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Case report

Encapsulated pleural effusion due to *Haemophilus influenzae* biotype II in a child with trisomy 21: A case report and literature review

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ABSTRACT

Haemophilus influenzae (Hi) can colonize in the upper respiratory tract and cause severe pulmonary infections, especially among immunocompromised children. Herein, we report a case of left encapsulated pleural effusion (EPE) due to Hi in a 24-month-old girl with trisomy 21. She was already vaccinated against Hi type b. The Hi biotype II was isolated from both the blood and aspirated sputum obtained upon admission. Ampicillin/sulbactam 180 mg/kg/day was administered intravenously for 34 days with oxygen supplementation for 4 days. She clinically recovered without undergoing thoracic drainage. One month after discharge, the girl developed acute otitis media, and the throat swab was cultured. Nontypeable Hi with the same biotype II was isolated, and the infection was controlled by administering antimicrobials. In this report, a literature review regarding the EPE due to Hi in children is also summarized. Pediatric clinicians should be aware of the possibility of Hi-related EPE because of its rapid progression, although it is rare in clinical settings. In addition, they need to consider the possibility of repetitive respiratory infections with Hi in a child with trisomy 21.

Introduction

Haemophilus influenzae (Hi) including the capsule type b (Hib) occasionally colonize the upper respiratory tract and can cause severe pulmonary infections and meningitis among infants and preschool children. Therefore, Hib vaccination has been introduced to the children, and its preventive intervention is very popular in Japan. Okada et al. [1] reported the radiological findings using thin-section computed tomography (CT) scans in acute pulmonary infections due solely to Hi, which was extracted from 211 patients in Japan. The main CT features were ground-glass opacity (n = 185, 87.7%), bronchial wall thickening (n = 181, 85.8%), centrilobular nodules (n = 137, 64.9%), and consolidation (n = 112, 53.1%); however, pleural effusion (PE) was found in 22 (10.4%) patients. Thus, PE involvement is uncommon.

Encapsulated PE (EPE) is confirmed as an extrapleural sign formed on the chest roentgenogram, and this sign is not changed between standing and lateral decubitus positions, in which the roentgenograms are taken. This situation might be induced by the fibrous adhesion between the parietal and visceral pleura.

Herein, an EPE formed in the left pleural space due to Hi in a 24-month-old girl with trisomy 21 was described. In addition, a literature review regarding Hi-related EPE in pediatric patients was also presented.

Case report

A 24-month-old Japanese girl, who was previously diagnosed with trisomy 21, was admitted to our hospital because of high fever and shortness of breath. Her past medical history revealed that she had repetitive lower respiratory tract infections (bronchiolitis or pneumonia) and post-cardiac repair operation for ventricular septal defect. She was already vaccinated against Hib. The patient had been ill with high fever and cold-like symptoms for 4 days before the emergent admission. Physical examinations revealed cyanosis and chest retraction when breathing, tachycardia (150 beats/min), tachypnea (53 breaths/min), and high fever (body temperature 39.4 °C).

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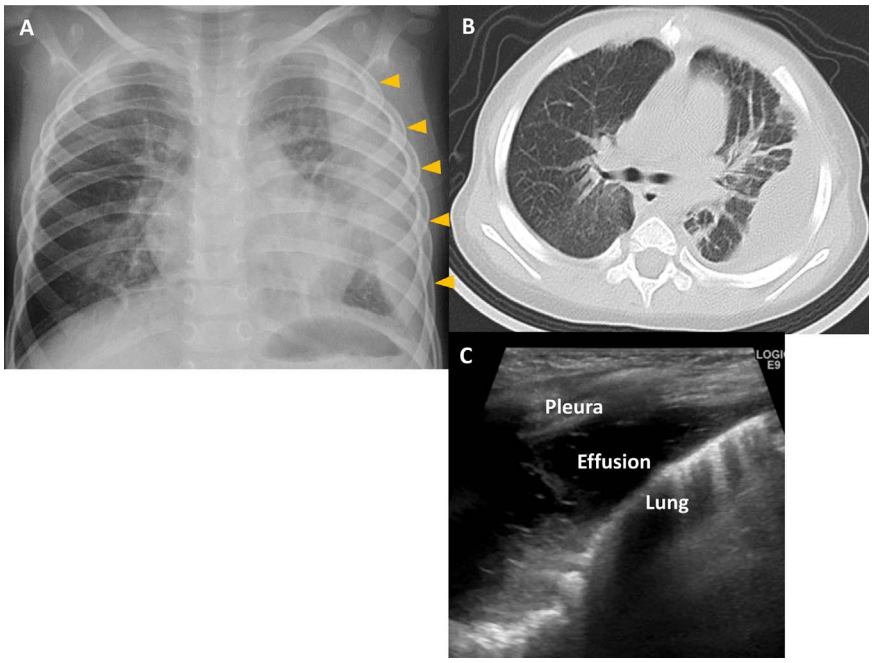

Fig. 1. Encapsulated pleural effusion formed in the left pleural space demonstrated by chest roentgenogram **(A)**, an image of thoracic computed tomography **(B)**, and an image of chest wall echography **(C)**. Arrowheads indicate an extrapleural sign.

