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Meningococcal disease in one soldier patient: case report from Vietnam

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Abstract:

Meningococcal disease is caused by an infection with *Neisseria meningitidis (N. meningitidis*) bacteria, which is responsible for two major forms of the disease including meningitis and/or septicaemia. *N. meningitidis* remains a significant cause of an endemic and leads to significant morbidity and mortality. Diagnosis of meningococcal disease may be challenging due to clinical signs that vary widely and are often similar to those of other illnesses. Meningococcal disease persists in Vietnamese military populations despite the availability of antibiotics and vaccines. The rate of meningococcal disease in Vietnam is low and no meningococcal sepsis case has yet been reported from Vietnam. Herein, we describe the first meningococcal sepsis case in a Vietnamese military unit and emphasize the beneficial application of a molecular method in the diagnosis of *N. meningitidis* and the successful use of antibiotic treatment.

Keywords: **meningitis, meningococcal disease, *Neisseria meningitidis*, sepsis.**

Classification number: **3.2**

Background

Neisseria meningitidis (*N. meningitidis*) is a Gram-negative diplococcus and aerobic or facultative anaerobic bacterium [1]. Humans are the only natural host of *N. meningitidis* and approximately 10% of adults and 24% of adolescence are infected [2, 3]. *N. meningitidis* infection is responsible for two major forms of disease including meningitis and septicaemia globally [4]. This disease mainly affects infants, preschoolers, and young people [5]. Humans can carry *N. meningitidis* in their nose and throat without any clinical symptoms [1, 3] and thus they are the main source of *N. meningitidis* spread. *N. meningitidis* is transmitted through close contacts such as among family members and military populations [6]. *N. meningitidis* can cause sporadic cases, infect small groups, or cause large epidemics over the world with seasonal variations and the prevalence of asymptomatic carriers varies among countries [7].

Rapid recognition and treatment of meningococcal infection are very important in reducing morbidity and mortality [8]. Therefore, understanding the signs of infection is particularly crucial in Vietnam where the prevalence of disease is low and doctors are likely to ignore [9]. Also, meningococcal disease is an uncommon infection in Vietnam, especially in military units. Sporadic cases of meningococcal disease in soldiers have been reported globally [10-12] but no meningococcal disease case in soldiers has been reported from Vietnam so far. In this report, we provide an attention to this disease in Vietnam and to discuss the clinical aspects such as diagnosis and treatment related to this meningococcal case.

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Case presentation

Medical history

A 23-year-old male soldier residing in an army unit located in Phu Man village, Quoc Oai district, Hanoi metropolis, Vietnam was admitted to the the 103 Military Hospital of the Vietnam Military Medical University (VMMU). In the last few years, this military unit had several soldiers infected with *N. meningitidis*. He did not have a history of any infection or travelled to other areas with reported epidemics or exposure to individuals with meningitis.

Clinical features

On May 1st, 2020, the patient presented with a sore throat, a sudden high fever, chills, impaired consciousness, and haemorrhagic rash on the body. He was taken to a local hospital where he was treated with antipyretics and antibiotic injection (cefotaxime 2 g powder for solution). Once stabilized, he was immediately referred to the 103 Military Hospital of the VMMU and was admitted to the Department of Infectious Disease in critical condition on May 2nd, 2020. On admission, the patient was found with a stiff neck, high fever, confusion, headaches, hypotension (80/50 mmHg), nasal bleeding, oral bleeding, oliguria, and haemorrhagic rash on the body but no photophobia, no nausea, and no vomiting (Fig. 1). Heart rate was increased with a regular rhythm and no rubs, murmurs, or gallops were heard. The lungs were clear to auscultation, the abdomen was tender to palpation, and bowel sounds were positive but no significant distention.

