Case Report

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A Fatal Spontaneous Gas Gangrene due to *Clostridium perfringens* during Neutropenia of Allogeneic Stem Cell Transplantation: Case Report and Literature Review

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Most cases of gas gangrene caused by *Clostridium* species begin with trauma-related injuries but in rare cases, spontaneous gas gangrene (SGG) can occur when patients have conditions such as advanced malignancy, diabetes, or immunosuppression. *Clostridium perfringens,* a rare cause of SGG, exists as normal flora of skin and intestines of human. Adequate antibiotics with surgical debridement of infected tissue is the only curative therapeutic management. Mortality rate among adults is reported range of 67-100% and majority of deaths are occurred within 24 hours of onset. We experienced a case of SGG on the trunk, buttock and thigh in a neutropenic patient with acute lymphoblastic leukemia. His clinical course was rapid and fatal during pre-engraftment neutropenic period of allogeneic stem cell transplantation.

Key Words: Gas Gangrene; *Clostridium perfringens;* Neutropenia; Stem Cell Transplantation

Introduction

Gas gangrene, or clostridial myonecrosis, is one of the most serious infectious diseases, characterized by rapidly progressive destruction of soft tissue and production of gas within the tissues. It is usually caused by traumatic injury, however spontaneous gas gangrene (SGG) is rarely reported [1]. Recognized risk factors are gastrointestinal diseases, cancer chemotherapy, lympho-proliferative disorders, radiation therapy, acquired immunodeficiency syndrome (AIDS) and neutropenic state [1]. The anaerobic gram-positive bacillus *Clostridium perfringens,* one of the causative pathogens of gas gangrene, is normal flora of skin or intestines. In SGG, source of the infection is usually the bowel [1]. We experienced a case of fatal SGG in

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patient with acute lymphoblastic leukemia (ALL) during pre-engraftment period of allogeneic stem cell transplantation (SCT). The Institutional Review Board at Seoul St. Mary's Hospital approved this case report and exempted patient consent (No. KC13ZISE0088).

Case Report

A 57-year-old male was admitted for unrelated peripheral blood SCT in June 2012. He was diagnosed as Philadelphia-positive ALL in January 2012 and treated with remission-induction chemotherapy and five cycles of intra-thecal chemotherapy. He had no other underlying disease. On hospital day (HD) 1, initial vital signs were stable as follows: blood pressure 110/60 mmHg, pulse rate 80/min, respiratory rate 20/min, and body temperature 36.4°C. On HD 5, pre-transplant conditioning chemotherapy was started with fludarabine (30 mg/m^2) for 5 days, melphalan (70 mg/m^2) for 2 days and anti-thymocyte immunoglobulin (1.25 g/kg) for 2 days. Ciprofloxacin (500 mg po bid), itraconazole syrup (150 mg po bid) and acyclovir (5 mg/kg iv tid) were used as prophylaxis. From HD 13 to 14 (also represented as post SCT D1 to D2), SCT was done and neutropenia developed (absolute neutrophil count [ANC] 890/mm^3), and progressed after that day. He started to feel intermittent mild abdominal pain and diarrhea (3-4 times/day) from post SCT D4. Additional antibiotics for diarrhea was not prescribed because the patient's symptom was mild and controlled easily with medications other than antibiotics. And there were neither infection signs including fever nor increase of C-reactive protein. The patient also had suffered from chronic diarrhea before hospitalization and *C. difficile* toxin assay and culture done at HD 5 revealed negative results. On the morning of post SCT D7, he complained of severe pain at the left chest wall, left buttock and thigh with localized swelling, and the tissue edema was progressed rapidly. We examined the patient's body thoroughly, however we could not find any obvious traumatic injury. He had an intravenous Hickman catheter and there was no infectious signs at the exit site. Although he had no other signs of infection, we immediately started empirical antibiotics with piperacillin/tazobactam (4/0.5 g iv q8hr) and vancomycin (1 g iv q12hr). At that time, a complete blood cell count revealed hemoglobin of 9.3 g/dL, hematocrit of 25.2%, white blood cells of 10/mm^3 (ANC 0/mm^3) and platelet 61,000/mm^3. Ciprofloxacin which had been used as prophylactic antibiotics was stopped. Chest X-ray showed soft tissue swelling with air density on the left side of chest wall (Fig. 1). The patient's blood pressure began to fall to 92/60 mmHg, heart rate was 164/min and oxygen saturation

