

MUC5B Mutation Causes Mucociliary Dysfunction and Primary Ciliary Dyskinesia Like Illness in a Saudi Girl: A Case Report

Mukhtar G*, Alzaid M, Alsadoon H, Alenazi A, Eltahir S and Alotaibi W

Section of Pulmonary Medicine, Department of Pediatrics, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia

*Corresponding author:

Gawahir Mukhtar,
Pediatric Pulmonary Unit, Department of Pediatrics,
King Fahad, Medical City, Riyadh, Kingdom
of Saudi Arabia

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1. Abstract

1.1. Background: MUC5B is a major gel forming mucin in the lung that plays a key role in mucociliary clearance and host defense that is secreted from proximal submucosal glands and distal airway secretory cells. The MUC5B promoter variant is associated with enhanced expression of the MUC5B transcript in lung tissue from unaffected subjects and patients with idiopathic pulmonary fibrosis (IPF). In patients with IPF, excess MUC5B protein is especially observed in epithelial cells in the respiratory bronchiole and honeycomb cysts, regions of lung involved in lung fibrosis. However, it remains unclear how MUC5B leads to the development of IPF in adult. In mice, MUC5B is required for mucociliary clearance and for controlling inflammation after microbial exposure. The consequences of its loss in humans are unclear, however MUC5B homozygous variant has recently been reported in two affected siblings.

1.2. Case Presentation: We report an 8-year-old girl, from Saudi Arabia, a case of recurrent pulmonary exacerbation, bronchiectasis, and impaired mucociliary clearance secondary to homozygous variant in MUC5B. She presented with productive cough and recurrent pulmonary exacerbations. Her chest CT scan showed bronchiectasis in right upper posterior, right lower posterior and left lower posterior, associated with bronchial wall thickening as well as multiple centrilobular and tree-in-bud nodules more pronounced in the right lung, there is also mosaic sequencing study revealed homozygous variant in MUC5B gene. The patient has similar presentation to primary ciliary dyskinesia.

1.3. Conclusion: Homozygous variant in MUC5B was found to be associated bronchiectasis, impaired mucociliary clearance, and primary ciliary dyskinesia like illness in children. MUC5B cases were studied mainly in adult populations and few cases were reported in pediatrics. We recommended further studies regarding MUC5B mutation in children and to be considered in the diagnosis of a typical presentation of primary ciliary dyskinesia in children.

2. Introduction

MUC5B is a major gel forming mucin that is secreted from proximal submucosal glands and distal airway secretory cells in the lung, it plays a key role in mucociliary clearance and host defense [1]. It is a major contributor to the lubricating and viscoelastic properties of whole saliva, normal lung mucus and cervical mucus. This gene has been found to be up-regulated in some human diseases, including sinus mucosa of chronic rhinosinusitis (CRS), CRS with nasal polyposis, and Idiopathic Interstitial Pneumonia [2]. It was reported that bronchiectasis sputum exhibited increased percent solids, total and individual (MUC5B and MUC5AC) [3].

The MUC5B promoter variant is associated with enhanced expression of the MUC5B transcript in lung tissue from unaffected subjects and patients with idiopathic pulmonary fibrosis (IPF). In patients with IPF, excess MUC5B protein is especially observed in epithelial cells in the respiratory bronchiole and honeycomb cysts [4], regions of lung involved in lung fibrosis. However, it remains unclear how MUC5B leads to the development of IPF in adult.

In mice, MUC5B is required for mucociliary clearance and for controlling inflammation after microbial exposure. The consequences

of its loss in humans are unclear, however MUC5B homozygous variant has recently been reported in two affected siblings [5].

We report an 8-year-old girl, from Saudi Arabia, a case of recurrent pulmonary exacerbation with bronchiectasis secondary to homozygous variant in the MUC5B gene. The patient was labelled initially as primary ciliary dyskinesia based on her clinical history which was mainly due to mucociliary clearance dysfunction. Her whole exome sequencing study revealed homozygous variant in MUC5B gene, c.5145del p. (Thr1716Argf8*26). She has been treated with an airway clearance regimen and antibiotics as-needed basis. Mucolytic agents were trialed and she showed good response

MUC5B cases were studied in adult populations and few cases were reported in children.

3. Case Report

An 8-year-old girl, was referred from other hospital as a case of recurrent respiratory symptoms which started at early neonatal period, for further management.

She was outcome of uneventful pregnancy, full term, normal spontaneous vaginal delivery (NSVD), birth weight was 3 kg and mother had good antenatal care. No NICU admission after delivery, but she was admitted to hospital at the age of 10 days with history of fever, cough and shortness of breath. She had history of frequent admissions due to respiratory symptoms mainly cough and shortness of breath. Patient has persistent wet cough during the day time, and shortness of breath even with minimal activities. Her condition associated with persistent nasal discharge. She was treated as asthma with allergic rhinitis based on positive family history of asthma. Her response to asthma medications was variable. There was no history of recurrent ear infections, hearing loss, congenital heart disease, laterality defects, or gastrointestinal symptoms. The family history was significant for consanguinity, with her parents being first cousins, no family history of inherited disorders.

