Rare disease

Difficult to control asthma in the patient with pseudoachondroplasia

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Summary

Pseudoachondroplasia (PsA) is a type of short-limbed dwarfism resulting from mutations in the cartilage oligomeric matrix protein gene. Skeletal involvement in the PsA is well-described but there are not any published cases reporting airways involvement. The authors present a case of a female with the PsA and congenital anomalies of the respiratory tract resulting in the tracheobronchomalacia and a difficult to control asthma.

BACKGROUND

Pseudoachondroplasia (PsA) is a rare condition affecting about 4 people per million population.¹ According to the international nomenclature of constitutional disease of bone, PsA has been classified as a form of the osteochondrodysplasia identifiable in a later life. PsA was first described in 1959 but gene responsible for the condition was not identified till 1995.²

Disease arises from mutations in the cartilage oligomeric matrix protein (COMP) gene which is expressed primarily in the cartilage, ligament and tendon. Toxic intracellular retention of the extracellular matrix proteins leads to chondrocyte cell death and decreased linear bone growth.³

To our knowledge, there are not any published cases which would describe patients with PsA and extra skeletal involvement of the respiratory tract. We present a case of patient with PsA, tracheobronchomalacia, dysgenesis of the left pulmonary artery and a bronchial asthma which requires multidisciplinary input and raises important and challenging questions regarding the management and a long-term follow-up.

CASE PRESENTATION

A 47-year-old woman has had a respiratory follow-up since the early adulthood. She weighted 6 lbs 8 ozs at the birth and problems were not noted until she was about 3 years of age when an asthma attack brought her to medical attention for the first time. At that point, the patient was noted to have a small stature. Growth hormone estimations were done and found to be normal. She began her periods at 15 years of age and is intellectually normal. The patient is of a small stature, height 113 cm, sitting height 65.5 cm. Her head circumference is of normal proportions 50.6 cm. Spine is straight but short; limbs are also short with rhizomelic shortening. She has prominent joints with limitation of extension of elbows. There is a slight tibial bowing and relatively normal round face without dysmorphic features and a short neck with some limitation

of the lateral movement. Over years she had multiple consultations to establish the pathophysiology of her condition. At first the patient was under care of the Children Hospital and diagnosed with hypochondroplasia then with dyschondrosteosis. Subsequently, in her twenties she has been referred to the Regional Genetic Centre and finally diagnosed with PsA. Diagnosis was made based on the radiographs obtained in prepubertal stage including anteroposterior views of the hips, knees and hands as well as lateral views of the spine. Also clinical features with characteristic proportions of a body in respect to the limbs and spine supported the diagnosis of PsA. Unfortunately, genetic testing was not available at that stage and diagnosis was not challenged since then. Mutation which has led to PsA in this case is believed to be a de novo mutation as none of the parents was affected and the condition is known to be inherited in an autosomal dominant manner.

Regrettably the patient happens to suffer also from asthma and tracheobronchomalacia. Allergic asthma was confirmed by evidence of bronchial reversibility with a short acting β_2 agonist and positive radioallergosorbent test to house dust mite, dog dander and grass pollens. Over years she has had multiple admissions with asthma exacerbations but never required any form of the ventilation.

INVESTIGATIONS

Investigations with flexible bronchoscopies demonstrated a narrow trachea through its length and a triangular cross sectional appearance with the narrow main bronchi and prominence of the posterior membranes. The left main bronchus orifice was reduced to a pinhole size. There was no evidence of focal stenosis but the whole area was flexible. There was no evidence of the endobronchial lesions. Interval chest x-rays showed evidence of oligovolemic left lung.

Recent admission with a chest pain and hypoxia triggered request for the computed tomographic pulmonary angiography. Scan excluded pulmonary emboli but revealed the right lung vascular congestion (figure 1c), an

Figure 1 (a) V/Q scan presenting no ventilation to left lung, (b) V/Q scan presenting minimal perfusion to left lung, (c) CT thorax showing right lung vascular congestion, (d) CT thorax showing partial collapse of left main bronchus, (e) CT vascular tree reconstruction showing underdeveloped left pulmonary artery.

Figure 2 Flow-volume curves showing peripheral airways obstruction.

abnormal left pulmonary vein and a small left pulmonary artery (figure 1e) with narrowing of the left bronchus (figure 1d). Ventilation-perfusion (V/Q) scan confirmed almost complete absence of the perfusion with no ventilation to the left lung (figure 1a,b). Echocardiography revealed only hyperdynamic left ventricle with an elevated filling pressure but no valves or major vessels abnormalities. Latest spirometric readings showed: forced expiratory volume in the 1 s (FEV1) 0.28 (predicted 0.65) 43.2%, forced vital capacity (FVC) 0.46 (predicted 0.85) 54.3% with the FEV1/FVC ratio 60.78%. There was noticeable decline over years in the FEV1 and FVC. Flow-volume curves were consistent with a diagnosis of the peripheral airways obstruction (figure 2).

Investigations for the obstructive sleep apnoea including an overnight oximetry were normal. There was no evidence of type II respiratory failure at any stage.

TREATMENT

Developmental bronchial tree abnormalities are likely accountable for a difficult asthma control resulting from mucus retention in much narrowed airways therefore medical therapy had to be maximised. Over years, the treatment has been modified and at present the patient is established on a combination inhaler with inhaled corticosteroid/long-acting β 2 agonist, a leukotriene receptor antagonist, a long-term small dose of the macrolide antibiotic (azithromycin 125 mg daily) and on the maintenance dose of oral prednisolone (5 mg daily). She has a regular clinic follow-up in the respiratory medicine department.

