A young patient with wheezing and dyspnoea on exertion: is all that wheezes asthma?

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Case history

A 21-year-old nonsmoking male visited his GP complaining of dyspnoea on exertion. His symptoms had started 3 years earlier, but he had experienced several episodes of dyspnoea and wheezing in the previous 6 months, when he started participating in a strenuous exercise programme. His medical history included hayfever for the past 4 years and recurrent chest infections during childhood with a remission in adolescence.

Physical examination

Physical examination revealed a mild pectus excavatum and bilateral expiratory wheezing that was more prominent on the right hemithorax. His physical signs were normal and his arterial oxygen saturation in room air was 97%.

Task 1
What was the most probable diagnosis for this patient?
a) Asthma
b) Chronic obstructive pulmonary disease (COPD)
c) Bronchiectasis
d) Congestive heart failure

Answer 1
a) This is a correct answer. According to the definition of asthma by the Global Initiative for Asthma (GINA) [1] "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment". The patient had experienced episodes of dyspnoea and wheezing on exertion that resolved spontaneously. The history of recurrent chest infections during childhood and the presence of hayfever were also consistent with a subsequent development of asthmatic symptoms.
b) This answer is incorrect. The patient was a nonsmoker without a history of exposure to noxious particles or gases, which along with his young age excluded a diagnosis of COPD.
c) This answer is incorrect. The history of frequent infections in childhood would be compatible with bronchiectasis, yet the remission of symptoms during adolescence is not compatible with that diagnosis.
d) This answer is incorrect. Congestive heart failure remained a possibility at this point, yet the young age of the patient and the history of atopy and dyspnoea on exertion were more indicative of asthma.

Task 2
Which of the following investigations would be your first choice?
a) Skin tests with allergens for assessment of atopic status
b) Spirometry before and after bronchodilation
c) Chest radiography
d) Measurement of the exhaled nitric oxide fraction (*F*eNO)

Answer 2

a) This answer is incorrect. The assessment of atopic status is not a diagnostic tool for asthma, since a positive result does not necessarily confirm the connection between atopy and respiratory symptoms and a negative test does not exclude the presence of asthma.
b) This is a correct answer. Spirometry before and after bronchodilation was indicated for this patient with a history of dyspnoea on exertion and wheezing, in order to confirm airflow limitation and reversibility consistent with a diagnosis of asthma. A rapid-acting bronchodilator is used (*e.g.* salbutamol 400 µg) and an increase in forced expiratory volume in 1 s (FEV_1) ≥200 mL and ≥12% above the pre-bronchodilator value is considered consistent with a diagnosis of asthma [1].
c) This answer is incorrect. A chest radiograph would have been useful for the exclusion of other conditions that may have been causing dyspnoea in this patient; however, it is not a first-line examination for the diagnosis of asthma, being normal in the majority of asthmatics.
d) This answer is incorrect. The measurement of *F*eNO has been proposed for the management of patients with asthma [2] and has been evaluated as a screening tool for asthma in young adults [3], yet it is not routinely recommended for the diagnosis of asthma in clinical practice.

The results of spirometry before and after bronchodilation (administration of 400 µg of salbutamol) are presented in figure 1 and table 1. The findings were consistent with a moderate obstructive pattern with no significant response after bronchodilation (<200 mL and <12% of the baseline value). However, it is important to bear in mind that many patients with asthma will not exhibit significant reversibility at each assessment, and this test therefore lacks sensitivity [1].

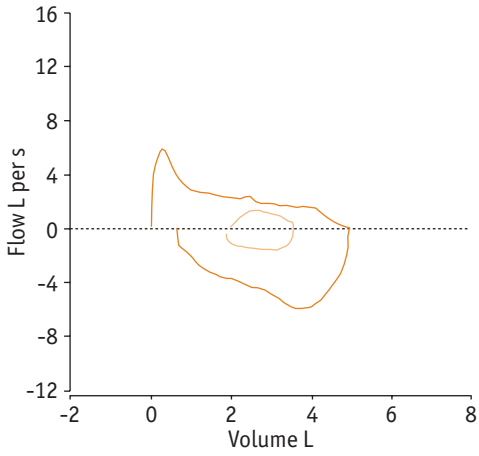

Figure 1
Flow–volume loop.

