Respiratory Bronchiolitis–Associated Interstitial Lung Disease in Childhood: New Sequela of Smoking

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abstract

Childhood interstitial lung diseases are rare disorders of largely unknown etiology characterized by variable types and degrees of parenchymal inflammation. Disease spectrum and prognosis considerably from those in adults. Respiratory bronchiolitis–associated interstitial lung disease (RB-ILD) is a well-described entity occurring almost exclusively in adults who are current heavy cigarette smokers. We describe an 11-year-old boy with failure to thrive, dry cough, and exertional dyspnea for 1 year who was diagnosed with RB-ILD due to heavy passive smoking exposure. Although RB-ILD is well defined in smoking adults, there are no reports in the English literature in nonactive smokers, especially in childhood.

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Dr Sismanlar conceptualized and designed the study and drafted the initial manuscript; Dr Aslan carried out the initial analyses and reviewed and revised the manuscript; Dr Turktas, Memis, and Griese analyzed and interpreted data; Dr Griese critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

www.pediatrics.org/cgi/doi/10.1542/peds.2015-1303

DOI: 10.1542/peds.2015-1303

Accepted for publication Jun 22, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No funding was secured for this study.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Childhood interstitial lung diseases (ILDs) are a heterogeneous group of rare chronic respiratory disorders characterized by variable types and degrees of interstitial and alveolar inflammation. The etiology of many entities is different from that of adults. Some of these diseases are very rare, and sometimes etiology cannot be identified.

Children with ILD usually present with failure to thrive, dry cough, dyspnea, and tachypnea and rales. With disease progression, chronic hypoxemia, cyanosis, and finger clubbing occur. The precise diagnosis is often difficult and frequently requires invasive procedures such as bronchoscopy, and in most cases, open lung biopsy.

Respiratory bronchiolitis–associated interstitial lung disease (RB-ILD) is a rare pulmonary disorder that occurs almost exclusively in current or former heavy adult smokers, usually between ages 30 and 70 years. The onset is usually insidious, with exertional dyspnea and progressive persistent cough, which may be nonproductive. On high-resolution computerized tomography (HRCT), central and peripheral bronchial wall thickening, centrilobular nodules, and patchy ground-glass opacities associated with upper lobe centrilobular emphysema are most frequently reported. Pulmonary function testing (PFT) usually demonstrates mixed, predominantly obstructive abnormalities, usually associated with a mild to moderate reduction in carbon monoxide diffusion capacity (DLCO). Histologically, RB-ILD is characterized by the accumulation of yellow-brown pigmented macrophages within the lumens of respiratory bronchioles and alveolar ducts, associated with a patchy submucosal and peribronchial chronic inflammation.[1]

Herein, we describe an 11-year-old boy diagnosed with RB-ILD due to heavy passive smoking exposure. Although RB-ILD is well defined in smoking adults, there are no reports on nonsmokers, especially in childhood, in the English literature.

CASE PRESENTATION

An 11-year-old boy was admitted to the pediatric pulmonology department

with failure to thrive, dry cough, and exertional dyspnea for 1 year. There was second-degree consanguinity. The physical examination revealed malnutrition (5th to 15th BMI percentile) and clubbing. Resting oxygen saturation (96%) was normal, and there was no desaturation (<93%) with exertion. Bilateral perihilar and peribronchial interstitial infiltrations were detected on chest radiograph. HRCT demonstrated fibrotic changes and associated ground-glass opacities in both apical lungs and both lower lobes anteriorly and posteriorly in the basal segments. There were 3 nodules in the central right upper lobe and lateral and lower lobe (Fig 1). Sweat chloride test was normal, there was no evidence of recurrent aspirations, upper gastrointestinal series was normal, and tuberculosis skin test was anergic. There was no exposure to bird allergen or fungi. He had no fever, and acute-phase reactants, blood cultures, and polymerase chain reaction for cytomegalovirus, herpes simplex virus, Epstein-Barr virus, *Pneumocystis jirovecii*, and mycobacteria (the latter 2 in lung biopsy) were negative. No primary humoral or cellular immunodeficiency was detected. Echocardiography was normal. Antinuclear antibody, anti–double-stranded DNA, and cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies were negative. Bone marrow cells were normal, and malignancy including histiocytosis was excluded. Arterial blood gas analysis was normal. PFT was compatible mixed, restrictive-obstructive pattern (forced expiratory volume in 1 second [FEV1]: 0.80 L (36%), forced vital capacity [FVC]: 0.86 L (35%), FEV1/FVC: 93%, forced expiratory flow [FEF] 25 to 75: 2.02 L/m (41%), DLCO: 25%, DLCO divided by alveolar volume [VA]: 72%; all results are given as volume or flows and percentage of predicted). Six-minute walk test distance was 378 m.

