CASE REPORT

Beyond the Cough: A Rare Case of Severe Pertussis With Hyperleukocytosis in a 30-day-old Malay Infant

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ABSTRACT

Pertussis infection can lead to hyperleukocytosis, characterized by a significant increase in white blood cell count. Hyperleukocytosis in pertussis is associated with disease severity and poor outcomes, particularly in young infants. Pertussis leukocytosis is caused by pertussis toxin released by *Bordetella pertussis* during infection, but the exact mechanisms are still unclear. We present a case of severe pertussis with hyperleukocytosis in a 30-day-old Malay infant, ultimately resulting in fatality due to severe complications. This case illustrates the severity and variability of pertussis in infants, particularly with the rare presentation of hyperleukocytosis. It demonstrates the link between leukocytosis treatment and outcomes, reinforcing the need for early detection and treatment, and highlights the critical role of vaccinations in preventing and mitigating the severity of pertussis infections.
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INTRODUCTION

Pertussis, commonly known as whooping cough, is a highly contagious respiratory illness caused by Bordetella pertussis and can be effectively prevented through vaccination. Despite vaccination efforts, there has been a global resurgence of pertussis infections in recent years, making it the most prevalent vaccine-preventable disease. According to the 2016 report from the World Health Organization, there were 139,535 reported cases of pertussis, with a mortality rate of 4% (1).

In its classic form, Pertussis is typically present in three phases: catarrhal, paroxysmal, and convalescent. The first week, known as the catarrhal phase, is characterized by nonspecific symptoms similar to a viral infection of the airways, including sneezing, runny nose, teary eyes, low fever, and a mild dry cough. In the second week, the paroxysmal phase begins, with characteristic episodes of intense, uncontrollable coughing and spasms that can last for two to six weeks. During this stage, there is an increase in lymphocyte count to over 20,000 leukocytes/mm3, although this may not be present in individuals who are partially immune or when a secondary bacterial infection occurs. The third convalescent phase is characterized by a gradual decrease in the number and severity of coughing episodes, typically lasting up to four weeks (2).

The clinical presentation in infants and children may show a spectrum of symptoms, ranging from being asymptomatic or having mild upper respiratory tract disease to severe and persistent coughing lasting for several weeks or even months. The presence of bacterial and viral co-infections, particularly with Adenovirus, Parainfluenza, and Respiratory Syncytial Virus can further complicate the clinical and laboratory findings, leading to delays in diagnosis and treatment, prolonged hospitalization, and an increased risk of complications. These co-infections are often facilitated

by the immunosuppressive effects of the pertussis toxin, which creates a favourable environment for secondary pathogens (2).

One such unusual presentation is hyperleukocytosis, defined as an elevated leukocyte count exceeding 100 x 10^9/L, compared to the normal range of 4 to 10 x 10^9/L in the general population. Hyperleukocytosis in pertussis is less commonly reported but can indicate a more severe disease course. The leukocyte differential in hyperleukocytosis often shows a predominance of immature white blood cells, such as lymphocytes and neutrophils, reflecting the body's acute response to the infection. In this case report, we describe a 30-day-old infant diagnosed with pertussis who exhibited an unusually critical elevation in leukocyte count, highlighting the need to consider atypical presentations in infants to guide timely and effective management.

CASE REPORT

A 30-day-old baby girl was admitted to our hospital with a history of cough, fever, and rapid breathing. Her symptoms began five days prior to admission, starting with a persistent cough. On the second day of illness, she developed a fever, reaching 38.0°C, and continued to experience worsening symptoms, including increased respiratory distress. The cough was initially described as mild but progressively became more severe, characterized by bouts of intense, paroxysmal coughing with a whooping sound. This was followed by difficulty breathing and noticeable respiratory distress. By the time of admission, the patient exhibited signs of acute respiratory failure. Notably, she experienced intermittent apnea episodes, marked by brief periods of cessation of breathing, which contributed to her overall clinical deterioration.

The patient had a sick contact with her mother, who had been suffering from a persistent cough for over a month. The infant had not yet received the pertussis vaccine due to her young age, which is below the recommended vaccination schedule. Her personal and family history was otherwise unremarkable.

On physical examination, she was febrile with a temperature of 38.0°C and exhibited tachycardia with a heart rate of 160 beats per minute. Her respiratory rate was 60 breaths per minute, and her oxygen saturation level on room air was 88%, which improved to 98% with supplemental oxygen through a nasal cannula. Lung auscultation revealed bilateral wheezing and crackles.

