Septic Shock Caused by Waterhouse-Friderichsen Syndrome Caused by *Neisseria meningitidis*

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Abstract

Background: *Neisseria meningitidis* is a rare but serious pathogen that leads to life-threatening septic shock. This infection can rapidly induce a critical condition.

Case 1: A 48-year-old male was transferred to our department with septic shock resulting from an unknown cause. A few days after admission, *Neisseria meningitidis* was detected in his blood culture. Because catecholamine or massive transfusion could not support his vital signs, plasma exchange was introduced. He recovered and was discharged on post-admission day 96 without extremity amputation.

Case 2: A 42-year-old male presented with sudden-onset whole-body cyanosis and shock. Although he was treated with several medications, he died on post-admission day two. *Neisseria meningitidis* was detected in his blood culture.

Conclusion: Prompt recognition and rapid therapy, including plasma exchange, might have the potential to treat patients with this infection.

Keywords: *Neisseria meningitidis*; septic shock

PURPURA FULMINANS rarely occurs in adults but is seen in patients with meningococcal infections, which have a high mortality rate. Because of its rarity, prompt recognition and early indication of treatment is important.

We treated two critically ill patients with septic shock caused by *Neisseria meningitidis*. Based on early goal-directed therapy, massive transfusion and early antibiotic agents were administered soon after blood culture. Although one patient who underwent plasma exchange treatment survived and recovered without amputation of the distal extremities, the other patient did not survive beyond 40 hours. We believe that our report may assist emergency clinicians in recognizing the condition promptly leading to early treatment, including plasma exchange.

Case 1

A 48-year-old male was transferred to our hospital because of unstable vital signs with unknown cause. He was unconscious at presentation with purpura in his extremities; intuba-

tion, massive transfusion, antibiotics (meropenem), a large amount of vasopressors, and continuous renal replacement therapy (CRRT) were administered quickly. His vital signs on arrival were as follows: heart rate, 140 beats per minute; blood pressure, 168/50 mm Hg; respiratory rate, 26 breaths per minute; body temperature, 40°C. His laboratory data are shown in Table 1. His arterial blood gas tests were as follows: pH: 7.042, pCO₂: 86.4 mm Hg, pO₂: 23.4 mm Hg, base excess (BE): –8.4 mmol/L; bicarbonate: 23.4 mmol/L, glucose: 41 mg/dL, and lactate level: 9.0 mol/L. Despite prompt therapy, his blood pressure deteriorated and his heart rate was worsened rapidly, followed by pulseless electric activity (PEA). After resuscitation with a few intervals of PEA, we decided to initiate plasma apheresis therapy because of refractory septic shock; his vital signs and laboratory data improved gradually. With tracheotomy, percutaneous endoscopic gastrostomy, and arteriovenous shunt because of acute kidney injury, he transferred to the rehabilitation hospital on post-admission day 96. Without amputation of his limbs, he recovered well and the purpura disappeared. His consciousness improved gradually. (See Fig. 1.)

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TABLE 1. LABORATORY DATA FOR CASE 1

Total protein	6.2	g/dL	WBC	14190	/mcL
Albumin	3.4	g/dL	RBC	553×10^6	/mcL
Total bilirubin	2.4	mg/dL	HGB	18.3	g/dL
AST	218	U/L	HCT	53.8	%
ALT	107	U/L	PLT	1.9×10^3	/mcL
LDH	853	U/L			
ALP	561	U/L	PT	< 10	%
γ -GTP	788	U/L	PT-INR	5.77	
AMY	626	U/L	APTT	> 180	second
CK	1985	U/L	Fib	< 50	mg/dL
BUN	10.5	mg/dL	D-dimer	> 80	ng/mL
Cre	3.78	mg/dL	AT-III	44	%
Na	146	mmol/L			
K	3.9	mmol/L	PCT	1347	ng/mL
Cl	104	mmol/L	HbA _{1c}	5.6	%
Ca	8.2	mg/dL	Pre-sepsin	2330	pg/mL
IP	4.9	mg/dL	feritine	4370	ng/mL
CRP	7.55	mg/dl			

AST=aspartate transaminase; ALT=alanine transaminase; LDH=lactate dehydrogenase; ALP=alkaline phosphatase; γ -GTP= γ -guanosine triphosphate; AMY=amylase; CK=creatine kinase; BUN=blood urea nitrogen; Cre=creatinine; Na=sodium; K=potassium; Cl=chloride; Ca=calcium; IP= ; CRP=C-reactive protein; WBC=white blood cell count; RBC=red blood cell count; HGB=hemoglobine; HCT=hematocrit; Plt=platelet; PT=prothrombin; PT-INR= ; APTT=activated partial thromoplastin time; Fib=fibrinogen; AT-III=angiotensin-III; PCT= ; HbA_{1c}=hemoglogin A_{1c}.