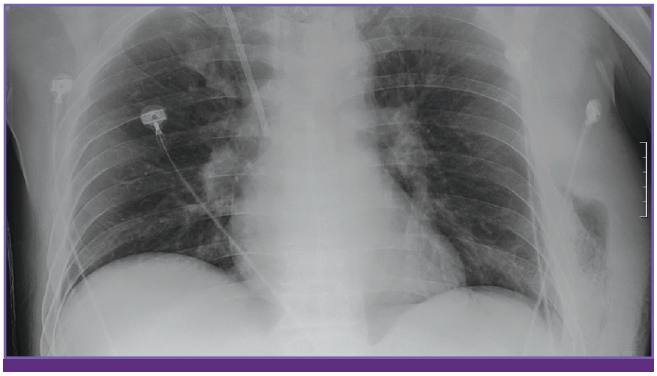

Figure 1. Chest X-ray shows soft tissue swelling on the left chest wall with internal air density.

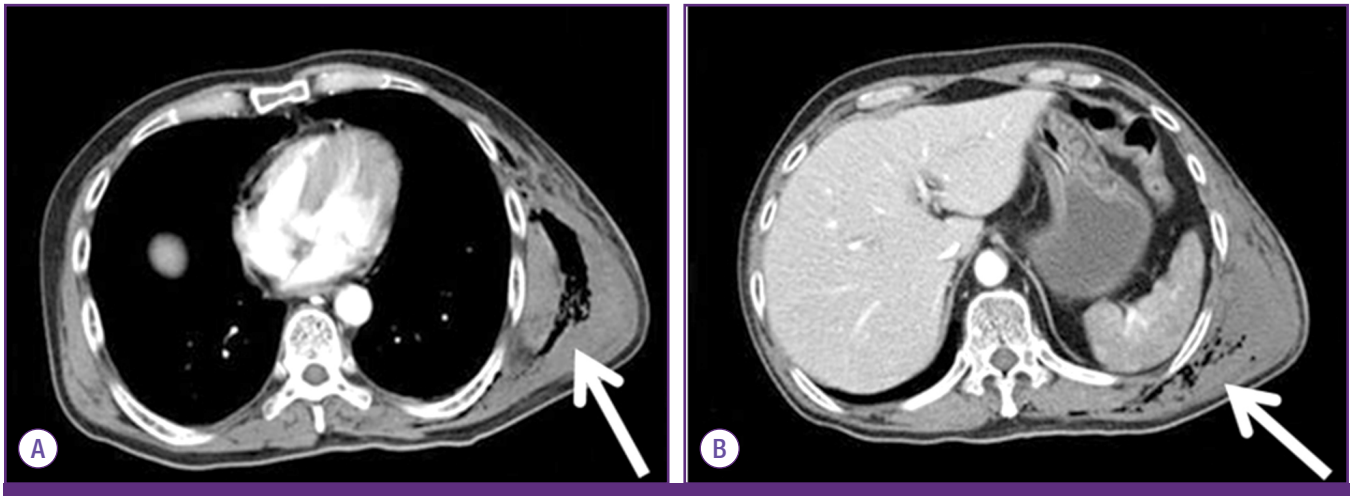

Figure 2. Computed tomography of chest and abdomen. Subcutaneous emphysema on (A) the left chest wall (arrow) and (B) left trunk (arrow).

was 83% at the room air. We pushed 500 mL of normal saline and applied 5 L of oxygen via a simple facial mask. After that, his vital signs stabilized again. Chest and abdominal computed tomography revealed multiple emphysematous soft tissue infection of left lateral chest wall, back, left buttock and thigh area (Fig. 2). After identification of the lesions, the needle aspiration was done from the soft tissue lesion to identify the causative organism in sterile environment. Ten hours after onset of pain, heart rate increased to 163/min despite blood pressure was not changed with 98/63 mmHg. He was planned to be transferred to intensive care unit to manage his sepsis. Cardiac arrest was occurred after approximately 12 hours from his first complaint of pain on those lesions. Cardiopulmonary resuscitation was done for over 30 minutes but he died without return of spontaneous circulation. Later, *Clostridium perfringens* was isolated from both blood cultures and culture of aspirated fluid from the lesion (BD BACTEC™ Plus Aerobic/F, Lytic/10 Anaerobic/F Culture Vials, Becton Dickinson, Sparks, MD, USA).