Thoracoscopic lung biopsy for definite diagnosis was performed. Lymphoid follicles around bronchioles and the respiratory bronchioles were detected, as well as accumulation of yellow-brown pigmented alveolar macrophages in respiratory bronchioles and alveolar spaces with minimal chronic inflammation in the bronchiolar walls (Fig 2). Biopsy was characteristic for RB-ILD.

After the histopathologic diagnosis, the patient's history was considered again regarding intensive passive or active smoke exposure. He was living with 11 people in the same house and he was the only child at home. All the adults were smoking at home and doing so sharing the same room.

First of all, indoor smoking was eliminated precisely. Steroid treatment was started (methylprednisolone 1 mg/kg/day). After 1 month, the patient was evaluated again. Chest x-ray, blood gases, lung function testing, and walking distance (390 m) were similar. He was followed closely, and there was no progression of the disease. Steroid treatment was tapered starting at the second month of treatment and was stopped at the seventh month.

At his last outpatient visit, 3 years after elimination of smoke exposure, he is a 14-year-old without any complaints. Physical examination revealed persistent clubbing. Arterial blood gases were normal. PFT showed FEV1: 45%, FVC: 45%, FEV1/FVC: 92%, FEF 25 to 75: 56%, DLCO: 44%, and DLCO/VA: 105%, but 6-minute walk test distance was 770 m. Chest x-ray and CT had similar images; there was no progression. He is now in the 50th to 75th BMI percentile and is followed without any treatment. There is no passive and active smoke exposure, as demonstrated by his cotinine level in urine (34 ng/mL, normal limit <500 ng/mL).

Written consent was obtained from the parent.

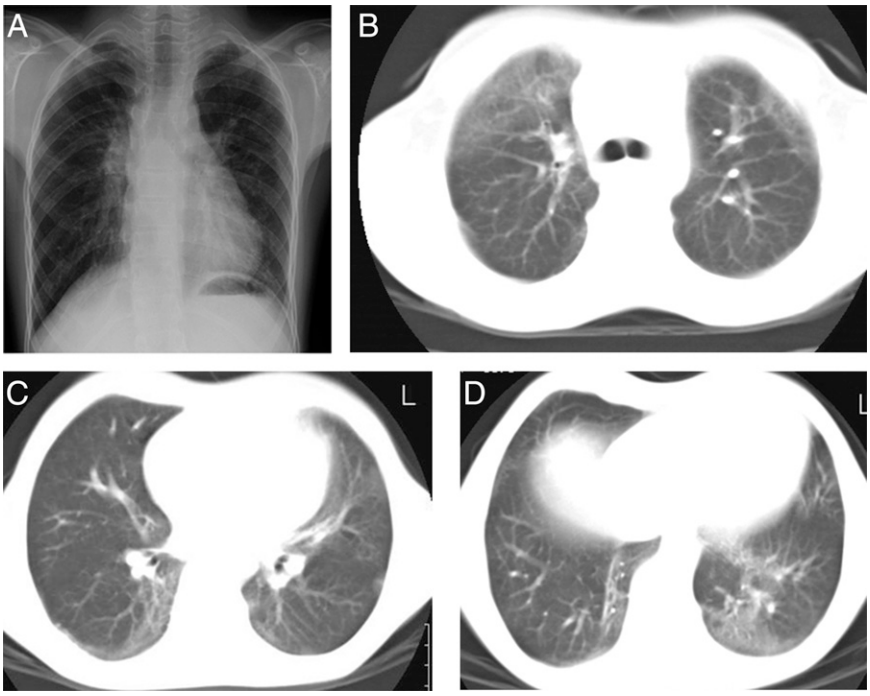

FIGURE 1

A, Bilateral perihilar and peribronchial interstitial infiltrations on chest radiograph at diagnosis. B, Apical fibrotic changes in both lungs, both lower lobe anteriorly. C, Peripheral regions of the basal segments including ground-glass opacity. D, Hyperaeration in other areas on HRCT.

