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【 CASE REPORT 】

Haemophilus influenzae Non-type b Infection in an Adult Patient with Systemic Lupus Erythematosus

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Abstract:
A 40-year-old man with systemic lupus erythematosus taking consecutive oral corticosteroids developed a high-grade fever and disorder of consciousness following acute rhinitis. *Haemophilus influenzae* type f (Hif) was found and isolated from the blood and cerebrospinal fluid by culture, leading to a diagnosis of meningitis. The prevalence of *H. influenzae* type b (Hib) infections has decreased due to routine immunization. As a result, the prevalence of invasive non-Hib, including Hif infection, is increasing as a common *H. influenzae* infection in children and adults. Physicians should be aware of non-Hib *H. influenzae* infection, even though the Hib vaccine is widely used in Japan.

Key words: *Haemophilus influenzae* type f, Hib vaccination, bacterial meningitis, systemic lupus erythematosus

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Introduction

Haemophilus influenzae is a Gram-negative bacillus classified into two types, depending on the possession of a capsule. *H. influenzae* with a capsule is also divided into six types (a-f) based on the capsulated strains. Of these capsular strains, type b (Hib) causes invasive infections most frequently, such as meningitis and epiglottitis, which can be fatal even in adults.

The Hib vaccine was developed to prevent critical complications due to Hib, and with its introduction, Hib infections have recently become uncommon in Western countries (1-3). However, patients infected with invasive *H. influenzae* due to types other than b or non-type *H. influenzae* (NTHi) remain relatively common (1-5). Since vaccination against Hib started in Japan in 2008, invasive *H. influenzae* infection by non-type b is increasing, in line with Western countries. In adults, invasive *H. influenzae* infection prevalently occurs in compromised hosts, such as patients receiving immunosuppressants for an autoimmune disease or those receiving chemotherapy for cancer (2, 3).

We herein report an adult patient with systemic lupus erythematosus (SLE) who developed meningitis caused by *H. influenzae* type f (Hif), which initially infected the upper respiratory tract as acute rhinitis and then translocated to the brain as meningitis. This case can be a useful model for considering invasive non-Hib infection even in adult patients, especially those under immunosuppressive treatment.

Case Report

The patient was a 40-year-old man who had been diagnosed with SLE at 32 years old based on pancytopenia, the presence of serum anti-nuclear antibodies, anti-DNA antibodies, and seizure disorder as a neuropsychiatric SLE (NPSLE) at the disease onset. Following the diagnosis, high-dose methylprednisolone with tacrolimus was administered as an induction therapy, after which methylprednisolone tapering was started. During the maintenance therapy with

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Table 1. Urine and Serum Data upon Hospital Admission.

Urine		Biochemistry		Immunity	
UP (1+)		TP	6.1 g/dL	CRP	19.22 mg/dL
UB (±)		Alb	3.4 g/dL	PCT	3.27 ng/mL
WBC	<1 /HPF	AST	33 U/L	IgG	984 mg/dL
		ALT	33 U/L	IgA	129 mg/dL
CBC		LDH	238 U/L	IgM	13 mg/dL
WBC	7,100 /μL	BUN	24.5 mg/dL	C_3	67 mg/mL
Lymp	490 /μL	Cr	1.39 mg/dL	C_4	16 mg/mL
Hb	14.3 g/dL	Glu	93 mg/dL	CH50	25 U/mL
Plt	123,000 /μL	Na	144 mEq/L	ADNA	6.1 IU/mL
Coagulation		K	4.0 mEq/L	C1q	1.6 μg/mL
PT-INR	1.00	Cl	110 mEq/L		
APT	25.3 s				
FIB	702 mg/dL				
FDP	4.70 μg/mL				
D-dimer	1.69 μg/mL				

UP: urinary protein, UB: urinary blood, Lymp: lymphocytes, PLT: platelet, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, FIB: fibrinogen, FDP: fibrinogen degradation products, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cr: creatinine, Glu: glucose, CRP: C-reactive protein, PCT: procalcitonin, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, CH50: 50% hemolytic unit of complement, ADNA: anti-DNA antibodies, C1q: immune complex quantified by C1

Table 2. Cerebrospinal Fluid CSF Data on Hospital Admission.

