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Primary Ciliary Dyskinesia with Refractory Chronic Rhinosinusitis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 49-year-old
Final Diagnosis: Situs inversus
Symptoms: Cough • nasal congestion • nasal obstruction
Medication: —
Clinical Procedure: —
Specialty: Otolaryngology

Objective: Rare disease

Background: Primary ciliary dyskinesia (PCD) is a rare genetic disease associated with abnormalities in the structure and function of cilia. The common clinical presentation of PCD is characterized by otitis media, chronic rhinosinusitis (CRS), chronic bronchitis, and infertility due to impaired ciliary motility. PCD is a complex disease and its diagnosis is complicated. However, there are some clinical features that are strong indicators of PCD, namely situs inversus, chronic otitis media, CRS, and chronic bronchitis with wet cough.

Case Report: A 49-year-old male who had already received 3 operations for refractory CRS presented with nasal discharge, post nasal discharge, and chronic wet cough. Since childhood, he had suffered from otitis media, rhinosinusitis, and bronchitis. He also had a family history of CRS. He was diagnosed as having male infertility at another hospital, but the details were unknown. We performed a fourth surgery and obtained the nasal mucosa for electron microscope analysis during the operation. The transmission electron microscopic findings of the nasal cilia revealed several abnormalities in structure including a central complex defect, microtubular disorganization, and an inner dynein arm defect. Based on these findings and clinical courses, we made the definitive diagnosis of PCD.

Conclusions: When faced with refractory CRS cases with characteristic clinical symptoms that are associated with otitis media, chronic bronchitis, and infertility, clinicians should consider the possibility of PCD.

MeSH Keywords: Kartagener Syndrome • Macrolides • Microscopy, Electron, Scanning • Sinusitis

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Background

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disease caused by mutations of genes related to the motile cilia. The prevalence of PCD is estimated to be between 1: 2000 and 1: 40 000 [1]. The common clinical presentation of PCD is chronic bronchitis, bronchiectasis, chronic rhinosinusitis (CRS), chronic otitis media from infancy, and male infertility. Situs inversus is observed in almost half of patients with PCD [2,3]. PCD is a complex disease and its diagnosis is complicated. However, there are some clinical features that are strong indicators of PCD, namely situs inversus, chronic otitis media, CRS, and chronic bronchitis with wet cough. Chronic and repeated airway infection from childhood could ultimately lead to dysfunction of the lungs and heart. Although a standardized treatment for PCD has not been defined, early diagnosis is important so patients can receive appropriate treatment of upper and lower airway diseases to prevent the progression of bronchiectasis and lung dysfunction. We present the case of a patient with PCD who was diagnosed after 4 operations for refractory CRS.

Case Report

A 49-year-old male presented with nasal discharge, nasal obstruction, post nasal discharge, and chronic wet cough. He was an ex-smoker with allergic rhinitis and had a past history of male infertility, which was diagnosed at another hospital but the details were unknown. He also had a family history of CRS, with his mother, sister, and brother also suffering. Since childhood, he had a history of repeated rhinosinusitis and otitis media. Three times, at 28, 33, and 43 years of age, he received endoscopic sinus surgery (ESS) for CRS at another hospital. After the ESS treatments, his symptoms were temporary relieved but they relapsed within a few months after the procedures. At 49 years of age, he was referred to our institution for his refractory CRS, 6 years after he received his third ESS treatment.

Blood examination findings showed that the eosinophil percentage was 1.1% (reference value: 0-6%) and serum IgE level was 109 IU/mL (reference value: <170 IU/mL). The otoscopic findings revealed that both of his tympanic membranes were thickened and perforated (Figure 1A, 1B). A pure tone audiogram test showed 26.7 dB (right) and 25.0 dB (left), with mild mixed hearing loss (average of 500, 1000, and 2000 Hz). Nasal endoscopy showed abundant white viscous nasal discharge and yellowish bulges on the region of both sides of the middle nasal meatus (Figure 2A–2C). Lung function tests showed decreased%FEV_1 49.55% (reference value: >70%). A chest computed tomography (CT) scan showed diffuse small nodular shadows in both lung fields, but did not show situs inversus (Figure 3A, 3B). Sinus CT scan revealed soft-tissue shadows in the bilateral paranasal sinuses and sphenoid sinus hypoplasia (Figure 4A–4D).

According to his past and family history, we suspected that his refractory CRS was caused by PCD. We consulted the respiratory physician to evaluate the lower airway condition. They diagnosed him with diffuse panbronchiolitis due to his persistent cough and sputum, coexistence of CRS, lung function test results, and characteristic findings of the chest CT scan [4]. We performed ESS and submucosal turbinectomy. The inferior turbinate mucosa was obtained during the operation and was used for transmission electron microscopic analysis. The transmission electron microscopic analysis was performed according to the previously reported method [5].