Case 2

A 42-year-old man presenting with whole-body cyanosis and shock was admitted to our emergency department. He had no notable medical history before admission. Because change of mental status and mottled skin were remarkable in the emergency department, intubation and massive crystalloid transfu-

sion were administered. His vital signs on arrival were: heart rate, 130 beats per minute; blood pressure, 145/96 mm Hg; respiratory rate, 24 breaths per minutes; oxygen saturation, unmeasurable. His laboratory data were as follows: white blood cell count: 2,170 per microliter, hemoglobin: 17.2 g/dL, hematocrit: 49.1%, platelets: 5.6×10^4 per microliter, prothrombin time: 39.6%, D-dimer: 50.75 mcg/mL. His arterial blood gas

FIG. 1. Clinical course of case 1. CRRT=continuous renal replacement therapy; HD=hemodialysis; AV=arteriovenous; PEG=percutaneous endoscopic gastrostomy; SOFA=sequential organ failure assessment; PE=plasma exchange; VP=vasopressors.

data were as follows: pH: 7.183, pCO₂: 36.9 mm Hg, pO₂: 94.2 mm Hg, bicarbonate: 13.3 mmol/L, BE: -14.2 mmol/L, and lactate level: 9.8 mmol/L. Although antibiotics (meropenem and minocycline), recombinant thrombomodulin, anti-thrombin, vasopressor, and CRRT were administered quickly, purpura in the peripheral extremities and trunk worsened rapidly. The patient died within 40 h of hospitalization. Two days later, the patient's blood culture presented *Neisseria meningitidis* infection. Adrenal gland hemorrhage was identified in both cases in computed tomography (case 1) and morbid anatomy (case 2).

Discussion

Septic shock caused by *Neisseria meningitidis* infection, defined as Waterhouse-Friderichsen syndrome in 1946 [1], has a high mortality rate of between 21% and 44% [2]. *Neisseria meningitidis* cause a fulminating fatal infection, frequently with few or no signs or pre-conditions. The presenting clinical picture is frequently pharyngitis, fever, and gastrointestinal symptoms, which are non-specific symptoms, followed by rapid widespread petechiae and whole-body cyanosis. The progress of the condition in these cases is so rapid that commonly death occurs within 12 to 24 h after the appearance of the first symptom. Ferguson et al. [3] reviewed 16 meningococcal patients and reported that almost all had died within 48 h.

A feature of systemic *Neisseria meningitidis* infection is rapid microvascular thrombosis in the peripheral extremities, called purpura fulminans. This symptom is provoked by bacterial lipopolysaccharide (LPS), which activates coagulation systems after inhibition of fibrinolysis. Hellum et al. [4] reported that tissue factor-bearing microparticles appear to contribute to the pathogenesis of this rapid disseminated intravascular coagulopathy [4]. Brandtzaeg et al. [5] demonstrated classification and pathogenesis of meningococcal infection. They reported the relation between plasma LPS level and fatality rate in patients with systemic meningococcal disease [5].

Adrenal hemorrhage is a most remarkable finding in Waterhouse-Friderichsen syndrome. Although the precise mechanism is obscure, the intrinsic vulnerability of hemorrhage is caused by anatomic factors. The adrenal gland is fragile to any increase of adrenal arterial and venous pressure after infections [6]. Neonates and pediatric patients are statistically at an increased risk for coagulopathy. [7]

Meningococcal septic shock occurs predominantly in young children and adolescents. In addition to the high mortality rate, amputation of digits or limbs may be necessary as a result of skin necrosis in patients who survive septic shock. Lindy et al. [8] reported long-term psychosocial outcomes in young adults who survived septic shock caused by *Neisseria meningitidis* during childhood. They concluded that 5%–20% of the patients still struggle with ongoing problems associated with the past illness. (8)

In addition to children, human immunodeficiency virus (HIV)-positive patients should also receive *Neisseria* vaccinations. Agrawal et al. [9] described a case of a 34-year-old man who had sex with men in the United States presenting with acute fulminant meningococcemia. They recommended prompt recognition and expanding vaccinations against *Neisseria meningitidis*.

Neisseria meningitidis infection is more frequent in children [10]. Villa et al. [11] reported a multi-center prospective descriptive study of patients admitted to pediatric intensive care units for sepsis. In 136 patients, the most common etiology was *Neisseria meningitidis* [11]. They concluded that patients with multiple organ failure, neutropenia, and purpura had a worse prognosis.

Hirono et al. [12] reviewed patients with meningococcemia without meningitis in Japan. Compared with other countries, the incidence of meningococcal infection and number of carriers in Japan is low, occurring in 0.4% [13,14].

It was demonstrated that poor prognosis of septic shock caused by *Neisseria meningitidis* is related to low protein C level [15,16]. Vaccarella et al. [17] described a case of an 18-year-old male with meningococcal sepsis and purpura fulminans (17). Because protein C and anti-thrombin levels were extremely low, replacement with protein C concentrates was begun, leading to uneventful discharge.

Protein C concentrate is not available commercially in Japan, therefore, institution of protein C concentrate was not possible with our cases. Based on this, we treated the patient in case 1 with plasma apheresis, but the patient in case 2 could not receive plasma apheresis because of acute deterioration of his vital signs. To our knowledge, no reports about the association between plasma apheresis and septic shock caused by *Neisseria meningitidis* have been published. Plasma apheresis might be a key therapy when confronting septic shock patients with meningococcemia.

Conclusion

Neisseria meningitidis infection is a rare but serious illness, therefore, emergency clinicians should be aware of this unspecific condition. Early recognition and early treatment of purpura fulminans are necessary.

Based on our case reports and previous reports, plasma apheresis might have the potential to treat refractory septic shock caused by *Neisseria meningitidis* successfully. Further reports and evidence are needed.

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T.N. designed this manuscript of this case report. H.S., K.S., and H.N. participated in the treatment of these patients. J.K. made a decision of final approve in this manuscript. All authors read and approved the final manuscript. H.S., K.S., and H.N. are clinicians. H.N. is an assistant professor at Hyogo College of Medicine. J.K. is a professor at Hyogo College of Medicine.

Author Disclosure Statement

All authors declare no conflict of interests.

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Abbreviations Used

BE = base excess

CRRT = continuous renal replacement therapy

LPS = lipopolysaccharide

PEAS = pulseless electric activity

IV = intravenous

TPN = total parenteral nutrition

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