Cell	385/μL (Mono 1% Poly 99%)
Turbidity	(+)
blood	(-)
Protein	513 mg/dL
Glucose	16 mg/dL
IgG-IDX	0.77
Oligoclonal band	(-)
MBP	<31.3 pg/mL

CSF: cerebrospinal fluid, IDX: index, MBP: myelin basic protein

methylprednisolone (18 mg/day), the patient presented to the community clinic with symptoms he described as "runny nose"; subsequently, he was diagnosed with acute viral rhinitis. He developed a high fever and progressive disorder of consciousness 10 days following his clinic visit. He was urgently transported and admitted to the authors' university hospital.

An assessment of his social history revealed no prehospitalization contact with children, and he did not live or work with children. Upon admission, the patient's vital signs were as follows: temperature, 40.9℃; blood pressure, 142/98 mmHg; pulse, 130 bpm; and respiratory rate, 32 breaths/min. Oxygen saturation was 98% on room air, and his Glasgow coma scale score was E4V1M4. On a physical examination, the findings in the chest and abdomen were normal, but significant neck stiffness was noted. On a neurologic examination, the patient's eyes exhibited conjugate deviation to the right. In addition, involuntary movements on both arms were observed.

The laboratory results revealed lymphopenia and thrombocytopenia (Table 1, 2). In addition, the patient had mild renal failure based on the definition for acute renal injury (6). Because his C-reactive protein (CRP) and procalcitonin concentrations were extremely high, the development of severe systemic inflammation was initially suspected, such as sepsis or SLE complications. However, stable anti-DNA antibody concentrations indicated a low level of SLE activity.

Because meningitis was strongly suspected due to the significant neck stiffness, lumbar puncture was performed. A cerebrospinal fluid (CSF) analysis revealed polynuclear leukocyte-dominant leukocytosis and significantly low glucose CSF concentrations compared with serum. A latex agglutination test (Pastorex Meningitis; Bio-Rad Laboratories, Hercules, USA) with CSF was negative for all antigens, including Hib, *Streptococcus pneumoniae*, Group B *Streptococcus, Neisseria meningitidis* type A/C/Y/W-135, and *Escherichia coli* with K1 capsular polysaccharide antigen. To exclude parenchymal lesions causing disorder of consciousness due to other diseases, such as NPSLE, brain magnetic resonance imaging was performed, which revealed high intensities in the right temporal lobe on diffusion-weighted imaging and high intensities scattered over the sulcus of the cerebral hemisphere on fluid-attenuated inversion recovery, suggesting bacterial meningitis (7) (Figure).

The patient was diagnosed with bacterial meningitis based on significant neck stiffness, high CRP level, polynuclear

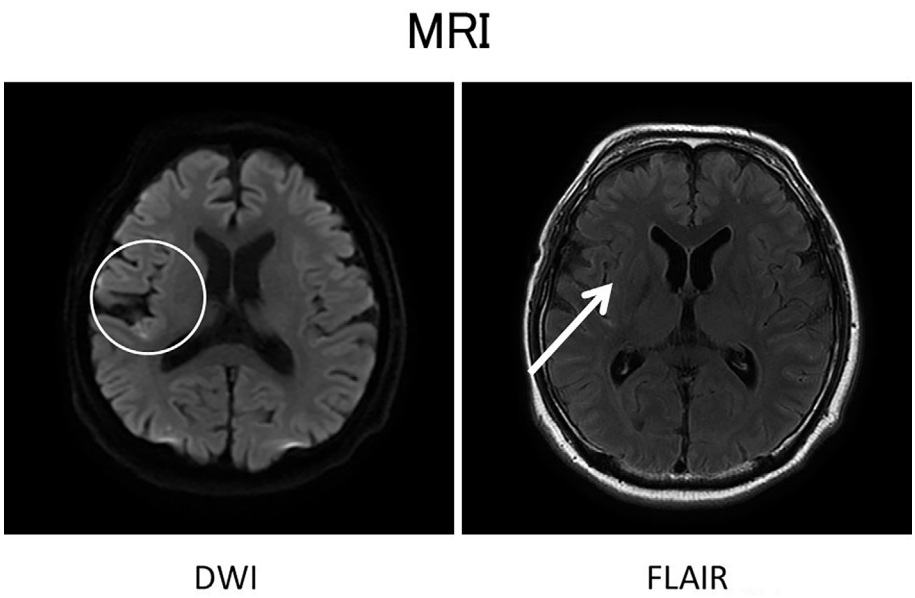

Figure. **Magnetic resonance imaging findings at admission. High intensities in the right temporal lobe on DWI (circle) and high-intensity areas in the sulcus of the cerebral hemisphere on FLAIR imaging (arrow), indicating bacterial meningitis. DWI: diffusion-weighted imaging, FLAIR: fluid-attenuated inversion recovery**