Surgical findings showed that abundant white viscous nasal discharge occupied the nasal cavity, and there were several capsulated yellowish lesions that contained viscous mucin and necrotic debris on the both sides of the middle nasal meatus. We performed the bilateral full-house ESS and inferior nasal meatus antrostomy, and removed thickened paranasal mucosa and cystic lesions using forceps, a microdebrider, and a CT-assisted navigation system.

The transmission electron microscopic findings of the nasal cilia showed several abnormal structures of the cilia including a central complex defect, microtubular disorganization, and an inner dynein arm defect (Figure 5A–5D). We suggested genetic and semen analysis for PCD, but the patient did not want to undergo any further examinations, including family investigation.

Based on these findings and clinical courses, we made the definitive diagnosis of PCD in this patient. After the surgical procedure, we initiated low-dose and long-term clarithromycin (200 mg/day) medication and daily self-administered nasal irrigation with saline to be maintained for 12 months. No mucoactive drugs or bronchodilators were prescribed. At 12 months after the final ESS procedure and with these conservative treatments, his symptoms were well controlled.

Discussion

PCD is a rare hereditary autosomal disease associated with structural and functional abnormalities of the motile cilia [6–8]. The clinical presentations of PCD are diverse and include situs inversus, CRS, otitis media, chronic bronchitis, and infertility. Although Kartagener syndrome was formerly known as a classical phenotype of PCD with the Kartagener triad, namely, situs inversus, CRS, and bronchiectasis, situs inversus is observed in approximately half of patients with PCD [1,8]. However, the diagnosis of PCD is often delayed or missed – even in children who showed the characteristic clinical courses of PCD – due in

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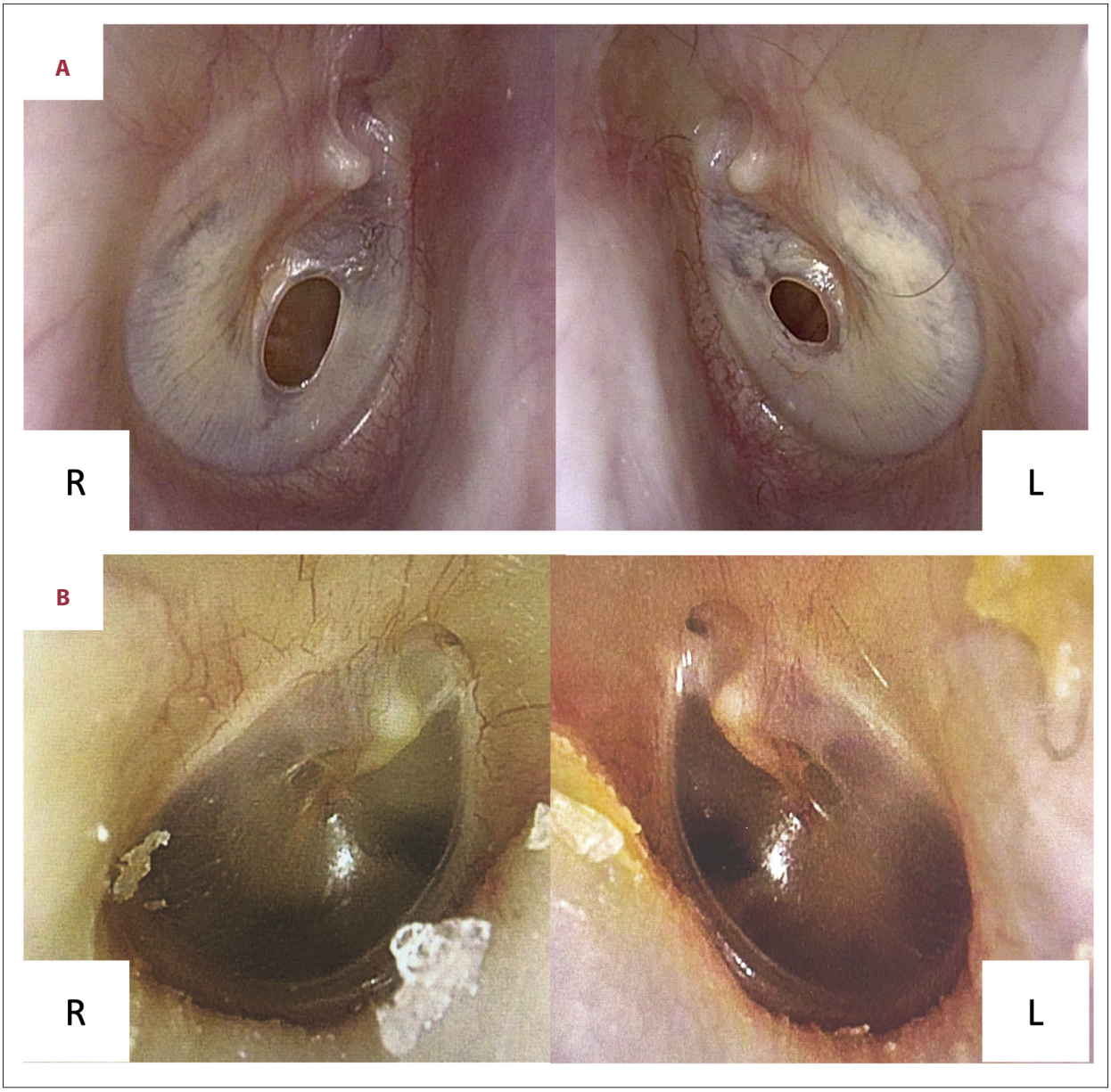