Task 3

What would be the next step in the management of this patient?

a) Evaluation of a trial of inhaled corticosteroids for 4 weeks
b) Referral for methacholine challenge testing
c) Evaluation of peak expiratory flow (PEF) variability
d) Chest radiograph

Table 1 Spirometry results

	Predicted	Actual before BD	% pred	Actual after BD	% pred
FEV_1 L	4.65	2.78	60	2.84	61
FVC L	5.55	4.95	89	4.99	89
FEV_1/FVC %	83	56	67		57
$FEF_{25-75\%}$ L per s	5.18	2.04	39	2.23	43

Pred: predicted; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow over the middle 50% of the FVC; BD: bronchodilation.

Answer 3

a) This is a correct answer. The absence of an initial response to bronchodilation does not exclude a diagnosis of asthma and the evaluation of the response to effective controller treatment may be an acceptable alternative in a primary care setting.

b) This is a correct answer. Measurement of airway hyperresponsiveness may serve as a tool for the exclusion of asthma, especially in patients with normal lung function, due to the high sensitivity of this test. However, the low specificity of bronchial challenge testing for a diagnosis of asthma (*e.g.* the positive results in patients with allergic rhinitis, as was the case for this patient) limits its usefulness in this case. Moreover, the low FEV_1 of this patient (60% predicted) represents a relative contraindication for the performance of methacholine challenge testing, according to the American Thoracic Society guidelines [4].

c) This is a correct answer. PEF variability may be used to confirm a diagnosis of asthma. Diurnal variation of PEF >20% is indicative of asthma in patients with diagnostic uncertainty.

d) This is a correct answer. After the absence of a response to a bronchodilator, a chest radiograph may be valuable for the exclusion of alternative diagnoses (*e.g.* chronic obstructive pulmonary disease (COPD), bronchiectasis).

The patient's general practitioner decided to prescribe a combination of long-acting β-agonist (formoterol 12 μg *b.i.d.*) and inhaled corticosteroid (budesonide 800 μg per day) to the patient. The patient took the inhaled medication for 4 weeks and returned to his GP reporting a mild improvement of his symptoms; however, there was no improvement in spirometry. The GP increased the dose of budesonide to 1,600 μg per day for another 4 weeks without any further improvement of the patient's symptoms. During this time, the patient experienced several episodes of dyspnoea on exertion and received relief medication for these episodes at least 3–4 times per week.

Task 4

What should the subsequent evaluation of this patient include?

a) Evaluation of compliance with treatment

b) Reassessment of the diagnosis of asthma

c) Evaluation of concomitant conditions

d) Referral to an asthma specialist

The patient was referred by his GP to an asthma clinic in a tertiary hospital for further evaluation. The findings on physical examination did not differ from those reported by his GP and his oxygen saturation in room air was 97%. Complete blood count and routine biochemistry provided normal results and his ECG was normal. His spirometry results did not differ from these presented in figure 1 and table 1, with no response to bronchodilation. Compliance to treatment was confirmed by the patient's prescriptions and a careful history for possible comorbidities was not indicative for the presence of any of the aforementioned conditions that are related to inability to achieve control. The patient's chest radiograph is presented in figure 2.

Table 2 Common alternative causes of recurrent wheezing that may mimic asthma [1]

Children	Adults
• Chronic rhinosinusitis	• Hyperventilation syndrome and panic attacks
• Gastro-oesophageal reflux disease	• Large airway obstruction (*e.g.* tracheal tumours)
• Recurrent viral lower respiratory tract infections	• Inhaled foreign bodies
• Cystic fibrosis	• Vocal cord dysfunction
• Bronchopulmonary dysplasia	• COPD
• Tuberculosis	• Bronchiectasis
• Congenital malformation causing narrowing of the intrathoracic airways	• Cystic fibrosis
• Foreign body aspiration	• Bronchiolitis
• Primary ciliary dyskinesia syndrome	• Nonobstructive forms of lung disease (*e.g.* diffuse parenchymal lung disease)
• Immune deficiency	• Nonrespiratory causes of symptoms (*e.g.* left ventricular failure, congenital abnormalities)
• Congenital heart disease	• Churg–Strauss syndrome
	• Allergic bronchopulmonary aspergillosis

