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Case Report

Invasive meningococcal disease due to ciprofloxacin-resistant *Neisseria meningitidis* sequence type 4821: The first case in Japan

Yu Kawasaki [a, *], Kousaku Matsubara [a], Hideyuki Takahashi [c], Masatomo Morita [c], Makoto Ohnishi [c], Masayuki Hori [a], Kenichi Isome [a], Aya Iwata [a], Hiroyuki Nigami [a], Mami Ikemachi [b], Go Yamamoto [b], Kiyofumi Ohkusu [d]

[a] Department of Pediatrics, Kobe City Nishi-Kobe Medical Center, 5-7-1 Kojidai, Nishi-ku, Kobe, 651-2273, Japan
[b] Department of Clinical Laboratory, Kobe City Nishi-Kobe Medical Center, 5-7-1 Kojidai, Nishi-ku, Kobe, 651-2273, Japan
[c] Department of Bacteriology I, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku-ku, Tokyo, 162-8640, Japan
[d] Department of Microbiology, Tokyo Medical University, 6-1-1 Shinjuku, Shinjuku-ku, Tokyo, 160-8402, Japan

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ABSTRACT

We present a 4-year-old girl who developed invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* serogroup C sequence type (ST)-4821. She was hospitalized due to fever, vomiting, rash and altered consciousness. Serogroup C *N. meningitidis* was isolated from blood culture taken on admission and was confirmed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry, a biochemical test, and molecular microbiological analysis. The patient was successfully treated with 50 mg/kg ceftriaxone every 12 hours for 7 days without any complications. The isolate was susceptible to a wide variety of β-lactams and rifampin but was resistant to ciprofloxacin. The isolate harbored *gyrA* T91I and *parC* S87I mutations at the quinolone-resistance-determining regions. Multi-locus sequence typing revealed the isolates as ST-4821, which was identical to an endemic clone frequently detected in China. However, neither the patient nor her family members had traveled abroad. To our knowledge, this report is the first to describe an IMD patient caused by ciprofloxacin-resistant *N. meningitidis* ST-4821 in Japan, and is the first community-acquired IMD case due to this strain outside of China. The high proportion of ciprofloxacin resistance and hypervirulent features of this ST-4821 strain raise special public health concerns. We still consider ciprofloxacin is still appropriate drug for post-exposure chemoprophylaxis in Japan. However, nationwide surveillance for susceptibility of IMD isolates is necessary to establish the regional antibiogram, and thereby to avoid chemoprophylaxis failure.

1. Introduction

Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* is a serious infection with significant morbidity and mortality; however, the epidemiology of IMD considerably varies geographically and over time. Although over 4000 IMD cases were reported annually before World War II in Japan, a recent nationwide surveillance in 2014 showed that the incidence was low at 0.028/100,000 even without the introduction of the meningococcal vaccine [1]. In Japan, national surveillance system for meningococcal diseases has changed. In 1999, meningococcal meningitis was designated as a notifiable disease regulated by the Infectious Disease Control Law, and since April 2013, bacteremia has been added to a reportable condition with meningococcal meningitis and categorized as IMD [1]. This surveillance also showed that the fatality rate was approximately 19%, and that serogroup Y (42%) was the most dominant serogroup followed by C (12%), B (7%) and W (3%) [1].

Ciprofloxacin is one of three antibiotics recommended for chemoprophylaxis worldwide; the other two are rifampin and ceftriaxone [2]. Although a number of ciprofloxacin-resistant *N. meningitidis* strains have been isolated in Greece, Argentina, Australia, Spain, Singapore, China, and the United States [3–9], they remain rare in other countries including Japan [10]. The use of

* Corresponding author. Department of Pediatrics, Kobe City Nishi-Kobe Medical Center, 5-7-1 Kojidai, Nishi-ku, Kobe, 651-2273, Japan.
E-mail address: ky26ky225@nmc-kobe.org (Y. Kawasaki).

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multi-locus sequence typing (MLST) has contributed substantially to our understanding of the molecular epidemiology of *N. meningitidis*, such as indentifying isolates from different serogroups but with similar antigenic or disease phenotypes [11,12]. In China, multiple outbreaks of *N. meningitidis* serogroup C or B sequence type (ST)-4821 resistant to ciprofloxacin have been documented since 2003 [8,13,14]. Although it is endemic in China, the circulation of ST-4821 strains has not been observed in other regions except for two imported cases found in Canada [15]. We identified the first IMD case caused by ciprofloxacin-resistant *N. meningitidis* serogroup C ST-4821 in Japan. Notably, this was not an imported case but a community-acquired case.

2. Case report

A previously healthy 4-year-old girl presented with fever, rash, and mental deterioration in February 2017. The patient had been fully immunized by 4 doses of 7-valent conjugate pneumococcal vaccine, conjugate *Haemophilus influenzae* type b vaccine, and diphtheria-pertussis-tetanus- inactivated polio vaccine. The patient had been healthy until the early morning of the day of admission when she had fever and vomiting. A primary pediatrician noticed rash on her trunk and subsequently prescribed an antiemetic agent. Approximately 12 hours after the onset of fever, she became drowsy and was transferred by ambulance to the emergency department of our hospital.

