American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2024; 25: e942444
DOI: 10.12659/AJCR.942444

Received: 2023.09.05
Accepted: 2024.01.01
Available online: 2024.02.01
Published: 2024.03.24

Cystic Lung Changes, Bronchiectasis, and a Heterozygous-Primary Ciliary Dyskinesia-Associated Variant in the *DNAH5* Gene: A Diagnostic Challenge

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BEG 1 Manal Albalawi
ABD 2,3 Abdullah Al-Shamrani
EF 4 Ahmed Sarar Mohamed
ACDF 2,3 Sarar Mohamed

1 Department of Pediatrics, College of Medicine, Tabuk University (TU), Tabuk, Saudi Arabia
2 Department of Pediatric Pulmonology, Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia
3 Al Faisal University, Riyadh, Saudi Arabia
4 College of Medicine, The National University, Khartoum, Sudan

Corresponding Author: Manal Albalawi, e-mail: Dr-manal00@hotmail.com
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 6-year-old
Final Diagnosis: Probable PCD
Symptoms: Asthma • clubbing
Clinical Procedure: —
Specialty: Pulmonology

Objective: Unknown etiology

Background: Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disease that can present at different ages with different phenotypes. Missed and delayed diagnoses are fairly common. Many variants in the *DNAH5* gene have been described that confirm the diagnosis of PCD. Advances in medicine, especially in molecular genetics, have led to increasingly early discoveries of such cases, especially in those with nonclassical presentations.

Case Report: This report describes a patient with bronchiectasis, lung cysts, finger clubbing, and failure to thrive who was misdiagnosed for several years as having asthma. Many differentials were suspected and worked up, including a suspicion of PCD. Genetic tests with whole-exome sequencing (WES) and whole-genome sequencing (WGS) detected a heterozygous, likely pathogenic, variant in the *DNAH5* gene associated with PCD.

Conclusions: Despite a thorough workup done for this case, including a genetic workup, a PCD diagnosis was not established. We plan to reanalyze the WGS in the future, and with advent of technology and better coverage of genes, a genetic answer for this challenging case may resolve this diagnostic quandary in the future.

Keywords: Ciliary Motility Disorders • Cystic Disease of Lung • DNAH5 Protein, Human • Lung Diseases • Bronchiectasis • Cilia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/942444

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Introduction

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive genetic disorder of ciliary motility. Although its prevalence is low, it varies widely between different ethnicities. One study [1] on over 182 000 individuals showed a prevalence that ranged from 1 in 9906 in Africans and African Americans to 1 in 16 309 in Latinos. The overall prevalence was estimated to be 1 in 7554 [1].

The mutated DNAH5 gene results in impairment of ciliary function. This dysfunction has diverse phenotypic forms leading to a wide array of changes in the cilia structure. Structural defects include missing dynein arms, central microtubule pairs, inner sheath, radial spokes, or nexin links, whereas functional defects include non-synchronous or asynchronous ciliary beating [2,3]. Ultimately, impaired ciliary motility results in defective mucociliary clearance in cilia-lining tracts. These changes cause recurrent respiratory tract manifestations [3]. PCD causes rhinitis, sinusitis, otitis media, and, ultimately, hearing impairment, in addition to lower respiratory tract infections and bronchiectasis [4]. Other conditions associated with PCD include infertility, hydrocephalus, and retinitis pigmentosa [4].

There are several ways of diagnosing PCD, each with its benefits and drawbacks. In addition to the clinical features, electron microscopic examination of ciliary ultrastructure is frequently used to support the diagnosis of PCD [5]. A less invasive investigation used to aid the diagnosis is nasal nitric oxide measurements [6]. Molecular genetic studies have been widely used to confirm the diagnosis of PCD [7,8]. With the clinical and genetic heterogeneity of PCD, diagnosis may sometimes be a challenge. In this paper, we present an interesting case with a clinical suspicion of PCD and unsolved diagnostic odyssey.

Case Report

Patient Information

The index patient was an 11-year-old girl. She presented to the Emergency Department of Prince Sultan Military Medical City (PSMMC), in Riyadh, with mild asthma exacerbation precipitated by flu-like illness, according to the Emergency Department doctor's impression, when patient's main concern was cough. She received inhaled bronchodilators and oral steroid and was referred to the pulmonary outpatient department (OPD).

Her past medical history revealed that she was born of a full-term pregnancy, normal vertex delivery with 2.8 kg birth weight and had no neonatal concerns. Her parents were first cousins with no family history of genetic or chronic lung disease. At the age of 4 years, she was diagnosed by her primary health care physician with seasonal asthma and allergic rhinitis, especially in winter. Furthermore, she had unexplained allergy when exposed to animals and grasses, with swollen eyes and runny nose. At the age of 6 years, she developed unexplained finger clubbing and mild stuttering. Her respiratory symptoms were controlled with no previous admission. She remained on episodic asthma therapy, especially during winter. She remained active like her siblings and developmentally normal.