Discussion

The proportion of anaerobic bacteremia was 0.5-12% depending on researchers [2] and *Clostridia* are the second common anaerobes (20.7%) following *Bacteroides fragilis* group (36.7%) [3, 4]. Park et al. [2] reported recent trends of anaerobic bacteria isolated from blood culture specimens in a university hospital of Korea. Of the 84 anaerobic isolates, *B. fragilis* (28.6%, 24 of 84 isolates) and *C. perfringens* (25%, 21 of 84 isolates) were the most frequently isolated organisms [2]. *C. perfringens* was not a rare causative organism of anaerobic bacteremia. However, the clinical significance of *C. perfringens* is not yet fully understood.

C. perfringens is a spore-forming gram positive rod that causes disease by toxin production and regional tissue destruction [3, 5]. It can cause wide range of diseases from a self-limited gastroenteritis to a life-threatening gas gangrene [3, 5]. We found 7 case reports of human diseases caused by *C. perfringens* from Koreamed (www.koreamed.org); they were about emphysematous hepatitis, massive intravascular hemolysis associated with sepsis, pseudomembranous colitis and endocarditis as well as more common food poisoning and diarrhea. To the best of our knowledge, this is the first case of SGG with bacteremia caused by *C. perfringens* in Korea.

We did a literature review to find case reports of SGG of which the pathogen was *C. perfringens*. Three reports were found and these are described in Table 1 including this case [6-8]. All of the cases in the table had one or more risk factors of clostridial SGG such as diabetes, atherosclerosis, malignancies or immunosuppression. Of the 5 SGG patients, four had underlying hematological malignancies.

We suppose that the portal of entries of *C. perfringens* in SGG might be gastrointestinal tract. Because *C. perfringens* is normal flora of skin and gastrointestinal tract of human and none of the 5 patients listed in Table 1 had no identifiable skin

Table 1. Summary of spontaneous gas gangrene cases caused by *Clostridium perfringens* (including this case)

	García-Suárez *et al*. [6]	Temple *et al*. [7]		Niimi *et al*.[8]	Present report
Age/sex	43/male	18/male	16/male	54/male	57/male
Underlying diseases	Non-Hodgkin's lymphoma (diffuse large B-cell lymphoma)	Lymphoblastic lymphoma	Acute lymphoblastic leukemia	Atherosclerosis obliterans, Diabetes mellitus, Mitral valve stenosis with atrial fibrillation	Acute lymphoblastic leukemia
Initial symptoms	Fever, diaphoresis, tachycardia, anxiety	Fever, right calf pain	Left thigh pain	Fever, chill, pain on the left thigh	Pain on left buttock, thigh and chest wall
Bacteremia	Proven	Not proven	Not proven	Proven	Proven
Antibiotics	Ceftriaxone Amikacin Clindamycin Penicillin G	Cefepime Clindamycin Gentamicin Penicillin (added later)	Cefepime Clindamycin Gentamicin	Piperacillin Imipenem/cilastatin	Piperacillin/tazobactam Vancomycin
Surgery	Done	Done	Done	Done	Not done
Final outcome	Died	Recovered	Died	Died	Died

injury. In this case, the patient had suffered from chronic diarrhea that was aggravated over time after admission. Therefore, infection caused by *C. perfringens* might be started from the gastrointestinal tract, and spread rapidly to the bloodstream through possible mucosal breaks of intestine. And this process could be accelerated by the patient's immunocompromised state related to lymphoblastic leukemia. We suppose that underlying diseases of cases listed on Table 1 might be one of the causes of damaged gastrointestinal tract. Initial symptoms include fever and/or pain at specific areas of body such as calf, thigh and chest wall. Crepitus or gas formation identified from imaging had been a clue for suspecting SGG that enabled more aggressive surgical management. Four patients died despite the administration of proper antibiotics and concurrent surgical debridement (Table 1).

