Case Report

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A Case of Meningococcal Sepsis and Meningitis with Complement 7 Deficiency in a Military Trainee

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Complement component 7 (C7) deficiency leads to the loss of complement lytic function, and affected patients show increased susceptibility to encapsulated organisms infection, especially *Neisseria meningitidis*. Recently, we have experienced a 20-year-old military trainee with meningococcal sepsis and meningitis who was diagnosed as having C7 deficiency based upon the undetectable serum C7 protein on radioimmunoassay. This case emphasizes that although C7 deficiency is rare immune disorder, it is important to be aware of possibility about late complement deficiency among patients who present with meningococcal disease.

Key Words: *Neisseria meningitidis,* Complement 7 deficiency, Meningitis, Sepsis

Introduction

Humans are the only host for *Neisseria meningitidis* which colonizes the nasopharynx and it is transmitted from human to human by infected respiratory secretions or saliva via airborne respiratory droplets. *N. meningitidis* invades the blood stream in certain individuals among the nasopharyngeal carrier and causes meningitis or sepsis which leads to death within a few hours to days. Despite the appropriate antibiotic treatment, the mortality rate is about 9-12%, in particular, the mortality rate for sepsis is up to 40% [1]. Meningococcal disease is most prevalent at age 4 or younger and 15 through 24 years of age. Especially, military trainees around the age of 20 and college freshmen residing in the dormitories are a well-known high risk group. The incidence of meningococcal disease increases as those high risk age groups from different geological areas start communal living [2].

Apart from these environmental factors, host factors such as complement deficiency are one of the risk factors of meningococcal disease. The complement system can be divided into early and late complement components according to the activation process, and C5b, C6, C7, C8 and C9, which belong to the late complement components, form the membrane attack complex (MAC) and lyse microorganisms. A deficiency in late complement components (C5–C9) or alternative pathway factors including properdin or factor D leads to the impaired

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formation of the membrane attack complex and eventually increases the incidence of meningococcal disease [3].

In Korea, there were 4 reported cases of meningococcal disease with complement deficiency, but all of the cases involved pediatric patients between the ages of 7-12 [4-7]. We are reporting first young adult case diagnosed with meningococcal sepsis and meningitis accompanying C7 deficiency.

Case Report

A 20-year-old trainee at a military training center was admitted to the hospital with fever, nausea, vomiting and headache which started 30 hours before admission. The patient entered at the military training center 5 weeks prior to his visit, and there was no other past medical history apart from a history of viral meningitis when he was 6 years old.

The patient's vital signs at admission were as follows: a temperature of 38.5°C, a blood pressure of 113/64 mmHg, a pulse rate of 86 beats/min and a respiratory rate of 16 breaths/min. Despite normal consciousness and orientation, his neck was stiff and the Kernig and Brudzinski signs were positive. Dermatologically, about 1~2 mm of petechial lesions were observed all over his body including the palms of his hands and feet (Fig. 1). In addition, pharyngeal injection and tonsillar hypertrophy were observed. The laboratory test results were as follows: white blood cell (WBC) 27,000 /mm^3 (neutrophil 87%), hemoglobin 15.0 g/dL and platelets 151×10^3 /mm^3. Blood chemistry tests showed an increase in the C-reactive protein at 25.0 mg/dL, but the other results were within the normal range: glucose 128 mg/dL, albumin 4.4 mg/dL, total bilirubin 1.6 mg/dL, AST 28 IU/L, ALT 26 IU/L, BUN 20 mg/dL and creatinine 1.2 mg/dL. PT/aPTT from the blood coagulation test was 14.4 sec/ 38.2 sec and it was also within the normal range.

