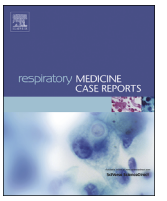
Respiratory Medicine Case Reports 45 (2023) 101909

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

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

Kwan Fung Lam [a, *], Shun Chan [b], Lok Sang Kam [c], Janette Kwok [d], Pamela Pui-Wah Lee [e], David Shu Yan Lam [f]

[a] Department of Paediatrics and Adolescent Medicine, Caritas Medical Centre, Hong Kong, China
[b] Department of Surgery, Tuen Mun Hospital, Hong Kong, China
[c] Department of Clinical Pathology, Tuen Mun Hospital, Hong Kong, China
[d] Division of Transplantation and Immunogenetics, Department of Pathology, Queen Mary Hospital, Hong Kong, China
[e] Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[f] Department of Paediatrics and Adolescent Medicine, Tuen Mun Hospital, Hong Kong, China

ARTICLE INFO

Handling Editor: DR AC Amit Chopra

Keywords:
Endobronchial nodules
Activated phosphatidylinositol 3-kinase delta syndrome (APDS)
Bronchial actinomycosis
Cobblestone airway

ABSTRACT

In this report, we describe a case of a 5-year-old girl with poor growth and unresolving pneumonia. Bronchoscopy showed numerous endobronchial mucosal nodules, consisting of dense lymphoid infiltrates. Bacterial culture of the nodule biopsy suggested endobronchial actinomycosis. Genetic test confirmed the diagnosis of APDS.

1. Introduction

The condition of diffuse endobronchial nodules is rare in children. It can be a respiratory manifestation of activated phosphatidylinositol 3-kinase delta syndrome (APDS), an immunodeficiency condition. Nonetheless, it has never been reported that actinomycosis was a possible contributing factor of the pathogenesis of the endobronchial nodules in APDS patients. Here we describe a case of a 5-year-old girl with poor growth and unresolving pneumonia. Bronchoscopy showed numerous endobronchial mucosal nodules, consisting of dense lymphoid infiltrates. Bacterial culture of the nodule biopsy suggested endobronchial actinomycosis. Genetic test confirmed the diagnosis of APDS.

2. Case presentation

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) (Fig. 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.

* Corresponding author.
E-mail address: lkf166@ha.org.hk (K.F. Lam).

https://doi.org/10.1016/j.rmcr.2023.101909
Received 12 April 2023; Accepted 11 August 2023
Available online 15 August 2023

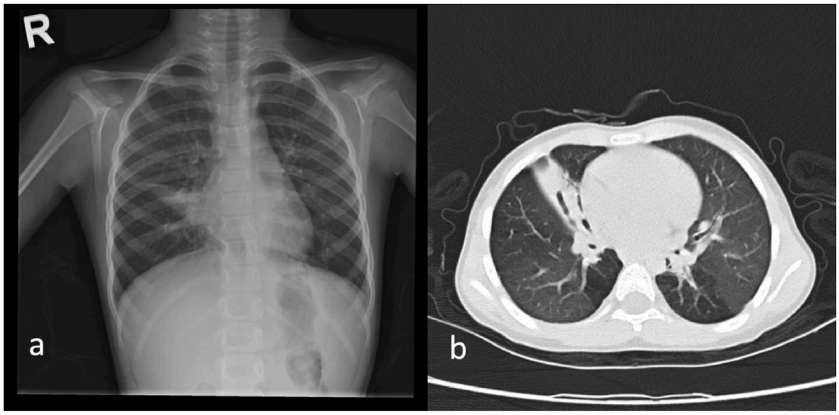


Fig. 1. a. Chest x-ray
b. HRCT thorax.

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 (Fig. 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 (Fig. 2a–b). On air injection, the RML bronchus opened and pus came out.

Table 1
Immunological workup.

Blood test	Result	Reference range
White blood cell	4.7	3.0–18.0 × 10^9/L
Neutrophil	2.9	1.5–8.5 × 10^9/L
Lymphocyte	1.3	1.5–7.0 × 10^9/L
Monocyte	0.4	0.2–1.8 × 10^9/L
Eosinophil	0.1	0.0–0.4 × 10^9/L
Basophil	0.0	0.0–0.1 × 10^9/L
RBC	4.5	3.3–6.0 × 10^12/L
Platelet	222.0	150–400 × 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	