Surgical debridement is the mainstay of therapy in SGG because necrotic tissues are poorly perfused due to vascular thrombosis, which made tissue concentration of antibiotics suboptimal. Prompt surgical management is the key factor for survival. Although limited effect of antibiotics in gas gangrene, its early application is emphasized because bacteremia might be preceded to gas gangrene. Initially, the broad spectrum antibiotics are desirable until the pathogen is identified in laboratory. When clostridial infection is identified, penicillin (3-4 million units iv q 4 hours) and clindamycin (600-900 mg or 15 mg/kg iv q 8 hours) is a drug of choice [5, 9] and it is suggested that tetracycline, erythromycin, rifampin, chloramphenicol and metronidazole were more efficacious than penicillin in experimental myonecrosis models [5]. In this case, our empirical choice of antibiotics was piperacillin/tazobactam and vancomycin which have broad-spectrum coverage in neutropenic patients and known to be susceptible in *Clostridium* species [5]. Although we could not perform surgical intervention because of rapid and fatal clinical course, aggressive surgical debridement is an important part in management of SGG.

SGG shows higher mortality than traumatic gas gangrene because of two important reasons. First, when compared with traumatic gas gangrene, diagnosis is often delayed in SGG. Crepitus on physical examination or identifiable gas from imaging might be clues to suspect the diagnosis but they are late manifestation during the clinical course of SGG. When physicians can recognize SGG, patients already have bacteremia and often progressed to severe sepsis accompanying multiorgan failure. And the other reason is that the patients with SGG usually have other serious comorbidities which make difficulties in coping with his fatal condition. In this case, the patient was in prolonged neutropenia which made it difficult to do procedures or surgical management.

In conclusion, patients with hematological diseases, especially in neutropenic state after SCT, can encounter various infectious diseases and its complications. As in this case, SGG caused by *C. perfringens* can be developed in patients with predisposing factors and resulted in fatal outcome. We emphasize here that if patient complains about soft tissue swelling and pain with predisposing factors of SGG such as diabetes, atherosclerosis, malignancies or immunosuppression, SGG can be a disease as a high priority even in cases without trauma history. And if the patient has symptoms of gastrointestinal tract, that also makes high index of suspicion to clostridial infection because gastrointestinal tract can be a portal of entry in most cases.

Conflicts of Interest

No conflicts of Interest.

References

1. Bryant AE, Stevens DL. Gas gangrene and other clostridial infections. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson L, Loscalzo J, eds. Harrison's Principles of Internal Medicine, 18th ed. New York: McGraw-Hill; 2012; 1204-10.
2. Park Y, Lee Y, Kim M, Choi JY, Yong D, Jeong SH, Kim JM, Lee K, Chong Y. Recent trends of anaerobic bacteria isolated from clinical specimens and clinical characteristics of anaerobic bacteremia. Infect Chemother 2009;41:216-23.
3. Murray PR, Rosenthal KS, Pfaller MA. Clostridium. In: Murray PR, Rosenthal KS, Pfaller MA, eds. Medical microbiology. 7th ed. Philadelphia: Elsevier Saunders; 2013;327-38.
4. Fenner L, Widmer AF, Straub C, Frei R. Is the incidence of anaerobic bacteremia decreasing? Analysis of 114,000 blood cultures over a ten-year period. J Clin Microbiol 2008;46:2432-4.
5. Stevens DL, Aldape MJ, Bryant AE. Life-threatening clostridial infections. Anaerobe 2012;18:254-9.
6. García-Suárez J, de Miguel D, Krsnik I, Barr-Alí M, Hernanz N, Burgaleta C. Spontaneous gas gangrene in malignant lymphoma: an underreported complication? Am J

Hematol 2002;70:145-8.
7. Temple AM, Thomas NJ. Gas gangrene secondary to *Clostridium perfringens* in pediatric oncology patients. Pediatr Emerg Care 2004;20:457-9.
8. Niimi M, Ikeda Y, Kan S, Takami H. Gas gangrene in patient with atherosclerosis obliterans. Asiancardiovasc Thorac Ann 2002;10:178-80.
9. Bryant AE, Stevens DL. Clostridial myonecrosis: new insights in pathogenesis and management. Curr Infect Dis Rep 2010;12:383-91.