Blood laboratory tests showed leukocytosis (28,700/μL), elevated C-reactive protein levels (17.75 mg/dL), and hypoxemia. Chest roentgenogram indicated lobar consolidation with a small amount of PE on the left lung. On hospital day 2, both the aspirated sputum and blood cultures yielded the growth of Hi. After starting an intravenous administration of 180 mg/kg/day ampicillin/sulbactam (ABPC/SBT) and oxygen supplementation combined with β-stimulant inhalation, her general conditions ameliorated within the next 2 days. On hospital day 4, although the percutaneous oxygen saturation was improved, the left vesicular sound was poorly auscultated and inflammatory blood markers still remained high. On hospital day 6, chest roentgenogram (Fig. 1A) and CT (Fig. 1B) showed remarkable EPE formed in the left pleural space.

She was immediately transferred to a tertiary hospital for further management of the EPE. Percutaneous needle aspiration was performed using an echography of the left chest wall (Fig. 1C), and a small amount of fluid was aspirated. Laboratory tests on the fluid revealed white cell count of 800/μL (not suggesting high-levels of inflammation in EPE), lactate dehydrogenase (LDH) level of 488 IU/L, and glucose (Glu) concentration of 4 mg/dL. The Gram-staining and culture results were both negative. Based on these data, we decided no performance of the chest tube placement to improve the EPE. Investigation regarding the immune system was done, and the serum levels of immunoglobulin G (IgG), IgA, and IgM were found to be 1197 mg/dL, 117 mg/dL, and 152 mg/dL, respectively. We considered the potential contribution of polymicrobial anaerobic pathogens to the EPE, and continued to intravenously administer ABPC/SBT (180 mg/kg/day) as the use of anti-anaerobic antibiotic. Thickening of the chest wall appeared to be due to local fibrinolysis, which might be induced by Hi-related inflammation. After continuously administering intravenous ABPC/SBT with the same dose for 1 month, the EPE disappeared. She had no EPE relapse during the 5-month follow-up period after discharge.

Microbiological analyses

Upon the emergent admission, blood and aspirated sputum specimens were immediately obtained to identify the causative microorganisms. Then, Gram-negative bacilli were isolated from the blood culture bottles, and both of the blood and sputum cultures yielded small gray/white-colored colony formations on the chocolate agar plate, but not on the sheep blood agar plate, which were incubated in a 5% CO_2 atmosphere at 37 °C for 24 h. These isolates required both the X (hemin) and V factors (nicotinamide adenine dinucleotide) for their growth. These characteristics were compatible with the biochemical properties of Hi. The blood-origin isolate was accurately identified using a commercially available manual identification kit (ID-test HN-20 rapid, Nissui Pharmaceutical Co., Ltd., Tokyo, Japan), and its profile No. was 7501040 (% probability, 100%). The Hi species has routinely been subdivided into eight biotypes (I–VIII) based on the combined properties of urease production, ornithine decarboxylase activities, and indole production [2,3], and these isolates were biotype II. Antimicrobial susceptibility testing was performed using the broth microdilution method (Dry plate Eiken DP34, Eiken Chemical Co., Ltd., Tokyo, Japan), and both isolates were β-lactamase-negative ampicillin-susceptible (BLNAS) strain.

To determine the capsular type, the throat swab was cultured 1 month after discharge, because the patient developed mild infection (acute otitis media [AOM]) of the upper respiratory tract again. This Hi isolate from the throat swab indicated the profile No. 7501040, biotype II, and antimicrobial susceptibility result of BLNAS, which were identical to those in the blood-origin isolate. The polymerase chain reaction-based amplification of several genes (*bexA*, *bexB*, and *acs–fcs*) was performed in regions I and II of the capsule locus with the amplification of *pepN* (a DNA-positive control) as previously described [4,5], and this isolate was a nontypeable Hi (NTHi). However, it still remained unclear whether or not this NTHi isolate from the throat was the same genetic lineage to the blood-origin isolate. Her infection was controlled by an oral administration of antimicrobials.

Discussion

Table 1 summarizes the literature review regarding the EPE caused by Hi in children [6]. A 6-month-old boy with Hib pneumonia followed by EPE received thoracic drainage for 8 days, and then, he clinically recovered [6]. On the other hand, our case was treated using an antimicrobial treatment alone without performing the thoracic drainage. Richard WL [7] described that parapneumonic PE and pleural empyema could be divided into classes 1–7 based on the pH, Glu concentration, LDH level, Gram-staining, and effusion culture data. When either the pH of < 7.0, Glu concentration of < 40 mg/dL, positive staining/

Table 1
Review of encapsulated pleural effusion due to Haemophilus influenzae in children.