Figure 1. The otoscopic findings. (**A**) Both tympanic membranes were thickened and perforated. (**B**) Normal findings of tympanic membrane. R – right, L – left.

part to the limitation of the available diagnostic examination, the technical expertise required for an accurate diagnosis, and a lack of physician knowledge [3,9–11]. Because there are diverse clinical presentations of PCD, physicians should also consider a differential diagnosis, such as cystic fibrosis, asthma, allergic rhinitis, gastroesophageal reflux disease and aspiration, immunodeficiency, and interstitial lung disease [12]. In our case, the patient had not been diagnosed with PCD before receiving his fourth surgery at our institution because, although he showed characteristic clinical symptoms of PCD, he did not show situs inversus. At present, PCD cases without situs inversus are sometimes left undiagnosed.

The gold standard for diagnosis of PCD has not been established, however European and North American evidence-based guidelines for PCD do exist [9,13]. Therefore, comprehensive examination including both structural and functional evaluation of the cilia and genetic analysis is important. A definitive diagnosis can be made when patients present characteristic clinical features and transmission electron microscopic analysis shows structural abnormalities, or when gene analysis shows mutations in genes associated with PCD. Transmission electron microscopic analysis is not easy because healthy subjects could sometimes show abnormal structures in cilia, such as compound cilia. Additionally, the findings of transmission

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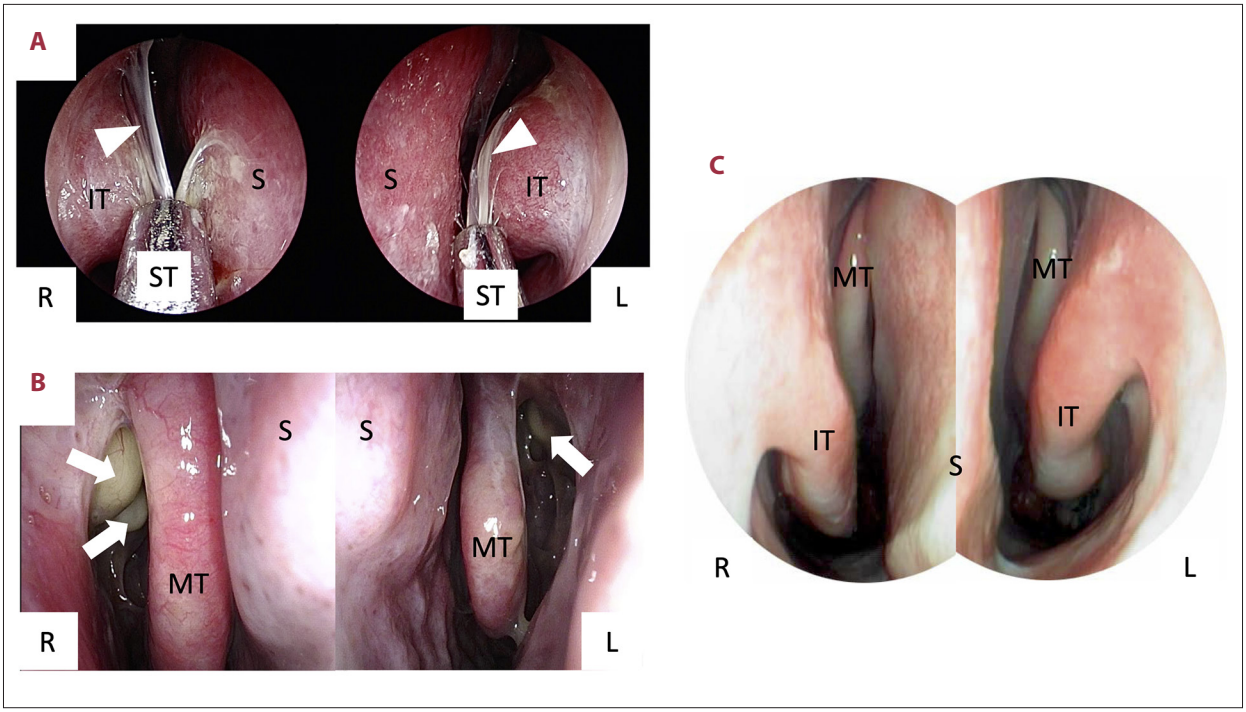

Figure 2. The nasal endoscopic findings. (**A**) White viscous nasal discharge secreted in both sides of the nasal cavity (white arrow heads). (**B**) Yellowish bulging lesions occupied both sides of the middle nasal meatus (white arrows). (**C**) Normal findings of nasal cavity. IT – inferior turbinate, MT – middle turbinate, S – septum, ST – suction tube.

