeruginosa* NF, which was diagnosed after minor trauma of the lower extremities. Almost all cases of *P. aeruginosa* NF affect the perineum, ocular adnexa, head, and neck, but it rarely affects theextremities. The rare causes of *Pseudomonas* NF in immune compromised hosts are varicella skin infections, penetrating trauma, surgery, colonic perforation, heroin skin popping, and insect bites[8-14]. More than half of previously reported cases of *P. aeruginosa* NF had concomitant bacteremia and a quarter of patients with *Pseudomonas* infection died[3-6,22]. The concept of locus minoris resistentiae might explain *Pseudomonas* NF without an obvious local wound opening in the current case and suggests that *P. aeruginosa* NF could occur in the extremities after a small superficial skin trauma.

Host factors are the main stay of monomicrobial *Pseudomonas* infection, especially in severely immune compromised conditions. The present case presented with many risk factors, such as poorly controlled diabetes mellitus with complications of DKA/HHS, a history of steroid exposure, lung cancer, and post-chemotherapy, despite the non-neutropenic condition. In previous reports, almost all cases of *Pseudomonas* NF were from Fournier's gangrene, and orbital and ocular adnexa infection. Moreover, a half of *Pseudomonas* NF cases presented in hematological malignancy patients, including acute lymphocytic leukemia, acute myeloid leukemia, neutropenic patients after myeloablative chemotherapy, bone marrow transplant, renal transplantation, solid tumors, and others immunocompromised conditions such as paraneoplastic hypercortisolism, alcoholism, diabetes mellitus, malnutrition, infancy, and immunodeficiency patients, (AIDS, leukocyte adhesion deficiency, congenital immunodeficiency)[3,15,23-29]. According to a surveillance culture report, almost half of patients with marrow disease who had *P. aeruginosa* recovered compared with 14% with lymphoma and 20% with solid tumors. The trend in incidence of *P. aeruginosa* infection in patients with positive surveillance cultures was higher than that in negative cultures and explained *P. aeruginosa* infection in many patients with cancer[30]. Almost all *P. aeruginosa* NF cases are nosocomial and polymicrobial infections. Clinical characteristics of NF may be subtle and difficult to clearly distinguish from minor soft tissue infection. This is especially the case in immunocompromised conditions until rapid progression of infection, appearance of typical features, and appearance of systemic findings[21]. Although the LRINEC score in the current case exceeded 6, it was reasonable for diagnosing NF, and it suggested a high mortality rate, the high LRINEC score in this case was almost from extreme laboratory results. The clinical diagnosis was still the most important for diagnosing NF[29,31-34]. In the present case, the patient had serious

complications of NF, including hematogenous spreading, septic shock, disseminated intravascular coagulation, and multiple organ dysfunction syndrome, such as acute kidney injury and respiratory failure.

The predominant distinguishing clinical feature for diagnosising *P. aeruginosa* NF in this case and in many cases is ecthyma gangrenosum. This condition is a common pathognomonic dermatological manifestation of *P. aeruginosa* hematogenous spreading and is described as cutaneous vasculitis caused by an organism invading the intima media and adventitia of the vascular wall.

Management of NF cases can be at a disadvantage if clinicians do not have high index of suspicion of early NF, especially in *P. aeruginosa* NF. Although the surgical debridement is the key of treatment; in the largest report in the year of 2012[3], only 45% of *P. aeruginosa* NF patients were treated with antibiotic and surgical resection which had 47% of mortality in this group. No study discussed about role of immune reversal therapy not only decreasing or stop immunosuppressive agents; but also, corrected immunocompromised condition such as well controlled blood sugar level. The early achievement of clinical and microbiological outcome when combined standard NF treatment and immune reversal therapy was showed in this case. Mortality of *P. aeruginosa* NF can be increased if physicians delay in diagnosis, resuscitation, prompt broad spectrum and anti-pseudomonal antibiotic treatment, and early aggressive surgical debridement.

Many guidelines describe management of patients with Fournier's gangrene and neutropenic patients with NF[35]. However, there is no definite recommended guideline for management of *P. aeruginosa* NF in non-neutropenic hosts, including the Infectious Diseases Society of America practical guidelines[16,35] for skin and soft tissue infections. According to the setting of cancer centers, such as where the current case was treated, many patients with cancer have numerous pseudomonal risk factors, such as neutropenia, post-chemotherapy, and corticosteroid use. Therefore, clinicians should be concerned about pseudomonal skin and soft tissue infection, and close monitoring of progression to NF in these cancer cases is required. In the current patient, correction of DKA and sustained good blood sugar control were the major adjunctive therapies. Because *P. aeruginosa* NF is associated with many immunocompromised conditions, immune reversal therapy is important for a better treatment outcome of *Pseudomonas* NF therapy. Achievement of diagnosis and treatment is obtained by a combination of a high index of suspicion of host factors, prompt diagnosis, and multimodal treatment, including early anti-pseudomonal antibiotic treatment, good resuscitation, immune reversal therapy, and immediate surgical debridement.

Conclusion

This case highlights monomicrobial *P. aeruginosa* NF in a patient with cancer who was diagnosed after minor trauma at the extremities and who had multiple compromising risk factors. Ecthyma gangrenosum is an important clinical clue representing *P. aeruginosa* bacteremia and leads to diagnosis of *Pseudomonas* NF. The cornerstone of excellent outcomes of this condition is a combination of a high index of suspicion of host factors, prompt diagnosis, and multimodal treatments.

What is already known on this topic?

NF is clinically diagnosed and many authors consider that a high LRINEC score help to diagnose NF. Almost all cases of *P. aeruginosa* NF are nosocomial and polymicrobial infections. Previously reported cases of *Pseudomonas* NF developed after surgical wound infection, bacteremia, periorbital infection, or Fournier's gangrene, additionally, these cases could be associated with risk factors of various immuno-compromised conditions, especially in patients with hematological malignancy with myeloablative regimen or neutropenia. Aprominent distinguishing clinical feature of *P. aeruginosa* NF is ecthyma gangrenosum, representing *P. aeruginosa* bacteremia, leading to diagnosis of *Pseudomonas* NF. Surgical debridement is the main treatment along with antibiotics therapy.

What this study adds?

Community-acquired monomicrobial *P. aeruginosa* NF should be suspected in immuno-compromised hosts who present with soft tissue infection. In patients with solid malignancy who have multiple immunocompromised risk factors and show colonization of *P. aeruginosa*, clinicians should have a high index of suspicion for *P. aeruginosa* infection, especially NF. Immune reversal therapy for immunocompromised conditions is important for a better outcome. Although no guidelines recommend management for *P. aeruginosa* NF, the cornerstone of an excellent outcome Is prompt diagnosis in the suspected host and multimodal treatment, including early broad spectrum anti-pseudomonal antibiotic

treatment, good resuscitation, immune reversal therapy, and immediate necrotic tissue resection.

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Potential conflicts of interest

The authors declare no conflict of interest.

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