Year of case report (ref. No.)	Country	Clinical samples for isolation	Capsular type of *H. influenzae* (biotype)	Antimicrobial susceptibility result	Age & gender	Comorbid illness	Involvement of effusion (white cell count on the fluid)	Antimicrobial treatment (dose & duration)	Thoracic drainage (duration)	Outcome
2007 (6)	Japan	Blood, pleural fluid, nasopharyngeal swab	b (NA)	BLNAR	6-month, boy	Healthy	Left (3330/μL)	Meropenem (75 mg/kg/day, 15 days)	Performed (8 days)	Cured
This case	Japan	Blood, aspirated sputum	NA[a] (II)	BLNAS	24-month, girl	Trisomy 21	Left (800/μL)	Ampicillin/sulbactam (180 mg/kg/day, 34 days)	None	Cured

NA, not available; BLNAR, b-lactamase-negative ampicillin-resistant; BLNAS, b-lactamase-negative ampicillin-susceptible.
[a] Capsular type was not determined, because those from the blood and sputum during hospitalization were not stored.

culture, or the presence of empyema was observed, invasive procedures (i.e., thoracic drainage or de-capsulation using the video-assisted thoracoscopic surgery) should be recommended. Whether or not these invasive procedures should be performed in a large number of pediatric patients with EPE remains to be evaluated.

Table 2 shows the yearly prevalence of various Hi biotypes (2011–2017), which were isolated at our hospital. These strains were isolated mainly (97.9%) from the upper and lower respiratory tract samples of all clinical specimens. Biotypes II (48.8%) and III (32.2%) followed by I (9.6%) were prevalent, whereas biotype VIII were not observed in this study. Another Japanese study results [1] were consistent with our findings that the prevalent types III (48.9%) and II (45.6%) followed by I (3.3%) were isolated from the lower respiratory tract and caused acute pulmonary infections. In a previous study conducted in Iran [3], types II (42.1%), I (18.4%), and III (15.8%) were well known, while types VI and VII were not found. A Japanese study concerning the capsular types of Hi isolates from pediatric patients with respiratory tract infections showed that all encapsulated strains (types b and f) displayed biotype I [8]. Of the 30 Hib isolates from the cerebrospinal fluid of Japanese children with meningitis, 22 (73.3%) were characterized as biotype I [9]. Thus, this biochemical phenotypic assay is useful to assess the prevalent type of Hi based on the data combined with the capsular genotypes.

In our case, the NTHi strain with biochemical properties (No. 7501040 and biotype II) and BLNAS result, which were both identical to those in the invasive isolate during the hospitalization, was isolated from the throat, since she developed AOM 1 month after discharge. However, it still remained unclear whether or not this NTHi isolate from the throat was the same genetic lineage to the blood-origin isolate. As most of the systemic Hi infections among children are caused by the Hib, NTHi is also considered as one of the respiratory tract pathogens common in local infections (AOM, pneumonia, acute exacerbation of chronic respiratory disease, and other otorhinolaryngologic infections) [10]. Furthermore, this NTHi strain can cause severe invasive diseases, including meningitis and bacteremia in a healthy child [11] as well as in an immunocompromised host. A review of literature on the Hi epidemiology from the 1990s onward indicates that NTHi induces significant morbidity in pediatric AOM, sinusitis, conjunctivitis, and lower respiratory tract infections in Japan [10]. In fact, 118 (96.7%) NTHi strains were found among 122 tested isolates from pediatric patients with respiratory tract infections [8]. Moriyama et al. [12] demonstrated a biofilm formation of clinical NTHi isolates from AOM children, suggesting that the biofilm production plays an important role in persistent or intractable clinical course of AOM. However, invasive NTHi isolates are genetically and phenotypically diverse, and certain genetic loci are frequently associated with NTHi strains [13,14]. Thus, further investigations should be conducted to clarify the virulent factors shared among the invasive NTHi isolates, because preventing severe invasive diseases due to NTHi strains is difficult.

Conclusions

Pediatric clinicians should be aware of the possibility of Hi-related EPE because of its rapid progression, although it is rare in clinical settings. In addition, they need to consider the possibility of repetitive respiratory infections with Hi in a child with trisomy 21.

Informed consent

The patient's parents gave their informed consent before this article was written.

Conflicts of interest

The authors have disclosed no relevant financial relationships.

Table 2
Prevalence of various *Haemophilus influenzae* biotypes by each year.