On clinical examination, she was in respiratory distress and was failing to thrive. No dysmorphic features were noted, but she had clubbing. Her vital signs showed tachypnea, and she had reduced air entry bilaterally and bilateral crackles on auscultation. Her other systemic examinations including cardiovascular examination were unremarkable.

Initial basic laboratory workup was normal. Other investigations including immunoglobulin, flow cytometry, celiac profile and sweat chloride test were normal.

The possibility of primary ciliary dyskinesia was raised based on persistent wet cough and nasal discharge, especially when her images including CXR and high-resolution thin-section chest computed tomography scan (HRCT) showed multifocal bilateral

bronchiectatic changes associated with bronchial wall thickening as well as multiple centrilobular and tree-in-bud nodules more pronounced in the right lung (Figure 1-4).

Pulmonary function testing showed moderately irreversible obstructive pulmonary function with a predicted FEV1 of 46% predicted (Figure 5).

Sputum cultures repeatedly grew *S. aureus*, and never grew *Haemophilus influenzae* or *Pseudomonas aeruginosa*.

The patient had extensive work up for primary ciliary dyskinesia including genetic tests and nasal/bronchial brush biopsies for electronic microscopy.

The biopsies for electronic microscopy were done two times, the first nasal brush biopsy showed small fragments of squamous epithelium only. No ciliated epithelium found after multiple deeper section.

The Second biopsy (bronchial brush): Showed possible shortened or absent inner dynein arms in more than 50% of the cross sections.

The Primary Ciliary Dyskinesia panel (PCD Panel) was sent and a potentially relevant heterozygous variant was detected (DNAAF5). Segregation analysis for the parents was done for DNAAF5, and the result came as mother was heterozygous for DNAAF5, and father was negative.

Cardiac assessment and echocardiogram showed mild Tricuspid Regurgitation with PG = 25 mmHg. No sign of pulmonary hypertension (PHTN). Tympanometry and visual examination of the ear drums were normal.

The patient had regular follow up in primary ciliary dyskinesia clinic, as she was labelled initially as primary ciliary dyskinesia (PCD) based on the previous mentioned investigations, and she was treated accordingly. She was admitted many times electively for pulmonary exacerbations and for workup because her picture was not fully matching with primary ciliary dyskinesia (PCD). A whole exome sequencing came homozygous of uncertain significance in MUC5B, c.5145del p. (Thr1716Argf8*26).

She has been treated with an airway clearance regimen and antibiotics as-needed basis. Mucolytic agents were trialed and she showed good response.



Figure 1: CXR: Showed bilateral airspace infiltration and peribronchial thickening