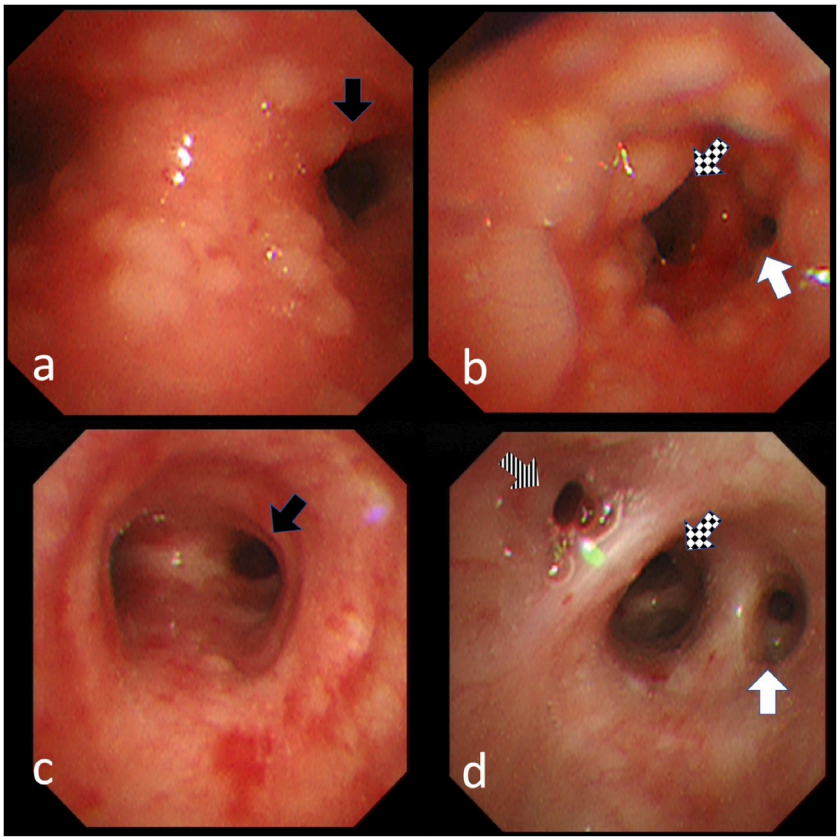


Fig. 2. Bronchoscopic images (black arrow: right main bronchus; white arrow: superior segment of the right lower lobe (RLL); checked arrow: basal segment of RLL; striped arrow: right middle lobe (RML))
a. Carina, at diagnosis
b. Bronchus intermedius and the opening of RLL, at diagnosis; The RML opening was obliterated by the endobronchial nodule and not visible.
c. Lower trachea and carina, after the 7 months of antibiotic treatment
d. Bronchus intermedius and the opening of RML and RLL, after the 7 months of antibiotic treatment.

The biopsy of the endobronchial lesions showed dense lymphoid infiltrates and some polymorphs in the underlying stroma (Fig. 3a). The lymphoid cells included mixed populations of $CD3^+$ and $CD20^+$ cells (Fig. 3b–c). 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.

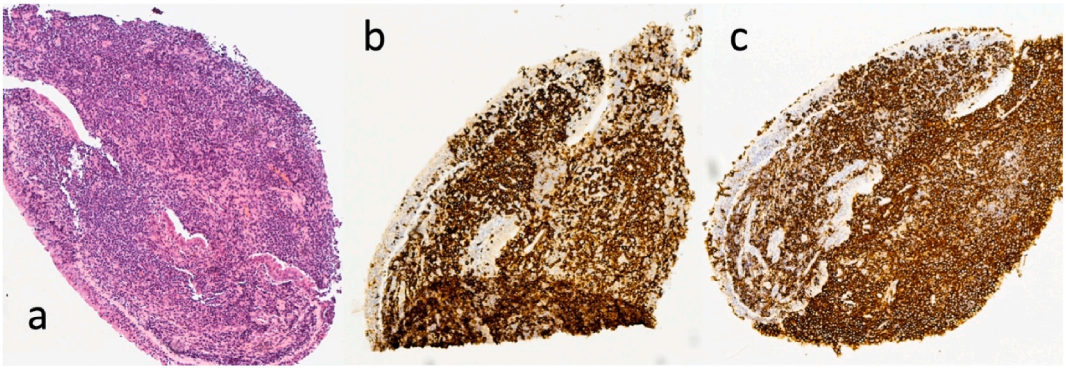


Fig. 3. Microscopy of the biopsy of an endobronchial nodule
a. Hematoxylin-eosin staining, x10, showing dense lymphoid infiltrates
b. Immunohistochemical CD3 staining, x10
c. Immunohistochemical CD20 staining, x10.

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 (Fig. 2c–d). 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.

3. Discussion

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

There are reports of adult cases about its association with chronic eosinophilic pneumonia [1,2], Churg-Strauss syndrome [3], hypereosinophilic syndrome [4], lymphoma [5], Sjögren's syndrome [6], pulmonary sarcoidosis [7], neurofibromatosis type 1 [8], and tracheobronchopathia osteochondroplastica [9]. On the other hand, Dave et al. described that tracheal cobblestoning in otherwise healthy children is common, and not associated with GERD or respiratory infection [10].