Chest X-ray showed diffuse bilateral infiltrates consistent with pneumonia, which was suggestive of superimposed bacterial infection. This finding was corroborated by elevated inflammatory markers, including a C-reactive protein (CRP) level of 50 mg/L (normal range <10 mg/L). These findings indicated an acute inflammatory response, which could be attributed to secondary bacterial pneumonia.

Laboratory findings included a complete blood count showing hyperleukocytosis with a white blood cell count of 101.3 x 10^9/L. The differential count was 41.9% neutrophils, 44.0% lymphocytes, and 12.6% monocytes. Hemoglobin was 9.5 g/dL, and the platelet count was 465 x 10^9/L (Table I). The peripheral blood smear examination revealed neutrophilia with abundant mature lymphocytes with sparse cytoplasm, condensed chromatin, and nuclei displaying clefts (Figure 1). A multiplex Polymerase Chain Reaction (PCR) test on nasopharyngeal aspiration confirmed the presence of Bordetella pertussis (Table II).

Table I: Complete blood count

Parameters	Result	Normal range (Unit)
Hemoglobin (Hb)	9.5	12.0 -15.0 g/dL
Mean Corpuscular Volume (MCV)	93.8	83 – 101 fL
Mean Corpuscular Haemoglobin (MCH)	30.9	27 -32 pg
Platelet	465	150 - 410 x10^9/L
Total White Blood Cell (WBC)	101.3	5 -19 x10^9/L
Neutrophils	41.9	40.0-80.0%
Lymphocytes	44.0	20.0-40.0%
Monocytes	12.4	2.0-10.0%
Eosinophils	1.6	1.0-6.0%

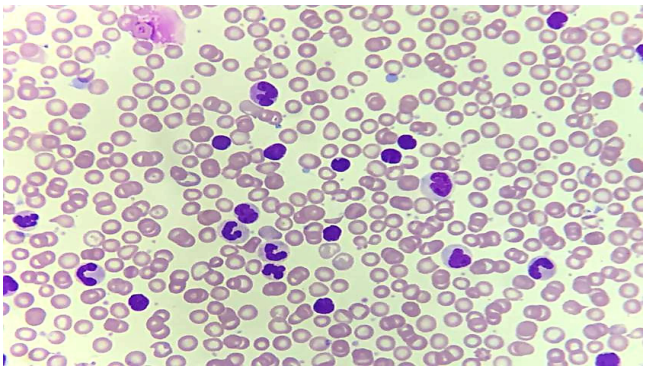

Figure 1: Peripheral blood smear showed an abundance of mature lymphocytes characterized by sparse cytoplasm, condensed chromatin pattern, and nuclei displaying clefts (red arrow). (Magnification x40, Wright stain)

Table II: PCR test for respiratory pathogens

Parameters	Result
Adenovirus	Not detected
Bocavirus	Not detected
Coronavirus	Not detected
Human metapneumovirus	Not detected
Influenza A	Not detected
Influenza B	Not detected
Parainfluenza virus	Not detected
Respiratory syncytial virus	Not detected
Bordetella pertussis	Detected

The patient was diagnosed with severe pertussis

complicated by acute respiratory failure. She was treated with intravenous azithromycin and intravenous ceftriaxone. Despite aggressive treatment, the patient's condition deteriorated rapidly. On the third day of admission, she developed severe respiratory failure requiring mechanical ventilation support. Her oxygen saturation fluctuated, and despite adjustments in ventilator settings, she continued to exhibit severe respiratory distress.

Inotropic support was initiated due to cardiovascular instability, but her general condition continued to decline. By the fourth day of illness, she showed signs of multi-organ failure. Despite ongoing intensive care, including respiratory and cardiovascular support, the patient's condition did not improve. She succumbed to death on the fifth day of hospitalization due to complications from severe pertussis and superimposed bacterial pneumonia.

DISCUSSION

Pertussis, caused by the bacterium Bordetella pertussis, is a severe respiratory infection. In 2008, it accounted for approximately 16 million cases and 195,000 deaths globally. This infectious disease is endemic in both developing and developed nations, with sporadic outbreaks occurring regularly across the world (3). The responsible agents for pertussis are Bordetella pertussis and Bordetella parapertussis, belonging to the family Alcaligenaceae and encompassing ten genetically distinct species (3). Pertussis is transmitted rapidly through airborne droplets from person to person. Both commensal bacteria and pathogens, including Bordetella pertussis, can colonize the human nasopharynx. When infected individuals cough or sneeze, they aerosolize droplets containing pertussis, which can further spread the disease (3,4).