Answer 4

a) This is a correct answer. Compliance with treatment is a major issue in asthmatic patients, especially in adolescents and young adults, and should be re-evaluated every visit. The technique used for the administration of inhaled medication should also be evaluated. Incorrect or inadequate use of medications remains the most common reason for failure to achieve control.

b) This is a correct answer. This is particularly important in patients who are unresponsive to effective anti-asthmatic treatment, as was the case for this patient. Interestingly, in a series of 100 patients with difficult-to-treat asthma evaluated in a single tertiary asthma specialist centre, 12 had a diagnosis other than asthma [5]. Alternative causes of recurrent wheezing that may mimic asthma are included in table 2.

c) This is a correct answer. In patients with difficult-to-treat asthma, it is important to determine whether environmental factors and concomitant disorders may be exacerbating asthma. In a study of 136 patients with difficult-to-treat asthma, factors associated with frequent exacerbations included severe nasal sinus disease, gastro-oesophageal reflux disease, recurrent respiratory infections, psychological dysfunctioning and obstructive sleep apnoea. Severe chronic sinus disease and psychological dysfunctioning were the only independently associated factors in multivariate analysis [6]. Such conditions should be evaluated meticulously in all patients with a diagnosis of difficult-to-treat asthma.

d) This is a correct answer. All patients who don't respond to the initial asthma treatment, especially after stepping up to a high dose of inhaled corticosteroids and long-acting B_2-agonists, may be referred to a health professional with expertise in the management of asthma for investigation of alternative diagnoses and/or causes of difficult-to-treat asthma.

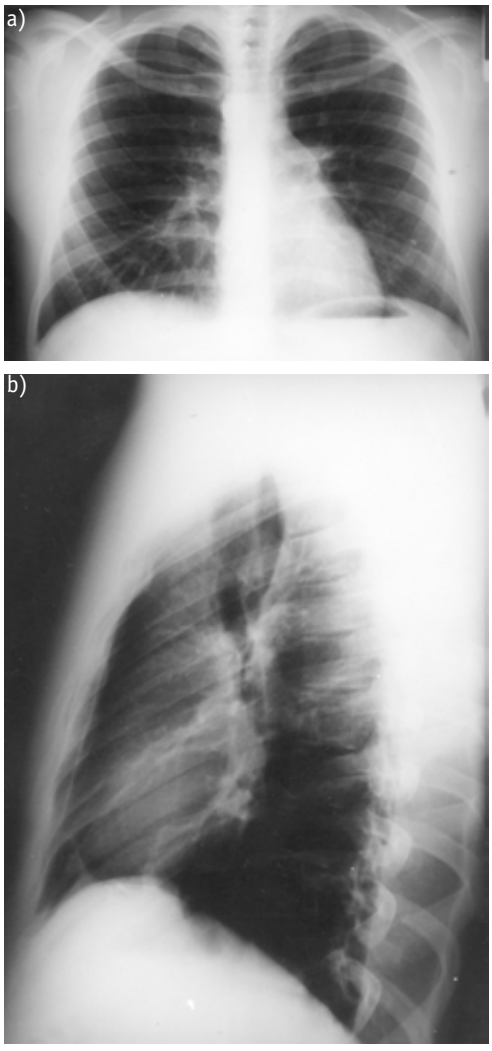

Figure 2
Posteroanterior (a) and lateral (b) chest radiographs.

Task 5
Interpret the patient's chest radiograph (figure 2).

Task 6
Which of the following investigation(s) would you order now?

a) Arterial blood gases
b) Bronchoscopy
c) Referral to the cardiology department for evaluation
d) Computed tomography (CT) of the chest

Answer 5

A right-sided aortic knob in a relatively high position, consistent with a right-sided aortic arch, is observed in the posteroanterior view of the chest radiograph (figure 2a). Additionally, a possible compression of the posterior wall of the trachea by the aortic arch can be observed in the lateral view (figure 2b). No abnormal findings from the lung parenchyma or the chest wall were observed.

