Fatal malignant pertussis with hyperleukocytosis in a Chinese infant
A case report and literature review
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Abstract
Rationale: Pertussis has re-emerged on a global scale and is an ongoing public health problem, even in countries with high rates of vaccination. Hyperleukocytosis [white blood cell (WBC) count > 100 × 10^9/L] is a rare complication that strongly predicts mortality in cases of severe pertussis.

Patient concerns: We report a case of severe pertussis in an infant who initially presented with persistent cyanotic cough, tachypnea, and grunting. The infant’s condition deteriorated rapidly, and she was transferred to the pediatric intensive care unit (PICU) during her third hour of hospitalization. On the third hospital day, her WBC count had increased to 101.85 × 10^9/L with a lymphocyte count of 36.76 × 10^9/L, and her hemoglobin level had fallen to 6.9 g/dL. Bone marrow examination found no evidence of tumor cells. Her initial echocardiogram showed no abnormal findings; however, a subsequent echocardiogram 10 days later revealed pulmonary hypertension.

Diagnoses: The patient was diagnosed with severe pneumonia, which was confirmed to be pertussis based on a persistent cough in the infant’s mother and the polymerase chain reaction and culture of the infant’s nasopharyngeal secretions being positive for Bordetella pertussis.

Interventions: The infant was treated with supportive care, early macrolide antibiotics, and broad-spectrum antibiotics before being transferred to the PICU for further management, including continuous venovenous hemodiafiltration.

Outcomes: Unfortunately, the infant died as a result of pulmonary hypertension and multiorgan failure.

Lessons: Exchange transfusion should be considered in all infants who present with severe pertussis with hyperleukocytosis. This guideline is supported by the findings of a comprehensive literature review, which is included in this article, as well as newly published criteria for exchange transfusion therapy. Finally, we hope that adults in China will be vaccinated against B. pertussis in order to prevent the infection of infants within their households.

Abbreviations: CVVHDF = continuous venovenous hemodiafiltration, ET = exchange transfusion, Hb = hemoglobin, PCR = polymerase chain reaction, PICU = pediatric intensive care unit, WBC = white blood cell.

Keywords: exchange transfusion, leukocytosis, pertussis

1. Introduction
Pertussis (whooping cough) is a highly contagious, vaccine-preventable, respiratory illness caused by Bordetella pertussis. In recent years, pertussis infections have re-emerged worldwide.[1,2] Pertussis has now become the most common vaccine-preventable disease.[3] In 2016, the World Health Organization reported 139,535 cases of pertussis, with a mortality rate of 4%.[4] In our department, we treated 595 infants with pertussis between January 1, 2016, and October 31, 2017; only 1 of these infants died. Here, we report the first case of severe pertussis with hyperleukocytosis in a Chinese infant. The patient was a 42-day-old infant, who eventually died as a result of severe complications. The main objectives of this report are to highlight the importance of treating hyperleukocytosis associated with pertussis and to review the literature regarding the usefulness of exchange transfusion (ET) for patients with severe pertussis with hyperleukocytosis.

2. Patient information and clinical findings
A 42-day-old (4.8kg) girl was admitted to the Shenzhen Children’s Hospital because of cough, tachypnea, and grunting. She was born at term via normal vaginal delivery with no remarkable neonatal events and exhibited good health at home until 4 days before admission. On examination, she exhibited a respiratory rate of 64 breaths/min; her oxygen saturation was 88% on room air, which improved to 97% upon receiving 3L of oxygen via face mask. Her heart rate was 156 beats/min, and she demonstrated poor peripheral perfusion. The infant’s body temperature was 37.8°C, and she exhibited a poor mental response. Bilateral wheezing and crackles were detected by lung
auscultation. The remainder of her physical examination was normal. The infant was diagnosed with severe pneumonia, and she was treated with intravenous cefoperazone-sulbactam and supplemental oxygen by face mask. Pertussis was suspected because of the infant’s persistent cyanotic cough, a persistent cough in the infant’s mother, and because the infant was too young to have been vaccinated.

3. Diagnostic assessment

Polymerase chain reaction (PCR) and culture of the infant’s nasopharyngeal secretions were both positive for *B. pertussis*. A chest radiograph on admission showed right lobe collapse and left lobe consolidation. Routine blood tests on the day of admission revealed a hemoglobin (Hb) level of 8.3 g/dL, white blood cell (WBC) count of 77.19 × 10^9/L, neutrophil count of 35.63 × 10^9/L, and platelet count of 793 × 10^9/L; the lymphocyte count could not be determined. Two days later, her WBC count had increased to 101.85 × 10^9/L with a lymphocyte count of 36.76 × 10^9/L, her Hb level had fallen to 6.9 g/dL, and a blood smear revealed hyperleukocytosis, anemia, and thrombocytosis. Bone marrow examination found no evidence of tumor cells. The infant’s clotting profile was initially normal. Her sodium level was 126 mmol/L, but all other electrolytes were within normal limits. Tests for common pathogens, including *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, respiratory syncytial virus, influenza, cytomegalovirus, Epstein–Barr virus, adenovirus, hepatitis B virus, as well as sputum bacterial cultures, were negative. An echocardiogram found no abnormalities.

