Masood Ur Rasool[1], Iftikhar Nadeem[2], Usman Feroze Khatana[3], Sadiyah Hand[4]

Iftikharnadeem49@gmail.com

Case report

An unusual case of breathlessness

A 39-year-old advanced nurse practitioner in the accident and emergency department presented with influenza-like symptoms, shortness of breath, cough, fatigue and generalised arthralgia. Her cough was non-productive and nocturnal in nature. There was no history of fever, chest pain, haemoptysis, night sweats, weight loss or joint swelling.

She had a past medical history of asthma, which was diagnosed clinically 9 years ago by the respiratory team. At the time of diagnosis, she had displayed symptoms of cough, chest tightness, shortness of breath, diurnal variation in peak expiratory flow rate and an improvement in these symptoms with inhaled corticosteroid (ICS) inhaler.

She had never smoked and had no pets. She denied any occupational exposures. She had no history of symptoms of allergic rhinitis or reflux disease.

On examination, oxygen saturation was 95% on air, respiratory rate was 18 breaths·min^{-1}, heart rate was 94 beats·min^{-1}, blood pressure 135/76 mmHg and she was afebrile. Her chest was clear and she had no wheeze. The rest of her systemic examination was unremarkable. Peak expiratory flow (PEF) was >75% of her average best. Her BMI was 22.81 kg m^{-2}.

Her asthma had been well controlled until the year before this admission. From the time of diagnosis until the year before this presentation, she only had two severe asthma exacerbations requiring steroids. She had never previously been admitted to the intensive care unit (ICU); however, this year she had four admissions. On her first admission she was found to have influenza B, triggering exacerbation of her asthma. It took her around 3 months after discharge to recover back to baseline. She received intravenous magnesium sulphate on each admission and intravenous aminophylline twice. During each admission, the asthma nurse specialist team saw her, and issues of inhaler techniques and adherence were addressed.

In response to these recurrent admissions, the asthma team had increased her therapy. She was now on the maximum dose of ICS/long-acting β_2 agonist (LABA)/long-acting muscarinic antagonist (LAMA) inhalers, *i.e.* Symbicort (budesonide/formoterol) 400/12 µg two puffs twice daily, Spiriva (tiotropium) 18 µg once daily, montelukast 10 mg once daily, theophylline 250 mg twice daily, azithromycin 500 mg on Mondays, Wednesdays and Fridays, as well as multiple intermittent courses of prednisolone. She was not a candidate for biological therapy as her eosinophils and immunoglobulin (Ig) E were never raised.

Her quality of life (QoL) was severely impaired because of these recurrent hospitalisations. Her asthma control test (ACT) score was 7. On occasion, during her inpatient stays, nursing staff reported episodes of severe shortness of breath at night (respiratory rate >22 breaths·min^{-1}). However, no drop in oxygen saturation was recorded during any of these episodes, although the patient stated that her oxygen saturation dropped to 85% on at least

Cite as: Ur Rasool M, Nadeem I, Khatana UF, *et al*. An unusual case of breathlessness. *Breathe* 2021; 17: 200344.

@ERSpublications

We present the case of an asthmatic patient who continued to present with breathlessness and received multiple courses of steroids for her presumed asthma exacerbations. After multiple investigations, we made the diagnosis of TBM secondary to relapsing polychondritis. https://bit.ly/3b8Uw1O

one occasion. Clinical examination of her respiratory system, performed by different clinicians, was always documented as normal and wheeze was never heard on any presentations.

The patient was anxious about recurrent admissions and scared by her episodes of sudden breathlessness. She was also fearful that the medical teams, which were looking after her, did not believe her account of illness and this was very distressing for her. The medical team was concerned that her adherence with medication was poor, which made her very upset and more anxious.

Task 1

What would be the reason for these recurrent admissions?

a) Another exacerbation of asthma
b) Functional breathlessness
c) Asthma overlapped with a different pathology
d) Poor adherence with asthma treatment causing frequent exacerbations
e) All the above

Answer 1
e.

