Case Report

Diffuse Panbronchiolitis in a 10-Year-Old Boy

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Summary. Diffuse panbronchiolitis is a progressive fatal respiratory disease of unknown cause seen predominantly in Southeast Asian adults. We report this condition in a 10-year-old child of Korean birth because of the uncommon presentation at this age and the favorable outcome associated with early diagnosis. Our objective was also to demonstrate the gradual but complete resolution of the disease and sustained remission from early institution of azithromycin. **Pediatr Pulmonol.** © 2015 Wiley Periodicals, Inc.

Key words: pulmonary function testing (PFT); lung pathology.

CASE REPORT

This 10-year-old boy, born at 36 weeks gestation in South Korea, was adopted by non-smoking professional American parents as a 4 month old infant. When first seen by us, he had a 6 month history of fatigue, cough, sputum production, wheezing, and severe exertional dyspnea. He had previously been in good health, normally active, and had no prior history of respiratory problems. He was now unable to keep up with friends during school recess or take part in physical activities.

Physical exam demonstrated a boy of normal appearance consistent with his ethnicity. Abnormal findings were limited to nasal congestion and polyphonic wheezing with coarse crackles throughout all lung fields. Spirometry showed airway obstruction (Table 1) that did not improve with bronchodilator.

Two trials of oral prednisone, courses of antibiotics, several inhaled corticosteroids, salmeterol, ipratropium, montelukast, levalbuterol, fexofenadine, and irrigations for purulent rhinitis had provided no benefit prior to our first contact. Opacification of all paranasal sinuses had been seen by computerized axial tomography (CT) imaging. A chest radiograph 3 months prior to our evaluation was read as normal. A chest CT 3 weeks prior to his initial visit to our clinic showed irregular patchy peripheral reticulonodular densities, bronchial wall thickening, and non-tapering bronchi consistent with early cylindrical bronchiectasis (Fig. 1).

With no apparent diagnosis, a flexible bronchoscopy and bronchoalveolar lavage (BAL) were performed. No anatomical abnormalities were seen. However, mucus was present in bronchi of multiple lobes. A lavage was performed in the right lower lobe. Cytologic examination of the lavage fluid showed 1,408 neutrophils per cubic millimeter (mm^3), 393 lymphocytes/mm^3, and 485 macrophages/mm^3. Culture grew 3 million colony-forming units per milliliter of fluid (cfu/ml) of *Streptococcus pneumoniae* and 500,000 cfu/ml of *Pseudomonas aeruginosa*. Erythrocyte sedimentation rate, C-reactive protein, IgA, IgM, IgG subclasses, IgE, cold agglutinin, and rheumatoid factor were all within normal limits. A 2 week course of amoxicillin/clavulanate and ciprofloxacin, based on sensitivities of the organisms found in the BAL, was associated with subsequent absence of those organisms in sputum but without clinical improvement and actual worsening of physiology. Both pulse oximetry and spirometric measurements decreased (Table 1). Pulmonary function decreased from that of the initial visit. Because the BAL culture had grown *Pseudomonas aeruginosa*, a sweat

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TABLE 1— Pediatric Pulmonology

	9/2/10 initial evaluation	10/21/10 14 days ciprofloxacin and Augmentin	12/3/10 43 days azithromycin	9/26/11 11 months azithromycin	3/22/12 17 months azithromycin	6/28/13 32 months azithromycin	6/6/14 ~1 year no medication
FVC (% predicted)	106	102	115	110	111	115	100
FEV1 (% predicted)	85	77	107	100	95	98	99
FEV1/FVC (%)	70	66	81	77	84	79	81
FEF25–75 (% predicted)	41	29	79	64	54	75	84
DLCO (% predicted)	68	64	66	98	80	79	100
Pulse ox (% saturation)	96	92			99	99	98
Cultures	BAL 9/3/10 3×10^6 cfu/ml S. pneumoniae; 5×10^5 cfu/ml *Pseudomonas aeruginosa*	Sputum 3×10^5 cfu/ml S. mucilaginosis; 2.5×10^6 cfu/ml alpha-hemolytic streptococci; 4×10^5 cfu/ml diphtheroids	Sputum 3×10^5 cfu/ml S. mucilaginosa 1×10^5 cfu/ml *H. parainfluenzae* 4.5×10^6 cfu/ml mixed flora	No sputum production	No sputum production	No sputum production	No sputum production

chloride was collected by quantitative pilocarpine iontophoresis. Normal values of 19 and 21 meq/L chloride were reported. Consideration was given to DNA sequencing to examine for mutations of cystic fibrosis transmembrane mutations, but the extreme rarity in someone with Korean parentage and the common presence of Pseudomonas aeruginosa associated with diffuse panbronchiolitis made a macrolide trial for that disease of greater importance. Moreover, cessation of symptoms and normalization of pulmonary function from a macrolide would serve to confirm the diagnosis, and make a lung biopsy superfluous.

