Endobronchial mucosal nodules and actinomycosis in a child with activated phosphatidylinositol 3-kinase delta syndrome (APDS)

Kwan Fung LAM¹, Shun CHAN², Lok Sang KAM², Janette Kwok³, Pamela Pui-Wah LEE⁴, and David Shu-yan Lam²

¹Caritas Medical Centre
²Tuen Mun Hospital
³Queen Mary’s Hospital Department of Pathology and Department of Microbiology
⁴The University of Hong Kong Department of Paediatrics and Adolescent Medicine

March 21, 2023

Abstract

A 5-year-old girl had poor growth and unresolving pneumonia. There was persistent collapse-consolidation of the right middle lobe. CT thorax revealed bilateral bronchial wall thickening and dilatation. Bronchoscopy showed numerous endobronchial mucosal nodules, consisting of dense lymphoid infiltrates. Bacterial culture of the nodule biopsy suggested endobronchial actinomycosis. She had T-cell lymphopenia. Genetic test confirmed the diagnosis of activated phosphatidylinositol 3-kinase delta syndrome (APDS), an immunodeficiency condition.

Title: Endobronchial mucosal nodules and actinomycosis in a child with activated phosphatidylinositol 3-kinase delta syndrome (APDS)

Authors:

<table>
<thead>
<tr>
<th>Author</th>
<th>Affiliations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwan Fung LAM</td>
<td>Department of Paediatrics and Adolescent Medicine, Caritas Medical Centre, Hong Kong</td>
</tr>
<tr>
<td>Shun CHAN</td>
<td>Department of Surgery, Tuen Mun Hospital, Hong Kong</td>
</tr>
<tr>
<td>Lok Sang KAM</td>
<td>Department of Clinical Pathology, Tuen Mun Hospital, Hong Kong</td>
</tr>
<tr>
<td>Janette KWOK</td>
<td>Division of Transplantation and Immunogenetics, Department of Pathology, Queen Mary Hospital,</td>
</tr>
<tr>
<td>Pamela Pui-Wah LEE</td>
<td>Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine,</td>
</tr>
<tr>
<td>David Shu-yan LAM</td>
<td>Department of Paediatrics and Adolescent Medicine, Tuen Mun Hospital, Hong Kong</td>
</tr>
</tbody>
</table>

Abstract: A 5-year-old girl had poor growth and unresolving pneumonia. There was persistent collapse-consolidation of the right middle lobe. CT thorax revealed bilateral bronchial wall thickening and dilatation. Bronchoscopy showed numerous endobronchial mucosal nodules, consisting of dense lymphoid infiltrates. Bacterial culture of the nodule biopsy suggested endobronchial actinomycosis. She had T-cell lymphopenia. Genetic test confirmed the diagnosis of activated phosphatidylinositol 3-kinase delta syndrome (APDS), an immunodeficiency condition.

Keywords:

Endobronchial nodules
Activated phosphatidylinositol 3-kinase delta syndrome (APDS)
Bronchial actinomycosis

Cobblestone airway

A 5-year-old Chinese girl had persistent cough for a few months following an acute episode of pneumonia, despite multiple courses of oral and intravenous antibiotics. The serial chest X-rays (CXR) showed non-resolving consolidation of the right middle lobe (RML) (Figure 1a). The inflammatory markers including white cell count, neutrophil count, C-reactive protein, erythrocyte sedimentation rate and procalcitonin were normal. *Haemophilus influenzae* and *Moraxella Catarrhalis* were isolated from two respiratory specimens respectively, and antibiotics had been given accordingly. The workup for pulmonary tuberculosis was negative.

In retrospect, she had poor growth and recurrent wet cough since 3 years old, recurrent snoring since infancy, and self-limiting febrile illnesses 2-3 times per year. She did not have swallowing dysfunction.

On physical examination, she did not have respiratory distress, finger clubbing, chest deformity, lymphadenopathy, hepatomegaly, or splenomegaly. Her breath sound was normal. Her oral and dental condition was good. There was bilateral grade 3 tonsillar hypertrophy. Her oxygen saturation was normal.

The immunological workup showed T-cell and NK cell lymphopenia (table 1).

