Case Reports - When bronchial obstruction in the young adult is not asthma and inhalers do not help

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Case Reports – When bronchial obstruction in the young adult is not asthma and inhalers do not help.

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Abstract

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Case study: We describe two younger patients treated unsuccessfully for asthma and eventually diagnosed with localised bronchoconstriction.

Results: Bronchoscopy revealed bronchoconstriction: Tracheobronchomalacia in case 1 and fixed obstruction in case 2.

Conclusion: A systematic approach to the asthma patient with absent response to therapy facilitates rational use of therapeutic and diagnostic resources.
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Running title: No COPD but asthma inhalers do not help.

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Abstract:

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Introduction:

Asthma is a common, inflammatory disease of the bronchial mucosa, leading to airway muscle constriction and general narrowing of the internal diameter of the peripheral bronchial tree (1). Asthma mimicking conditions do not respond to high-intensity asthma treatment and may therefore easily be mistaken for severe asthma (2). In the absence of response to pharmacological treatment of asthma, careful evaluation of adherence to therapy, potency of treatment, co-morbidity, exposure, as well as asthma diagnosis are mandatory (1,3). Inconsistencies between history, physical features and spirometry should heighten suspicion of an alternative diagnosis (4).

In the following, we describe two younger patients treated unsuccessfully for asthma and eventually diagnosed with localised bronchoconstriction.

Case study:

Case 1: A 17-year old female was referred from her general practitioner (GP) due to refractory asthma. Since age 12, she had suffered from exercise-induced dyspnoea, becoming increasingly pronounced with age, paralleled by louder expiratory sounds. Birth and childhood were unremarkable with normal physical and mental development. She was physically active in and after school and was not the slowest runner in her class. She had no history of allergic conditions and no family history of cardio-pulmonary disease or allergy. She had been treated by her GP with inhaled corticosteroid and bronchodilators without subjective benefit. At physical examination, she had no signs of respiratory stress, or any trait suggesting developmental disorders. Lung auscultation was normal. Spirometry showed partly reversible airway obstruction (pre-[post] beta 2 agonist FEV₁ 2.0 L (62% of expected) [2.2 l (69%)]; FEV₁/FVC 70% [74%], Δ FEV₁ 11% (figure 1). A cardiac murmur was noted, but echocardiography revealed no signs of congenital or other heart diseases. Basic blood samples (haematology, liver and kidney function, and TSH) were all normal. A trial of 3 months of increased inhaled corticosteroids (ICS, dry powder 800 µg budesonide b.d.) and oral montelukast
q.d. failed to improve symptoms or spirometric values. High resolution (HR-)CT thorax, metacholine challenge test, exhaled nitrogen oxide (e-NO), and peak-flow diary were all normal. At 6-months follow-up, FEV$_1$ had decreased to 60% of expected level. A flexible video-bronchoscopy in light sedation was performed (see results). She was referred for evaluation by thoracic surgeons who recommended watchful waiting until age 21. Medication was tapered off within a month without adverse events. Now, at age 20, her FEV$_1$ is stable, and she only experiences tolerable exercise-related dyspnoea.

**Case 2:** A 39-year-old never-smoking woman with X-linked hypohidrotic ectodermal dysplasia (a rare genetic, usually X-linked recessive disorder affecting several ectodermal structures (5)). The patients mother had same genetic disorder and was lung transplanted 15 years earlier) with slight facial abnormality, chronic sinusitis (treated surgically by ENT specialist) and chronic laryngitis (treated by logopedist) was admitted from specialized ENT-centre for asthma work-up. She had experienced slowly progressive exercise-induced dyspnoea and night-time coughing, interpreted as asthma by her GP and treated with terbutaline dry powder inhalation as needed. She was known allergic to grass pollen and had recurrent sinusitis with staphylococcus species. At physical examination, she presented a slight inspiratory stridor with predominance corresponding to right upper lobe bronchus, and lung function showed mild airway obstruction (FEV$_1$ 1.8 L (63%); FEV$_1$/FVC 63%) with no reversibility but flattening of inspiratory flow-volume curve suggesting intra-thoracic airway obstruction (figure 3a). Peak-flow was reduced to 200 mL (60% expected) but without diurnal variability. HR-CT was normal. Metacholine challenge was omitted. Body-plethysmography showed increased residual volume (160%) but was otherwise normal. She had normal basic blood samples including eosinophil count, except a mannose binding lectin just below lower limit. Intrathoracic obstruction was suspected, but she refused the offered bronchoscopy. Though not much pointed towards asthma, the patient and pulmonologist agreed on a trial of three months of inhaled ICS/LABA (dry powder budesonide 800 μg + formoterole 9 μg b.d.). At follow-up, FEV$_1$ had decreased
to 1.6 L. Bronchoscopic evaluation was re-offered but refused. She accepted referral for lung physiotherapy, and ENT re-evaluation (revealing insignificant slight oedema and reddening of first tracheal ring, but no stenosis). Five months later, she accompanied her mother at a consultation to the Regional Transplant Unit. Our colleagues noticed the clearly audible stridor and offered a bronchoscopy that she accepted. This confirmed a fixed bronchostenosis (see results). Medication was tapered off during 2 months without relapse. Now, 24 months later she maintains a normal lung function. She still has recurrent staphylococcal upper airway infection. Unfortunately, no endoscopic photos were saved.

Results:

Case 1: A flexible video-bronchoscopy revealed weakened cartilage structure between the right upper lobe bronchus - which continued to segment 2 only - and the right lateral part of the distal trachea where an abnormal bronchus led to the right segments 1 and 3. At forced expiration and voluntary coughing, we observed an almost complete collapse of the anterior wall of the lower trachea distally to the tracheal right overlap bronchus (figure 2).