Table 3. **Antimicrobial Susceptibility Testing of *Haemophilus influenzae* Type f.**

Antibiotics	MIC (μg/mL)	Interpretation
Ampicillin	>16	R
Cefotaxime	2	S
Ceftriaxone	≤1	S
Imipenem	≤0.5	S
Meropenem	≤0.125	S
Clarithromycin	≤4	S
Levofloxacin	≤1	S

MIC: minimal inhibitory concentrations, R: resistant, S: susceptible

leukocyte-dominant leukocytosis, and low glucose concentrations in the CSF. The patient was intravenously administered meropenem 6 g/day and vancomycin 2 g/day with betamethasone 40 mg/day based on the guidelines for bacterial meningitis (8). On hospital Day 2, Gram-negative bacilli were detected in his primary smear preparation, and *H. influenzae* was detected from both the CSF and blood culture. The administration of betamethasone for 3 days was completed according to the guidelines, and then the administration of methylprednisolone 18 mg/day was started again as maintenance therapy for SLE. Vancomycin was discontinued on hospital Day 4, as no Gram-positive cocci were detected. On hospital Day 5, Hif was confirmed in both the CSF and blood by the latex agglutination test. The patient was diagnosed with an invasive *H. influenzae* infection, and accordingly, the case was reported to the Public Health Center as a Category V Infectious Disease. On hospital Day 10, elevation of serum creatinine was observed, and meropenem was changed to ceftriaxone 4 g/day, based on the susceptibility tests (Table 3).

The CSF leukocyte count decreased to 6/μL following the 10-day administration of antibiotics. During follow-up, 25 days after hospital admission, pancytopenia was documented that was thought to have been caused by ceftriaxone. Treatment was changed to ciprofloxacin 800 mg/day, which reversed his pancytopenia. After the CSF leukocyte count dropped below the upper limit during follow-up, 32 days after admission, antibiotic therapy was halted with no subsequent disease recurrence.

Discussion

H. influenzae type b is a significant cause of invasive bacterial infections and can occasionally cause fatal invasive infections, such as meningitis and acute epiglottitis (9). Studies have shown that Hib vaccination can reduce the rate of invasive Hib infections from about 80% to 20% in Western countries (2). Since the Hib vaccine was first introduced and has been used for more than 10 years in Western countries, non-type b *H. influenzae* infections are expected to be the more prevalent type of *H. influenzae* infections worldwide. Indeed, some evidence suggests that non-type b, NTHi, and Hif are as common as *H. influenzae* infections. According to recent reports, one of the most common causes of invasive infections by *H. influenzae* in older adults was Hif, following NTHi in Western countries (1, 2, 4). In Japan, routine immunization against Hib started in 2013, and the annual incidence of invasive Hib infections drastically decreased from 98.2% to 5.0% in children younger than 5 years old (10). However, the same report also demonstrated that

Table 4. Cases of Invasive *Haemophilus influenzae* Type f Infections in Adults since 2013.

Case	Reference	Age	Sex	Nation	Focus	Comorbidities	Antibiotics	Prognosis
1	18	36	F	JPN	meningitis	None	VCM+ABPC+CTRX →CTRX	Recovered
2	19	66	M	JPN	Cellulitis	IgG4-RD	MEPM→CTRX+ABPC	Recovered
3	20	73	F	USA	infective endocarditis, septic arthritis	DM, OA	VCM+MEPM→CTRX	Recovered
4	21	58	M	USA	artery aneurysm	DM, COPD	VCM+PIPC/TAZ→CTRX	Recovered
5	22	73	F	USA	septic arthritis	OA	CTRX	Recovered
6	23	63	F	USA	Necrotizing Fasciitis	Breast cancer	VCM+CTRX →CLDM+CFPM→CTRX	Recovered
7	24	58	M	USA	Mycotic Aortic Aneurysm	DM, COPD	CTRX	Recovered

