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중증혈관내용혈을 동반한 *Clostridium perfringens* 패혈증 1예

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A Case of *Clostridium perfringens* Septicemia with Fatal Hemolytic Complication

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Massive intravascular hemolysis secondary to *Clostridium perfringens* septicemia is rare but often fatal. We report a case of a fatal clostridial hemolytic complication in a 71-year-old woman with probable refractory anemia. The patient was admitted to the emergency room due to a comatose mental state and a high fever. Laboratory analysis showed massive hemolysis. She died from severe anemia two hours after admission. The next day, blood cultures grew gram positive cocci and boxcar-shaped gram positive rods, which were identified as coagulase-negative staphylococci and *C. perfringens*, respectively. ***(Korean J Lab Med 2006;26:358-61)***

Key Words : *Clostridium perfringens, Massive hemolysis, Septicemia*

INTRODUCTION

Massive intravascular hemolysis is a rare but often fatal complication of *Clostridium perfringens* bacteremia[1]. This feature is reported in the groups of patients who have undergone abortion, childbirth, or trauma, who are immunocompromised because of diseases such as diabetes and malignancy including leukemias, and who are apparently healthy but are found at autopsy to have a portal of entry for the bacteria, such as liver or spleen abscess, endocarditis, cholecystitis, gastrointestinal arteriovenous malformations, or pleural effusions[2-4]. But we could find only one case of such complication in a patient with refractory anemia[5]. We report a case of a 71-year-old woman with probable refractory anemia who presented with massive intravascular hemolysis and died from severe anemia 2 hr after admission.

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CASE

A 71 year-old-woman with jaundice and coma of recent onset was admitted to emergency room. She had been diagnosed of probable refractory anemia about 6 months before, when her white blood cell count (WBC) was 1.28 $\times 10^9$/L (neutrophils 22%, lymphocytes 72%, and blasts 2%), hemoglobin (Hb) 9.0 g/dL, hematocrit 26.8%, mean corpuscular volume (MCV) 100.9 fL, mean corpuscular hemoglobin (MCH) 33.9 pg, and platelets 42 $\times 10^9$/L. Bone marrow aspiration and biopsy were not attained because of her refusal. She was followed up for months, and received on the average 2 units of packed red cells a month.

On the present admission, she was icteric, and her lips were cyanotic. The blood pressure was 106/49 mm Hg, heart rate 120/min, and body temperature 40.5℃. One blood culture set was drawn immediately and laboratory analysis was performed. Her WBC was 6.21×10^9/L (neutrophils 24%, lymphocytes 50%, and atypical lymphocytes 24%), Hb 2.2 g/dL, hematocrit 1.4%, MCV 84 fL, and platelets 28×10^9/L. The serum and plasma was red-colored. Other laboratory results are shown in Table 1. Peripheral blood smear demonstrated a markedly decreased number of the red cells (not more than 10 red cells per high power field [×400]) with spherocytosis, and occasional extracellular microorganisms (Fig. 1), but gram stain was not performed with blood smears. The patient was transfused 2 units of packed red cells, but thereafter became asystolic, and died 2 hours after admission. No additional laboratory test or postmortem examination was performed. The next day blood culture grew bacteria.

Within five minutes of the patient's admission, the blood drawn from a peripheral vein was infused into a blood culture set consisting of a BACTEC Aerobic/F culture bottle (Becton Dickinson, Sparks, Maryland, USA) and a BacT/Alert anaerobic culture bottle (bioMerieux, Durham, North Carolina, USA). Culture bottles were incubated in BACTEC 9240 system (Becton Dickinson) and BacT/Alert 3D system (bioMerieux). The next day, bacteria grew in the culture bottles. The bacteria were gram positive cocci and gram positive rods. Gram positive cocci were subcultured onto blood agar and identified as coagulase-negative staphylococci. Gram positive rods were boxcar-shaped and were subcultured onto brucella vitamin K1 blood agar (BRBA) in Anaerobic Pouch System (Oxoid Ltd., Basingstoke, Hampshire, England). Incubated for 48 hr, colonies showed irregular edge and double zone of hemolysis (Fig. 2). The rods were identified as *C. perfringens* (profile code: 4501404030; %id: 99.9; and T index:

Table 1. Results of laboratory tests except complete blood count

Tests	Results	Reference ranges	Units
Prothrombin time	56.4	10.8-13.9	sec
INR	9.15	0.64-1.17	
aPTT	240	27-4	sec
Sodium	136	136-145	mmol/L
Potassium	6.4	3.5-5.1	mmol/L
Chloride	114	98-107	mmol/L
AST	368	<35	IU/L
ALT	24	<35	IU/L
Total bilirubin	9.7	<1.3	mg/dL
Direct bilirubin	7.0	<0.3	mg/dL
BUN	22	<20	mg/dL
Creatinine	1.4	<1.2	mg/dL
Glucose	101	80-115	mg/dL
pH	6.83	7.35-7.45	
PO_2	267	72.0-104.0	mmHg
PCO_2	16	32.0-45.0	mmHg
DAT	Negative		
IAT	Negative		
Urine protein	Positive (4+)		
Urine RBC	5-9	0-2	/HPF
Urine nitrite	Positive (1+)		
Urine bilirubin	Positive (1+)		

Abbreviations: INR, international normalized ratio; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; DAT, direct antiglobulin test; IAT, indirect antiglobulin test; RBC, red blood cell.

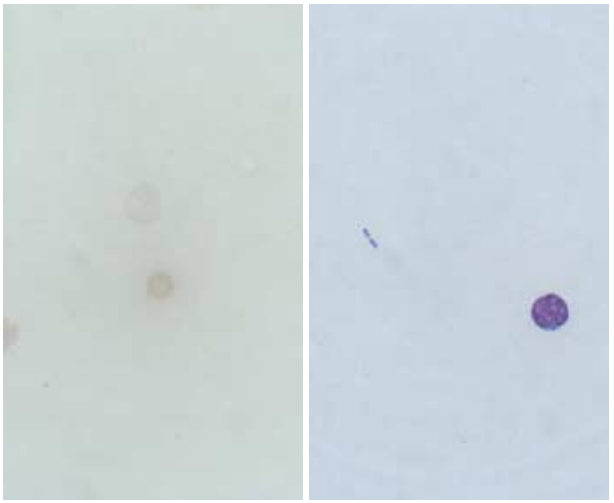

Fig. 1. Peripheral blood smear showed rare intact red cells with spherocytes, and occasional rod-shaped microorganisms (× 1,000). But it was not determined whether the microorganisms were pathogens or contaminants.

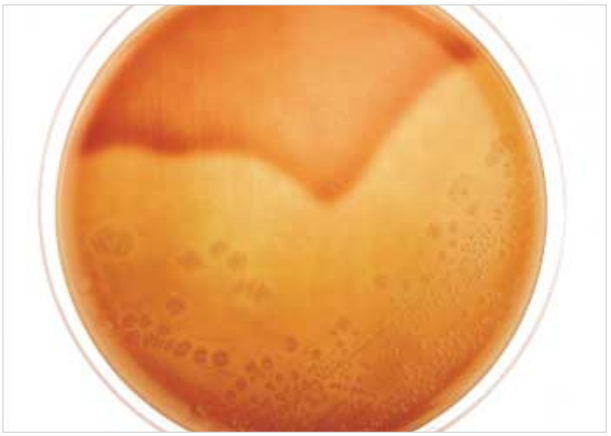

Fig. 2. Colonies grown on blood agar plate showed double zone hemolysis, which comprised an inner zone of complete hemolysis and an outer zone of incomplete hemolysis.

0.42) by a commercial identification kit, API ID 32 A (bioMerieux, Marcy-l'Etoile, France).

DISCUSSION

Clostridia account for only about 10% to 12% of the anaerobic bacteria isolated from properly selected and collected clinical specimens[6], and less than 3% of all blood cultures[7]. *C. perfringens* is the most common clinical isolate of *Clostridium*[2, 6, 7], but as many as 50% of isolates from the blood are assessed to be contaminants[7]. *C. perfringens* is nonmotile and generally has a distinctive box-car appearance on gram stain of clinical material or subcultures[7], It is commonly found among the normal flora of the gastrointestinal tract, therefore, the vast majority of infections are of endogenous origin[3, 6]. Usually the bacteria gain entrance to the body through penetrating wounds or mucosal defects in the gastrointestinal, genitourinary, or hepatobiliary tract[1], and break the gut barrier with ease in patients with leukemia, malignancy, or hepatic cirrhosis, especially when there is a loss of integrity of the bowel[3]. In neutropenic patients including our case, the organisms can readily enter the blood stream, even in the absence of obvious gut pathology[3]. But we could not find a report that describes the relationship between refractory anemia and *C. perfringens*-induced massive hemolysis.

