Fulminant pertussis in very young infants: two cases and review of the literature

Muhammet Şükrü Paksu[1], Muhammet Akgün[2], Adil Karadağ[3], Nazik Aşılıoğlu[1], Nurşen Belet[2], Gülnar Şensoy[2]

[1]Pediatric Intensive Care Unit, [2]Division of Pediatric Infectious Diseases, Department of Pediatrics and [3]Department of Clinical Microbiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey. E-mail: sukrupaksu@yahoo.com

SUMMARY: Paksu MŞ, Akgün M, Karadağ A, Aşılıoğlu N, Belet N, Şensoy G. Fulminant pertussis in very young infants: two cases and review of the literature. Turk J Pediatr 2013; 55: 426-429.

Pertussis is one of the leading causes of death that can be prevented by vaccination. More than 600,000 deaths from pertussis occur annually, with a disproportionate number appearing in unvaccinated infants. Pertussis is particularly troublesome because it does not necessarily present itself in its commonly known classical stages. Therefore, in very young and non-immunized children, the disease may have a fulminant process characterized by severe leukocytosis, neurologic involvement and serious cardiopulmonary failure that can be accompanied by pulmonary hypertension, persistent hypoxia and death. This article describes two infants with fulminant pertussis; they were admitted for acute respiratory failure and severe leukocytosis and ultimately died from multi-organ failure.

Key words: fulminant pertussis, child, severe leukocytosis, cardiopulmonary collapse.

Pertussis is a highly contagious bacterial respiratory infection caused by a gram-negative bacillus, *Bordetella pertussis*[1-3]. The primary source of infection in non-immunized young children is infected adults who live in the same household. The major clinical manifestation of the disease is protracted cough that lasts for several weeks[1]. Unfortunately, though, in very young and non-immunized children, the disease may present through a fulminant process. Accordingly, the patient would exhibit symptoms that are not consistent with classical pertussis, making it difficult to diagnose[4-6]. Malignant pertussis is defined by a rapidly evolving combination of pneumonia, cardiopulmonary failure, severe leukocytosis, neurologic involvement, and finally, severe pulmonary hypertension leading to death, despite intensive therapeutic measures[7]. Previous reports establish that age younger than two months and severe leukocytosis (white blood counts >100,000/mm^3) are the predictors of poor outcomes[8-12].

This article identifies two infants with fulminant pertussis. Both suffered acute respiratory failure and massive leukocytosis and ultimately died from multi-organ failure. We wish to alert clinicians about pertussis, an important preventable cause of death, especially as concerns the non-immunized infant.

Case 1

A 2.5-month-old girl was admitted with complaints of cough, vomiting, and dyspnea. She had these symptoms for five days prior to admission. She was treated for pneumonia for one day in a state hospital, and when her condition worsened, she was referred to our hospital. Her medical and family histories were unremarkable. She had not been vaccinated against pertussis. The clinical and laboratory findings of the patient are shown in Table I.

She was admitted to the pediatric intensive care unit (PICU) with the diagnoses of pertussis and pneumonia. She was intubated and underwent mechanical ventilation. Intravenous treatment with cefotaxime, ampicillin, and clarithromycin was started. A bone marrow examination, which was performed to rule out congenital leukemia, was normal. Circulatory collapse (bradycardia and hypotension) and persistent hypoxia occurred within hours despite high airway pressures in mechanical ventilation, with a worsening of her chest clinical and radiological findings during the follow-up. Despite aggressive fluid resuscitation and

Table I. Clinical Features and Laboratory Data of the Two Patients

	Case 1	Case 2
Temperature (°C) (axillary)	36.5	36.5
Heart rate (beats/min)	180 (tachycardia)	172 (tachycardia)
Respiratory rate (breaths/min)	58 (tachypnea)	Intubated
SO_2 by pulse oximeter (%)	95	92
Respiratory system findings	Dyspnea, nasal flaring, subcostal retractions, prolonged expiration, bilateral rales, and typical whooping cough	Respiratory insufficiency (intubated) and bilateral rales
Hemoglobin (g/dl)	9.5	9.6
White blood counts/mm^3	106.000	89.600
Platelet counts/mm^3	777.000	784.000
pH	7.34	7.25
PO_2 and PCO_2	74 & 35	86 & 52
HCO_3 (mmol/L) and BE (mEq/L)	19 & -6	21 & -6
Lactate (mg/dl) [normal range:4-20]	27	9
Peripheral blood smear	Lymphomonocytic leukocytosis	Lymphomonocytic leukocytosis
C-reactive protein (mg/dl) Normal range (0-5)	14	48
Chest X-ray	Bilateral diffuse infiltration*	Bilateral diffuse infiltration**
Echocardiography	Normal	Normal
Length of PICU stay (hours)	24	40