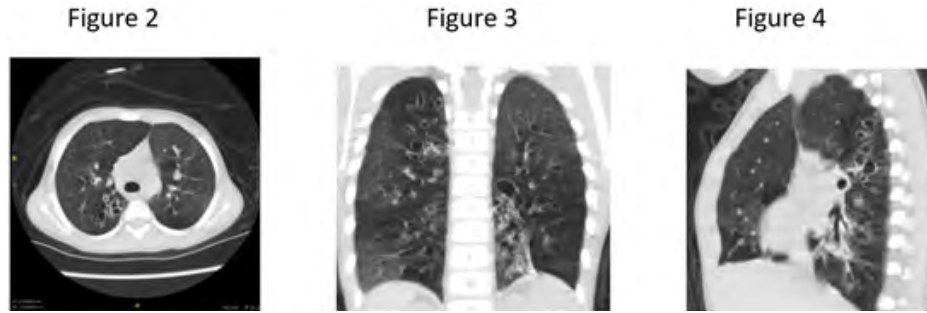


Figure 2,3 & 4: HRCT showed bilateral bronchiectasis, bronchial wall thickening

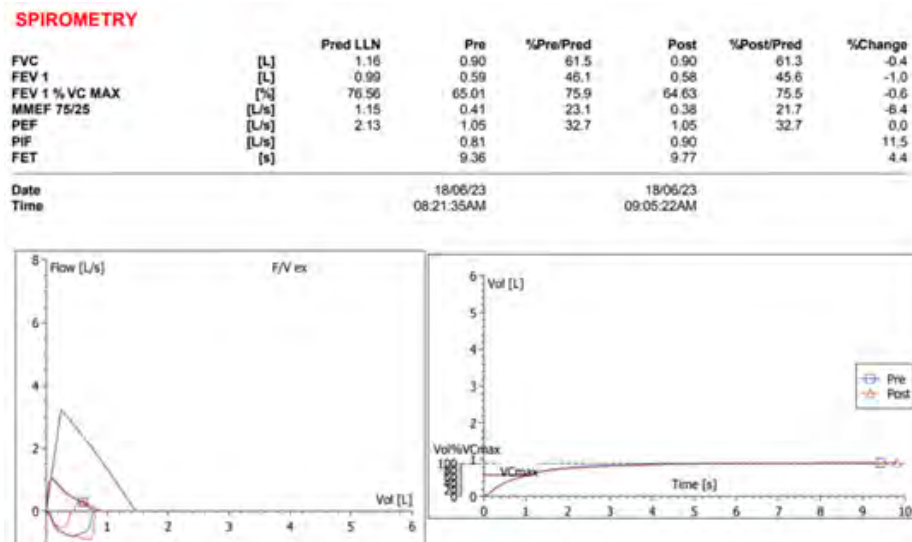


Figure 5: Spirometry showed moderate irreversible obstructive lung disease

4. Discussion

In the normal lungs, mucus is responsible for clearance of trapping inhaled particles and organisms, and transporting them out of the airways by ciliary and cough-driven forces. Mucins are the glycosylated proteins in mucus, are primarily responsible for giving mucus their viscoelastic properties. Up to now, about 20 mucin genes have been identified. Among these, 11 are expressed in the lungs, including MUC1, 2, 3, 4, 5AC, 5B, 6, 7, 8, 13, and 19 [6]. Among these, MUC2, MUC5AC, MUC5B, and MUC19 are secreted, and MUC5AC and MUC5B are the major mucins.

MUC5AC and MUC5B are synthesized by surface goblet cells and submucosal glandular cells. They are expressed throughout the upper and lower respiratory tract. In distal airways, MUC5B is the dominant gel-forming mucin, and little MUC5AC is present.

Mucus overproduction contributes to the morbidity of many airway diseases, the most common are chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis (CF) [7]. In addition, the overproduction of MUC5B contributes to the development of IPF resulting from excessive lung injury and aberrant repair [8]. Although the mechanisms remain unclear, the associated hypotheses or possibilities are consistent.

First, excessive MUC5B compromises the mucosal host defense and reduces lung clearance of inhaled particles and microorgan-

isms. Over time, reduced clearance may lead to scar tissue formation and persistent fibroproliferation and subsequent interstitial injury.

Second, excessive MUC5B in the respiratory bronchioles may interfere with alveolar repair either by interfering with the interaction between type II alveolar epithelial cells and the underlying matrix or by interfering with the surface-tension properties of the surfactant [9]. The damaged alveoli could enhance the collapse and fibrosis of bronchoalveolar units and lead to the development of idiopathic pulmonary fibrosis (IPF).

The changes of MUC5B in the distal conducting airways potentially enhance injury or disrupt repair responses in alveoli. The two mechanisms are plausible and may act alone or together to contribute to the development of idiopathic pulmonary fibrosis.

Up to now, extensive genome-wide linkage scanning has identified a single nucleotide polymorphism (SNP) in the promoter region of the MUC5B gene (rs35705950) that is the principal risk factor for developing IPF, accounting for 30–35% of the risk [10]. Many individuals with this SNP rs35705950 that do not develop to IPF [11] therefore, even sharing the same genetic variant, different individuals do not necessarily have the same disease pattern. In this situation, other risk factors include environmental factors include occupational exposure such as asbestos, cigarette smoking,

and some viruses such as hepatitis C, adenovirus, and herpesvirus. These environmental factors change the expression of MUC5B [12].

Daniel Song and his coworkers tried to understand the individual role of MUC5B and MUC5AC in mucus transport, and they found that MUC5B deficiency leads to impaired mucus clearance, whereas MUC5AC deficiency leads to transport that lacks spatial coordination, demonstrating the importance of each mucin to airway clearance [13].

People with the MUC5B promoter variant produce higher quantities of MUC 5B in lung parenchyma and airways. The mechanisms that linking the MUC5B promoter variant with IPF risk are still under investigation, the relative overabundance of the MUC5B protein may lead to local recruitment of immune cells that leads to long-term damage and lung fibrosis [14].

In adult population, the MUC5B promoter polymorphism is the strongest and the most replicated genetic risk factor for idiopathic lung fibrosis (IPF), appears to be protective and predictive in this disease, and is likely involved in IPF pathogenesis through an increase in MUC5B expression in terminal bronchi and honeycombed cysts [15]. It also was found to be associated with interstitial lung disease in the general population, this association was more apparent in old age population [16].

Regarding the effects of other mutations on MUC5B Expression, mutations in the genes for surfactant protein C (SPC) and surfactant protein A2 (SPA2) have been described in association with familial interstitial pneumonia (FIP) and rarely with sporadic idiopathic pulmonary fibrosis (IPF). Liptzin et al. showed that MUC5B was increased in bronchoalveolar lavage (BAL) and lung tissues of pediatric IPF patients with SPC mutations compared with the controls, indicating that MUC5B may play a role in the development of IPF in patients with SPC mutations [17].

