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Postinfectious Bronchiolitis Obliterans Misdiagnosed as Bronchial Asthma in a Pediatric Patient

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Bronchiolitis obliterans is a chronic obstructive respiratory disease involving stenosis or occlusion of the bronchioles and smaller airways. The prognosis of bronchiolitis obliterans is poor, and the patient might require home oxygen therapy and/or lung transplantation. Bronchiolitis obliterans has various etiologies; in children, the most common causes are infections by respiratory pathogens like adenoviruses. In such cases, the condition is termed as postinfectious bronchiolitis obliterans. A 7-year-old girl was diagnosed with bronchial asthma at the age of 1 year and was on a regimen of a leukotriene receptor antagonist and an inhaled corticosteroid. At 1 year of age, she was admitted to our hospital with a respiratory syncytial virus infection, and despite continued treatment with the above drugs, she required frequent readmissions. At the age of 7 years, she was diagnosed with postinfectious bronchiolitis obliterans based on the following findings: mosaic perfusion on high-resolution chest computed tomography and ventilation-perfusion mismatch on ventilation-perfusion scintigraphy. A lung biopsy was not performed due to its invasiveness. It has been suggested that appropriate treatment during the early stage improves the prognosis of bronchiolitis obliterans. This disease might be misdiagnosed as bronchial asthma because of the clinical similarities. In patients who do not respond to the treatment for bronchial asthma, pediatricians should consider other diseases with similar signs and symptoms, such as bronchiolitis obliterans, in the differential diagnosis.

Keywords: bronchial asthma; bronchiolitis obliterans; mosaic perfusion
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Introduction

Bronchiolitis obliterans is a chronic obstructive respiratory disease involving stenosis or occlusion of the bronchioles and smaller airways. The prognosis of bronchiolitis obliterans is poor, and the patient might require home oxygen therapy and/or lung transplantation. Bronchiolitis obliterans can be idiopathic; however, known etiologies include prior infection, prior transplantation, Stevens-Johnson syndrome, systemic disease (such as Sjögren syndrome), toxic fumes inhalation, and drugs. In children, the most common cause of bronchiolitis obliterans is infection by respiratory pathogens like adenoviruses; in such cases, the condition is termed postinfectious bronchiolitis obliterans. Bronchiolitis obliterans is clinically similar to bronchial asthma, and in some cases, bronchiolitis obliterans might be misdiagnosed as bronchial asthma (Onay et al. 2020). Herein, we report a pediatric case of postinfectious bronchiolitis obliterans misdiagnosed as bronchial asthma.

Case Presentation

Informed consent forms were signed by the patients' guardians before treatment administration and publication of this report.

A 7-year-old girl treated with pranlukast and budesonide, a leukotriene receptor antagonist and an inhaled corticosteroid, respectively, was diagnosed with bronchial asthma. She was born at a gestational age of 35 weeks and 6 days and was admitted to the neonatal intensive care unit because of respiratory distress. Her peripheral capillary oxygen saturation (SpO_2) levels declined after birth, and she was diagnosed with transient tachypnea of the newborn. However, the symptoms improved within a few days with oxygen therapy alone.

She was subsequently admitted to our hospital at the age of 1 year with a respiratory syncytial (RS) virus infection, which was detected in samples from the patient's

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nasopharynx using a rapid antigen test. She was readmitted due to wheezing and respiratory distress next month. After this episode, she was diagnosed with bronchial asthma and initiated on pranlukast (a leukotriene receptor antagonist) and budesonide (an inhaled corticosteroid). Subsequently, she had several episodes of hospitalization due to wheezing, respiratory discomfort, and tachypnea; 6 times at the age of 1 year, 5 times at the age of 2 years, 7 times at the age of 3 years, and 6 times at the age of 4 years. From the age of 4 years, her symptoms at the time of acute exacerbation were mainly respiratory discomfort and tachypnea without wheezing. Home oxygen therapy was also administered for respiratory distress from the age of 4 years. She was admitted once at the age of 5 years, and 6 times at the age of 6 years. She was treated with systemic corticosteroids for several days during each episode. She also experienced exertional dyspnea; hence, she was taken to school by car and was unable to attend physical education classes. She had no episodes of previous adenovirus infection, no recurrent episodes of otitis media, rhinitis, or sinusitis. At the age of 7 years, she was hospitalized again due to dyspnea.