Case 2: Bronchoscopy showed narrowing of right main bronchus. Bronchoscopic dilatation with inflatable water balloon was repeated four times at the transplant unit, and FEV₁ increased to 2.7 L (93%) and index 83% (figure 3b).
Discussion:

It is of little surprise that the two patients were suspected having asthma by our non-specialist colleagues. Asthma is the most common chronic respiratory disease in adolescents and younger adult non-smokers (6, 7). GINA guidelines support that asthma diagnoses can be based solely on presence of asthma-like symptoms though preferably with supportive objective tests (8). As no symptom is pathognomonic for asthma, and differential diagnoses are numerous (1, 2, 4, 8), a careful and critical revision of the diagnosis is mandatory when patients are seen in tertiary units due to treatment failure (2, 4). The importance of considering asthma-mimicking conditions when asthma treatment does not work has been convincingly illustrated by Bel et al who presented an algorithm to optimise discrimination between difficult-to-manage-asthma and severe refractory asthma (2). Keeping the many differential diagnoses of difficult-to-manage-asthma in mind (table 1), Bel et al highlights the necessity of a systematic and extensive approach: Thorough medical history, medication adherence assessment, physical examination, spirometry, and bronchial challenge tests form the initial assessment; if negative, supplemented by a variety of targeted modalities to address differential diagnoses and co-morbidities and - lastly, tapering off asthma medication (1,2,3,4,7,9).

Luks et al have presented a simple flowchart for stepwise reduction of asthma medications, and showed that nearly 30% of patients with primary care-diagnosed asthma referred to a pulmonology service had neither positive objective tests nor asthma symptoms after terminating medication (9).

Keywords to alternative diagnoses for our two women were excellent self-reported adherence supported by prescription data from pharmacies, futile trials of guidelines-supported increases in anti-asthmatic treatment, presence of stridor in history, localised/fixed stridor at physical examination, and evident obstruction at spirometry with inspiratory flow-volume curves (10).

Relevant differential diagnoses were addressed by medical history, physical examination, HR-CT and ENT evaluation. The gold standard for diagnosing localised bronchial abnormalities is bronchoscopy.
However, expiratory CT imaging and virtual tracheobronchoscopy have promising sensitivities above 97% (11,12) but are not performed on a routine basis in our institution.

Our two cases illustrate differences between dynamic and fixed obstruction. The first patient has tracheobronchomalacia (TBM), which is a weakness in the bronchial wall, defined as a narrowing of the lumen exceeding 50% in the expiratory phase (13). TBM is most commonly congenital, and this is probably the cause of TBM in our patient as well. TBM affects both bronchial and tracheal wall. Isolated bronchomalacia is rare. Secondary TBM may be caused by intubation, tracheotomy or infection or can be a result of prolonged compression including malignancy (13). Treatment depends on symptoms, cause and patient’s age: Tracheostomy, continuous positive airway flow +/- mechanical ventilation, stents or surgical removal of affected area (13). In adults, the symptoms are generally milder than in patients with fixed obstruction, bronchostenosis. This too may be caused by intubation, tracheostomy or infection, as well as systemic inflammation or malignancy (10). Our patient suffered from a genetic disorder and had recurrent staphylococcal sinus infections: Neither have previously been reported to be associated with bronchostenosis. Microaspiration could be a possible but unproven mechanism. Treatment is based on severity and cause: Balloon dilatation, heat therapy, stenting or surgery. Our patient was eligible for balloon dilatation, and the treatment remains efficacious 24 months later.
Conclusion:

In summary, localised bronchial obstruction is a rare differential diagnosis to asthma. Localised bronchial obstruction may be dynamic or fixed. Knowledge of asthma mimicking condition and a systematic approach to the asthma patient with treatment failure facilitates rational use of therapeutic and diagnostic resources (1, 2, 4, 8, 9).

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References:


Fig. 3a

Fig. 3b
Table 1

**Children**
- Dysfunctional breathing/vocal cord dysfunction
- Bronchiolitis
- Recurrent (microl)aspiration, reflux, swallowing dysfunction
- Prematurity and related lung disease
- Cystic fibrosis
- Congenital or acquired immune deficiency
- Primary ciliary dyskinesia
- Central airways obstruction/compression
- Foreign body
- Congenital malformations including vascular ring
- Tracheobronchomalacia
- Carcinoid or other tumour
- Mediastinal mass/enlarged lymph node
- Congenital heart disease
- Interstitial lung disease
- Connective tissue disease

**Adults**
- Dysfunctional breathlessness/vocal cord dysfunction
- Chronic obstructive pulmonary disease
- Hyperventilation with panic attacks
- Bronchiolitis obliterans
- Congestive heart failure
- Adverse drug reaction (e.g. angiotensin-converting enzyme inhibitors)
- Bronchiectasis/cystic fibrosis
- Hypersensitivity pneumonitis
- Hypereosinophilic syndromes
- Pulmonary embolus
- Herpetic tracheobronchitis
- Endobronchial lesion/foreign body (e.g. amyloid, carcinoid, tracheal stricture)
- Allergic bronchopulmonary aspergillosis
- Acquired tracheobronchomalacia
- Churg-Strauss syndrome
Figure- and table captions:

**Figure 1. Case 1:** Lung function test showing flattened expiratory curve with near-significant reversibility for beta-2-agonists.

**Figure 2. Case 1:** Bronchoscopic view of open right main bronchus during unforced breathing (a), but closed during forced expiration (b).

**Figure 3. Case 2:** Forced flow-volume and volume time curves showing flattened, “box-like” inspiratory and expiratory curves before balloon dilatation (a), and normalization hereafter (b).

**Table 1:** Diseases that can masquerade as severe asthma. Reproduced from Reference 4 with the permission of the publisher.