High-resolution computed tomography (HRCT) of the thorax revealed diffuse bronchial wall thickening and RML collapse. There was mucus plugging and bronchiectasis of both lower lobes. It also showed mosaic attenuation of both lungs, suggestive of small airway disease. (Figure 1b)

Bronchoscopy found numerous whitish mucosal nodules from the trachea to the bilateral major segmental bronchi, resembling cobblestone appearance. The RML opening was completely obliterated by the nodules (Figure 1d-e). On air injection, the RML bronchus opened and pus came out.

The biopsy of the endobronchial lesions showed dense lymphoid infiltrates and some polymorphs in the underlying stroma (Figure 1c). The lymphoid cells included mixed populations of CD3+ and CD20+ cells. There was no light chain restriction by immunostaining. There was no granuloma or malignancy. Bacterial culture of the biopsy yielded *Actinomyces odontolyticus*, whereas the AFB culture was negative.

She was treated with intravenous benzylpenicillin (300,000 units/kg/day) for four weeks, followed by oral amoxicillin (45mg/kg/day) for six months. Her cough and snoring resolved, and she had better weight gain. On follow-up bronchoscopy, the endobronchial nodules became remarkably fewer and smaller (Figure 1f). The appearance in CT thorax also improved notably.

We suspected she had inborn error of immunity, as she had T-cell and NK cell lymphopenia, failure to thrive, endobronchial actinomycosis (not typical in children), non-resolving pneumonia, and atypical endobronchial appearance.

Genetic testing by next generation sequencing gene panel revealed de novo nucleotide substitution c.3061G>A of exon 24 in the *PIK3CD* gene. This missense variant caused a substitution of a glutamic acid residue with lysine at codon 1021 of the *PIK3CD* protein (pGlu1021Lys), which is a hotspot mutation. The diagnosis of activated phosphatidylinositol 3-kinase delta syndrome (APDS) was made. She was put on long-term sirolimus and monthly immunoglobulin infusion. She remains free of pneumonia, frequent infection, or atypical infection.

Discussion

In the literature, there is limited information about the condition of diffuse endobronchial nodules, or ‘cobblestone airway’, especially in children.

In adults, there are reports about its association with chronic eosinophilic pneumonia, Churg-Strauss syndrome, hypereosinophilic syndrome, lymphoma, Sjogren’s syndrome, pulmonary sarcoidosis, neurofibromatosis type 1, and tracheobronchopathia osteochondroplastica.
In children, some reports suggest that it is caused by mucosal irritation resulting from factors like gastroesophageal reflux (GERD) or pulmonary infection. Contrasting, Dave et al described that tracheal cobblestoning in otherwise healthy children is common, and not associated with GERD or respiratory infection.

Meanwhile, some authors reported that diffuse endobronchial nodules were seen in individuals with APDS and actinomycosis respectively.

In a series of 53 individuals with APDS, five (9%) had mucosal nodular lymphoid hyperplasia in the lower airway visualized as cobblestone-like plagues or polyps. Biopsy specimens from the mucosal lesions showed follicular hyperplasia. The most common findings in CT thorax in this series are air-space opacity, tree-in-bud opacities, bronchial wall thickening, bronchiectasis, mosaic attenuation, and mediastinal lymphadenopathy.

Thoracic actinomycosis, occurring mostly in adults, usually presents as slowly progressive chronic pneumonia or chest wall mass. Despite this, Kalai et al described an adult case of bronchial actinomycosis with diffuse mucosal nodules in the lower airway.

In our case, the CT and endoscopic appearance improved significantly following targeted antibiotic therapy against actinomycosis, even before the diagnosis of immunodeficiency was made. We believe that both APDS and actinomycosis contributed to the pathogenesis of the diffuse endobronchial nodules.