The results of the blood tests showed a white blood cell count of 6,900/μL, (eosinophils 9.6%), a KL-6 level of 204 IU/mL, total immunoglobulin E (IgE) level of 681 UA/mL, house dust mite-specific IgE level of 6.85 UA/mL, and aspergillus-specific IgE level of less than 0.1 UA/mL. The sputum was not examined for eosinophils, and sputum culture showed no pathogenic bacteria. A chest roentgenogram revealed hyperinflation, indicating air trapping (Fig. 1). High-resolution chest computed tomography images depicted mosaic perfusion (Fig. 2). Respiratory function test results included a forced expiratory volume in the first second of 56.6%, %V75 of 36.7%, %V50 of 21.5%, and %V25 of 16.5%, indicating obstructive airway disease. The administration of bronchodilators did not improve the respiratory function. The fractional nitric oxide concentration in

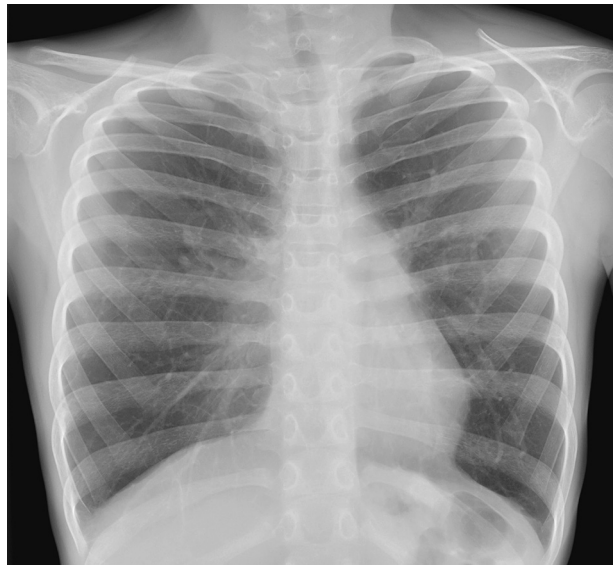

Fig. 1. A chest roentgenogram.
The chest roentgenogram reveals hyperinflation and flattening of the diaphragm, indicating air trapping.

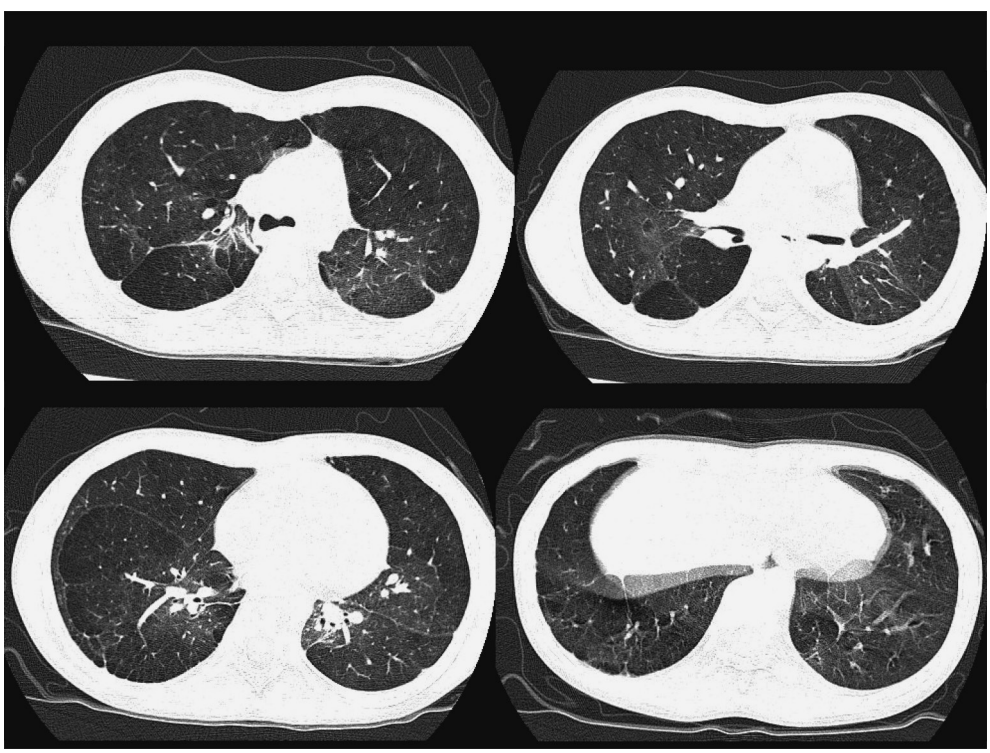

Fig. 2. High-resolution chest computed tomography scan.
High-resolution chest computed tomography image depicts mosaic perfusion.