BE: Base excess. PICU: Pediatric Intensive Care Unit.

maximum inotropic support, clinical worsening continued and multi-organ failure occurred. The patient died 24 hours after admission. A nasopharyngeal swab culture that had been obtained at admission and polymerase chain reaction (PCR) both detected B. pertussis.

Case 2

A 36-day-old male infant was transferred from a local hospital with a history of fever, cough, wheezing, and dyspnea. These symptoms had started two weeks before but had worsened considerably in the previous five days. The patient was hospitalized with the diagnosis of bronchiolitis, and oxygen treatment was started. Because of the increase in respiratory distress, she was referred to our hospital. Her medical and family histories were unremarkable; she was not vaccinated against pertussis. Clinical and laboratory findings of the patient are shown in Table I and Figures 1 and 2. The patient was admitted to the PICU. Mechanical ventilation and intravenous treatment with ceftriaxone, teicoplanin, and clarithromycin were started. Fluid resuscitation was given for hypotension and tachycardia, and inotropic support was started. Peritoneal dialysis was started 12 hours after admission due to oliguric renal failure. A bone marrow examination, which was performed to rule out congenital leukemia, was normal. The patient worsened progressively and died 40 hours after admission. B. pertussis was recovered from the nasopharyngeal swab culture of the patient.

Discussion

Pertussis is a contagious and vaccine-preventable infection that is common throughout the world and mainly affects the respiratory and circulatory systems[3,6]. The disease usually begins in the form of upper respiratory tract infection. This may be followed by progressive cough, typical "whooping cough" and episodes of apnea[7,8]. The initial symptoms are variable in young children. Feeding disability and mild respiratory distress may be the sole findings or patients may present with bronchopneumonia[8,10]. As our patients revealed, the disease may have a fulminant process especially in small infants, so-called malignant pertussis. Malignant

pertussis is characterized by severe leukocytosis, neurologic involvement and cardiopulmonary failure accompanied by severe pulmonary hypertension, leading to refractory hypoxemia, multi-organ failure and finally death, despite intensive therapeutic measures[1,2,8,9]. The exact mechanism of pulmonary hypertension in these patients is unknown[1]. The most commonly accepted hypotheses are toxins produced by the bacillus that cause direct pulmonary damage, hyperviscosity syndrome caused by increased leukocytes and leukocyte thrombi, or hypoxia alone[1,9,13].

In many studies, a high leukocyte count was associated with poor prognosis[8-12]. Reports reveal that hyperleukocytosis-induced vascular infiltration or vascular stasis in pulmonary vessels due to leukocyte thrombi may play an important role in pulmonary hypertension, hypoxia, and heart failure[1,11,12,14-16]. Sawal et al.[17] reported that the time between hospital admission and intubation averages one day in patients with malignant progression. Our patients had severe leukocytosis and significant respiratory distress at admission, and were started on mechanical ventilation support on the same day.

Antibiotic therapy, oxygenation, and ensuring hemodynamic stability constitute the typical courses of action for treatment. Unfortunately, pertussis is a toxin-related infection, and therefore, the effect of antibiotic treatment on the duration and severity of the disease is limited[18]. Due to severe leukocytosis playing a role in the pathogenesis of the fulminant process, treatment modalities reducing the number of leukocytes may contribute to positive outcomes[8,9,16,19]. Rowlands et al.[9] suggested double-volume exchange transfusion for clinically stable patients with hyperleukocytosis until the leukocyte count becomes less than 50,000. By contrast, Sawal et al.[17] suggested a more complex physiopathological mechanism of the disease. They reported that exchange transfusion only reduces the number of leukocytes, whereas it does not remove chemokine- and cytokine-induced endothelial injury, and therefore may be useful only in the early period. There is a consensus that vascular stasis caused by an excessive number of leukocytes is reduced by exchange transfusion. We also believe that an exchange transfusion may reduce the burden of toxins and cytokines that damage the vascular endothelium and pulmonary epithelium. In addition, we propose