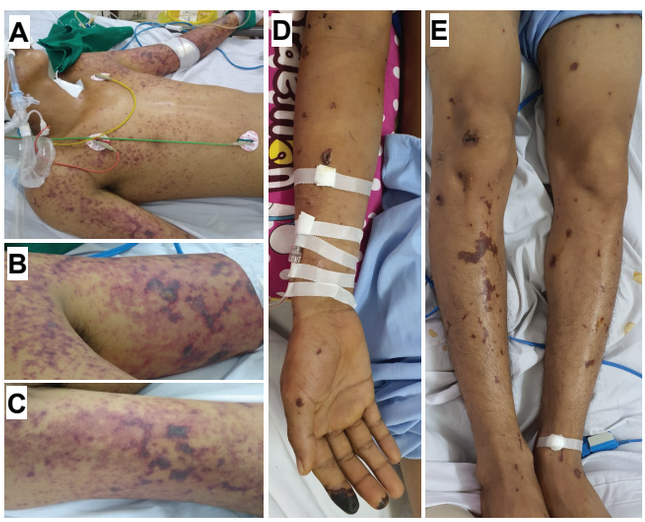

Fig. 1. Widespread purpuric and ecchymotic rash (on day 2). (**A**) Upper body; (**B**) Upper left limb; (**C**) Right limb; (**D**) Right arm; (**E**) Lower limbs.

Identification of meningitis

Bacterial culture, Gram staining and real-time PCR were immediately performed with the peripheral blood, spinal fluid, and nasopharyngeal specimens. The collection and transport of these specimens and the culture method were followed according to WHO guidelines [13]. The results of the bacterial culture and Gram staining showed that the tested samples were negative for *N. meningitidis*. The real-time PCR results showed positive for *N. meningitidis* in peripheral blood sample only. For the real-time PCR, DNA extraction was performed using the automatic nucleic acid extraction system SaMag-12 (Sacace, Italia) according to the manufacturer's instructions. The real-time PCR assay was performed using the Meningitidis real-time PCR kit for *in vitro* diagnostics (IVD) on the SaCycler-96 real-time PCR system (Sacace, Italia) according to manufacturer instructions.

Laboratory tests

The results from the laboratory blood tests during hospitalization are shown in Table 1. On admission (day 2 or D2), the laboratory tests showed anaemia, low haemoglobin level, leukopenia, lymphocytopenia, neutrophilia, thrombocytopenia, coagulopathy, decreased fibrinogen and prothrombin levels, and increased international normalized ratio (INR) and activated partial thromboplastin time (APTT) levels. Increased lactate levels revealed tissue hypoperfusion and the increased creatinine and urea nitrogen levels revealed an acute renal failure. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were in the normal range, which revealed normal liver function. There were significantly increased inflammatory markers such as C-reactive protein and procalcitonin. Arterial blood gas showed acidosis with pH of 7.29 (reference range: 7.35-7.45), bicarbonate of 17.7 mEq/l (reference range: 22-26 mEq/l), and base excess of -9.1 mEq/l (reference range: -2 to +2 mEq/l). Normal values for $PaCO_2$ (36.3 mm of Hg) and PaO_2 (85.7 mm of Hg) were observed. Laboratory parameters also showed leukocytosis on day 3 (D3), day 4 (D4), and extreme leukocytosis on day 6 (D6) and day 8 (D8) as well as impaired myocardial function (significant increase of total Creatine Kinase (CK) and CK subunits M and B (CKMB) on D4). Real-time PCR was negative for *N. meningitidis* on day 15 (D15). Other parameters appeared within the normal range except for liver function and anaemia on D18 (Table 1).

Table 1. Laboratory data of biochemical and clinical tests.