Azithromycin, 500 mg initial dose, followed by 250 mg daily for 2 weeks, was given. A subsequent maintenance dose of 500 mg on Monday, Wednesday, and Friday was continued for 3 years. During that time, symptoms, sputum production, and pulmonary function progressively improved and remained normal for one year following cessation of the azithromycin (Table 1).

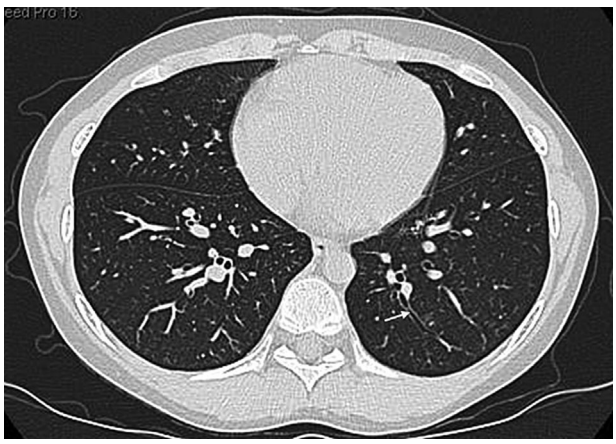

Fig. 1. Thin-sectioned axial chest CT image obtained 2 weeks prior to our evaluation reveals areas of cylindrical bronchiectasis (arrow) and bronchial wall thickening in both lower zones and right middle lobe; irregular patchy peripheral reticulonodular densities were also seen in other cuts.

DISCUSSION

Diffuse panbronchiolitis is an idiopathic rare progressive potentially fatal lung disease first described in Japan.[1] Subsequently found predominantly in several Southeast Asian countries, the prevalence in Japan is estimated to be about 1 per 10,000.[2] The average age of onset is 40 years. We found only 2 previous cases reported in children. A 13-year-old Chinese girl was described as the first child in the Chinese literature with diffuse panbronchiolitis.[3] She had a slowly progressive course over a 12 year period. Lung function was described as severely compromised with a FVC of 58%, an FEV1 of 45%, and a PaO2 of 65 mmHg. Clinical improvement with low-dose erythromycin was described with only a 6 month period of follow-up. The first description of a child in the English-language literature was a 12-year-old Caucasian Turkish girl of first-degree consanguineous parentage who was diagnosed with diffuse panbronchiolitis after a 5 year history of productive cough with purulent sputum and chronic sinusitis.[4] She had substantial irreversible lung

disease by that time and continued to deteriorate despite use of clarithromycin.

Our case is the youngest child with diffuse panbronchiolitis reported to date and uniquely provides the results of a bronchoalveolar lavage. Additionally, pulmonary function was repeated over a 4 year period during and subsequent to treatment with azithromycin (Table 1). Complete clinical and pulmonary function reversibility was obtained following 3 years of continuous azithromycin with remission for over 1 year to date following cessation of treatment. In contrast to the 2 previously reported cases in children, the early diagnosis and intervention in our patient with azithromycin was associated with complete reversibility of symptoms and signs of the disease without evidence for persistent respiratory compromise.

Clinical improvement of diffuse panbronchiolitis was reported with low-dose, long-term erythromycin in 1984 with publication of that experience in 1987.[5] Prior to that, 5 year survival was 51% and only 8% in advanced diffuse panbronchiolitis with *Pseudomonas aeruginosa* infection.[6] Subsequently, azithromycin therapy was associated with remission or improvement and a five-year survival of 94% in a cohort of 51 cases in Shanghai China.[7]

Since a prolonged period of diffuse panbronchiolitis is associated with progressive lung damage, our experience with this patient illustrates the importance of early diagnosis and documentation of remission. The standard of care for this disease therefore requires an index of suspicion based on the clinical presentation, bronchoscopy, and BAL to document neutrophilia and relevant microbiology. A typical clinical picture and an impressive response to azithromycin monotherapy provides a clinical diagnosis that readily differentiates this disease from cystic fibrosis or other causes of chronic lung disease. A study of histopathology from lung biopsies was reported to be potentially useful only when there was difficulty in diagnosis.[8] That report concluded that most cases can be diagnosed by clinical criteria. This case met the diagnostic clinical criteria included in a recent review of diffuse panbronchiolitis.[9]

Considering the current state of still limited knowledge for this disease, long-term, probably life-long, follow-up is essential since we don't know the duration of remission induced by azithromycin.

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