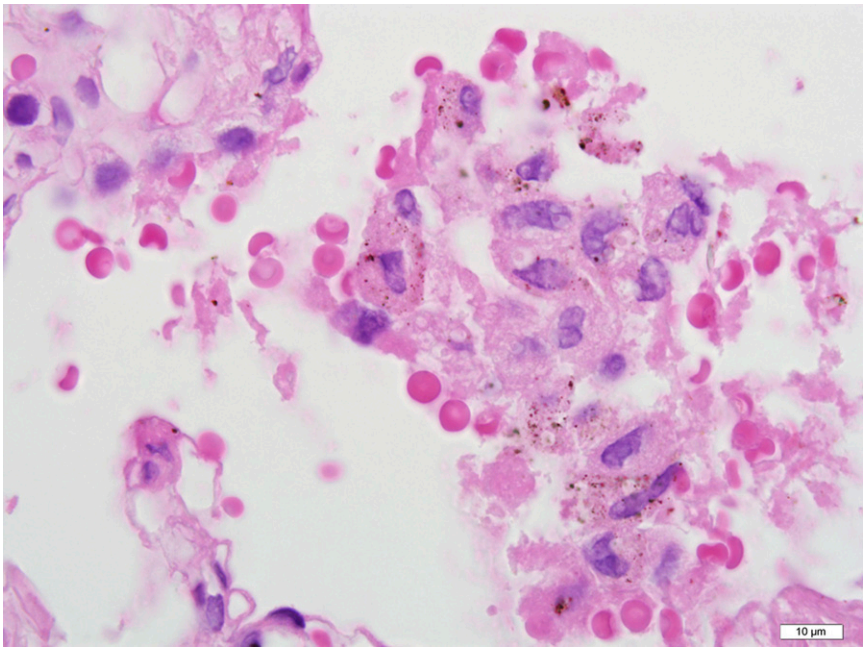

FIGURE 2
Lymphoid follicles around bronchioles and the respiratory bronchioles were detected, as well as accumulation of yellow-brown pigmented alveolar macrophages in respiratory bronchioles and alveolar spaces with minimal chronic inflammation in the bronchiolar walls.

DISCUSSION

Active smoking in adults is well known to lead to lung cancer, chronic obstructive pulmonary disease, and also less frequently to smoking-related interstitial lung diseases. The latter include desquamative interstitial pneumonia (DIP), pulmonary Langerhans cell histiocytosis, acute eosinophilic pneumonia, and RB-ILD. Of these, DIP and pulmonary Langerhans cell histiocytosis have also been identified in children with cigarette smoke exposure.[2,3] To our knowledge, RB-ILD has not yet been described in children. In adults, it is a well-described clinicopathological entity that occurs exclusively in current heavy cigarette smokers. The diagnosis can be based on the combination of clinical evidence of interstitial lung disease, CT findings of centrilobular nodularity and mild ground glass attenuation, pulmonary function abnormalities, and biopsy specimen showing accumulation of pigmented macrophages within the bronchioles and the peribronchial alveolar spaces in association with minimal chronic inflammation in the bronchial walls and the neighboring interstitium, which is rarely seen in nonactive smokers.[4] Although the etiology of ILD in childhood is very wide and has some differences from that in adults, RB-ILD had not been reported in children before and thus needs to be better described in the literature.

Passive smoking has been causally linked to increased risks of respiratory tract infections, middle ear infections, sudden unexplained death in infancy, and asthma, but the relation between smoking and ILD is not clear in childhood.[5] In the literature, only a few reports were found about the relation between passive smoking and childhood ILD, eg, Langerhans cell histiocytosis[3] and DIP.[4] Respiratory disorders caused by smoking in adults may occur with passive smoking in childhood. Smoking bans are implemented in public places, but elimination of smoke exposure at home is very difficult, albeit of great importance to protect children.

It is important to emphasize that many experts consider RB-ILD and DIP the same disease with variable intensity and lung involvement. The distinction between RB-ILD and DIP is mostly based on the extension of smoker's macrophages: in RB-ILD they are restricted to the centrilobular area, and in DIP they involve in the lobule more diffusely. Interstitial fibrosis, eosinophils, and giant cells are more frequent in DIP than RB-ILD.[6,7] Another point to remember is that children with surfactant deficiency can be at risk for similar findings. Mutation in surfactant protein B or C or transporter ABCA3 could present with DIP or resemble RB-ILD in its initial stages of the milder phenotype. In such cases, exposure to cigarette smoke may cause coincidental findings such as the golden-brown dusty granules in macrophages. However, these children tend to have a more extensive alveolar involvement and protracted clinical course.

RB-ILD usually presents with mild symptoms and is associated with a good prognosis. Smoking cessation causes significant improvement in symptoms and lung function tests, and no deaths have been reported.[7,8] In this patient, with smoking cessation and initial steroid treatment, mild improvement in pulmonary function tests and apparent improvement in 6-minute walk test were observed. The role of steroid therapy in RB-ILD is unclear, as results reported vary, and up to now no controlled clinical studies have been performed. Smoking cessation is considered the most important factor in the management of RB-ILD.

In conclusion, in children with interstitial lung diseases, it is important to consider passive smoking exposure as a potential etiology. We describe a first case of RB-ILD associated with passive smoke exposure in childhood.

ABBREVIATIONS

DIP: desquamative interstitial pneumonia
DLCO: carbon monoxide diffusion capacity
FEF: forced expiratory flow
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
HRCT: high-resolution computerized tomography
ILD: interstitial lung disease
PFT: pulmonary function testing
RB-ILD: respiratory bronchiolitis–associated interstitial lung disease
VA: alveolar volume

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Pediatrics 2015;136;e1026; originally published online September 7, 2015;
DOI: 10.1542/peds.2015-1303

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