electron microscopic analysis are likely obscured due to section thickness and angle, and the abnormal structures of cilia could sometimes be observed under the condition of inflammation or infection [14]. Several types of cilia abnormalities including deletion of the outer dynein arms, inner dynein arms, and central microtubes have been identified in patients with PCD. Among these findings, defect of the outer dynein arms is most frequently observed in PCD (approximately 40%) [8]. The 2 classes of transmission electron microscopic diagnostic defects for PCD were identified by an expert consensus group. Class 1 defects are considered the hallmark defects confirming a diagnosis in a patient with symptoms of the condition. Class 1 defects are an outer dynein arm defect, outer and inner dynein arm defect, or microtubular disorganization and inner dynein arm defect. Class 2 defects indicate a diagnosis of PCD in a patient with other supporting evidence. Class 2 defects are a central complex defect, mislocalization of basal bodies with few or no cilia, microtubular disorganization defect with inner dynein arm present, outer dynein arm absence from 25% to 50% of cross sections, or combined inner and outer dynein arm absence from 25 to 50% of cross sections. In the present case, microtubular disorganization and inner dynein arm defect were observed in a hallmark transmission electron microscopic defects diagnosis [2,15].

More than 30 genes related PCD mutations have been identified, including DNAH5 (15–29%), DNAH11 (6–9%), CCDC39 (4–9%), DNAI1 (2–10%), and CCDC40 (3–4%) [7]. Even if patients received gene analysis, many cases would not lead to the definitive diagnosis of PCD because the genes responsible for PCD are not singular and there are many responsible genes which are unknown. Therefore, the significance of gene analysis is to increase the accuracy of definitive PCD diagnosis when the patient shows structural abnormalities of the cilia, because the phenotype of structural abnormality of cilia depends on the responsible genes. The core axoneme structure of both the motile cilia and sperm tail has the same ultrastructural feature. It was recently reported that the comparative disease phenotype between cilia and sperm does not correlate in all cases, although it appears that many PCD genes have an effect on male fertility [3,10,11,16–18].

It is also reported that the evaluation of nasal nitric oxide (NO) level is useful for screening for PCD because patients with PCD show lower nasal NO levels [2,16,20]. However, we could not evaluate the patient's nasal NO levels because our department was not equipped with a nitric oxide analyzer. In addition, high speed video and immunofluorescence would have been helpful to confirm PCD because cilia rotate and have an absence of human radial spork genes [21]. There are some clinical characteristics that can help to diagnose PCD including the hypoplasia of the frontal sinuses and the sphenoid sinuses [22]. In this study, sinus CT scan showed hypoplasia of the sphenoid sinuses (Figure 4B). This finding also supported the definitive

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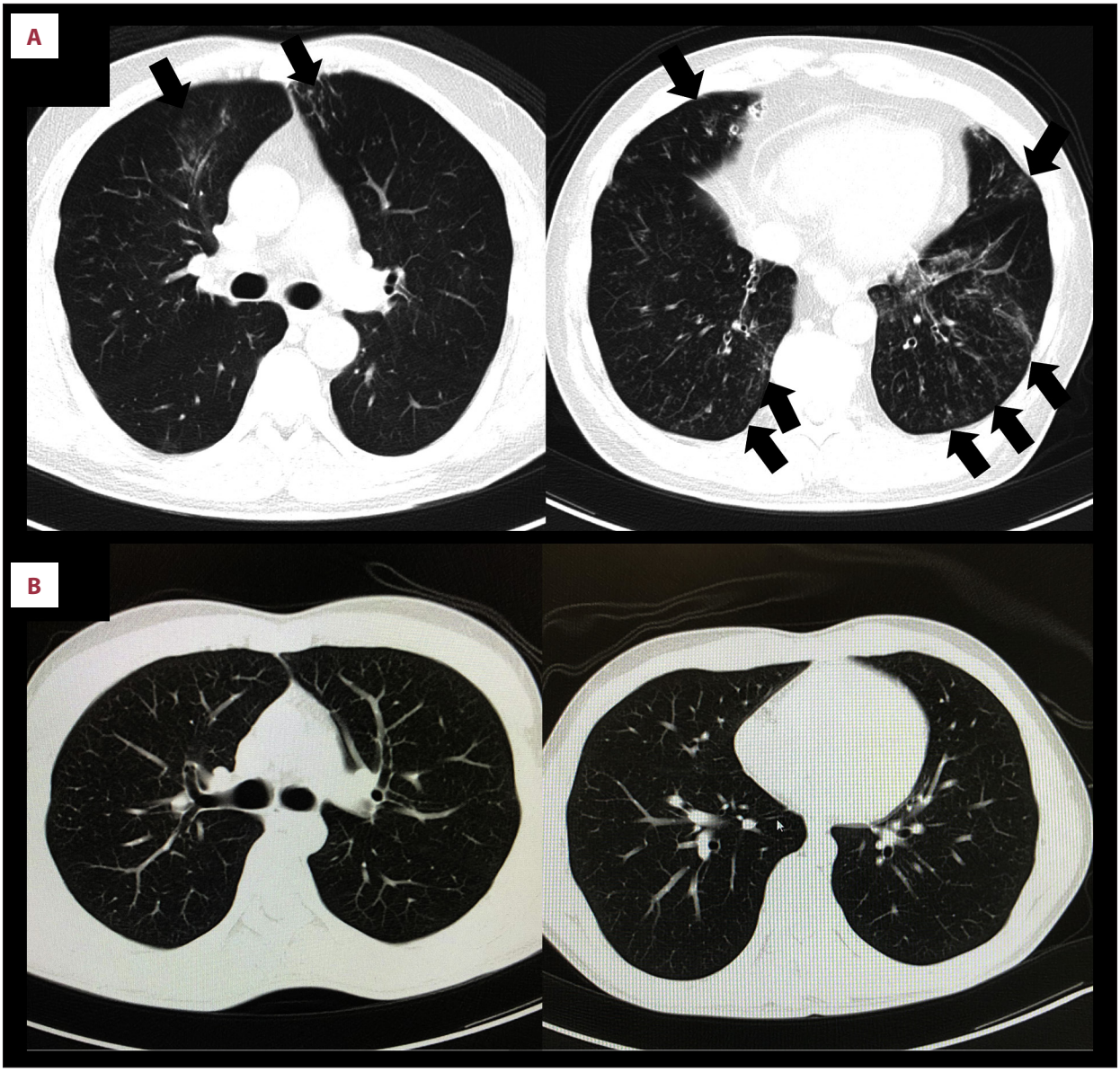