4. Therapeutic intervention and outcomes

Due to the patient’s worsening respiratory distress in her third hour of hospitalization, she was transferred to the pediatric intensive care unit (PICU) for further management. In the PICU, she was treated with continuous positive airway pressure and intensive care unit (PICU) for further management. In the PICU, she was initially normal. Her sodium level was 126 mmol/L, but all other electrolytes were within normal limits. Cough for 4 days

WBC: 77.19 × 10^9/L, Hb: 8.3 g/L

bio PCR: 1.07E+5 copies/mL

BM: no tumor cells,

Bp PCR: 1.02E+4 copies/mL

5. Discussion

An elevated and rapidly rising WBC count is suggested as a predictor of severe *B. pertussis* infection in young infants, making early and repeated WBC count determinations critical in the evaluation of all infants with suspected or proven pertussis.[5] Leukocytosis is associated with the need for mechanical ventilation, pulmonary hypertension, and eventual mortality; pulmonary hypertension may be an independent risk factor of mortality in cases of severe pertussis.[6] An increased WBC count is observed in nearly all cases of pertussis; however, hyperleukocytosis (WBC count >100 × 10^9/L) is a rare complication of pertussis, which is thought to be caused by the pertussis toxin.[7] This is the first report of pertussis resulting in hyperleukocytosis in a Chinese infant.

Multiple therapies have been described to treat leukocytosis in severely ill infants, including hyperhydration.[9] However, few
Leukocytosis is strongly associated with fatal cases of pertussis in infants. Early recognition of pertussis-associated leukocytosis and treatment with appropriate leukoreduction therapy are critical for preventing mortality. This report highlights the importance of aggressive supportive care, as well as early implementation of ET, during the management of infants who are at a high risk of severe pertussis with hyperleukocytosis. Moreover, this report suggests that adults in China should be vaccinated against *B. pertussis* in order to prevent the infection of infants within their households.

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**References**

[1] Sealey KL, Belcher T, Preston A. Bordetella pertussis epidemiology and evolution in the light of pertussis resurgence. Infect Genet Evol 2016;40:136–43.

[2] Althouse BM, Scarpino SV. Asymptomatic transmission and the resurgence of Bordetella pertussis. BMC Med 2015;13:146.

[3] Kilgore PE, Salim AM, Zervos MJ, et al. Pertussis: microbiology, disease, treatment, and prevention. Clin Microbiol Rev 2016;29:449–86.

[4] World Health Organization. Surveillance and Burden: Pertussis. Available at: http://www.who.int/immunization/surveillance/en/Updated. Accessed August 27, 2017.

[5] Murray EL, Nieves D, Bradley JS, et al. Characteristics of severe Bordetella pertussis infection among infants ≤90 days of age admitted to pediatric intensive care units: Southern California, September 2009–June 2011. J Pediatric Infect Dis Soc 2013;2:1–6.

[6] Berger JT, Carcillo JA, Shanley TP, et al. National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCRN)/Critical pertussis illness in children: multicenter prospective cohort study. Pediatr Crit Care Med 2013;14:356–65.

[7] Kerr JR, Matthews RC. Bordetella pertussis infection: pathogenesis, diagnosis, management, and the role of protective immunity. Eur J Clin Microbiol Infect Dis 2000;19:77–88.
[8] Lashkari HP, Karuppaswamy S, Khalifa K. Pertussis-related hyperleukocytosis: role of hyperhydration and exchange transfusion. Clin Pediatr (Phila) 2012;51:987–90.
[9] Oñoro G, Salido AG, Martínez IM, et al. Leukoreduction in patients with severe pertussis with hyperleukocytosis. Pediatr Infect Dis J 2012;31:873–6.
[10] Romano MJ, Weber MD, Wesse ME, et al. Pertussis pneumonia, hypoxemia, hyperleukocytosis, and pulmonary hypertension: improvement in oxygenation after a double volume exchange transfusion. Pediatrics 2004;114:e264–6.
[11] Cherry JD, Wendorf K, Bregman B, et al. An observational study of severe pertussis in 100 infants ≤ 120 days of age. Pediatr Infect Dis J 2018;37:202–3.
[12] Donoso AF, Cruces PL, Camacho JF, et al. Exchange transfusion to reverse severe pertussis-induced cardiogenic shock. Pediatr Infect Dis J 2006;25:846–8.
[13] Sawal M, Cohen M, Irazusta JE, et al. Fulminant pertussis: a multi-center study with new insights into the clinico-pathological mechanisms. Pediatr Pulmonol 2009;44:970–80.
[14] Rowlands HE, Goldman AP, Harrington K, et al. Impact of rapid leukodepletion on the outcome of severe clinical pertussis in young infants. Pediatrics 2010;126:e816–27.
[15] Kundrat SL, Wolek TL, Rowe-Telow M. Malignant pertussis in the pediatric intensive care unit. Dimens Crit Care Nurs 2010;29:1–5.
[16] Martinez M, Rochat I, Corbelli R, et al. Early blood exchange transfusion in malignant pertussis: a case report. Pediatr Crit Care Med 2011;12:e107–9.
[17] Guillot S, Descours G, Gillet Y, et al. Macrolide-resistant Bordetella pertussis infection in newborn girl, France. Emerg Infect Dis 2012; 18:966–8.
[18] Taffarel P, Bonetto G, Haimovich A. Severe pertussis, progression and exchange transfusion as an alternative treatment. Case reports [in Spanish]. Arch Argent Pediatr 2012;110:327–30.
[19] Nieves D, Bradley JS, Gargas J, et al. Exchange blood transfusion in the management of severe pertussis in young infants. Pediatr Infect Dis J 2013;32:698–9.
[20] Kuperman A, Hoffmann Y, Glikman D, et al. Severe pertussis and hyperleukocytosis: is it time to change for exchange. Transfusion 2014;54:1630–3.
[21] Assy J, Seguela PE, Guillet E, et al. Severe neonatal pertussis treated by leukodepletion and early extra corporeal membrane oxygenation. Pediatr Infect Dis J 2015;34:1029–30.
[22] Kazantzis MS, Prezerakou A, Kalamitsou SN, et al. Characteristics of Bordetella pertussis infection among infants and children admitted to paediatric intensive care units in Greece: a multicentre, 11-year study. J Paediatr Child Health 2017;53:257–62.