Answer 6

a) This answer is incorrect. Arterial blood gases were not indicated in this patient presenting with oxygen saturation of 97% in room air.

b) This answer is incorrect. Bronchoscopy is not routinely indicated for diagnostic purposes in patients with asthma. However, it may be indicated for the re-evolution of the diagnosis of severe asthma. It may be used for the exclusion of alternative diagnoses, such as a foreign body in the airways, and the more prominent wheezing in the right hemithorax of this patient may be indicative of a local cause for wheezing. However, less invasive imaging studies should precede the performance of bronchoscopy.

c) This is a correct answer. The patient's cardinal symptoms were wheezing and dyspnoea on exertion and cardiac causes of dyspnoea should be excluded. Moreover, the presence of a right-sided aortic arch was indicative of a possible congenital malformation.

d) This is a correct answer. The presence of a right-sided aortic arch and the compression of the posterior wall of the trachea rendered imperative the visualisation of the large airways and the large mediastinal blood vessels.

The evaluation by the cardiologists did not provide any remarkable findings, with the exception of mild pulmonary valve regurgitation in the echocardiogram. The CT scan of the chest demonstrated a right-sided aortic arch in a relatively high position, compression of the posterior wall of the lower intrathoracic part of the of the trachea and the right main bronchus by the descending aorta and no abnormal findings from the lung parenchyma (figure 3). On more careful examination at this point, the expiratory limb of the flow–volume curve presented a plateau, consistent with (but not typical of) a variable intrathoracic pattern of airways

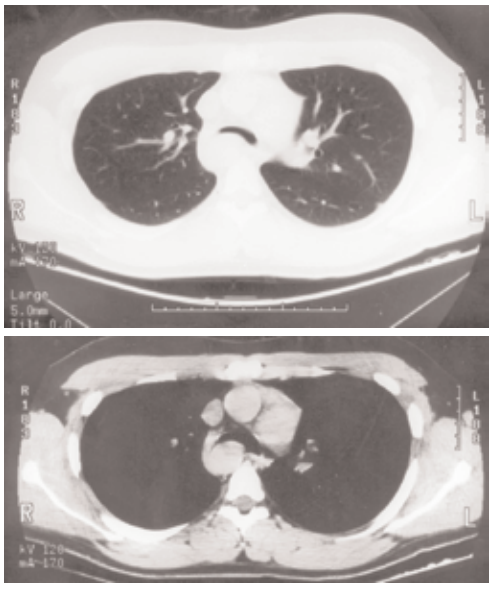

Figure 3

CT scan showing the right aortic arch and the compression of the posterior wall of the lower intrathoracic part of the trachea by the descending aorta.

obstruction (figure 1) [7]. However, it must be admitted that this is not a textbook example of tracheal compression and it may well be misinterpreted.

The patient subsequently underwent fibreoptic bronchoscopy, where a pulsatile compression of the lower third of the posterior tracheal wall with a "comma-like" appearance of the tracheal lumen was observed (figure 4). On expiration there was a significant aggravation of the stenosis. The mucosa throughout the right bronchial tree was suggestive of inflammation with an erythematous appearance and abundant mucous secretions. No other abnormalities were found. A magnetic resonance imaging (MRI) scan of the chest provided similar findings. The patient was given a diagnosis of a right aortic arch with possible formation of a vascular ring involving the right aortic arch, the ligamentum arteriosum and the descending aorta that compresses the trachea, more prominently during exercise. The patient was referred for surgical treatment involving the division of the ligamentum arteriosum and presented marked improvement of his symptoms a few months after the procedure.