The laboratory findings of leukocytosis with a predominance of lymphocytes are well-documented in severe pertussis, with cases reported from the 1900s to the present. There is a strong correlation between leucocytosis and severe pertussis. Moreover, leukocytosis is associated with the requirement for mechanical ventilation, the onset of pulmonary hypertension, and eventual mortality in cases of severe pertussis. Although it is a common finding in nearly all pertussis cases, hyperleukocytosis—defined as a white blood cell count exceeding 100 x 10^9/L—is a rare complication associated with pertussis, triggered by the pertussis toxin. In this case, our patient exhibited hyperleukocytosis with a white blood cell count of 101.3 x 10^9/L, predominantly lymphocytes (44.0%) which is relatively rare and is often associated with severe disease and poor outcomes. The predominance of lymphocytes in our patient reflects the typical response in pertussis; however, it is important to note that neutrophilia or an abnormal neutrophil count could have indicated a superimposed bacterial infection or other complications.

In cases of pertussis with hyperleukocytosis, the differential diagnosis must consider potential superimposed infections such as bacterial pneumonia or sepsis. The challenge lies in distinguishing these secondary infections, as symptoms of pertussis can overlap with those of pneumonia. Our patient's chest X-ray revealed diffuse bilateral infiltrates, consistent with pneumonia, and elevated inflammatory markers, including CRP, supported this diagnosis. These findings highlight the difficulty in rapidly diagnosing superimposed infections and underscore the need for careful monitoring and comprehensive diagnostic evaluation in critically ill patients with pertussis. Ventilatory support in severe pertussis patients is critical for managing severe respiratory failure. The decision to use mechanical ventilation should be based on the clinical severity of respiratory compromise.

The gold standard for diagnosing pertussis is identifying bacterial growth on culture, boasting a specificity of 100%. However, the sensitivity of this method varies depending on several factors such as the disease stage, the onset of antimicrobial treatment, sampling technique, quality of the material used for sampling, conditions during sample transport to the laboratory, and the laboratory's proficiency. Sensitivity can span from 12% to 60%, reflecting the variability introduced by these diverse influencing factors (5). Another method, as recommended by the World Health Organization (WHO), is using PCR, which has reported sensitivity and specificity ranging from 70-99% and 86-100%, respectively (5). In our patient, bacterial growth was not detected on pertussis culture media. However, the PCR respiratory tract panel showed the presence of Bordetella pertussis.

Macrolides, including erythromycin, clarithromycin, and azithromycin, are the preferred treatment for pertussis in individuals aged 1 month and older. Trimethoprim-sulfamethoxazole is considered an alternative for those aged 2 months and older. Critically ill infants with leukocytosis can be treated using leukapheresis that stands out as an effective intervention for lowering the overall leukocyte mass. According to the Advisory Committee on Immunization Practices (ACIP), all children, including those with immunocompromised, should receive a five-dose DTaP schedule. Infants should be given three doses of DTaP at 2, 4, and 6 months. The fourth dose is recommended for toddlers aged between 15 and 18 months, while the fifth dose is advised for children aged 4 to 6 years. It is important to follow the recommended schedule to ensure that children are protected against diphtheria, tetanus, and pertussis. In this case, the patient has not yet received the pertussis vaccine as the age of the patient falls below the recommended vaccination schedule. Pertussis vaccination typically commences at two months of

age as part of the routine immunization schedule. The delayed immunization may have contributed to the severity of the infection, emphasizing the critical importance of timely vaccination in preventing and mitigating the impact of pertussis in infants.

Overall, this case underscores the importance of timely diagnosis and management of pertussis and its complications. It also highlights the critical need for vaccination and early intervention to prevent severe outcomes in at-risk populations, especially in unvaccinated infants.

CONCLUSION

In conclusion, this case report underscores the clinical variability and potential severity of pertussis in infants. The atypical presentation of hyperleukocytosis with a lymphocytic predominance highlights the diverse manifestations of this infectious disease. The association between leukocytosis and adverse outcomes, emphasizes the importance of early recognition and intervention. This case serves as a reminder of the ongoing importance of vaccination efforts, not only in preventing the primary infection but also in reducing the severity of the disease in breakthrough cases.

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SA, NR and LPC participated in the sequence alignment and drafted the manuscript. AD, KAJ, MHN, NRR and RH participated in the sequence alignment. All authors read and approved the final manuscript.

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