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A typical Presentation of Haemophilus *influenzae* Septic Arthritis: A Case Report

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INTRODUCTION

Septic arthritis (SA) caused by *Haemophilus influenzae* (*H. influenzae*)is amonga few known orthopedic emergencies that can result in significant joint and cartilage destruction. *H.influenza* is a small, non-motile, Gram-negative, pleomorphic opportunistic bacterium, a strict human pathogen that commonly inhabits the upper respiratory tract and istransmitted via airborne droplets or direct contact with respiratory secretions. It can exist both as encapsulated and non-encapsulated (non-typeable) strains, latter being associated with most of the non-invasive infections. Based on the unique polysaccharide capsule of encapsulated strains, they are divided into 6distinct serotypes, “a” through “f.” H. influenzae type b (Hib) is most known for causing severe invasive diseases, including acute epiglottitis, meningitis, pneumonia, septic arthritis, and bacteremia, particularly in non-immunized pediatric populations [1]. Infections due to other encapsulated serotypes (e.g., types a, c, d, e, and f) and non-typeable strains have been increasingly reported, particularly in immunocompromised individuals and older adults. Septic arthritis can be caused secondary to bacterial, viral or fungal infections, *Staphylococcus aureus*implicated as the most common cause among bacterial etiological agent [2]. Less commonly, it can be caused by bacteria such as *Kingellakingae*, *Group A Streptococcus, H. influenzae non-type b (NTHi), Neisseria gonorrhoeae*, and *Mycobacterium tuberculosis* [3]. While most cases of septic arthritis occur in previously healthy individuals, immunodeficiency significantly increases the risk of infection, especially with less common organisms. Patients with

conditions such as Combined Variable Immunodeficiency (CVID) or other agammaglobulinemia are particularly vulnerable due to their impaired ability to produce antibodies [4]. Risk factors for *H.influenzae* infection includeextremes of age, underlying immunocompromising conditions (ie, complement deficiency, hypogammaglobulinemia, sickle cell anemia, functional asplenia, HIV, malignancy), chronic pulmonary disease, smoking, HIV, alcoholism during pregnancy [5].

The most common pathogens isolated in cases of SA include *Staphylococcus aureus* and *Streptococcus pneumoniae*. Other less common pathogens include Gram-negative bacilli, mycobacteria, Gram-negative cocci, Gram-positive bacilli, and anaerobes.*Haemophilus influenzae* has been identified as a rare cause of SA, which had previously decreased in prevalence secondary to *H influenzae* serotype b (Hib) conjugate vaccine development in 1986 [6,7]. *H influenzae* is an encapsulated, pleomorphic Gram-negative rod with multiple capsular serotypes and commonly colonizes the human respiratory tract.While Hib is considered the most virulent serotype, other serotypes and non-typable *H influenzae* have been implicated in the development of invasive disease. Some invasive infections include meningitis, bacteremia, epiglottitis, SA, cellulitis, purulent pericarditis, endocarditis, and osteomyelitis [8].
Therefore, the early identification and treatment of *H influenzae* SA is crucial in preventing significant morbidity and mortality. Here we discuss a case of septic arthritis caused by *Haemophilus influenzae* having unusual presentations, highlightingthe importance of its accurate diagnosis for the efficient management of such rare cases.
CASE REPORT - A 17-year-old male child, resident ofHardoi district, Lucknow, presented in Immunology OPD of SGPGIMS, Lucknow,with complaints of pain in rt.elbow, fever, cough and epistaxis.The patient was apparently healthya week prior when he started experiencing low-grade fever, which wascontinuous in nature, was relieved with antipyretics,had no diurnal variation,no history of chills and rigors,no history of rashes and no aggravating or relieving factors.He suddenly experienced pain in his Rt. elbow joint a week earlier,that was continuous in nature and got aggravated on movement. His pain restricted him from lifting any item, howeverit did not radiate to other adjoining structures. He gave no history of any trauma or joint surgery.

