IDCases 31 (2023) e01656

Contents lists available at ScienceDirect

IDCases

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Case report

Non-serogroupable *Neisseria meningitidis* pneumonia in an immunocompetent patient with severe COVID-19 pneumonia: A case report

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ARTICLE INFO

Keywords:
N. meningitidis
Meningococcal pneumonia
Non-serogroupable
Non-capsulated
Immunocompetent
Coronavirus disease 2019 (COVID-19)

ABSTRACT

Background: Non-serogroupable *Neisseria meningitidis* (*N. meningitidis*), the most common type of *N. meningitidis* in asymptomatic carriers, rarely causes infections. Most reported cases of infection are in patients with immunodeficiency, primarily complement deficiencies.

Case presentation: A 54-year-old immunocompetent man was transferred to our hospital to treat severe coronavirus disease 2019 (COVID-19). The patient presented with cough producing a large amount of purulent sputum, which was considered an atypical presentation of COVID-19. Gram staining of the sputum revealed a large number of gram-negative diplococci phagocytosed by many neutrophils, and a diagnosis of bacterial pneumonia was established. The culture yielded non-serogroupable *N. meningitidis,* and the patient was diagnosed with non-serogroupable *N. meningitidis* pneumonia. Potential immunodeficiency was considered; however, testing including human immunodeficiency virus and complement factors showed no abnormalities.

Conclusions: We report herein a rare case of non-serogroupable *N. meningitidis* pneumonia that occurred in an immunocompetent patient during the course of severe COVID-19. We consider impaired T cell function attributable to COVID-19 and dexamethasone administration may have triggered a transient immunosuppressive state and led to non-serogroupable *N. meningitidis* pneumonia.

Introduction

Neisseria meningitidis is considered an endemic worldwide and results in an estimated 1.2 million cases with up to 135,000 deaths per year globally [1]. The key factor in the virulence of *N. meningitidis* is the polysaccharide capsule; the serogroups of *N. meningitidis* are classified into 12 serogroups based on the serologic differences in the capsule [2]. Pathogens that lack polysaccharide capsules are termed non-serogroupable *N. meningitidis*. It is the most common type of *N. meningitidis* in asymptomatic carriers [3]. The reported cases of non-serogroupable *N. meningitidis* infection are low, with an annual incidence of less than 10 % of all *N. meningitidis* infections in the United States as reported in 2019 [4]. Most reports of non-serogroupable *N. meningitidis* infection occur in patients with immunodeficiency; inherited or acquired deficiencies of the terminal complement pathway are reported in most cases [5,6]. Herein, we report a rare case of non-serogroupable *Neisseria meningitidis* pneumonia in an immunocompetent patient with severe coronavirus disease 2019 (COVID-19) pneumonia in Japan.

Case

The patient was a 54-year-old man with a history of type 2 diabetes controlled without medication. He had no known immunodeficiency or past episodes of recurrent infections. He did not smoke or consume alcohol. He had not received vaccination for either COVID-19 or *N. meningitidis*. He had no known sick contact within the last few months. The patient had no recent trauma.

In August 2021, he developed fever and cough (herein after referred to as day 1). On day 2, a nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 by reverse transcription-polymerase chain reaction (PCR) returned positive. On day 4, he developed dyspnea and was admitted to a nearby hospital. He was hypoxic on admission, and he received supplemental oxygen and was started on

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https://doi.org/10.1016/j.idcr.2022.e01656
Received 22 September 2022; Accepted 30 November 2022
Available online 1 December 2022

intravenous dexamethasone 6.6 mg once daily and intravenous remdesivir 100 mg once daily (first dose: 200 mg). Despite treatment, respiratory failure deteriorated. On day 7, the patient was transferred to our hospital for further treatment.

On presentation, he was alert, afebrile with a body temperature of 36.8 ℃, tachypneic with a respiratory rate of 28/min, and had an oxygen saturation of 93 % with a 10-L/min non-rebreathing mask. He complained of severe cough with excess purulent sputum, which was considered an atypical presentation of COVID-19. He had no headache on admission or during the clinical course. Respiratory investigation revealed diffuse bilateral coarse crackles. Physical examination was otherwise normal. Abnormal skin lesions or neck stiffness were not observed. Blood pressure was 171/109 mmHg and pulse rate was 85 beats/min. Laboratory tests showed lymphopenia with an absolute lymphocyte count of 241/μL (reference range (RR), 1000–4800/μL), normal level of leukocytes (4300/μL; RR, 3100–8400/μL), elevated D-Dimer level of 1.4 μg/mL (RR < 1.0 μg/mL), elevated lactate dehydrogenase level of 472 IU/L (RR 124–222 IU/L), elevated C-reactive protein level of 5.63 mg/dL (RR < 0.3 mg/dL), and elevated ferritin level of 360.0 ng/mL (RR < 160 ng/mL). Chest X-ray showed bilateral consolidation.