When spinal puncture was carried out to test the cerebrospinal fluid (CSF), the initial opening pressure was raised to 29 cmH_2O and its color was turbid yellow. The following results were obtained from CSF analysis: WBC count of 3,850 /mm^3 (polymorphonuclear neutrophils 80%, lymphocytes 20%), red blood cells (RBC) count of 390 /mm^3, glucose level of 66 mg/dL, and protein level of 106.8 mg/dL. From the latex agglutination test (Murex®, Wellcome Diagnostics Limited, Darford, U.K.), the meningococcal antigen was not detected and bacteria were not detected even on the gram stain.

Clinically, meningococcal sepsis and meningitis were suspected and the manifestation of severe sepsis or septic shock was not observed in the initial physical examination and laboratory test. As empirical antibiotics, ceftriaxone of 2g and vancomycin of 1g were intravenously injected twice a day. From the intermediate blood culture results on day 2 of the hospital admission, a gram negative diplococci was cultured and eventually *N. meningitidis* was cultured on day 4 of the hospital admission. Vitek2 ID-NH card (BioMérieux, France) was used for the blood culture system. The serogroup was confirmed as W-135 using the Pastorex® meningitis (Bio-Rad, USA) kit. However, the result from the CSF culture was negative. The patient's fever became better from day 3 of the hospital admission, and his other vital signs were stable. Therefore, only ceftriaxone was continued while vancomycin was stopped.

To confirm the patient's complement function, a complement system test was carried out with a radioimmunoassay. The following results from the complement system test were

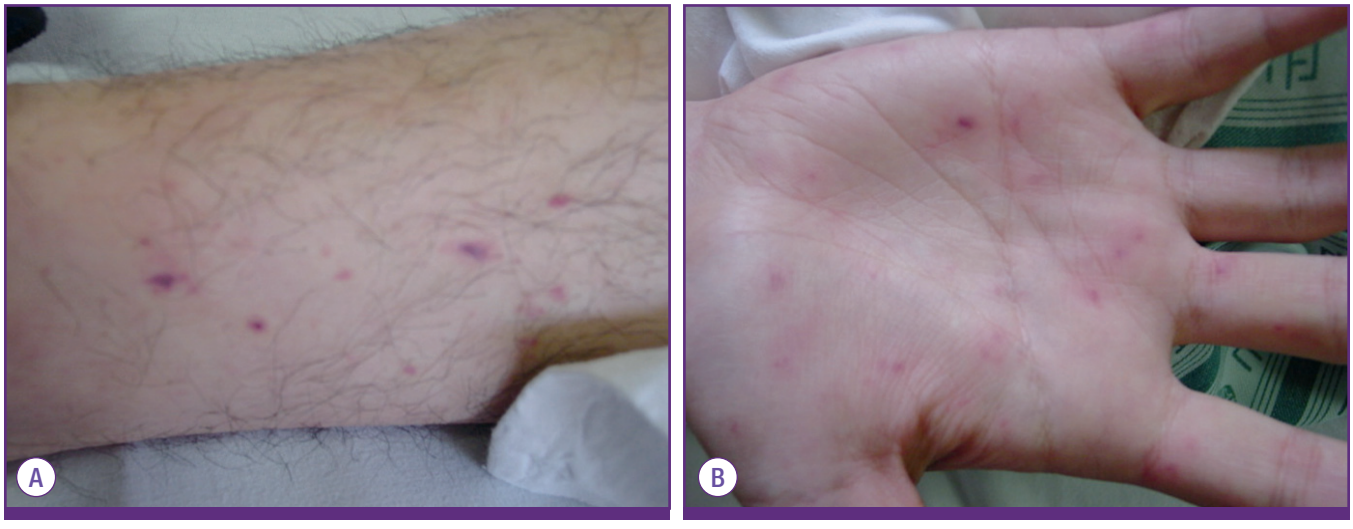

Figure 1. The patient show scattered small sized petechial lesions. (A) on the right lower extremity, (B) on the right hand.