Activated phosphoinositide 3-kinase delta syndrome (APDS) is a combined immunodeficiency syndrome. One cause is a gain-of-function mutation in PIK3CD, a phosphoinositide 3-kinase (PI3K) gene encoding p110δ. PI3Ks are enzymes involved in cellular functions. Class IA PI3Ks involve in lymphocyte signaling by activating protein kinase B (PKB, also known as AKT) in the PI3K/AKT/mTOR/S6K pathway, which plays a major role in controlling lymphocyte proliferation, differentiation, function, and survival. This group of PI3Ks comprise of a catalytic (variants include p110α, β, and δ) and a regulatory subunit (variants include p85α, p85β, and p55). PI3Kδ, a class IA isoform comprising of p110δ and p85δ, is expressed predominantly in leukocytes. Mutations in PIK3CD result in the hyperactivation of the PI3K/AKT/mTOR/S6K signaling pathways in the leukocytes, causing aberrant differentiation of B cells and T cells. These lymphocytes have abnormal proliferation, poor functioning and die earlier than usual.

The hallmark of APDS is low naïve CD4 and CD8 T cells. Affected individuals usually have recurrent sinopulmonary infections, bronchiectasis, lymphadenopathy, nodular lymphoid hyperplasia in mucosal tissues, increased incidence of EBV and CMV infections, autoimmunity, lymphoma, neurodevelopment delay and growth retardation.

Management options include antibiotic prophylaxis, immunoglobulin replacement, immunosuppressive therapies (such as steroids and rituximab), mTOR inhibition with sirolimus, and hematopoietic stem cell transplantation. Targeted therapies like selective PI3Kδ inhibitors are under development.

In the past, many APDS cases were diagnosed some years after the initial presentation, when complications and structural damages had already been established. Some patients remained undiagnosed until adolescence and adulthood. With advances in genetic testing, APDS (and many other conditions of inborn error of immunity) can be diagnosed timely. Early recognition of the disease presentation and prompt referral for immunological and genetic evaluation help to improve the outcome of these children.

Table 1: Immunological workup

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Result</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell</td>
<td>4.7</td>
<td>3.0-18.0 x 10^9/L</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>2.9</td>
<td>1.5-8.5 x 10^9/L</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>1.3</td>
<td>1.5-7.0 x 10^9/L</td>
</tr>
<tr>
<td>Monocyte</td>
<td>0.4</td>
<td>0.2-1.8 x 10^9/L</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>0.1</td>
<td>0.0-0.4 x 10^9/L</td>
</tr>
</tbody>
</table>
Basophil                  0.0  0.0-0.1 x 10^9/L
RBC                      4.5  3.3-6.0 x 10^12/L
Platelet                 221.0 150-400 x 10^9/L
Haemoglobin              12.8  9.5-16.5 g/dL
IgG                      1332.0 724-1380 mg/dL
IgA                      100.0  68-229 mg/dL
IgM                      198.0  88-275 mg/dL
IgE                      <30  <100 IU/mL
B-cells (CD19) %          31.0  14-21%
B-cells (CD19) number     422.0 300-500 /uL
CD3 T-cell %              59.8  64-72.5%
CD3 T-cell number         805.0 1300-2200 /uL
CD4 T-cell %              35.4  29.5-35.5%
CD4 T-cell number         477.0 600-1100 /uL
CD8 T-cell %              21.6  24-33.5%
CD8 T-cell number         291.0 500-1000 /uL
CD4:CD8                  1.6  0.9-1.4
NK cells (CD16/CD56) %    8.2  11-23%
NK cells (CD16/CD56) number 111.0 300-500 /uL
T-cell recombination excision circles (TREC) study Normal
Kappa-deleting recombination excision circles (KREC) study Normal

Figure 1.

a. Chest x-ray
b. HRCT thorax
c. Microscopy of the biopsy of an endobronchial nodule (Hematoxylin-eosin staining, x10), showing dense lymphoid infiltrates
d. Bronchoscopic image of the carina, at diagnosis
e. Bronchoscopic image of the bronchus intermedius and the opening of right lower lobe (RLL), at diagnosis; The RML opening was obliterated by the endobronchial nodule and not visible.
f. Bronchoscopic image of the bronchus intermedius and the opening of RML and RLL, after the 7 months of antibiotic treatment

(black arrow: right main bronchus; white arrow: superior segment of RLL; grey arrow: basal segment of RLL; stripe arrow: RML)
Reference


Hosted file