Figure 3. (**A**) Chest computed tomography images showing diffuse small nodular shadows in both lung fields (black arrows). (**B**) Normal findings of chest computed tomography images.

diagnosis of PCD in this patient. We diagnosed this patient as having PCD from the characteristic clinical course, which included male infertility and transmission electron microscopic findings of multiple structural abnormalities of the cilia.

Although there is no specific treatment for PCD at present, it is likely that the prognosis is improved when patients are diagnosed early and their complications are managed properly [8,23,24]. Early diagnosis also enables patients and their families to receive appropriate genetic counseling. Screening and adequate prevention and treatment, including vaccination and life guidance for PCD-associated otitis media, rhinosinusitis, pulmonary diseases, and infertility, may delay the onset and progression of these conditions, thus improving patient quality of life and health [2,8,9]. Therefore, physicians should aggressively consider the necessity of an early and appropriate diagnosis approach for PCD in suspected patients.

Otitis media with effusion is often complicated by PCD. Usually, middle ear diseases associated with PCD are intractable in children and mild but persistent in adults [7]. In the present case, the patient had a history of repeated otitis media with effusion in childhood and received myringotomy and the insertion of ventilation tubes.

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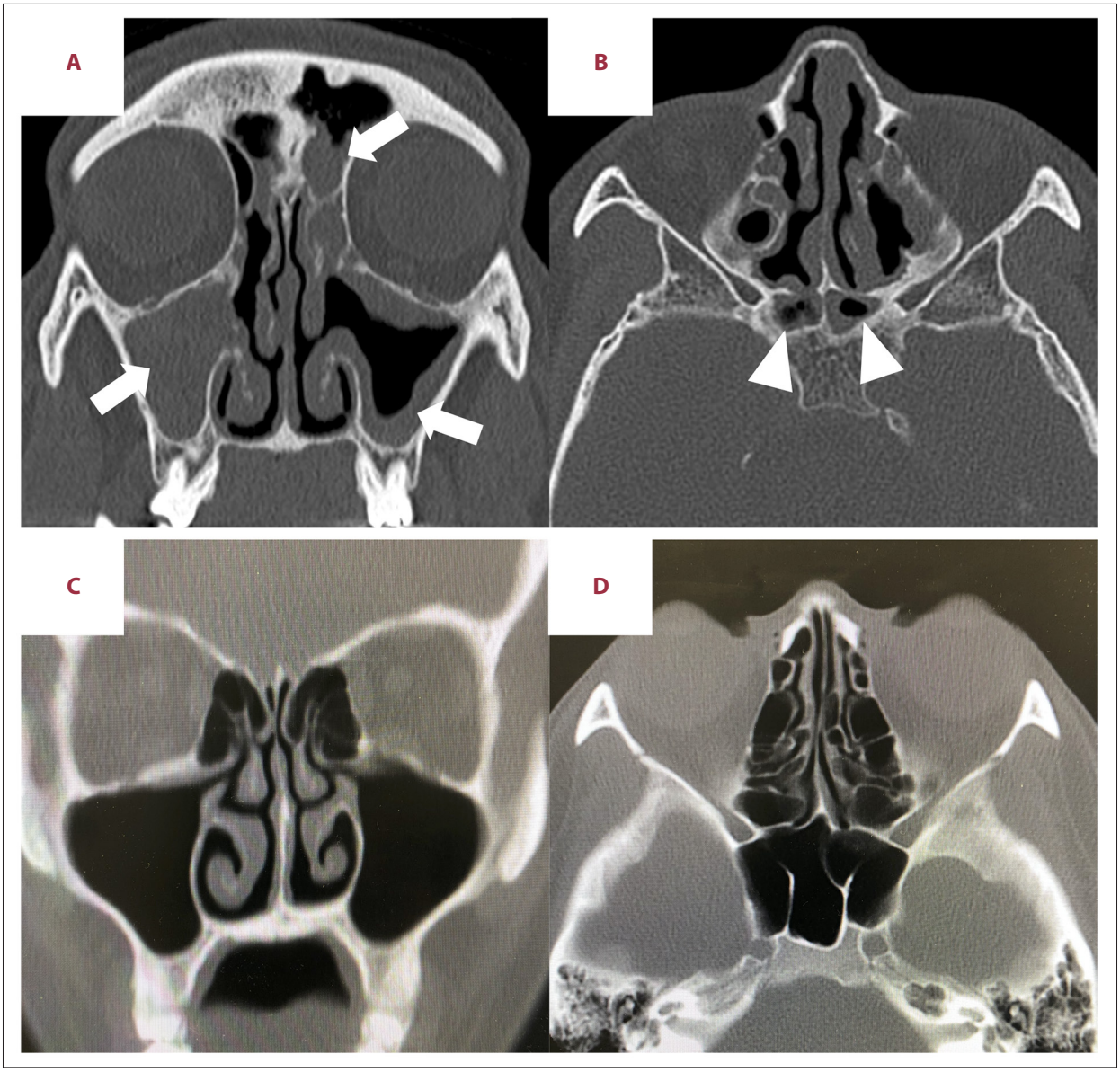