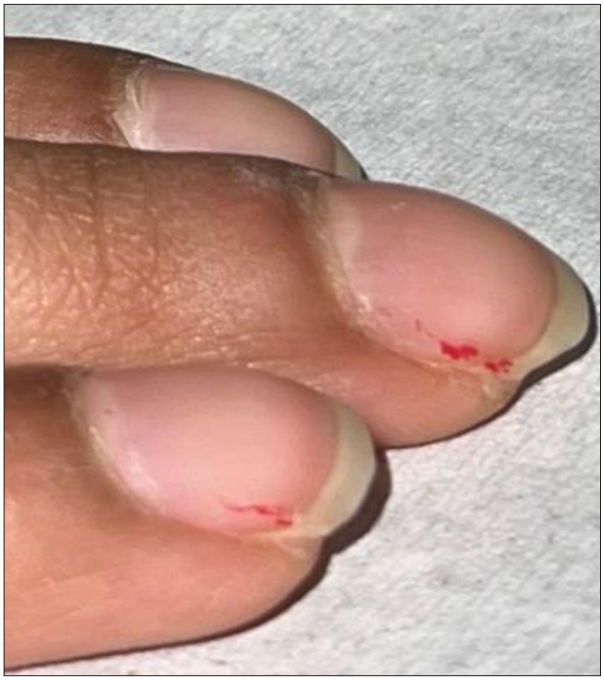

Figure 1. Grade 4 finger clubbing.

Physical Findings

The clinical assessment showed that our patient was healthy-looking with no respiratory distress. Her general examination showed grade 4 finger clubbing (**Figure 1**). She weighed 24 kg, 3 standard deviations below the mean, and she was 141 cm tall at the 50th centile. She had a BCG scar on her left arm. Her respiratory rate was 18 breaths/min with 98% oxygen saturation on room air. Her chest shape was normal, and chest auscultation revealed that the breath sounds were slightly reduced on the left side with no added sounds. The rest of the examination results were normal.

Diagnostic Assessment

The patient was investigated thoroughly in our pulmonary unit. A chest X-ray revealed multiple cavitations and cystic changes that were markedly worse, especially over the left upper lobe (**Figure 2**). A chest CT showed multiple cysts with different shapes and sizes. The largest cyst involved almost the whole left upper lung zone with bilateral bronchiectasis (**Figure 3**). As

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

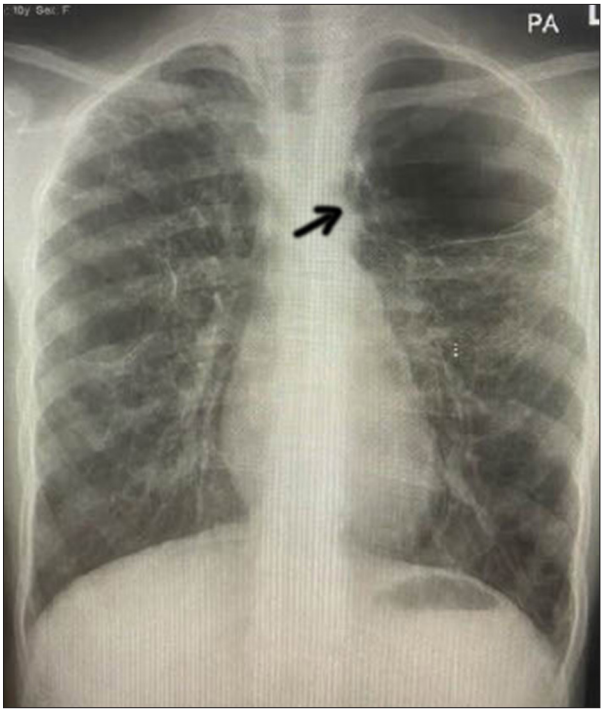

Figure 2. Chest X-ray with marked hyperinflation and marked radiolucency in the left upper zone, with no vascular vessels suggestive of a localized cyst (black arrow). Furthermore, multiple cavitations in the right upper and middle zones were observed.

per the radiologist's verbal report, there were bronchiectasis in some cuts bilaterally, which was hard to see because of the numerus cysts occupying both lung fields. Echocardiography was unremarkable with no evidence of pulmonary hypertension. Abdominal ultrasound was unremarkable with no evidence of internal organ cysts.

Blood test results revealed normal complete blood count with normal leukocyte, eosinophil, and absolute lymphocyte counts. Liver and kidney function tests were within normal limits.