On arrival, the general appearance was ill. Physical examinations showed the following measurements: body temperature, 39.4 °C; heart rate, 132/min; blood pressure, 88/51 mmHg; and Glasgow coma scale, 12 (E3V4M5). The petechial rash spread over her trunk, face, and proximal extremities (Fig. 1). The petechiae were also noted on the bulbar conjunctiva and hard palate. Nuchal rigidity or Kernig signs were negative. Laboratory findings showed the following results: white blood cells, 3.9×10^9/l, hemoglobin, 12.4 g/dl, platelet, 170×10^9/l; C-reactive protein, 7.0 mg/dl; and blood glucose, 126 mg/dl. Fifteen minutes after arrival, generalized tonic-clonic convulsions occurred but were alleviated by intravenous diazepam. We tentatively diagnosed her as having purpura fulminans and meningitis caused by an unknown bacterial pathogen. According to the recommendation in the Practical Guideline for Bacterial Meningitis 2014 in Japan [16], empirical treatment with intravenous ceftriaxone and panipenem-betamipron was initiated after blood cultures were obtained. Head computed tomography and magnetic resonance imaging showed no abnormal findings. A cerebrospinal fluid (CSF) examination was performed 1 hour after the start of antibiotic treatment and showed pleocytosis (polymorphonuclear cells, 27/μl; mononuclear cells, 7/μl) with normal protein (16 mg/dl) and glucose (100 mg/dl) levels. Gram staining and antigen detection using a latex agglutination kit (Pastorex, Bio-rad Laboratories, USA) were negative. CSF culture yielded negative results. Furthermore, PCR-based methods using specific primers for *N. meningitidis* and their major 5 serogroups (A, B, C, Y, and W) [17,18] did not detect the organism in the CSF.

On the day after admission, the patient recovered normal consciousness and her fever subsided. Proline aminopeptidase-positive, γ-glutamyl aminopeptidase-positive, gram-negative cocci

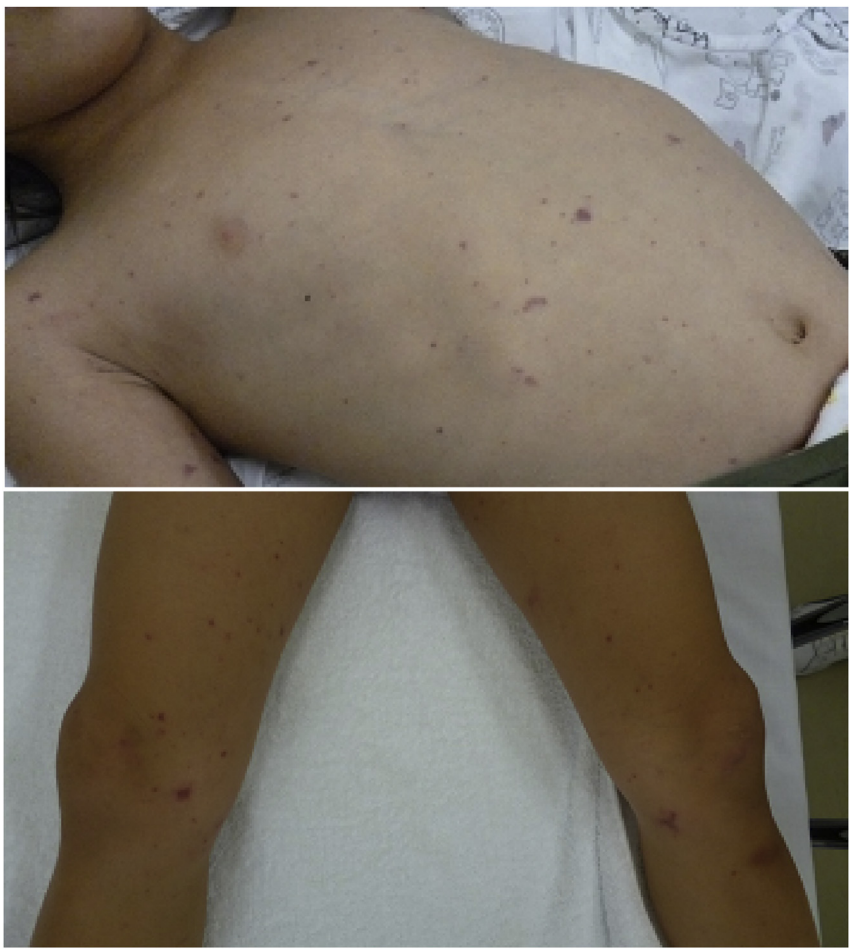

Fig. 1. Macular and non-blanching petechial rashes spreading on the trunk (upper panel) and lower extremities (lower panel) on admission.

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