Laboratory data	Reference range	D2	D3	D4	D5	D6	D7	D8	D11	D14	D15	D18
Red blood cells (t/l)	4.2-6.0	4.1	4.3	3.9	-	3.9	-	3.76	3.62	-	-	3.58
Hemoglobin (g/l)	130-170	122	128	113	-	116	-	110	105	-	-	104
White blood cells (g/l)	4.0-10.0	3.8	23.6	16.5	-	30.6	-	30.2	14.7	-	-	8.2
Neutrophil (%)	43-76	89.7	91.6	89.3	-	87.1	-	80.9	79.3	-	-	66.2
Lymphocytes (%)	19-48	8.8	5	6.5	-	4.6	-	10.6	11.3	-	-	22.06
Platelet count (g/l)	150-350	51	12	25	-	73	-	129	257	-	-	494
Fibrinogen (g/l)	2-4	1.68	3.2	6	-	6.9	-	-	-	-	-	-
Prothrombin (%)	70-140	40	42	55	-	89	-	79	89	-	-	-
INR	0.8-1.2	1.9	1.86	1.5	-	1.08	-	1.16	1.08	-	-	-
APTT (sec)	30-40	55	104	37	-	29	-	-	-	-	-	-
Urea (mmol/l)	2.5-7.5	9.2	9	8.9	-	9.7	-	-	-	-	-	-
Creatinine (mmol/l)	62-120	206	159	141	-	102	-	93	70	-	-	56
Glucose (mmol/l)	3.9-6.4	5.1	5.6	5.6	-	6.6	-	8.8	6.6	-	-	4.4
Total bilirubin (mol/l)	3.4-17.1	15.7	17	16	-	-	-	18.8		-	-	-
Bilirubin direct (µmol/l)	0-7	4	3	4	-	-	-	-	-	-	-	-
Total protein (g/l)	60-80	51.4	-	-	-	-	-	-	-	-	-	-
Albumin (g/l)	38-54	28.3	32	32	-	-	-	36	30.6	-	-	-
AST (U/l)	10-40	42	49	179	-	260	-	-	-	-	-	49
ALT (U/l)	10-40	38	37	53	-	96	-	158	178	-	-	77
Total CK (U/l)	38-174	-	-	6395	-	5274	-	-	-	-	-	-
CKMB (U/l)	1-25	-	-	82	-		-	-	-	-	-	-
Procalcitonin (ng/ml)	<0.05	>100	>100	>100	64.6	-	11.6	-	-	0.44	-	-
CRP (mg/l)	0.5-10	56	-	-	-	-		107	-	-	-	11.2
pH	7.35-7.45	7.29	7.31	7.48	-	-	7.56	-	-	-	-	-
HCO_3 (mEq/l)	22-26	17.7	18.4	28	-	-	34.1	-	-	-	-	-
Base excess (mEq/l)	-2- +2	-9.1	-7.9	4.3	-	-	11.8	-	-	-	-	-
Lactat (mmol/l)	<2.1	7.3	4	2.7	-	-	1.6	-	-	-	-	-
Gram stain*	Negative	Negative	-	-	-	-	-	-	-	-	-	-
Realtime PCR*	Negative	Positive**	-	-	-	-	-	-	-	-	Negative	-

*: Gram stain and real-time PCR to detect *N. meningitidis* in spinal fluid, blood, and throat specimens; **: positive with peripheral blood sample; (-): not available; CRP: C-Reactive Protein.

Treatment and intervention

Because of sepsis shock, the patient had to undergo a gastrostomy and tracheotomy. To avoid delay, antimicrobial therapy was initiated as quickly as possible after the performance of the lumbar puncture and collection of peripheral blood. The patient was initially treated with IV meronem 2 g/24 h and IV ciprobay 800 mg/24 h. Once *N. meningitidis* had been definitively identified, ciprobay was stopped and meronem was continued. The patient became hemodynamically unstable with a blood pressure of 80/50 mmHg, therefore noradrenalin and dobutamin were administered. In addition, other supportive therapies were used including saline infusions, electrolytes, antipyretics, and oxygen therapy. He also had begun to receive one unit of platelet transfusions on day 2 (D2). Consequently, the patient showed clinical improvement and was discharged after 20 days. He underwent another blood test after 20 days, which showed normal ranges, and had good mental status and was without the presence of haemorrhagic rash.

Discussion

In this case, the patient only presented nonspecific prodrome of fever, sore throat, and a nonspecific rash. Therefore, it was difficult to distinguish meningococcal disease from other common bacterial and viral febrile illnesses.