Case: A typical Presentation of Haemophilus *influenzae* Septic Arthritis

Patient was a follow up case of a rare Syndromic Disease under evaluation at KGMU, Lucknow since childhood. He had history of birth asphyxia and cerebral palsy due to which, hismilestones were delayed.The patient was fully immunized as per the national immunization schedule. However, in the past 17 years, he had experienced multiple episodes of recurrent infections like: meningitis -3 episodes of Tuberculous meningitis at the age of 1.5 years, 2.5years and 9 years respectively, 1 episode of Pneumonia at the age of 10 and repetitive episodes of diarrhea.He had also suffered from multiple episodes of bilateral knee arthritis since age of 10, 1st episode of which was treated as septic arthritis, whereas, 2nd and 3rd episode was identified as a case of Juvenile idiopathic arthritis (JIA). There was history of two fatalityin his family (2º male siblings) at younger age due to an unknown syndrome.On his follow-up visit to KGMU with persistent bilateral knee pain, he was advised for whole exome sequencing (Chennai)which revealed that he was suffering from a primary immunodeficiency disorder: X-linked Agammaglobulinemiacaused by Bruton's tyrosine kinase deficiency. (O'Toole D, Groth D, Wright H, et al. X-Linked Agammaglobulinemia: Infection Frequency and Infection-Related Mortality in the USIDNET Registry. J Clin Immunol. 2022;42(4):827-836. doi:10.1007/s10875-022-01237-1). This patient was then referred to SGPGI Genetics department for further evaluation and managementthat in-turn suggested him to consult immunology department in the view of suspected rt. elbow arthritis.

Comprehensive laboratory tests were done which included - TLC (12.8),DLC (80/20/6),Platelet(10,000 cells count),ESR(30), all of which were deranged, however, rest testedwithin normal limits.

Microbiological evaluation of the patient's synovial fluid from the affected joint,blood, and sputum were requested and the respective samples were sent to microbiology laboratory on the day of admission. Bactec Blood culture,reported sterile after five days of aerobic and anaerobic incubation. Sputum was assessed for the presence of any bacterial, mycobacterial or fungal infectious agents, all of which were reported as negative after processing according to the

standard laboratory protocol.

Patient's synovial fluid was inoculated and sent in Bactec vial. The same was incubated which flagged positive on third day . It was then subculture on blood agar which grew tiny transparent, circular, dome-shaped colonies after 48 hours of incubation.Grams stain from the colonies showed pleomorphic Gram-variable coccobacilli. It was further sub cultured twice on blood agar and chocolate agar to recover the organism as the cultures were either getting contaminated or the organism was very scanty for further processing. With the differential diagnosis of *Haemophilus influenza* in mind,it was tested for Satellism phenomenonby streaking *S.aureus* across the culture plate, thatcame as positive.Colonies were also subjected to MALDI TOF MS for further evaluation, where it was identified as *Haemophilus influenza.* The isolates were then processed for antibiotic susceptibility testing on blood agar by disc diffusion method where it showed susceptibility towards Ampicillin, Ampicillin-sulbactam, Ceftriaxone, Ceftazidime, Ciprofloxacin, Ertapenem, Imipene and resistance towards Trimethoprim-sulfamethoxazole.

Definitive diagnosis was made as *Haemophilusinfluenzae*associated acute septic arthritis linked with X linked Agammaglobulinemia- Bruton's tyrosine kinase deficiency.

Empirically, the patient was receiving Inj. Amikacin 500mg iv OD, Vancomycin 500 mg iv BD, Azithromycin 500mg OD along with management of other constitutional illnesses.On receiving report from microbiology department, the treatment was revised and Ceftriaxone was started 1g i.v BD together with Vancomycin and Azithromycin. Within 3 days of changing the antibiotics, patient's symptoms started to improve. His fever subsided and Rt. elbow pain improved with return of joint movement.The patient was discharged for weekly follow up of IVIg and then monthly dosing.

DISCUSSION

This case report demonstrates a rare presentation of *H. influenzae* septic arthritis in an immunocompromised child. *H. influenzae*is a pathogenic upper and sometimes lower respiratory tract organism. However, it is not uncommon for it to invadethe bloodstream. Bacteremia can in turn lead to seeding of the agent in the joint leading to septic arthritis which can progress to a polyarthritic infection. Therefore, early recognition and aggressive management combining surgical and medical modalities are often needed for optimal recovery [5].

Immunocompromised patients are known to be more susceptible to certain infections, with patients with X-linked agamma globulinemia and as plenic individuals more predisposed to encapsulated bacteria such as H. influenzae and Streptococcus pneumonia [1,9].