The patient was intubated and treated with neuromuscular blockade and prone positioning. He received dexamethasone for 10 days and remdesivir for 5 days. He developed a new onset of fever on day 8, and respiratory failure deteriorated from day 8 to day 10. Elevated leukocytes (10,300/μL, RR 3100–8400/μL) and C-reactive protein level (14.59 mg/dL, RR < 0.3 mg/dL) were detected on day 10. A large amount of purulent sputum was noted; a sputum sample was collected for Gram staining and culture. Gram staining results (Fig. 1) revealed a large number of gram-negative diplococci phagocytosed by numerous neutrophils. No other pathogen was detected upon Gram staining. Based on the Gram staining findings and the clinical course, bacterial pneumonia was diagnosed, and intravenous cefepime (1 g every 8 h) was initiated. The culture was dominated by gram-negative diplococci, identified as *N. meningitidis* by the ID-test HN-20 Rapid system (Nissui, Tokyo, Japan). The blood culture results were negative. Antimicrobial drug susceptibility tests for *N. meningitidis* were performed using the Etest (bioMerieux, Lyon, France). Antimicrobial susceptibility was interpreted according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing [7]. The isolate was susceptible to ceftriaxone (minimal inhibitory concentration [MIC] < 0.016 μg/mL), minocycline (MIC = 0.064 μg/mL), chloramphenicol (MIC = 0.50 μg/mL, and meropenem (MIC = 0.016 μg/mL), and was resistant to benzylpenicillin (MIC = 0.25 μg/mL) and ciprofloxacin (MIC = 0.125 μg/mL). Based on the sputum culture and Gram staining results, *N. meningitidis* pneumonia was diagnosed. Antibiotic treatment was switched to intravenous ceftriaxone (2 g every 24 h) on day 14 and was administered for 6 days.

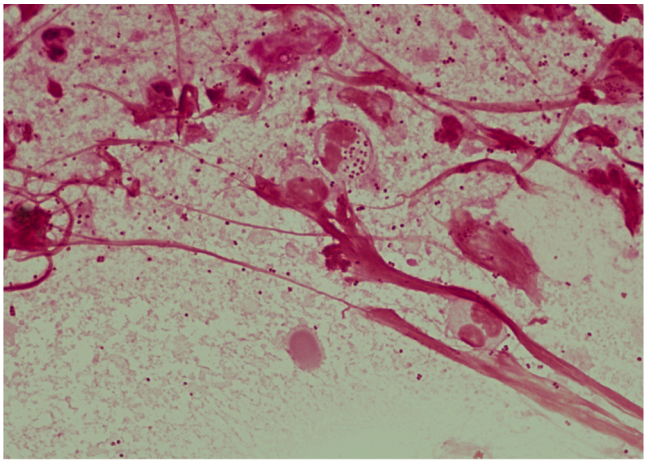

Fig. 1. Gram staining of the sputum sample. A large number of gram-negative diplococci are phagocytosed by numerous neutrophils.

A sample was sent to the Tokyo Metropolitan Institute of Public Health for further testing. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI Biotyper; Bruker Daltonics Inc., Billerica, MA, USA) detected *N. meningitidis*. Typing was performed for serogroups A, B, C, W, and Y by PCR, which were all negative. The PCR to detect the phytoene synthase gene (*ctrB*) was also negative. Owing to the lack of *crtB*, it was typed as non-serogroupable [2]. Multilocus sequence typing was performed according to the protocols on the Public databases for molecular typing and microbial genome diversity (PubMLST) website (https://pubmlst.org). The sequence type was assigned as ST-11026, a member of the ST-32 complex.

His clinical course improved gradually, and the patient was extubated on day 15. Fever and purulent sputum resolved on day 16, and the patient remained afebrile for the rest of the hospital course. Potential immunodeficiency was considered, and testing was performed. The human immunodeficiency virus test results were negative. Complement C3 and C4, and CH50 values tested on day 13 were normal. On day 25, the patient was transferred to another hospital for rehabilitation.

Discussion

This is a rare case of non-serogroupable *N. meningitidis* pneumonia that occurred in an immunocompetent patient during the course of severe COVID-19. The major risks for *N. meningitidis* pneumonia are immunodeficiencies, such as immunoglobulin or complement deficiencies, asplenia, preceding respiratory infections attributed to influenza, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and advancing old age [8]. The patient had no known immunodeficiency and no other risk of infection.