Her immunology workup was normal, including immunoglobulins and lymphocyte subsets. The sweat chloride test was normal (58 mmol/l).

Exhaled nitric oxide was 90 ppb (normal is less than 18 ppb). The 6-minute exercise test was 450 meters with mild restriction and a Borg scale of 0 (normal). Her pulmonary function test showed a mild obstructive airflow limitation with FEV1 64% predicted. The skin test was negative for common aeroallergen.

Whole-exome sequencing revealed a class 2, likely pathogenic, heterozygous variant, c.5503C >T, p.(Gln1835*) in DNAH5, which creates a premature stop codon. This finding was also confirmed by whole-genome sequencing.

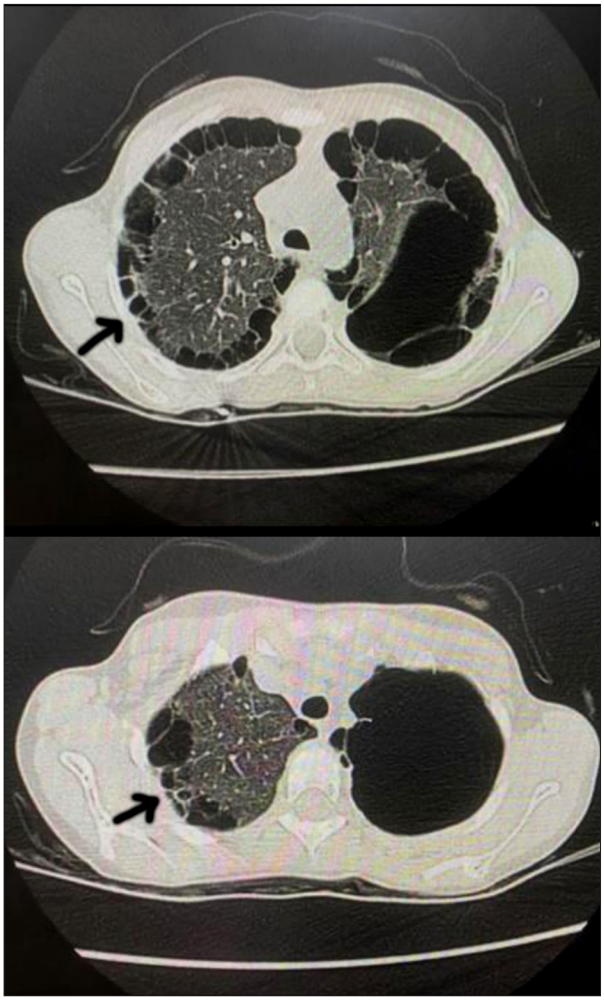

Figure 3. Axial chest CTs at different levels showing numerous subpleural (black arrows) and intraparenchymal lung cysts, worse on the left upper lobe.

Therapeutic Intervention

Our patient started asthma treatment as per step 2 asthma management according to SINA guidelines [9] (fluticasone 125 mg twice a day, a bronchodilator, inhaled nasal steroid spray, and normal saline). She was advised to avoid airplane travel, scuba diving, and strenuous exercises, knowing that pneumothorax is a potential complication that could occur at any time. Her repeated chest X-ray over a 1-year period did not show any change but was still alarming.

Discussion

In this report, we present a girl with chronic respiratory symptoms treated as asthma. However, her other symptoms and signs, including failure to thrive, clubbing, bronchiectasis, and lung cysts, were suggestive of another underlying chronic

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

pulmonary disease. Pulmonary tuberculosis, immunodeficiency, congenital lung malformations, and cystic fibrosis were initially considered. However, all these disorders were excluded after extensive workup. In view of the failure to thrive, clubbing, bronchiectasis, and lung cysts, the possibility of PCD was raised.

PCD is a heterogeneous hereditary disease that often presents with persistent tachypnea in the neonatal period which can resolve in a few weeks, followed by otitis media and speech delay due to conductive hearing loss in the second year, persistent sinus infection in toddlers, recurrent chest infection, and, eventually, infertility in adulthood [10]. Our patient did not pass through this classic course of PCD. Her neonatal history was unremarkable, and she did not develop recurrent otitis media as a toddler. Most PCD patients have a chronic productive cough as a prominent feature [11]. As effective cough could partially compensate for the impaired mucociliary clearance, the insult to the lungs will be milder and a bit later compared to CF patients [10-12]. Our patient had recurrent cough that resembled episodic asthma, which may suggest PCD. Clinical and radiographic evidence of bronchiectasis usually develops in patients with PCD as the disease progresses, often accompanied by digital clubbing. Our patient had a combination of bronchiectasis and finger clubbing, which makes PCD a likely diagnosis. *Pseudomonas aeruginosa* infection, including mucoid strains, has been reported in older PCD patients [11]. Despite sputum cultures, we were unable to confirm *Pseudomonas* infection in our patient. Furthermore, extensive immune workup was performed for our patient to exclude immune-related disorders that can present with a similar phenotype. Additionally, PCD and immunodeficiency do exist. A recent study reported the concurrence of PCD with panhypogammaglobulinemia in an adult patient with recurrent lower respiratory infections since childhood [13]. In a cohort of 168 patients, PCD and humoral immunodeficiency coexisted in 6.5% (11 patients) [14].