F: female, M: male, JPN: Japan, USA: The United States of America, IgG4-RD: IgG4-related disease, DM: diabetes mellitus, OA: osteoarthritis, COPD: chronic obstructive pulmonary disease, VCM: vancomycin, ABPC: ampicillin, CTRX: ceftriaxone, MEPM: meropenem, PIPC/TAZ: piperacillin/tazobactam, CFPM: cefpirome, CLDM: clindamycin

the frequency of invasive non-type b *H. influenzae* infections has been increasing (10). Interestingly, the numbers of invasive infections by *H. influenzae* are increasing, even in older adults in Japan (11, 12). This increase may be the result of decreased antibodies (13) and opsonization (14) against *H. influenzae* in the older adult population. In addition, the reported number of cases in Japan may have increased based on the revised Infectious Diseases Control Law in 2013, requiring the reporting of invasive *H. influenzae* infection. Thus, the relative increase in non-Hib infections in the pediatric population may be particularly associated with increased infections in the older adult population.

The Hib vaccine has reduced the prevalence of pediatric Hib infection (15), which may have led to a relative increase in non-Hib. In fact, invasive Hif infection is becoming the most common infection in adults among those with capsular strains (1, 2, 4). In the case of invasive Hif infection alone, about 75% of patients were reported to be ≥15 years old (16). The incidence of bacterial meningitis caused by Hif was also shown to be higher in adults than in children, most of whom had underlying diseases (16). In the present report, we described an adult patient with SLE who developed meningitis caused by Hif; the clinical features of our case were consistent with those in previous reports. Although the patient in this case survived, older adults and immunosuppressed patients have a higher mortality rate than healthy individuals (16, 17). Other reports have also shown that older adults have a higher frequency of invasive non-Hib infections, including Hif, and higher associated mortality rates with 1.5 to 2.5 folds (1-4). These findings suggest that the physicians must consider the possibility of *H. influenzae* infections in all populations. Technically, the latex agglutination test of CSF can only detect Hib, not non-Hib *H. influenzae*. Compared with Hib infection, Hif infection is more likely to cause bacterial meningitis in adults (16), leading to a poor prognosis. In addition, not only Hif infection but also other non-Hibs infections, such as NTHi, can cause bacterial meningitis in adults (1). Therefore, if the rapid latex agglutination test is negative for *H. influenzae*, clinicians should still consider *H. influenzae* meningitis caused by non-Hib infection.

Previous reports indicated that comorbid diseases, such as chronic obstructive pulmonary disease, malignancy, and immunosuppression, are risk factors for invasive infections caused by *H. influenzae* (3). To compare this case with the trend in recent invasive Hif infections, the authors surveyed case reports on PubMed using the search terms "*H. influenzae* type f" and "adult" and used the results to build a summary table (Table 4) of case report of invasive Hif infections since 2013, when routine immunization against Hib started in Japan (18-24). In these cases, the median age was 63 years old, with some differences in sex. Many of the patients had comorbid disease. Although the patient in the present case was younger than the age distribution in Table 4, he was immunocompromised with SLE and was using immunosuppressants.

As presented in Table 4, invasive Hif can cause a variety of types of organ damage in infected patients. Because older adults can have comorbidities similar to those noted previously, the risk of non-Hib infection in adults is expected to increase in Japan. Although 60-70% of adult cases of invasive non-Hib infections presented with pneumonia (1-4, 17), the absence of pneumonia cannot be used to rule out non-Hib infections. The patient in the present case had multiple risk factors for infection, including immunosuppressant use with corticosteroids and lymphopenia (25-27). In addition, patients with SLE have immunologic abnormalities in the complement system, which is associated with decreased protection against capsulated bacteria, including *H. influenzae* (28). The acquisition of Hif infection in the present case may have been associated with the widespread use of the Hib vaccine in Japan. In addition, the presence of multiple risk factors for immunocompromise likely led to the development of meningitis in our patient.

Conclusion

Although Hib vaccination is currently widespread in Japan, physicians should still consider the diagnosis of non-

Hib infection, especially in an immunocompromised host with multiple comorbidities. The incidence of invasive non-Hib infections is expected to increase in Japan (12), so clinicians should take care not to miss cases of non-Hib infections, given the associated high mortality rate in immunocompromised patients.

The authors state that they have no Conflict of Interest (COI).

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