The absence of wheeze, no improvement with standard asthma treatment, normal eosinophils and a normal IgE point towards something more than just asthma. Functional breathlessness is a possibility, but it is a diagnosis of exclusion. Hence, further work-up is essential to exclude other differentials [1]. Adherence and technique were checked on almost every admission. Poor adherence to medication and most importantly poor inhaler technique are important factors associated with recurrent exacerbation of asthma. Effective inhaler technique improves asthma control [2]. So, all of these could be possibilities.

The blood investigations profile is shown in table 1 and spirometry in table 2. Flow–volume loops are shown in figure 1.

Chest radiography was arranged during her last admission and it was compared with that which she had around 9 months ago. No lung parenchymal, pleural or tracheal deformity was reported; however, radiography was performed in the posterior–anterior view and no lateral films were taken (figure 2).

Task 2
What are the differential diagnoses?

a) Pulmonary embolism
b) Obstructive sleep apnoea
c) Congestive cardiac failure
d) Large airway structural disease
e) All the above

Table 1 *Blood investigations*

Investigations	Results	Notes
Haemoglobin	139 g L^{-1}	
White blood cells	8.7×10^9 cells L^{-1}	
Platelets	441×10^9 platelets L^{-1}	
Eosinophils	0.22×10^9 cells L^{-1}	Maximum ever 0.61×10^9 cells L^{-1} on one occasion only
Urea	7.4 mmol L^{-1}	
Creatinine	99 mmol L^{-1}	
Potassium	4.2 mmol L^{-1}	
Sodium	143 mmol L^{-1}	
Calcium	2.59 mmol L^{-1}	
Glucose	5.1 mmol L^{-1}	
TSH	0.90 mU L^{-1}	
FT4	14 pmol L^{-1}	
C-reactive protein	5 mg L^{-1}	Stayed normal during all admissions
Serum IgE	7 kU L^{-1} (normal)	
Aspergillus Screen	Negative	
ANA, ANCA (PR3 and MPO)	Negative	
Fractional exhaled nitric oxide	Negative (highest = 14 ppb)	
PCR throat swab	Negative	
Sputum C/S	Normal respiratory flora	

Table 2 *Spirometry*

Retrospective spirometry review	FEV_1	FVC	FEV_1/FVC
March 2011 (at the time of diagnosis)	2.71 L (88%)	2.89 L (81%)	93%
June 2016	2.70 L (92%)	3.05 L (90%)	88%
October 2018 (pre-admission	2.63 L (91%)	3.02 L (90%)	87%
December 2018 (post-admission)	2.86 L (95%)	3.16 L (91%)	89%

FVC: forced vital capacity.