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 [11], 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 [12]. Despite this, Kalai et al. described an adult case of bronchial actinomycosis with diffuse mucosal nodules in the lower airway [13]. Yilin et al. also described a case of pulmonary actinomycosis in a teenage presenting with a lump on the chest wall [14].

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, functioning, 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 p85α, 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 naive 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 [15,16].

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.

4. Conclusion

Diffuse endobronchial nodules, a rare condition in children, can be a manifestation of APDS. Actinomycosis is a possible contributing factor of the pathogenesis of the endobronchial nodules in our case. Obtaining biopsy of the nodule for histological and microbiological studies helps in identification of the aetiologies.

5. Declaration

This project did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None

References

[1] C.D. Martinez-Balzano, A. Sosa, S. O'Reilly, Y. Gong, R.A. Irwin, 66-Year-Old man with a past history of relapsing polychondritis presented with right upper lobe consolidation, nodular airway lesions, and a corticosteroid-responsive chronic cough, Chest 148 (5) (2015 Nov) e142–e147.

[2] F. Zhao, Y. Jiang, S. Ma, W. Zhang, Y. Jiang, A case with nodular airway lesions misdiagnosed as difficult-to-treat asthma, Ann. Allergy Asthma Immunol. 123 (2) (2019 08) 217–219.

[3] H. Matsushima, N. Takayanagi, K. Kurashima, et al., Multiple tracheobronchial mucosal lesions in two cases of Churg-Strauss syndrome, Respirology 11 (1) (2006) 109–112.

[4] H. Wakamaya, Y. Itoh, H. Maeda, et al., A case of hypereosinophilic syndrome presenting endobronchial lesion with multiple nodules and pulmonary lesion at onset, J. Jpn. Soc. Bronchol. 16 (4) (1994) 397–403.

[5] D. Gurminder, Z. Andrew, Endobronchial nodules: a rare manifestation of non-Hodgkin's lymphoma, Chest 150 (issue 4) (October 2016) supplement, 1064a.

[6] H. Hara, K. Kuwano, S. Minagawa, T. Numata, J. Araya, K. Nakayama, Macroscopic inflammatory tracheal and endobronchial nodules in Sjogren's syndrome, Thorax 72 (9) (2017 09) 864–865.

[7] K.H. Cho, J.H. Shin, S.H. Park, H.S. Kim, S.H. Yang, A case of pulmonary sarcoidosis with endobronchial nodular involvement, Tuberc. Respir. Dis. 74 (6) (2013 Jun) 274–279.

[8] H.M. Pascoe, P. Antippa, L. Irving, M. Christie, McCusker MW Rare manifestation of Neurofibromatosis type 1: a plexiform neurofibroma involving the mediastinum and lungs with endobronchial neurofibromata, J. Med. Imag. Radiat. Oncol. 63 (1) (2019 Feb) 76–78.

[9] S. Decalmer, A. Woodcock, M. Greaves, M. Howe, Smith J Airway abnormalities at flexible bronchoscopy in patients with chronic cough, Eur. Respir. J. 30 (6) (2007 Dec) 1138–1142.

[10] Dave MH, Gerber A, Bailey M, et al. Prevalence and characteristics of tracheal cobblestoning in children. Pediatr. Pulmonol.; 50(10):995–999.

[11] Coulter TI, Chandra A, Bacon CM, et al Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: a large patient cohort study. J. Allergy Clin. Immunol., 139 (2). 597-606.e4.

[12] David W. Kimberlin, Elizabeth D. Barnett, Lynfield Ruth, Mark H. Sawyer, "Actinomycosis", Red Book: 2021–2024 Report of the Committee on Infectious Diseases, Committee on Infectious Diseases, American Academy of Pediatrics, 2021.

[13] U. Kalai, V. Hadda, K. Madan, et al., A 35-year-old woman with productive cough and breathlessness, Lung India 32 (2015) 651–654.

[14] Z. Yilin, L. Xinyi, S. Longwei, Z. Hongwu, Pediatric pulmonary actinomycosis: a misdiagnosed case report, Front. Pediatr. 10 (2022) 955554.

[15] A.M. Condliffe, A. Chandra, Respiratory manifestations of the activated phosphoinositide 3-kinase delta syndrome, Front. Immunol. 9 (2018) 338, https://doi.org/10.3389/fimmu.2018.00338.

[16] Michalovich D, Nejentsev S Activated PI3 kinase delta syndrome: from genetics to therapy. Front. Immunol. 9:369. doi: 10.3389/fimmu.2018.00369.