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Case Study

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Invasive *Haemophilus influenzae* Infection in Immunocompromised Child

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A B S T R A C T

The gram-negative, capnophilic coccobacillus *Haemophilus influenzae* is a member of the Pasteurellaceae family. It can result in otitis media as well as serious invasive illnesses. Based on capsular antigens, *H. influenzae* strains can be categorized as typeable or non-typeable. We present a case of *H.influenzae* sepsis in 2 years old child with Acute Lymphoblastic Leukemia who was completely vaccinated for age. Patient presented with cough, cold and breathlessness. On respiratory system examination, bilateral diffuse crepitations was heard, subcostal and suprasternal retractions were seen. Blood culture bottle grew *Hemophilus influenzae*. The patient clinically improved with cefoperazone - sulbactam and repeat cultures sent were sterile. Non type-b strain or wanning immunity of *H.influenzae* type b(Hib) conjugate vaccine in immunocompromised state could be attributed to *H.influenzae* sepsis in this patient. Appropriate antimicrobial therapy is essential to reduce mortality and morbiditity. To prevent invasive disease, non-type b strains might need to be included in the Hib conjugate vaccination. Additionally, giving leukemia patients a booster dose of the Hib conjugate vaccination helps to prevent the invasive disease.

Introduction

Haemophilus influenzae is an oxidase-positive, fastidious bacterium that primarily causes respiratory tract infections in both children and adults (Mandell, *et al*., 2021). Strains of *H. influenzae* are categorized as typeable (serotypes a-f) or non-typeable, based on polysaccharide capsule. Historically, serotype b (Hib) was responsible for approximately 95% of severe invasive infections, particularly in children. However, following the widespread introduction of the Hib conjugate vaccine, the incidence of Hib-associated diseases have significantly declined in many countries. In recent years, there has been an increase in invasive disease caused by non-Hib serotypes and non-typeable strains (Li, *et al*., 2021). According to the European Centre for Disease Prevention and Control, in 2018, 78% of the 3,982 confirmed cases of invasive *H. influenzae* infection were attributed to non-typeable strains. The most common clinical presentation was septicemia (38%), followed by pneumonia (26%), meningitis, or a combination of septicemia and meningitis (8%) (MacNeil, *et al*., 2011).

Here, we report a case of *H. influenzae* sepsis in a 2-year-old child with acute lymphoblastic leukemia (ALL), who was fully immunized with three doses of the Hib conjugate vaccine.

Case Presentation

A 2-year-old child with Acute Lymphoblastic Leukemia (ALL), currently undergoing chemotherapy, presented with a history of cough, cold, and breathlessness. On examination, the patient appeared pale, with a pulse rate of 144 beats per minute and a respiratory rate of 42 breaths per minute. Oxygen saturation was 88% on room air. Respiratory system examination revealed bilateral diffuse crepitations, along with subcostal and suprasternal retractions. Other systemic examinations were unremarkable.

Laboratory investigations showed severe anemia (hemoglobin: 4.9 g/dL), leukopenia (WBC count: 0.34 × 10^3/µL), neutropenia (absolute neutrophil count: 0.19 × 10^3/µL), and thrombocytopenia (platelet count: 50 × 10^3/µL) (Table 1). Respiratory PCR panel and GeneXpert testing for tuberculosis were negative. Sputum culture showed no bacterial growth.

The patient was diagnosed with congestive cardiac failure secondary to severe anemia and lower respiratory tract infection. He was started on intravenous amoxicillin-clavulanic acid and cardiac medications. Packed red blood cell was transfused to correct severe anemia. Subsequently, the patient developed fever along with an increased heart rate and respiratory rate. Blood culture was sent and flagged positive after 20.4 hours of incubation (Table 2). Gram stain revealed gram-negative coccobacilli (Figure 1). MacConkey agar showed no growth, while blood agar demonstrated minute, non-hemolytic colonies exhibiting satellitism (Figure 2). The organism was identified as Haemophilus influenzae by MALDI-TOF MS, with a confidence interval of 99.9% (Figure 3).

Antimicrobial susceptibility testing revealed resistance to ampicillin and tetracycline, and susceptibility to ceftriaxone, ampicillin-sulbactam, cotrimoxazole, levofloxacin, and azithromycin. Procalcitonin levels were markedly elevated (15.95 ng/mL). In view of persistent fever and signs of septic shock, amoxicillin-clavulanic acid was discontinued, and the patient was started on cefoperazone-sulbactam and vancomycin. Following the blood culture report, cefoperazone-sulbactam was continued, and redundant antibiotics were discontinued. A repeat blood culture performed after 10 days of antibiotic therapy was sterile. The patient showed clinical improvement and was subsequently discharged.

Results and Discussion

Haemophilus influenzae is a facultatively anaerobic, pleomorphic, and capnophilic gram-negative coccobacillus belonging to the Pasteurellaceae family (4). It can cause a wide spectrum of illness, including otitis media, sinusitis, and invasive diseases such as meningitis and bacterial pneumonia. Despite appropriate treatment, the case fatality rate can reach up to 5%. Non-typeable *H. influenzae* (NTHi) strains colonize the upper and lower respiratory tracts, conjunctiva, and genital tract. Humans are the only known reservoir (Slack, *et al*., 2020).

H. influenzae type b (Hib), known for its polyribosyl ribitol phosphate (PRP) capsule, is responsible for approximately 95% of invasive diseases in children and over 50% in adults (Gozum, *et al*., 2020). Hib was estimated to cause around 8.13 million cases of severe illness and 371,000 deaths annually among children under five years of age.