Early signs of sepsis are hypotension and tachycardia and the distinguishing feature such as rash, which may initially appear as small lesions that may appear urticarial, macular, or papular. The rash can develop into petechiae, purpura, or ecchymosis. These may be early signs of thrombocytopenia and purpura fulminant. The sensitivity of Kernig's and Brudzinski's signs was only 55.5 and 53.3%, respectively, which makes them unreliable in excluding meningitis [14]. The nonspecific features progress to sepsis with signs of circulatory insufficiency, shock, and the pathognomonic purpuric rash in about 40-70% of patients with meningococcal diseases [15]. In this study, the patient presented hypotension, shock, tachycardia and purpura, he also had stiff neck and thrombocytopenia. The presence of a non-blanching haemorrhagic rash is pathognomonic of meningococcal disease and reflects coagulopathy with the decreased fibrinogen, prothrombin, and increased INR and aPTT. In this case, the haemorrhagic rash has developed into ecchymosis on day 2. The stiff neck presented in this patient is consistent with Magazzini's report that elderly patients are less likely to present with neck stiffness and are more likely to present with altered consciousness compared to those aged <30 years [16]. Shock due to meningococcal septicaemia is a consequence of several pathophysiologic processes including myocardial dysfunction and impaired cellular metabolism [17]. Septic shock can lead to the consequence of impaired myocardial function and metabolic derangements, which were also found in this case.

N. meningitidis can be identified by microbiological culture, real-time PCR, or Gram staining from a purpuric skin lesion, blood, or cerebrospinal fluid. Microbiological culture is considered the standard method for *N. meningitidis* detection, but the sensitivity is limited particularly when antibiotics were previously administered. Microbiological culture is time-consuming and is frequently compromised by previous antibiotic treatment. Although this method has been used for decades to detect *N. meningitidis*, testing of respiratory specimens to detect *N. meningitidis* using microbiological culture is often discouraged [18]. Gram staining was negative for *N. meningitidis* in blood likely due to the previous use of cefotaxime. Cefotaxime interferes the final transpeptidation step during the biosynthesis of bacterial cell walls, thus reduces their stability and causes bacterial lysis [19]. Real-time PCR is not affected by antibiotics used previously [20] and thus the use of real-time PCR has quickly identified *N. meningitidis* and improved the detection rate [21]. In this case, the positive result for *N. meningitidis* in the blood sample by real-time PCR significantly helped physicians provide appropriate antibiotic treatment for the patient.

Approximately 10% of the general population carry *N. meningitidis* without any signs of disease [3] but this rate is drastically higher in certain living environments such as college dormitories or military units [22, 23]. Meningococcal disease is relatively frequent in military units in Vietnam. The drug of choice for treatment of meningococcal disease used to be penicillin and chloramphenicol [24]. However, due to resistance to these and some other antibiotics, third-generation cephalosporins are currently the most common choice of treatment. These drugs, however, are not readily available in many medical units in Vietnam. Cefotaxime, ceftriaxone, and penicillin are preferred as initial therapy in patients clinically diagnosed with invasive meningococcal disease [25], thus cefotaxime was already used in this case. However, according to WHO, 88-97% of drug stores dispense antibiotics without a prescription despite prohibition of this in Vietnam. One-third of inpatients used an inappropriate antibiotic during their admission. Antibiotics account for more than 50% of drugs used and are the most commonly sold drugs in Vietnam [26]. According to the Vietnam Ministry of Health, penicillin resistance is common in Vietnam [27]. Empiric treatment with a third-generation cephalosporin is recommended in developed countries. Chloramphenicol and meropenem can be used in cases of penicillin allergy [25]. Ciprofloxacin antibiotic is the antibiotic of choice, and ceftriaxone is an alternative [5]. In this case, we used IV meronem in treatment as recommended by most national and international guidelines [28, 29] and the patient recovered after 20 days of treatment.

Conclusions

Meningococcal meningitis may persist in Vietnam military populations, particularly during periods of military recruits. This is the first meningococcal sepsis case among soldier patients in a Vietnamese military unit. The clinical presentations of *N. meningitidis* vary widely making it difficult to diagnose, especially in Vietnam military units. The source of *N. meningitidis* should be investigated to propose suitable deterrence methods for *N. meningitidis* infection.

Consent for publication

Written informed consent from the patient was obtained for publication of the case report, including any accompanying images.

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COMPETING INTERESTS

All authors declare no conflict of interests in this study.

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