The clinical spectrum of *C. perfringens* bacteremia ranges from a positive culture without associated symptoms to the syndrome of rapid shock and death[2]. *C. perfringens* produces one or more major lethal toxins (alpha, beta, epsilon, iota toxins, etc). Among these, alpha toxin (alpha-lecithinase, phospholipase C) is the most important toxin and produced by all types of *C. perfringens*[8]. Intravascular hemolysis is mediated by alpha toxin, which hydrolyzes sphingomyelin and lecithin to phosphoryl choline and diglyceride and lyses red blood cells, white blood cells, platelets, endothelial cells, and the plasma membranes of muscle cells[1, 3]. Automated blood counts might show disproportionately high hemoglobin levels in comparison with hematocrit, artificially increased MCH, and very low MCV [9]. In our case, the MCH and mean corpuscular hemoglobin concentration (MCHC) were spuriously increased to 136.5 pg and 162.5 g/dL, respectively, which is probably due to free plasma hemoglobin.

The definite treatment for clostridial septicemia is administration of antimicrobial agents and aggressive surgical debridement of any potential source of infection[1, 2]. High-dose penicillin, preferably by continuous intravascular infusion, was known as the drug of choice, but several studies have reported an increased resistance of *C. perfringens* to various antibiotics including penicillin G[2-4, 10]. Clindamycin, metronidazole, second or third generation cephalosporins, chloramphenicol, and imipenem will be alternative agents[1, 3, 4, 10]. Exchange blood transfusions with packed or washed red blood cells, and hyperbaric oxygen has also been tried[1, 4]. Despite all therapeutic efforts, the prognosis is poor, with reported mortality ranging from 35% to almost 100%[1, 8, 10, 11]. In our case, no empiric antimicrobials were started in spite of high fever. But even if any antibiotic treatment was started, the patient could hardly survive due to the rapid progression of intravascular hemolysis. Postmortem examination was not performed, and the infection source was not identified.

In Korea, there has been no reported case of massive intravascular hemolysis caused by *C. perfringens* infection, except for a case of liver abscess with sepsis and suspicious intravascular hemolysis by *C. perfringens*[12]. In our case, though only one blood culture set was drawn, fever, massive intravascular hemolysis, and rapid growth of bacteria are very well consistent with *C. perfringens* sepsis. In addition, there was no evidence of known causes of massive intravascular hemolysis, including malaria, bartonellosis, babesiosis, hemolytic uremic syndrome, blood transfusion, snake venoms, or extensive acute burns.

Gutierrez et al.[13] postulated that clinical physicians must suspect clostridial septicemia in a patient who presents with fever, jaundice, and intravascular hemolysis, especially with underlying malignant conditions or soft-tissue involvement. Although *C. perfringens*-induced hemolytic anemia is rare, early recognition of *C. perfringens* is very important because only a prompt antibiotic therapy before the anemia became life-threatening can rescue patients from an otherwise rapidly fatal outcome[9].

요 약

Clostridium perfringens 패혈증에 따른 중증혈관내용혈은 드물지만 치명적인 경우가 대부분이다. 저자들은 불응성빈혈의증이

있는 71세 여자 환자에게서 *Clostridium*에 의한 치명적인 용혈을 경험하였기에 보고하는 바이다. 환자는 발열과 혼수로 응급실에 입원하였다. 검사소견에서는 혈색소가 2.2 g/dL, 적혈구용적률 1.4%로 심한 용혈이 있었다. 환자는 입원한 지 2시간 만에 사망하였고, 다음날 혈액배양에서 그람양성구균과 그람양성간균이 관찰되었고 이 균은 coagulase 음성 포도구균과 *C. perfringens*인 것으로 동정되었다.

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