We searched ST-11026, the sequence type of *N.meningitidis* found in this patient, on the PubMLST website database (https://pubmlst.org/bigsdb?db=pubmlst_neisseria_isolates, accessed October 16, 2021). Five isolates of ST-11026 were reported, all of which were reported in Japan from 2014 to 2016. Thus, the acquisition of the organism in Japan was assumed. *N. meningitidis* infection is very rare in Japan, with only an average of 32 cases of invasive meningococcus infection (defined by *N. meningitidis* bacteremia or meningitis) annually as reported from 2013 to 2017 [9]. Infection of non-serogroupable *N. meningitidis* is extremely rare in Japan, with only one report found in PubMed [10].

Reported cases of non-serogroupable *N. meningitidis* infection nearly exclusively occurred in patients with immunodeficiencies; inherited or acquired deficiencies of the terminal complement pathway are reported in most cases [5,6]. Other researchers have reported alternative immunodeficiencies, such as post-transplant leukemia receiving immunosuppressants owing to graft-versus-host disease, and asplenia [11]. To the best of our knowledge, only two cases of *N. meningitidis* infection in an immunocompetent patient have been previously reported [12,13]. Since this patient had no known immunodeficiency, we assume that COVID-19 and treatment against COVID-19 pneumonia triggered a transient immunosuppressive state and led to non-serogroupable *N. meningitidis* pneumonia.

Three steps are required for *N. meningitidis* pneumonia: colonization of the oro-nasopharynx, translocation to the lower airways, and pulmonary damage mediated by the pathogen [14]. In normal hosts, ciliated cells prevent bacteria in the oro-nasopharynx from translocating to the lower airways. Viral pneumonia causes damage to the ciliated cells, thereby impairing mucociliary clearance and allowing the bacteria to translocate to the lower airways [15]. While the capsulated *N. meningitidis,* which is protected from phagocytosis and lysis by the polysaccharide capsule, could initiate virulence following translocation to the lower airways resulting in pneumonia [8], non-serogroupable *N. meningitidis*, which lacks the polysaccharide capsule, is killed by

opsonophagocytosis by antibodies and complements in normal hosts [16]. The lack of this process would be essential in the occurrence of infection. The activation of multiple complement pathways is seen in patients with severe COVID-19 [17]. Thus, the deficiencies of the complement pathways would not be considered the etiology for the development of non-serogroupable *N. meningitidis* pneumonia in this patient. In one report, T cell activation impairment was observed in patients with COVID-19 who developed secondary bacterial pneumonia [18]. We presume that the impaired T cell activation resulting in impaired B cell function and resultant loss of antibodies against non-serogroupable *N. meningitidis* led to impaired opsonophagocytosis, which could have contributed to the pathogenesis of non-serogroupable *N. meningitidis* pneumonia in this patient. Steroids impair T cell function as well [19], and an increased risk of secondary bacterial and fungal infection in COVID-19 patients related to the administration of steroids has been reported [20]. Thus, the administration of dexamethasone is also considered a contributory factor of infection in this patient.

In conclusion, we observed non-serogroupable *N. meningitidis* pneumonia, a rare infection among immunocompetent individuals, in an immunocompetent patient with severe COVID-19. We consider impaired T cell function attributed to COVID-19 and dexamethasone administration to be associated with the pathogenesis of non-serogroupable *N. meningitidis* pneumonia in this patient. Most cases of non-serogroupable *N. meningitidis* infection have been reported in patients with deficiencies of the terminal complement pathway, and this case indicates that impaired T cell function may be another factor in acquiring this infection. Further studies are needed to understand the relationship between COVID-19 and non-serogroupable *N. meningitidis* infection and determine the underlying mechanisms.

CRediT authorship contribution statement

Hiroki Kojima: Conceptualization, Writing – original draft. **Fukumi Nakamura-Uchiyama, Jun Makino:** Writing – review & editing, Supervision. **Tsukasa Ariyoshi:** Data collection, microbiological testing of the pathogen. **Atsushi Kosaka, Takuya Washino, Naoya Sakamoto, Sentaro Iwabuchi:** Writing – review & editing.

Ethical approval

The need for approval was waived by the Ethics Committee of Tokyo Metropolitan Bokutoh Hospital.

Consent

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

Funding

The authors did not receive any specific grant from funding agencies in the public,commercial, or not-for-profit sectors.

Conflicts of interest

None declared.

Acknowledgments

Not applicable.

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