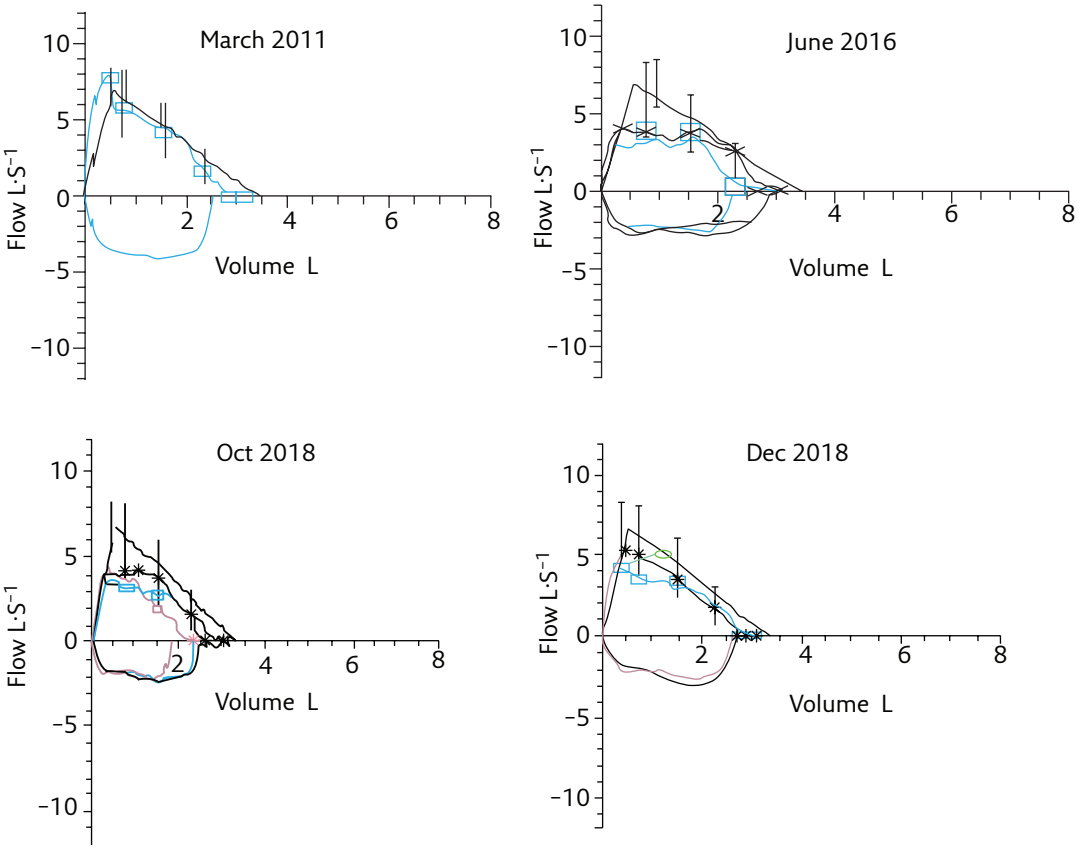

Figure 1 *Flow–volume loops.*

Answer 2

e.

These differential diagnoses were based on the important clues from history and examination. Persistent nocturnal cough could be the presenting feature of asthma, heart failure or OSA. No desaturation episode depicts that gaseous exchange seems to be least likely effected

Nocturnal increase in respiratory rate was significant and it will be explained later in this case.

Unremarkable chest examination by different clinicians was obviously worth considering an important inkling in moving towards final diagnosis.

So, the following specific investigations were arranged. A computed tomography pulmonary angiogram was negative for pulmonary embolism. There was significant tracheal narrowing and it showed crescent shaped trachea (figure 3). Inpatient overnight pulse oximetry did not reveal any evidence of apnoea/hypopnea. Echocardiography reported no evidence of cardiomyopathy or valvular pathology. Connective tissue disorder screen, *i.e.* anti-nuclear