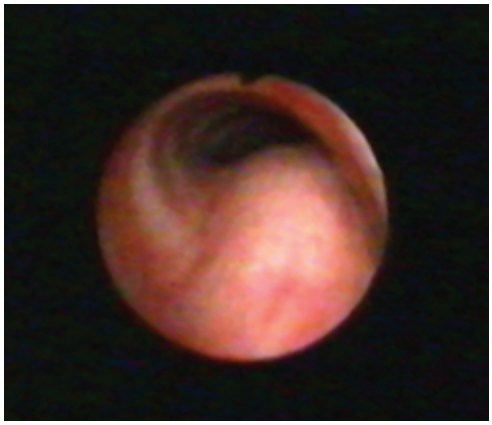

Figure 4
Bronchoscopic imaging of the patient's trachea showing the extrinsic compression of the posterior tracheal wall by the right-sided descending aorta and the "comma-like" appearance of the tracheal lumen.

Discussion

Vascular rings are developmental abnormalities involving partial or complete encirclement of the trachea or oesophagus by the aortic arch. The incidence of vascular rings is <0.2% annually. Gross [8] introduced the term vascular ring in 1945, after performing the first successful division of a vascular ring, which had resulted from a double aortic arch. A double aortic arch is the most common anomaly, followed by a right aortic arch, as was the case for this patient. The case reports of symptomatic adults without any previous symptoms are scarce [9–11]. The most common clinical findings reported in children when a taut vascular ring is formed are respiratory distress, stridor, apnoea, recurrent pulmonary infections and dysphagia [8, 12, 13]. These symptoms may mimic obstructive lung disease, especially when the patient becomes more active, as was the case for this patient.

In normal individuals, the left aortic arch passes in front and to the left of the trachea and the descending aorta is connected to the pulmonary trunk by the ligamentum arteriosum. In the abnormal situation, the aortic arch passes to the right and behind the trachea [10]. The vascular ring consists of the right aortic arch and the ligamentum arteriosum that runs from the pulmonary artery to the left of the trachea to join the descending aorta. No evidence of the presence of a ligamentum arteriosum forming a vascular ring with the right-sided aortic arch was seen using the imaging techniques used with this patient. However, the severity of the compression of the posterior tracheal wall and the location of the stenosis (lower third of the trachea) were consistent with the presence of a taut ligamentum arteriosum.

This patient presented exclusively with expiratory wheezing. During inspiration, the intratracheal pressure is higher than the extratracheal pressure. This pressure gradient results in dilatation of the trachea that compensates the external compression from the descending aorta. During expiration, the intratracheal pressure is lower than the extratracheal pressure, leading to narrowing of the trachea. Additionally, the turbulence and convective acceleration produced by the compressed segment in this patient resulted in further airway narrowing. During the forced expiratory manoeuvre of the flow–volume loop and in exercise, these phenomena were accentuated, resulting in airway narrowing sufficient to cause symptoms, whereas at rest these mechanisms did not limit airflow severely enough to cause symptoms [9]. Furthermore, the hyperkinetic circulation during strenuous exercise, responsible for the patient's symptoms on exertion, may have further aggravated the compression of the large airways.

The investigations indicated for the diagnosis of this malformation are CT, MRI, fibreoptic bronchoscopy and barium oesophagogram [10, 13, 14]. Our patient did not complain of any symptoms from the upper gastrointestinal tract, thus he was not subjected to barium swallow. MRI is considered the imaging technique of choice for accurate delineation of the vascular and tracheal anatomy [13, 14], but in this case it did not provide any further information. Echocardiography is increasingly used for the diagnostic evaluation of vascular rings, especially in younger patients, in order to rule out the presence of an associated cardiovascular anomaly. Finally, bronchoscopy is useful in the diagnostic evaluation of adult patients with a suspicion of a vascular ring, because it effectively excludes other conditions, such as endobronchial lesions.

The interesting element of this case is that significant facts needed for the final diagnosis were evident from the beginning of the evaluation of this patient. The absence of response to treatment, along with the shape of the expiratory limb of the flow–volume curve (consistent with variable intrathoracic airways obstruction) and the presence of a right aortic knob in the chest radiograph, could raise the suspicion of a right aortic arch and extrinsic tracheal

compression. Therefore, the fact that "all that wheezes is not asthma" should always be re-evaluated in cases of patients with "typical" symptoms and signs of asthma who do not respond to proper antiasthmatic treatment in the primary care setting.

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