

## Primary ciliary dyskinesia with complex abnormalities including cleavage of B-subfibers

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### Keywords

B-subfiber, genetic mutation, immotile cilia, primary ciliary dyskinesia, transmission electron microscope.

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### Abstract

A 25-year-old Japanese woman suffered from repeated respiratory tract infections. Because of her characteristic medical history and imaging findings, we suspected primary ciliary dyskinesia (PCD) and performed a transbronchial biopsy. The biopsy revealed complex abnormalities of the ciliary structure including cleavage of the B-subfibers observed by transmission electron microscopy analysis and the complete loss of ciliary motion by video analysis. Genetic examinations to diagnose PCD have progressed in recent years. However, in this case, the well-known genetic mutations in causal genes of PCD were not detected via whole-exome sequencing of the blood. Cleavage of the B-subfibers in patients with PCD has never been reported. This case appears to be the first report of this PCD subtype in humans.

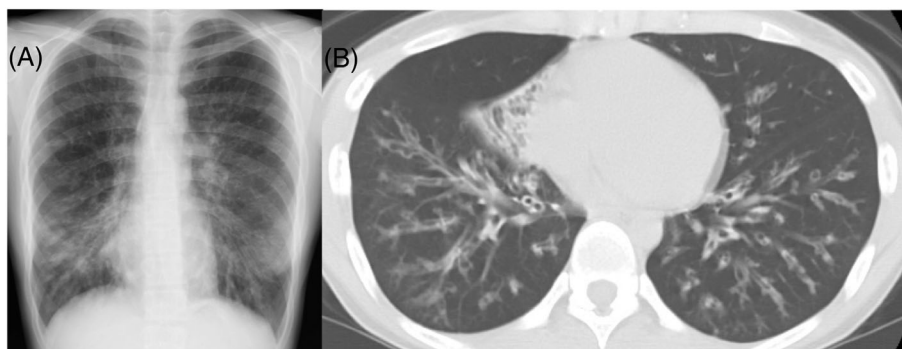
## Introduction

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disease caused by structural and functional abnormalities of motile cilia. PCD is associated with bronchiectasis, chronic rhinosinusitis, infertility, and situs inversus due to ciliopathy. The prevalence of PCD is approximately 1:15,000 live births. The common presentation is recurrent upper and lower airway infection beginning during childhood; as a result, PCD can lead to irreversible pulmonary dysfunction [1]. The most common abnormalities of ciliary structure are defects in the dynein arm. PCD with cleavage of B-subfibers has never been reported. We report a patient with PCD with complex abnormalities of the ciliary structure including cleavage of B-subfibers and complete immotile cilia.

## Case Report

A 25-year-old Japanese woman repeatedly suffered from severe respiratory tract infections with purulent sputum since

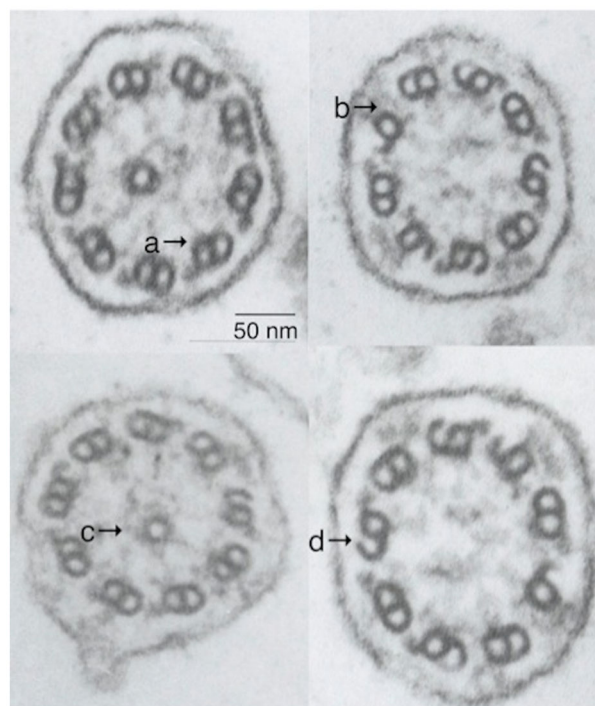
the age of 16. When she was 18 years old, her primary doctor diagnosed her with suspicion of PCD based on nasal mucosa biopsy results. Because her symptoms of dyspnea had gradually worsened, she was admitted to our hospital for a ciliary function assessment. She experienced recurrent otitis media and wheezing dyspnea during childhood, atopic dermatitis at the age of 10, and chronic sinusitis at the age of 18. Her mother was hearing impaired from youth, without symptoms originating in the respiratory tract. She was 169 cm tall with a mass of 50 kg. Her vital signs were as follows: body temperature – 36.7°C; respiratory rate – 16 breaths/min; blood pressure – 99/64 mmHg; pulse – 100 /min; and peripheral capillary oxygen saturation (SpO<sub>2</sub>) – 92%. Auscultation revealed bilateral coarse crackles. *Pseudomonas aeruginosa* was isolated from a sputum culture. The fractional nitric oxide concentration in her exhaled breath was 12 ppb (normal range < 22 ppb). Blood examination findings showed a white blood cell count of 15,820 cells/mm<sup>3</sup> (neutrophils: 14,630 cells/mm<sup>3</sup>; eosinophils: 270 cells/mm<sup>3</sup>) and a C-reactive protein level of 1.66 mg/dL (normal range < 0.3 mg/