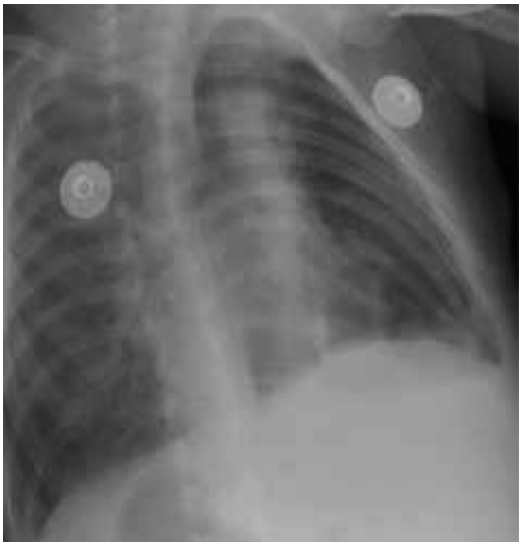

Fig. 1. Consolidation with air bronchograms in the left upper and middle zone, causing loss of cardiac borders and bilateral perihilar bronchovascular reticular opacities.

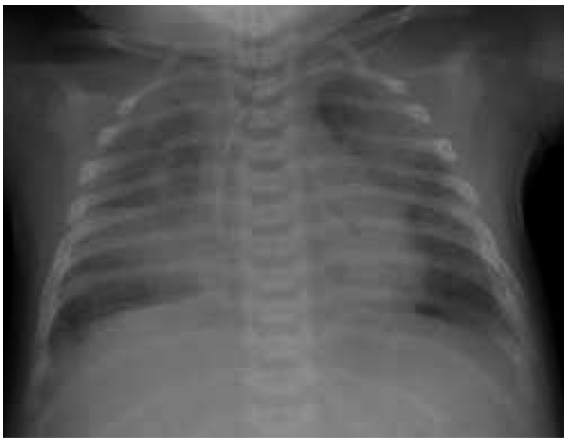

Fig. 2. Bilateral alveolar consolidation. Alveolar opacity is seen in the right lung middle zone, which moves from the hilum toward the periphery.

further investigation into whether or not the antibodies transferred from the donor during the transfusion have a positive contribution to the defense of a non-immune host.

Extracorporeal membrane oxygenation (ECMO) can be used in fulminant cases. Rowlands et al.[9] recommended ECMO either alone or together with leukofiltration, depending on the number of leukocytes in patients with severe cardiopulmonary failure who are unresponsive to other medical therapy. However, it has been reported that the results of ECMO in malignant pertussis are worse than in the other forms of cardiopulmonary failure[1,12,13]. Despite the use of ECMO and pharmacological therapies such as inhaled nitric oxide, sildenafil,

or phosphodiesterase inhibitors, malignant pertussis has a high mortality today[1,2,8]. This finding suggests that hypoxia is not the only factor that determines the severity of the disease in a patient. Because we do not have ECMO in our unit, we could not use it in our patients.

The disease is primarily transmitted by air droplets from the secretions of infected individuals. The primary source in non-immunized young children is infected adults who share the same house. It is for this reason that prevention of the disease is of great importance. Adolescents and adults are the major sources of pertussis infection in non-immunized young children. Therefore, in many developed countries, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) is used for adolescents. Recently, the Advisory Committee on Immunization Practices revised recommendations for the use of Tdap, recommending Tdap also for adults aged 65 years and older who have not received Tdap previously and have contact with infants less than 12 months old[20].

In conclusion, some cases of pertussis have a lesser-known fulminant process; therefore, traditional pertussis symptoms may not be present in a pertussis patient. To address this problem, physicians should consider a pertussis diagnosis for young patients exhibiting severe leukocytosis with severe respiratory distress. Treatments that reduce the number of leukocytes should be considered before cardiopulmonary collapse occurs. Additionally, booster doses of pertussis vaccine for pre-school children, adolescents and adults aged 65 years and older might be considered in our country as well.

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