Fig. 3. Ventilation-perfusion scintigraphy.
Ventilation-perfusion scintigraphy indicates mismatch between ventilation and perfusion.

the exhaled breath was normal (< 5 parts per billion). Ventilation-perfusion scintigraphy revealed a ventilation-perfusion mismatch (Fig. 3). A lung biopsy was not performed due to its invasiveness. The primary ciliary dyskinesia rule score (Behan et al. 2016) for the screening of primary ciliary dyskinesia was 4 (2 points for chest symptoms in the neonatal period and 2 points for admission to a neonatal unit). The genetic test was not performed because the score was below 6. The patient had no respiratory problems during infancy, and a chest CT scan revealed no typical findings indicative of bronchopulmonary dysplasia (BPD) such as cystic lesion at the age of 7 years; hence, the possibility of bronchopulmonary dysplasia was considered low. She had no episodes with signs and symptoms indicative of cystic fibrosis, such as meconium ileus, intestinal disorder, and recurrent respiratory infections. Hence, sweat examination and genetic examination were not performed. The patient was diagnosed with postinfectious bronchiolitis obliterans due to RS virus; consequently, systemic methylprednisolone was administered for 5 days, and the dyspnea gradually improved. Pulmonary function test showed no significant improvement 1 month later. However, she was readmitted to the hospital, and her quality of life continued to deteriorate because of exertional dyspnea.

Discussion

Bronchiolitis obliterans is clinically similar to bronchial asthma, and some cases of bronchiolitis obliterans might be misdiagnosed as bronchial asthma (Onay et al. 2020). Reports indicate that there are no differences in the clinical characteristics, such as the response to inhaled β2-agonist between patients with postinfectious bronchiolitis obliterans and those misdiagnosed with bronchial asthma. Only the duration of symptoms are significantly longer in cases of postinfectious bronchiolitis obliterans misdiagnosed with bronchial asthma than in cases of postinfectious bronchiolitis obliterans diagnosed correctly. This report suggests that bronchiolitis obliterans should be considered in cases refractory to asthma treatment, such as the use of inhaled corticosteroids. In the present case, pediatricians should have considered other diseases similar to bronchial asthma, such as bronchiolitis obliterans, because the patient's symptoms did not respond to the treatment for bronchial asthma. The differential diagnosis should be widened to include bronchiolitis obliterans in refractory cases of bronchial asthma even when indicators for bronchial asthma are positive, such as the slight sensitization to inhaled allergens as observed in the present case.

The diagnosis of bronchiolitis obliterans is usually based on a pathological assessment of the lung biopsy specimen; however, even this might fail to detect diffuse lesions. In recent times, cases of bronchiolitis obliterans have been diagnosed based on clinical symptoms and the use of less invasive examinations such as respiratory function tests and imaging (Fischer et al. 2010). Reports indicate that the evaluation of air trapping by high-resolution computed tomography during each inspiration and exhalation is useful for the diagnosis of bronchiolitis obliterans (Lee et al. 2000). Mosaic perfusion is considered a characteristic of bronchiolitis obliterans, and it might indicate uneven peripheral airway obstruction. The usefulness of ventilation-perfusion scintigraphy in the context of bronchiolitis obliterans has also been reported (Hasegawa et al. 2002). In current times, it is possible to establish a diagnosis by combining the results of these non-invasive examinations.

There is no established treatment for bronchiolitis obliterans. Inhaled corticosteroids are often administered, and some reports state that a combination of budesonide and formoterol fumarate hydrate (β2 adrenergic receptor agonist) is effective (Bergeron et al. 2007). Leukotriene receptor antagonists are effective after hematopoietic stem cell transplantation (Verleden et al. 2011). Although these treatments have evidently been effective in some cases, responses might vary depending on the cause and stage of bronchiolitis obliterans. In a mouse model of bronchiolitis obliterans, the bronchiolar epithelium was damaged after hematopoietic stem cell transplantation due to the infiltration of inflammatory cells and remodeling during the healing process, resulting in stenosis and occlusion of the bronchioles (Nicod 2006). Administration of pulse

methylprednisolone in patients with early-stage postinfectious bronchiolitis obliterans is reported to be effective (Tanou et al. 2015).

Owing to misdiagnosis, our patient had been on a regimen of a leukotriene receptor antagonist and an inhaled corticosteroid since the age of 1 year. However, she was repeatedly hospitalized and experienced exertional dyspnea daily. In this patient, the appropriate diagnosis of bronchiolitis obliterans and the commencement of alternative treatments should have been considered at an earlier stage, although the patient had the possibility of concomitant asthma. Therefore, further studies investigating the methods for the early diagnosis and effective treatment of bronchiolitis obliterans in pediatric patients are needed.

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Conflict of Interest

The authors declare no conflict of interest.

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