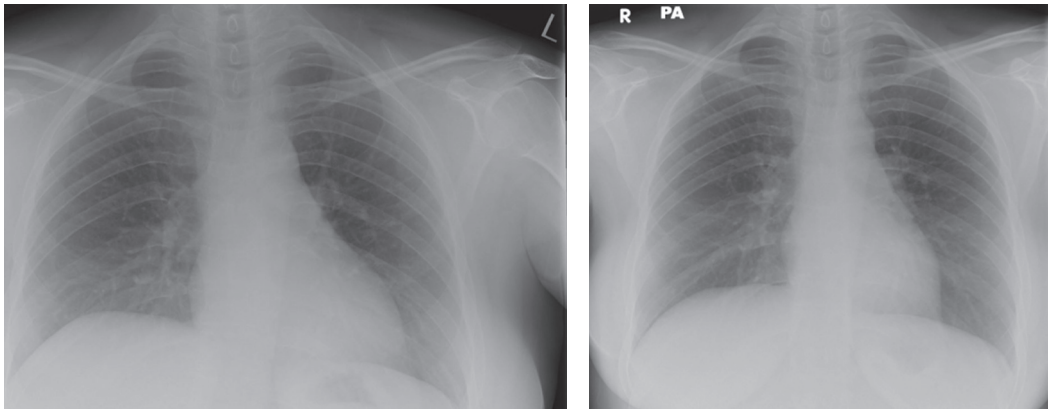

Figure 2 *Chest radiography posterior–anterior view.*

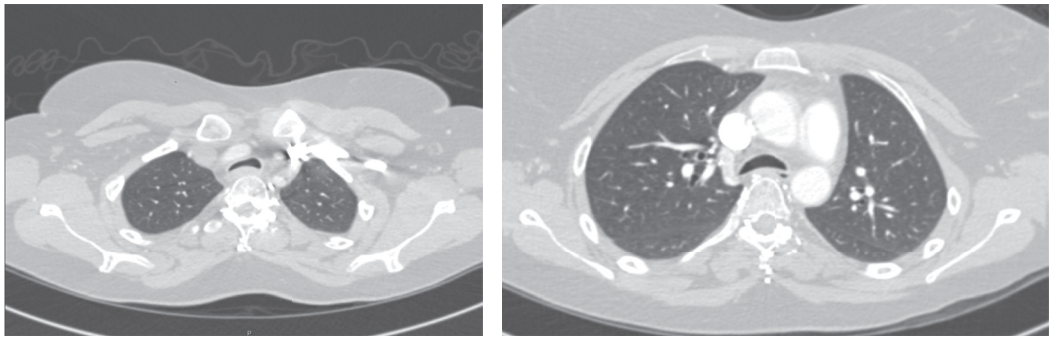

Figure 3 *Computed tomography pulmonary angiogram showing classic crescent sign consistent with tracheobronchomalacia.*

antibodies, anti-neutrophil cytoplasm antibodies and extractable nuclear antigen profile, was normal. So, these investigations excluded most of our differential diagnosis.

Task 3
What is the next best approach in this case?

a) Oesophageal manometry
b) Right heart catheterisation
c) Psychological assessment
d) Bronchoscopy
e) All the above

Answer 3
d.

In the absence of reflux symptoms, oesophageal manometry would not be next best investigation. Echocardiography reported normal right ventricular (RV) size and pressure so right heart catheterisation was not appropriate. Psychological assessment could be considered but after excluding organic cause of symptoms. So, bronchoscopy is the next investigation of choice here. Bronchial biopsies were arranged for histopathology to challenge the diagnosis of asthma, bronchial washings for atypical infection and for cell count (eosinophils). And, most importantly, to look for large airways structural pathology [3].

Bronchoscopy

The larynx was normal and the trachea was reported abnormal (figure 4). The posterior wall bowed in and almost completely occluded the lumen when the patient had a bout of coughing during the procedure.

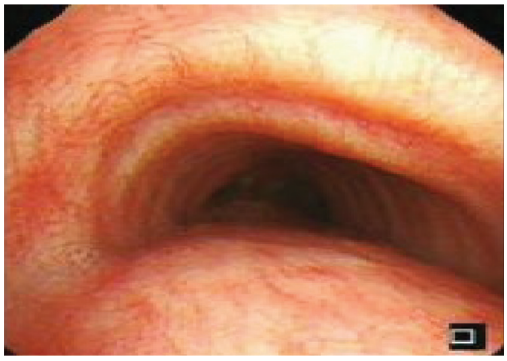

Figure 4 *Tracheal lumen narrowing on bronchoscopy.*

Microscopy

Five biopsies of bronchial mucosa with thickened basement membrane and scattered chronic inflammatory cells without eosinophils. Fungal stains are negative excluding allergic bronchopulmonary aspergillosis (ABPA). Biopsy results were consistent with asthma.

Hence bronchoscopic findings confirmed the diagnosis of tracheobronchomalacia.

She was then started on nocturnal continuous positive airway pressure (CPAP) at 10 cmH_2O. She was observed for next 2 nights and CPAP was tolerated well. She was discharged and follow-up was arranged with the local noninvasive ventilation team. Since beginning CPAP, her respiratory symptoms improved remarkably, and her exacerbation rate was also reduced. She was also referred to a regional large airway group for rigid bronchoscopy and stenting. Rigid bronchoscopy confirmed tracheobronchomalacia and results from tracheal biopsies showed nonspecific mild chronic inflammation. Albeit she initially improved with CPAP, she started having symptoms of shortness of breath and cough a few months later, limiting her exercise tolerance and causing more off work days. She also ended up having intermittent prednisolone courses. The case was discussed at multidisciplinary meeting and consensus was to asses her for tracheobronchial stenting to improve her symptoms and exercise tolerance. She subsequently had a Y-stent inserted.

Task 4
What is/are the cause/s of tracheobronchomalacia in this case?

a) Congenital
b) Acquired, steroids related
c) Mechanical-/trauma-related damage
d) Underlying connective tissue disorder
e) All the above

Answer 4
d.