After excluding common causes of our patient's presentation, we proposed that the possible diagnosis was PCD. The parents refused the ciliary sampling; therefore, a molecular diagnostic plan was proposed. Initially, we performed Sanger sequencing of the *DNAH5* gene, which is implicated in the pathogenesis of PCD. However, we opted to perform whole-exome sequencing to exclude other inherited monogenic disorders that can present with similar phenotypes. WES failed to confirm the diagnosis of PCD, as it detected a heterozygous rather than a homozygous variant in the *DNAH5* gene. We proposed that a second variant in the *DNAH5* gene may have been missed by WES, as it may have been a deep intronic or promotor region variant or possibly a copy number variant (CNV). Therefore, we performed whole-genome sequencing, which is known to identify deep intronic variants and CNVs. However, WGS failed to identify a second variant in the *DNAH5* gene, and we were unable to establish the genetic confirmation of autosomal recessive PCD. We plan to reanalyze the WGS in the future. With the advent of technology and better coverage of genes, a genetic answer for this challenging case may resolve this diagnostic challenge in the future. According to our knowledge and upon reviewing the literature, no similar cases have been reported with such clinical and genetic findings.

Conclusions

This report describes a patient with a clinical finding of extensive lung cysts, bronchiectasis, and finger clubbing. Many differential diagnoses were considered and excluded. PCD was one of the probable differentials but was not established despite extensive investigations. WGS detected a heterozygous, likely pathogenic, variant in the *DNAH5* gene associated with PCD. Our case is a diagnostic dilemma that we hope will be solved in the future with development of better genetic tests.

Department and Institution in Which the Work Was Done

Pediatric Pulmonary Department at Prince Sultan Military Medical City (PSMMC) Hospital, Riyadh.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Hannah WB, Seifert BA, Truty R, et al. The global prevalence and ethnic heterogeneity of primary ciliary dyskinesia gene variants: A genetic database analysis. Lancet Respir Med. 2022;10(5):459-68
2. Cowan MJ, Gladwin MT, Shelhamer JH. Disorders of ciliary motility. Am J Med Sci. 2001;321(1):3-10
3. Damseh N, Quercia N, Rumman N, et al. Primary ciliary dyskinesia: Mechanisms and management. Appl Clin Genet. 2017;10:67-74
4. Goutaki M, Meier AB, Halbeisen FS, et al. Clinical manifestations in primary ciliary dyskinesia: Systematic review and meta-analysis. Eur Respir J. 2016;48(4):1081-95
5. Olin JT, Burns K, Carson JL, et al. Diagnostic yield of nasal scrape biopsies in primary ciliary dyskinesia: A multicenter experience. Pediatr Pulmonol. 2011;46(5):483-88
6. 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(6):574-81
7. Kim RH, A Hall D, Cutz E, et al. The role of molecular genetic analysis in the diagnosis of primary ciliary dyskinesia. Ann Am Thorac Soc. 2014;11(3):351-59
8. Lucas JS, Davis SD, Omran H, Shoemark A. Primary ciliary dyskinesia in the genomics age. Lancet Respir Med. 2020;8(2):202-16

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

9. Al-Moamary MS, Alhaider SA, Alangari AA, et al. The Saudi Initiative for Asthma-2021 Update: Guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med. 2021;16(1):4-56
10. Knowles MR, Daniels LA, Davis SD, et al. Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. Am J Respir Crit Care Med. 2013;188(8):913-22
11. Leigh MW, Pittman JE, Carson JL, et al. Clinical and genetic aspects of primary ciliary dyskinesia/Kartagener syndrome. Genet Med. 2009;11(7):473-87
12. Raoof S, Bondalapati P, Vydyula R, et al. Cystic lung diseases: Algorithmic approach. Chest. 2016;150(4):945-65
13. Kumar S, Ray A, Kabra SK, Sinha S. Coexistence of pan-hypogammaglobulinaemia and primary ciliary dyskinesia. BMJ Case Rep. 2022;15(5):e248812
14. Boon M, De Boeck K, Jorissen M, Meyts I. Primary ciliary dyskinesia and humoral immunodeficiency – is there a missing link? Respir Med. 2014;108(6):931-34

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]