**Figure 1.** (A) A chest X-ray shows bilateral tram lines representing thickened bronchial walls. (B) Chest computed tomography shows diffuse bilateral bronchial wall thickening and bronchiectasis.

dL). A chest X-ray showed bilateral tram lines predominantly in the lower lung fields (Fig. 1A). A chest computed tomography showed diffuse bilateral bronchial wall thickening and bronchiectasis (Fig. 1B). Spirometry showed a forced vital capacity of 1.75 L (47.9% of predicted), a forced expiratory volume in 1 s of 0.98 L (30.9%), and a forced expiratory volume in 1 s/forced vital capacity ratio of 55.9%. Transmission electron microscopy analysis of the transbronchial biopsy showed complex abnormalities (Fig. 2) including the deletion of one

or two central pairs (100%), cleavage of the B-subfibers (28.7%), and deletion of the inner (82.4%) and outer dynein arms (23.1%). A video analysis revealed a complete loss of ciliary motion. Therefore, she was diagnosed with PCD. She left our hospital and began home oxygen therapy. Thereafter, she underwent medical observation monthly. Although we performed whole-exome sequencing of DNA from the patient and her mother's peripheral blood, the well-known genetic mutations that cause PCD were not detected.



**Figure 2.** Transmission electronic microscopy analysis shows multiple structural abnormalities of the cilia. Deletion of the inner dynein arms (a), deletion of the outer dynein arms (b), deletion of the central pair (c), and cleavage of the B-subfibers (d) are shown.

## Discussion

Primary ciliary dyskinesia is caused by structural and functional abnormalities of motile cilia. Transmission electron microscopy analysis is commonly used to assess structural abnormalities of cilia. Abnormalities of the outer dynein arms are the most frequent structural abnormalities, reported in approximately 40% of patients with PCD. Abnormalities in the radial spoke or the central pair are relatively rare. Furthermore, to our knowledge, the cleavage of B-subfibers in patients with PCD has never been reported in humans. Reportedly, the interaction of the B-subfibers with the dynein arms plays an important role in generating ciliary movement in the ciliate protozoa, *Tetrahymena* [2]. Furthermore, in the case of zebrafish (*Danio rerio*), when the B-subfibers are cleaved, severe dysfunction of ciliary motion occurs [3]. In our patient, in addition to other abnormalities, the cleavage of the B-subfibers possibly affected the movement of the cilia, which were completely immotile when observed by video analysis. Acute or chronic airway infection causes secondary ciliary dyskinesia with structural abnormalities, such as compound cilia and ciliary edema. However, the frequency of structural abnormalities is reported to be less than 5% in the cilia [4]. Because all cilia were abnormal in our case, we diagnosed this patient with PCD. Occasionally, the severity of structural abnormalities does not correlate with functional abnormalities, making a diagnosis of PCD difficult. Genetic examinations have progressed in recent years. According to a recent review paper, 31 genes have been reported to cause PCD, and modern genetic technologies allow for the identification of disease-causing mutations in approximately 60% of patients [5]. In this case, whole-exome sequencing did not reveal abnormalities in genes known to cause PCD, such as *DNAI1* and *DNAH5*, which can be found in approximately one-third of patients with PCD, and *RSPH4A*, which has been reported to cause absence of the central pair. Although *tll3* and *tll6* have been reported to cause cleavage of B-subfibers in zebrafish, our patient did not exhibit an abnormality in

these genes. Therefore, this case is likely the first report of this PCD subtype in humans. Indeed, causal genes cannot be detected in many cases, and further investigations via genetic analysis are needed.

A treatment strategy for patients with PCD has not been determined. Although the therapeutic effect of macrolides for patients with PCD has been reported, a standard treatment has not been established, especially for severe cases. We used macrolides and mucolytic drugs in this case, but we did not observe a remarkable effect. Although little progress has been made in the treatment of PCD, further investigation into the causal genes and pathophysiology is expected to ensure optimal treatment.

## Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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