Between 2000 and 2015, approximately 340,000 cases of Hib-related meningitis, pneumonia, and non-pneumonic bacteremia were reported in children under five, resulting in 29,800 deaths globally. During this period, Hib-related mortality declined by 90%, with India accounting for the highest number of deaths (15,600) (Abdi, *et al*., 2023).

Due to its potential to cause severe invasive infections, *H. influenzae* is listed among the WHO's top 12 priority pathogens. Non-typeable strains have now emerged as the leading cause of invasive *H. influenzae* disease. A study by Abd El Nour M *et al.,* reported that bacteremia is the most common presentation of *H. influenzae* infection in immunodeficient children, which is consistent with our case (Abd, *et al*., 2009). Following the introduction of the Hib vaccine, NTHi strain has replaced Hib with a gradual rise in invasive disease. It is well documented that vulnerable populations-including preterm infants, the elderly, immunocompromised individuals, cancer patients, and those with chronic respiratory or cardiovascular diseases-are more susceptible to invasive NTHi infections (Ladhani, *et al*., 2011). Among encapsulated *H. influenzae* strains, serotype f is currently the most common cause of invasive non-type b disease in children.

Figure.1 Gram staining of positively flagged blood culture showing gram negative coccobacilli

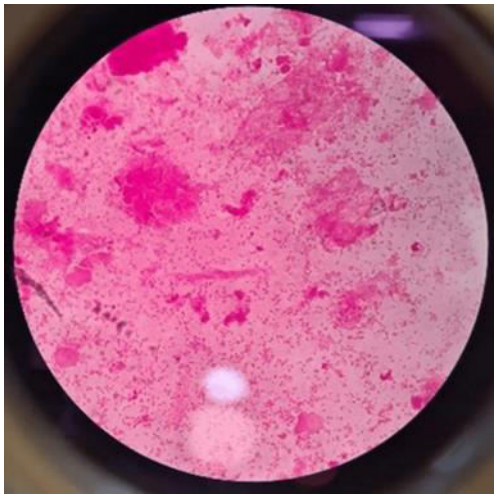

Figure.2 Blood agar showing satellitism

Table.1 Complete Blood Count

CBC	04-02-2025	05-02-2025	07-02-2025	10-02-2025	11-02-2025	12-02-2025	16-02-2025	Reference value
HB(g/dl)	4.9	9.6	8.9	7.1	8.1	7	11	13.1-17.2g/dL
RBC Count (x10^6/uL)	1.65	3.26	2.96	2.43	2.78	2.37	3.78	4.2-5.6 x10^6/uL
HCT (%)	15.4	28.6	27	22.2	24.6	20.9	34.4	38 - 50 %
WBC Count(x10^3/uL)	0.34	0.13	0.13	0.1	0.21	0.57	21.24	4.0 - 11.0x10^3/uL
Neutrophls (%)	55.9	53.8	46.1	45.4	38.2	49.1	79.6	40 - 75 %
Lymphocytes (%)	20.6	30.8	38.5	27.3	19	12.3	9.7	20 - 45 %
Eosinophils (%)	2.9	7.7	7.7	18.2	9.5	7	0.3	1 - 6%
Monocytes (%)	20.6	7.7	7.7	9.1	33.3	31.6	10.3	2 - 10 %

Table.2 Blood Culture Profile

Blood Culture	Time to Positivity	Organism Grown
04-02-2025	20.4 HRS	*Haemophilus influenzae*
05-02-2025	24.3 HRS	*Haemophilus influenzae*
11-02-2025	26.7 HRS	*Haemophilus influenzae*
13-03-2025	Not Flagged Positive	Sterile

Children are now more likely to develop disease from non-b strains because of increased Hib vaccination. There are also notable differences in clinical presentation. Type b strains are more frequently associated with meningitis and epiglottitis, whereas non-type b strains are more commonly linked to bacteremia and pneumonia (Heath, *et al*., 2001).

According to a study by McNair, *et al.,* 2010 children undergoing cancer chemotherapy are at increased risk of vaccine failure due to waning immunity against Hib and other pathogens. In this study patient, the infection would likely be caused by a non-type b strain not covered by the Hib vaccination or Hib strain itself with a possible explanation of waning vaccine-induced immunity in the context of immunosuppression.

However, the specific serotyping could not be performed, which is a limitation of our study. Among 91 children with leukemia, only 41% had protective Hib antibody titers after completing chemotherapy for at least one year. However, post-treatment immunization with the Hib conjugate vaccine (administered ≥6 months after chemotherapy) increased protective titers to 81-94% (10). This highlights that Hib immunization following chemotherapy may help prevent *H. influenzae* disease in immunocompromised patients.

In conclusion, with the advent of *Hemophilus influenza* type b conjugate vaccine, incidence of *Hemophilus influenza* type b disease has decreased in immunocompetent individuals. But, in an immunocompromised individual, *Hemophilus influenza* is still causing invasive disease. This could be due to decreased immunity of individuals or due to strain replacement. So Hib immunization after chemotherapy may prevent the disease. In order to lower mortality and morbidity, appropriate antibiotic therapy is necessary. Serotyping and epidemiologic surveillance are essential for tracking the evolving epidemiology of invasive disease caused by *H. influenzae*. To prevent invasive disease, vaccines for non-type b strains may need to be developed. A booster dose of the Hib conjugate vaccine helps patients with leukemia prevent the invasive disease.

Author Contributions

A. Benedict Vinothini: Conceived the original idea and designed the model the computational framework and wrote the manuscript; K. Sultan Basha: Formal analysis, writing review and editing; K.P.V. Hyma: Validation, methodology, writing—reviewing; , Aravindh Selladurai: Formal analysis, writing review and editing; Jaikumar Govindaswamy Ramamoorthy: Validation, methodology, writing—reviewing; Apurba S. Sastry: Formal analysis, writing review and editing.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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