within normal range: C3 112 mg/dL (normal range, 90-180 mg/dL) and C4 26 mg/dL (normal range, 10-40 mg/dL). However, the result from the total hemolytic component (CH50) was 2.0 U/mL or below (normal range, 23.0-46.0 U/mL); thus, the concentrations of individual late complement component (C 5 – 9) were measured. As a result, C5 (16.0 mg/dL (normal range, 6-20 mg/dL)), C6 (9.9 mg/dL (normal range, 7.1-12.8 mg/dL)), C8 (20.6 mg/dL (normal range, 10.7-24.9 mg/dL)), and C9 (26 mg/dL (normal range, 6-29 mg/dL)) were within the normal range; however, C7 (normal range, 4-11 mg/dL) was very low such that it was even impossible to measure.

The patient was administered ceftriaxone for a total of 14 days and discharged without any complications. The quadrivalent protein conjugate vaccine (Menactra®, Sanofi-Pasteur, France), which was introduced for the purpose of relief, was injected into the patient before discharge taking the patient's circumstances into consideration that the patient had continue his communal living. Recurrent episodes of meningococcal disease did not occur during 2 years of follow-up at an outpatient clinic.

Discussion

This case report was the first Korean case with confirmed complement deficiency in a 20-year-old military trainee who was diagnosed with meningococcal sepsis and meningitis. In this case report, although the patient had both high risk factors, joining the military and complement deficiency, for meningococcal disease at the same time, he did not progress to severe sepsis or septic shock and recovered without any complications.

The complement system is the humoral immune response that regulates antigen-antibody reactions, and it consists of a series of 19 plasma and 9 membrane proteins. The antibody for the bacterium and complement play an important role, for the *in vivo* defense mechanisms against encapsulated bacteria such as *N. meningitidis*. When an antibody is attached to a bacterium, the Fc receptors of the phagocytes such as neutrophils and macrophages get activated to engulf and remove the bacterium, and among this process, the early and late complement components are involved in opsonization which supports the engulfing process. The late complement components (C5-C9) form the MAC, which is capable of forming transmembrane pores, leading to cell lysis and cell death. During this process of activating the complement system, inflammatory mediators are released and those mediators gather neutrophils and other immunocytes around the inflammatory site. Therefore, with complement deficiency, the susceptibility to meningococcal disease increases due to dysfunctional opsonization or impaired formation of MAC [3, 8, 9] . The prevalence of complement deficiency varies in different races, C7 and C8β complement deficiencies were the most prevalent in Caucasians whereas C6 and C8α-γ complement deficiencies were the most prevalent in Blacks or Hispanics [10]. In Asians, C9 complement deficiency was quite common among Japanese, in which the prevalence was reported as 0.04-0.10% [3]. There is no report for the prevalence of complement deficiency in Koreans. However, there have been several case reports that confirmed different types of complementary deficiencies with meningococcal disease in children aged 7-12 years [4-7] (Table 1). With the presence of complement deficiency, the incidence of meningococcal disease is 10,000-fold greater than that in normal individuals and a higher recurrence rate has been reported (41% vs 0.34%) [3, 11]. However, the mortality rate in patients with complement deficiency was 10-

Table 1. Summary of cases on meningococcal disease with complement deficiency in Korea

No.	Year [reference]	Age / Sex	Past medical history	Diagnosis	Serogroup	Complement deficiency	Treatment	Outcome
1	2004 [4]	11/F	None	Meningitis	B	C7	Ceftriaxone, dexamethasone	Recovered without sequelae
2	2005 [5]	12/F	None	Meningitis	A	C9	Ceftriaxone, penicillin, dexamethasone	Recovered without sequelae
3	2006 [6]	7/M	None	Meningitis	Unknown	C3, C5	Ceftriaxone	Recovered with nephropathy
4	2009 [7]	11/F	None	Meningococcal sepsis, septic arthritis	Unknown	C7	Cefotaxime	Recovered without sequelae
5	Present case	20/M	None	Meningococcal sepsis, meningitis	W-135	C7	Ceftriaxone	Recovered without sequelae