Regarding the clinical presentations in adult, dyspnea is the most frequent symptom reported by patients with IPF at the initial visit. Several studies have shown correlations between the severity of dyspnea and quality of life and survival in patients with IPF [18]. Cough is also a common symptom in patients with IPF and is more prevalent in patients who have never smoked or in those who have more advanced disease. Cough is significantly associated with the presence of the minor allele of a MUC5B promoter polymorphism [19].

Fine crackles, predominantly in the lower posterior lung zones, are commonly reported in patients with IPF, and clubbed fingers are reported in 30%–50% of patients which was correlated with the extent of smooth muscle proliferation within areas of fibrotic change in lung biopsy specimens [20].

Changes in pulmonary function test are clearly an important predictor of mortality due to IPF, particularly declines in FVC, total lung capacity, alveolar–arterial gradient, and DLCO. A decline in

FVC over a period of 6 or 12 months reliably predicts mortality [21].

In pediatrics, no enough studies were reported for MUC5B mutations, however Gregory and his colleagues performed whole-genome sequencing in an adult patient with recurrent pulmonary exacerbations and unexplained bronchiectasis. Her symptoms started at early infancy with exacerbations every 1–2 months. Genotyping with reverse phenotyping was done for her and the eight family members. Immunofluorescence staining and mass spectrometry for mucins, were performed across accessible sample types. The patient, and her symptomatic sibling who also had extensive sinusitis with nasal polyps, were homozygous for a novel splicing variant in the MUC5B gene (NM_002458.2: c.1938 + 1G>A). MUC5B was absent from sputum, saliva, and nasal secretions. Mucociliary clearance was impaired in the patient. Three siblings were found to be heterozygous for the familial MUC5B variant and they were asymptomatic but had a shared pattern of mild lung function impairments [5].

In our proband, her symptoms started at early neonatal period with same presentation of recurrent pulmonary exacerbations, productive cough, and persistent nasal discharge. She developed bronchiectasis at age of 4 year. Sputum cultures repeatedly grew *S. aureus*, immune deficiency and cystic fibrosis were ruled out. Her pulmonary function test showed moderate reduction in FVC and FEV1. The possibility of Primary Ciliary Dyskinesia as a cause of her symptoms was raised based on the positive PCD Panel result, a potentially relevant heterozygous variant was detected (DNAAF5). Her electronic microscopy results were inconclusive, in the first nasal brush biopsy, no ciliated epithelium was found after multiple deeper section. The Second biopsy (bronchial brush) showed possible shortened or absent inner dynein arms in more than 50% of the cross sections. Segregation analysis for the parents was done for DNAAF5, and the result came as mother was heterozygous for DNAAF5). A whole exome sequencing was sent because PCD does not match her clinical presentation and it revealed homozygous of uncertain significant in MUC5B, c.5145del p. (Thr1716Argf8*26).

She has been treated with an airway clearance regimen and antibiotics as-needed basis. Mucolytic agents were trialed and she showed good response. Mucolytic treatment in adult results in acute clearance of inflammatory cells from the lungs, which is demonstrated by a significant and rapid diminishment in lung lavage leukocyte numbers. Hyper concentrated airway mucus is characteristic of subjects with bronchiectasis and hypertonic saline inhalation reduce non-cystic fibrosis bronchiectasis mucus concentration by 5% 3. Aggressive treatment of intercurrent infections is warranted, as antibiotics during periods of exacerbation would be expected to be lifesaving. Susceptibility to *S. aureus* infection may be increased. Currently our patient is receiving aggressive airway clearance, azithromycin as anti-inflammatory for bronchi-

ectasis, and mucolytic agents. She has regular follow up in a PCD multidisciplinary clinic.

Regarding the prognosis, MUC5B gene polymorphism appears to be predictive and prognostic in idiopathic pulmonary fibrosis (IPF) in adult populations. Georges et al studied the time to death in a cohort of patients diagnosed with IPF according to the presence or absence of the MUC5B gene polymorphism (G/T or T/T). They observed a trend for slower progression in the MUC5B group, this was not statistically significant as confounders like age, mood of treatment and follow up duration may have an impact on their finding [21].

5. Conclusion

Homozygous variant in MUC5B was found to be associated with bronchiectasis, impaired mucociliary clearance, and PCD like illness in children. MUC5B mutations were studied mainly in adult populations and few cases were reported in pediatrics. We recommended further studies regarding MUC5B mutation in children and the diagnosis should be considered on any child with bronchiectasis and recurrent pulmonary exacerbation after excluding PCD, CF, and primary immune deficiency.

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