Biotype	2011	2012	2013	2014	2015	2016	2017[a]	Total
I	10 (12.2)	13 (12.0)	7 (6.7)	6 (6.2)	7 (5.6)	17 (13.6)	8 (12.5)	68 (9.6)
II	29 (35.4)	56 (51.9)	66 (62.9)	31 (32.0)	47 (37.9)	50 (40.0)	37 (57.8)	316 (44.8)
III	29 (35.4)	32 (29.6)	26 (24.8)	43 (44.3)	46 (37.1)	36 (28.8)	15 (23.4)	227 (32.2)
IV	4 (4.9)	2 (1.9)	5 (4.8)	3 (3.1)	1 (0.8)	6 (4.8)	1 (1.6)	22 (3.1)
V	6 (7.3)	2 (1.9)	1 (1.0)	12 (12.4)	17 (13.7)	14 (11.2)	3 (4.7)	55 (7.8)
VI	2 (2.4)	1 (0.9)		2 (2.1)	2 (1.6)	2 (1.6)		9 (1.3)
VII	2 (2.4)	2 (1.9)			4 (3.2)			8 (1.1)
VIII								
Total	82 (100)	108 (100)	105 (100)	97 (100)	124 (100)	125 (100)	64 (100)	705 (100)

Percentages of the various biotypes are shown in parentheses.
[a] We analyzed the biotype data from January 1st to June 30th in 2017.

Ethical approval

Ethical approval was not required for this study.

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References

[1] Okada F, Ando Y, Tanoue S, Ishii R, Matsushita S, Ono A, et al. Radiological findings in acute *Haemophilus influenzae* pulmonary infection. Br J Radiol 2012;85:121–6.
[2] Doern GV, Chapin KC. Determination of biotypes of *Haemophilus influenzae* and *Haemophilus parainfluenzae:* A comparison of methods and a description of a new biotype (VIII) of *H. influenzae*. Diag Microbiol Infect Dis 1987;7:269–72.
[3] Mojgani N, Rahbar M, Taqizadeh M, Ashtiani MP, Mohammadzadeh M. Biotyping, capsular typing, and antibiotic resistance pattern of *Haemophilus influenzae* strains in Iran. Jpn J Infect Dis 2011;64:66–8.
[4] Falla TJ, Crook DW, Brophy LN, Maskell D, Kroll JS, Moxon ER. PCR for capsular typing of *Haemophilus influenzae*. J Clin Microbiol 1994;32:2382–6.
[5] Davis GS, Sandstedt SA, Patel M, Marrs CF, Gilsdorf JR. Use of *bexB* to detect the capsule locus in *Haemophilus influenzae*. J Clin Microbiol 2011;49:2594–601.
[6] Ohta E, Kouda M, Tanaka M, Yamaguchi S, Hirose S. An infant with *Haemophilus influenzae* b pneumonia complicated with encapsulated pleural effusion. Shouni Kansen Men-eki 2007;19:363–8. (in Japanese).
[7] Richard WL. Pleural diseases. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 151–81.
[8] Luong DC, Ishiwada N, Takeda N, Kohno Y. Serotypes of Haemophilus influenzae strains isolated from pediatric patients with respiratory tract infections. Tohoku J Exp Med 2004;202:245–54.
[9] Mitsuda T, Kuroki H, Ishikawa N, Imagawa T, Ito S, Miyamae T, et al. Molecular epidemiological study of *Haemophilus influenzae* serotype b strains obtained from children with meningitis in Japan. J Clin Microbiol 1999;37:2548–52.
[10] Sunakawa K, Takeuchi Y, Iwata S. Nontypeable *Haemophilus influenzae* (NTHi) epidemiology. Kansenshogaku Zasshi 2011;85:227–37. (in Japanese).
[11] Ito T, Shibata H, Nakazawa M, Myokai M, Ikegaya K, Tsuchiya K, et al. Meningitis and septicemia caused by nontypeable *Haemophilus influenzae* in a previously healthy 2-year-old girl. J Infect Chemother 2011;17:559–62.
[12] Moriyama S, Hotomi M, Shimada J, Billal DS, Fujihara K, Yamanaka N. Formation of biofilm by *Haemophilus influenzae* isolated from pediatric intractable otitis media. Auris Nasus Larynx 2009;36:525–31.
[13] Erwin AL, Nelson KL, Mhlanga-Mutangadura T, Bonthuis PJ, Geelhood JL, Morlin G, et al. Characterization of genetic and phenotypic diversity of invasive nontypeable *Haemophilus influenzae*. Infect Immun 2005;73:5853–63.
[14] Erwin AL, Sandstedt SA, Bonthuis PJ, Geelhood JL, Nelson KL, Unrath WC, et al. Analysis of genetic relatedness of *Haemophilus influenzae* isolates by multilocus sequence typing. J Bacteriol 2008;190:1473–83.