fold lower compared with healthy people. In this case report, the patient recovered after treatment without any complications. In the four reported cases in Korea, none of the patients have died and membranoproliferative glomerulonephritis (MPGN) was reported in only one case [4-7]. The reason for the low mortality rate in patients with meningococcal disease with complement deficiency has been suggested as a decrease in endotoxin production due to the inability to form the MAC in the case of complement deficiency [12]. The decrease in endotoxin levels could weaken the degree of septic shock, cerebral edema, coagulation disorder or tissue injury. However, there is a possibility of bias because patients recovering from meningococcal disease are highly likely to be diagnosed with complement deficiency compared to patients who die.

The CH50 test is not generally recommended for the patients with meningococcal disease [10]. The test for complement deficiency is required for patients with meningococcal disease who have a history of meningococcal disease, atypical progress and uncommon serogroups such as W-135, X, Y, or nongroupable strains. Age is an important factor, and in the case with patients with meningococcal disease by uncommon serogroups, the prevalence of complement deficiency is 15 times higher in patients aged 5 or older compared to the patients under 5 years old. Especially, patients with meningococcal disease in their late teenage years have been reported with the highest prevalence of complement deficiency [13]. Hence, it is possible that a complement deficiency was not confirmed because complement deficiency test was not done in the young adults who were diagnosed with meningococcal disease.

N. meningitidis are classified into 13 serogroups according to the different types of capsular polysaccharides, and mainly 5 serogroups, A, B, C, Y and W-135, account for most cases of disease. The distribution of serogroup causing meningococcal disease is different according to the timing and location. Serogroups B and C are the most common in America and Europe, and serogroups A and C mainly cause disease in Asia and Africa [14, 15]. The data on serogroups in Korean patients with meningococcal disease are very limited. From a prospective study carried out among patients with meningococcal disease in the Armed Forces Capital Hospital in 2000 and 2001, serogroups C and A were confirmed, but there was a limitation that those serogroups were confirmed in only 33% of the patients [16]. In the patients with community acquired meningococcal disease in 2002 and 2003, serogroup Y was the most common, but the serogroup was only confirmed in 9 cases out of 65 cases [17]. The serogroup in this case was W-135. From April to June in 2011, 2 cases with blood cultures out of 4 cases of meningococcal disease outbreak at a military training center were confirmed as W-135, and the serogroup W-135 has been confirmed in another proven case with meningococcal disease from the Armed Forces Capital Hospital in 2012. Those data on the changes in serogroups have a limitation in that the outcome was from a small group of patients, but it suggests that there is change in the types of serogroups according to the timing of the meningococcal infection in Korea as well. Hence, it provides evidence of the introduction of the quadrivalent protein conjugate meningococcal vaccine in military trainees since 2012.

The patient in this case report has recovered without any complications from the meningococcal sepsis and meningitis that occurred at the beginning of his military training, and continued his military service after immunization with the quadrivalent protein conjugate vaccine. The recurrent rate of meningococcal disease among military personnels is low under 2 %, but the recurrence rate in patients with complement deficiency is about 120 times higher than in patients without the deficiency [11, 18]. Until recently, the decision for a disability discharge from military service was based on the presence of secondary complications following meningococcal disease, as a result, the patient had no choice but to continue on duty after immunization with the quadrivalent protein conjugate vaccine. This is due to the absence of any evidence-based regulations for disability discharges from military service because there have been no cases of the complement deficiency in military patients with meningococcal disease. Therefore, in the future, evidence-based regulations for disability discharge from the military service or for transfer to different military bases are necessary taking into consideration the current circumstances that there is a high recurrence rate in meningococcal disease with complement deficiency and the 100 % efficacy of the vaccine is not expected even with vaccination [19]. In addition, for cases with meningococcal disease in military patients, a screening test for complementary deficiency must be considered.

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