OUTCOME AND FOLLOW-UP

Further management was discussed locally at the respiratory multidisciplinary meeting as well as in the tertiary centre for patients with a tracheobronchomalacia. The wait and watch approach with the optimisation of medical therapy was implemented. Trial of continuous positive airways pressure would be considered if there is an evidence of the respiratory failure.

DISCUSSION

Pseudoachondroplasia is an inherited bone dysplasia disorder preventing normal bone growth and extra skeletal complications are generally uncommon.^{3 4} It is usually diagnosed at the onset of walking at age 2–3 years with the recognition of a waddling gait. Patients present with marked short stature and deformity of the legs, short fingers, loose joints and ligamentous laxity. Delay in the ossification of annular epiphyses of the vertebrae results in a characteristic radiographic feature of beaking effect when viewed on a lateral projection. PsA is almost exclusively caused by mutations in COMP.⁵

The tracheobronchial tree develops as early as between 24 and 36 day of gestation.⁶ It is not uncommon that congenital anomalies of bronchial tree are associated with vascular dysgenesis which might explain underdevelopment of the left-sided bronchial and vascular pulmonary tree in our patient.

It has been shown that pulmonary hypoplasia results from deficient or incomplete development of the lung and is caused by factors that directly or indirectly compromise the thoracic space restriction. Bronchi and alveoli are still present, but their growth is restricted.⁷ Anomaly is often identified in the early life because of dyspnoea, recurrent lower respiratory tract infections, haemoptysis, or pulmonary hypertension.⁸ Only a few congenital cases have been reported as an initial diagnosis in adults.⁹ Pulmonary artery hypoplasia can lead to pulmonary hypertension and patients present with progressive dyspnoea especially in the early life. This group of patients often require stenting of the pulmonary artery.¹⁰ Underdeveloped pulmonary vasculature in our patient does not cause any symptoms. There is not any echocardiographic evidence of pulmonary hypertension and patient's dyspnoea is variable and correlates with times of asthma exacerbations.

Left side pulmonary hypoplasia and left pulmonary artery dysgenesis in our patient resulted probably from limited lung growth due to a thoracic cage underdevelopment caused by PsA (large lungs in a small thorax) and presence of the bronchial stenosis. One of the studies in patients with achondroplasia, another form of short limbs dwarfism showed reduced vital capacity of that predicted for normally proportionate females, suggesting that there is reduced chest wall compliance or abnormal lung growth.¹¹

Another pathology identified in this case is tracheobronchomalacia (TBM) which can be congenital or acquired and arises from the weakness of the cartilaginous rings, allowing collapse of the posterior membranous wall during expiration, leading to outflow obstruction and air trapping.¹² We hypothesise that TBM leading to intermittent airways collapse in our patient is congenital and resulted either from the reduction and/or atrophy of the longitudinal elastic fibres of the pars membranacea, or abnormal cartilage structure secondary to PsA.¹³ TBM is associated with a dynamic large airway collapse and leads to airways obstruction also asthma which is almost exclusively associated with a small airways involvement equally results in the airways obstruction. It is important therefore to distinguish asthma from TBM as both conditions can present with similar symptoms including wheeze, cough, dyspnoea, stridor and recurrent respiratory tract infections, but they require different treatment and a long-term follow-up. Patients with both a small and a large airway obstruction may respond to inhaled β 2 agonists when the small airways disease prevail but when large airways obstruction predominates they can experience worsening of symptoms.¹⁴

Pathophysiology of the asthma differs significantly from that of the TBM. Asthma is a chronic inflammatory disease which leads to hyperresponsiveness and remodelling, characterised by reversible lower airway obstruction. Physiologically, bronchial hyperresponsiveness is documented by decreased bronchial airflow after bronchial provocation or increased bronchial flow after bronchodilator challenge. Asthma leads to lung hyperinflation, smooth muscle hypertrophy, lamina reticularis thickening, mucosal oedema, epithelial cell sloughing, cilia cell disruption and mucus gland hypersecretion. Exacerbations of asthma lead to pulmonary tissue inflammation and injury which are followed by repair process causing long-term structural

changes ('remodelling') of the airways. Decline in the lung function in our patient who suffered multiple asthma exacerbations over years could be explained by these repeating injury–repair cycles.^{15 16}

It is also important to point out that in the group of patients with PsA there can be respiratory problems of different types then mentioned before including obstructive sleep apnoea/hypopnoea syndrome with upper airway obstruction, neurological problems due to cervicomedullary compression and adeno-tonsillar hypertrophy. Tracheal narrowing also has been described in association with marked thoracic deformity. All possible causes other than tracheobronchomalacia for a difficult asthma control in this case were ruled out with appropriate investigations.^{17 18}

Regardless of the aetiology this complex condition, which to our knowledge has not been described before, requires multidisciplinary approach to provide optimal care in order to reduce the rate of exacerbations and a lung function decline.

Learning points

- ▶ Patients with dwarfism can present with the respiratory problems of different types including obstructive sleep apnoea with an upper airway obstruction due to adeno-tonsillar hypertrophy, tracheal narrowing associated with marked thoracic deformity, possible tracheobronchomalacia secondary to an abnormal lung growth or cartilage abnormalities therefore careful assessment is required.
- ▶ Existence of congenital abnormality in one system such as skeletal involvement can be associated or influence abnormalities in the other systems.
- ▶ Common conditions like asthma even in the patients with congenital respiratory tract abnormalities require optimisation of treatment in a line with already established asthma guidelines.
- ▶ Asthma and tracheobronchomalacia can present with similar symptoms therefore it is important to investigate and distinguish both conditions in order to provide an optimal management.

Competing interests None.

Patient consent Obtained.

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