Figure 4. Sinus computed tomography images. (**A**) Coronal view showing soft-tissue shadows in the bilateral paranasal sinuses (white arrows). (**B**) Horizonal view showing sphenoid sinuses hypoplasia (white arrow heads). (**C**) Normal findings of coronal view. (**D**) Normal findings of horizonal view.

Evidence-based treatment for CRS associated with PCD is limited. The basic treatment strategy for CRS is the combined therapy of nasal irrigation, medication, and possible surgery. The low-dose, long-term 14- or 15-membered macrolide antibiotic treatment (macrolide therapy) is demonstrated to be effective for airway inflammatory diseases such as diffuse panbronchiolitis, bronchiectasis, chronic bronchitis, cystic fibrosis, asthma, and CRS [25–30]. Kido reported that macrolide therapy was effective in managing airway conditions in patients with PCD [31]. In the present case, we initiated macrolide therapy expecting an anti-inflammatory effect and improvement of mucociliary clearance instead of an antibacterial effect [32,33]. CRS associated with PCD is refractory despite adequate management including surgery because the cilia in the nasal cavity and paranasal sinuses could not sufficiently excrete mucus and inflammatory products due to its impaired mucociliary clearance. Therefore, patients with CRS associated with PCD often recur, although the nasal symptoms temporary improved after the treatment. It is reported that the ESS procedure could effectively manage refractory CRS associated with PCD [34,35]. However, it is also reported that patients with CRS associated with PCD need several operations over their lifetime [36]. In this case, the endoscopic findings of the nasal cavity showed the multiple yellowish cystic lesions that