Septic arthritis in the immunocompromised host is a challenging diagnosis. The classic presentation of septic arthritis of a warm, tender, swollen, erythematous joint and inabilityto bear weight may not be present on initial examination. Thus, clinical suspicion must remain high during evaluation in any patient with joint pain with a history of immunodeficiency. In the case of immunocompromise, septic arthritis may be associated with typical and opportunistic microorganisms [6,7]. Therefore, for investigation, a blood culture and synovial fluid should be sent for microbiological evaluation. Standardtreatment involves surgical debridement and culture of fluid and tissues with empiric antibiotic treatment based on the most likely causative organism [8]

Since H. influenzae typically resides in the nasopharynx, musculoskeletal infections caused by this pathogen typically arise from hematogenous spread from this region. Therefore, our patient likely developed septic arthritis secondary to bacteremia associated with a recent upper respiratory infection [9]. Immunocompromised patients are known to be more susceptible to certain infections, with patients with X-linked agamma globulinemia and asplenic individuals more predisposed to encapsulated bacteria such as H. influenzae and Streptococcus pneumonia [10]

With the widespread implementation of Hib conjugate vaccines, there has been a substantial reduction in invasive Haemophilus influenzae type b disease globally. However, invasive disease due to non-b serotypes and NTHi remains a concern, particularly in the immunocompromised, elderly, and unvaccinated populations. Reports indicate that serotype a (Hia) has become a notable cause of invasive disease in certain regions, particularly among Indigenous populations in North America. Surveillance data have also highlighted an increase in invasive infections caused by serotype f (Hif) and non-typeable strains [11,12].

There was another study which was in accordance to the present finding where the case demonstrates a rare presentation of *H influenzae* SA in an immunocompromised adult [8].

Prior studies have attempted to identify an appropriate cutoff for SF WBC count in the identification of SA. Margaretten et al published a systematic review analyzing the likelihood ratios (LR) for multiple different SF cutoff levels. They found a LR of 0.32 in adults with SF WBC count less than 25,000 vs SF WBC count greater than or equal to 25,000, which had a LR of 2.9 [13]. A newer review by Long et al found that nearly half of all patients with SA had a SF WBC count under 28,000 cells/mm^3 [14]. While the authors suggest using clinical judgment over laboratory cutoffs, this data illustrates how difficult the diagnosis of SA can be.

Other studies have shown how immunodeficiency further increases diagnostic difficulty due to changes in SF findings [15,16]. Notably, immunosuppression increases risk of infection while lowering SF WBC count, which complicates diagnosis. Zalavras et al identified consistently lower SF WBC count in HIV-positive patients with SA when compared to immunocompetent patients with average counts of 40,500 and 69,000 cells/mm^3, respectively.

Our patient was immunocompromised secondary to agammaglobulinemia and presented with polyarticular joint involvement.His immunoglobulins Ig A, IgG and IgM were decreased and B cell count was also very low, 0.1%

Despite the overall success of vaccination programs, H. influenzae remains capable of causing invasive disease, especially in immunocompromised hosts. Clinicians must maintain a high index of suspicion for H. influenzae infections, particularly in patients with underlying immunodeficiencies or chronic diseases, to ensure timely diagnosis and treatment. The continued evolution of H. influenzae epidemiology underscores the importance of ongoing surveillance, research into novel vaccines targeting non-typeable strains, and improved management strategies for high-risk populations.

Physicians must also consider immunocompromising comorbidities or potential immunocompromised states when analyzing synovial fluid results. Timely and accurate diagnosis of SA can decrease complications and improve patient outcomes. Therefore, clinical presentations that are suspicious for SA must prompt careful diagnostic consideration, despite inconsistent laboratory findings.

Septic arthritis in a newly diagnosed human immunodeficiency virus (HIV)-positive adult can progress to a polyarthritic infection and further invasive disease. Therefore, early recognition and aggressive treatment combining surgical and medical modalities is often needed for optimal recovery.

CONCLUSION

This case report highlights the importance of NTBHI serotypes, especially in immunocompromised patients. More studies are needed to determine these types' epidemiology and virulence and clinical relevance. For children diagnosed with an invasive disease caused by NTBHI, a workup for immunodeficiency could be warranted. There is a need for the development of a vaccine for non type b H. influenza, especially for immunodeficient patients.

DECLARATIONS:

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