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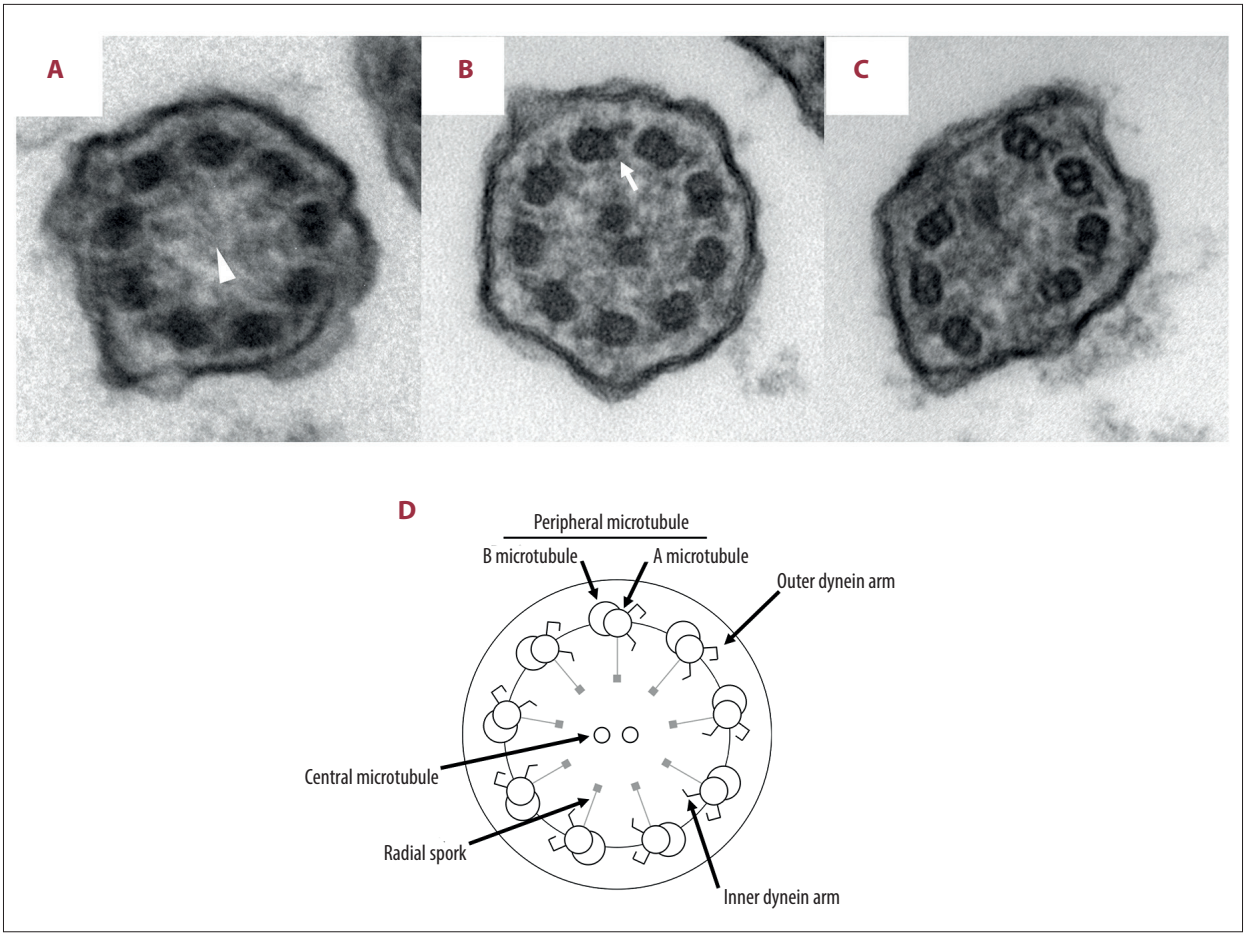

Figure 5. The electron microscopic analysis of the nasal cilia. (**A**) Central complex defect (white arrow head). (**B**) Inner dynein arm defect (white arrow). (**C**) Microtubular disorganization and inner dynein arm defect. (**D**) The schema of electron microscopic findings of normal cilia. Normal cilia have 2 central microtubules and 9 pairs of peripheral microtubules. A pair of peripheral microtubules consists of A microtubule and B microtubule. Outer and inner dynein arms are attached to A microtubules.

contained viscous mucins and necrotic debris occupied both sides of the middle nasal meatus. To remove irreversible lesions that are resistant to conservative treatment, it may be necessary to reoperate.

Several kinds of physicians may come in contact with PCD cases including respiratory physicians, pediatricians, and otolaryngologists. Among them, otolaryngologists have an important role in making a definitive diagnosis of PCD because they are able to precisely evaluate the upper airway and ear condition and perform biopsies necessary for the diagnosis by electron microscope.

Conclusions

When we face refractory CRS cases with characteristic clinical symptoms that are associated with otitis media, chronic bronchitis, and infertility, we should consider the possibility of PCD. Although a specific therapy for PCD is not available at present, it is important to make a precise diagnosis of PCD and provide appropriate control for patients. The role of otolaryngologists in making a definitive diagnosis of PCD is crucial, including the evaluation of the ear and upper airway and collection of nasal mucous membranes with biopsy or nasal brushing for electron microscopic analysis.

Conflict of interest

None.

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References:

1. Goutaki M, Meier AB, Halbeisen FS et al: Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis. Eur Respir J, 2016; 48: 1081–95
2. Lucas JS, Barbato A, Collins SA et al: European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. Eur Respir J, 2017; 49: 1601090
3. Pereira R, Barbosa T, Gales L et al: Clinical and genetic analysis of children with kartagener syndrome. Cells, 2019; 8: 900
4. Kudoh S, Keicho N: Diffuse panbronchiolitis. Clin Chest Med, 2012; 33: 297–305
5. Theegarten D, Ebsen M: Ultrastructural pathology of primary ciliary dyskinesia: Report about 125 cases in Germany. Diagn Pathol, 2011; 6: 115
6. Kennedy MP, Omran H, Leigh MW et al: Congenital heart disease and other heterotaxic defects in a large cohort of patients with primary ciliary dyskinesia. Circulation, 2007; 115: 2814–21
7. Takeuchi K, Kitano M, Ishinaga H et al: Recent advances in primary ciliary dyskinesia. Auris Nasus Larynx, 2016; 43: 229–36
8. Inaba A, Furuhata M, Morimoto K et al: Primary ciliary dyskinesia in Japan: Systematic review and meta-analysis. BMC Pulm Med, 2019; 19: 135
9. Shapiro AJ, Davis SD, Polineni D et al: Diagnosis of Primary Ciliary Dyskinesia. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med, 2018; 197: e24–39
10. Pereira R, Oliveira J, Ferraz L et al: Mutation analysis in patients with total sperm immotility. J Assist Reprod Genet, 2015; 32: 893–902
11. Pereira R, Oliveira ME, Santos R et al: Characterization of CCDC103 expression profiles: further insights in primary ciliary dyskinesia and in human reproduction. J Assist Reprod Genet, 2019; 36: 1683–700
12. Leigh MW, Pittman JE, Carson JL et al: Clinical and genetic aspects of primary ciliary dyskinesia/Kartagener syndrome. Genet Med, 2009; 11: 473–87
13. Shoemark A, Dell S, Shapiro A, Lucas JS: ERS and ATS diagnostic guidelines for primary ciliary dyskinesia: Similarities and differences in approach to diagnosis. Eur Respir J, 2019; 54: 1901066
14. Boon M, Jorissen M, Proesmans M, De Boeck K: Primary ciliary dyskinesia, an orphan disease. Eur J Pediatr, 2013; 172: 151–62
15. Shoemark A, Boon M, Brochhausen C et al: International consensus guideline for reporting transmission electron microscopy results in the diagnosis of Primary Ciliary Dyskinesia (BEAT PCD TEM Criteria). Eur Respir J, 2020; 55: 1900725
16. Sironen A, Shoemark A, Patel M et al: Sperm defects in primary ciliary dyskinesia and related causes of male infertility. Cell Mol Life Sci, 2019; 77(11): 2029–48
17. Pereira R, Barbosa T, Alves A et al: Unveiling the genetic etiology of primary ciliary dyskinesia: When standard genetic approach is not enough. Adv Med Sci, 2019; 65: 1–11
18. Sousa M, Oliveira E, Alves A et al: Ultrastructural analysis of five patients with total sperm immotility. Zygote, 2015; 23: 900–7
19. Shapiro AJ, Zariwala MA, Ferkol T et al: Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review. Pediatr Pulmonol, 2016; 51: 115–32
20. Leigh MW, Hazucha MJ, Chawla KK et al: Standardizing nasal nitric oxide measurement as a test for primary ciliary dyskinesia. Ann Am Thorac Soc, 2013; 10: 574–81
21. Frommer A, Hjeij R, Loges NT et al: Immunofluorescence analysis and diagnosis of primary ciliary dyskinesia with radial spoke defects. Am J Respir Cell Mol Biol, 2015; 53: 563–73
22. Pifferi M, Bush A, Caramella D et al: Agenesis of paranasal sinuses and nasal nitric oxide in primary ciliary dyskinesia. Eur Respir J, 2011; 37: 566–71
23. Bush A, Cole P, Hariri M et al: Primary ciliary dyskinesia: diagnosis and standards of care. Eur Respir J, 1998; 12: 982–88
24. Ellerman A, Bisgaard H: Longitudinal study of lung function in a cohort of primary ciliary dyskinesia. Eur Respir J, 1997; 10: 2376–79
25. Kudoh S, Azuma A, Yamamoto M et al: Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. Am J Respir Crit Care Med, 1998; 157: 1829–32
26. Wong C, Jayaram L, Karalus N et al: Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): A randomised, double-blind, placebo-controlled trial. Lancet, 2012; 380: 660–67
27. Shirai T, Sato A, Chida K: Effect of 14-membered ring macrolide therapy on chronic respiratory tract infections and polymorphonuclear leukocyte activity. Intern Med, 1995; 34: 469–74
28. Jaffe A, Francis J, Rosenthal M, Bush A: Long-term azithromycin may improve lung function in children with cystic fibrosis. Lancet, 1998; 351: 420
29. Yamada T, Fujieda S, Mori S et al: Macrolide treatment decreased the size of nasal polyps and IL-8 levels in nasal lavage. Am J Rhinol, 2000; 14: 143–48
30. Miyatake H, Taki F, Taniguchi H et al: Erythromycin reduces the severity of bronchial hyperresponsiveness in asthma. Chest, 1991; 99: 670–73
31. Kido T, Yatera K, Yamasaki K et al: Two cases of primary ciliary dyskinesia with different responses to macrolide treatment. Intern Med, 2012; 51: 1093–98
32. Tamaoki J, Chiyotani A, Sakai N et al: Effect of erythromycin on ciliary motility in rabbit airway epithelium *in vitro*. J Antimicrob Chemother, 1992; 29: 173–78
33. Kanoh S, Rubin BK: Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clin Microbiol Rev, 2010; 23: 590–615
34. Parsons DS, Greene BA: A treatment for primary ciliary dyskinesia: Efficacy of functional endoscopic sinus surgery. Laryngoscope, 1993; 103: 1269–72
35. Chen W, Shao C, Song Y, Bai C: Primary ciliary dyskinesia complicated with diffuse panbronchiolitis: A case report and literature review. Clin Respir J, 2014; 8: 425–30
36. Bush A, Chodhari R, Collins N et al: Primary ciliary dyskinesia: Current state of the art. Arch Dis Child, 2007; 92: 1136–40

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