No childhood infections/symptoms related to tracheobronchomalacia were reported, steroid-related tracheobronchomalacia is a relatively uncommon diagnosis and other differentials should be ruled out first. There was no history of accident or trauma; so, the most appropriate option would be underlying connective tissue disease [4]. However, the initial connective tissue screen was normal.

Her respiratory symptom burden was remarkably reduced but she was still having ongoing fatigue, tiredness and some nonspecific arthralgia. These symptoms were initially attributed to recurrent courses of steroids, tracheobronchomalacia and exacerbation related but her general practioner referred her to the rheumatology team, which found that she had stiffness and swelling in her metacarpophalangeal joints (MCP) and proximal interphalangeal joints (PIP), aching in her knees and pain in both interphalangeal joints (IPs). Her symptoms improved over time with nonsteroidal therapy but she was still stiff for an hour each morning. She often struggled to strap her 14-month-old niece into her car seat. She remained profoundly fatigued. The rheumatologist also noted that she had developed an inflammation of her pinna. Her nasal bridge and tracheal cartilages were exquisitely tender on examination.

Finally, it was concluded that she had relapsing polychondritis in context of having tracheobronchomalacia, pinna inflammation, joint symptoms and tracheal biopsy results. She was also noted to have deranged renal functions, which were normal previously. She was reviewed by a nephrologist and a diagnosis of chronic kidney disease stage two was made. This was attributed to her relapsing polychondritis.

She was started on methotrexate 20 mg·week^{-1} injection and 17.5 mg prednisolone oral tablets with the aim of reducing the dose gradually. A positron emission tomography scan was arranged which did not show any uptake in cartilages or large vessel, suggesting that her relapsing polychondritis was coming under control with treatment. She is under regular follow-up with the rheumatologist and being planned for addition of further steroid sparing drugs. She is also under the care of a cardiothoracic surgeon for possible of surgery down the line.

Discussion

This is a complex and unique case of relapsing polychondritis in a patient with asthma and tracheobronchomalacia.

Relapsing polychondritis is rare, with an estimated incidence of 3.5 cases per million [5, 6]. It is an immune-mediated systemic disease, characterised by recurrent inflammatory episodes of cartilaginous tissues of the ear, nose, peripheral joints and tracheobronchial tree, which results in functional impairment and destruction of the involved structures [7]. Relapsing polychondritis has associations with other autoimmune diseases; *i.e.* rheumatoid arthritis being one of the commonest ones [8]. Diagnosing relapsing polychondritis is still a critical challenge for the physicians and can be missed very easily. There is no specific laboratory test to diagnose relapsing polychondritis. Anaemia, if present, can be normochromic normocytic and acute phase reactants can be helpful. Patients can have peripheral eosinophilia [4]. Interestingly, our patient did not have anaemia, no peripheral blood eosinophilia, normal fractional exhaled nitric oxide, normal acute phase reactants and normal kidney functions, so it was quite challenging to get to a diagnosis in our patient's case. The diagnosis is clinical and usually does not depend on investigations.

McAdam *et al*. [4] suggested that the diagnosis of relapsing polychondritis can be made if three or more of the six clinical features (auricular chondritis, nonerosive inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory tract chondritis and audiovestibular damage) are present.

This was later modified by Damiani and Levine [9], who concluded that the presence of at least one McAdam criterion and positive histological confirmation, or two McAdam criteria and positive response to administration of corticosteroids or dapsone will be sufficient to confirm a diagnosis of relapsing polychondritis.

Tracheobronchomalacia, relapsing polychondritis and asthma

Tracheobronchomalacia occurs when the walls of the airways are weak and it can lead to collapse of airways. There are two forms of tracheobronchomalacia:

1) Primary tracheobronchomalacia: develops during infancy or early childhood.
2) Secondary tracheobronchomalacia: seen in adults due to underlying conditions.

Primary tracheobronchomalacia has been reported in people with genetic conditions (mucopolysaccharidoses, Ehlers–Danlos syndrome, chromosome abnormalities, prematurity and a tracheoesophageal fistula) [10].

Secondary tracheobronchomalacia is occasionally observed in respiratory conditions (asthma, emphysema, COPD), inflammatory condition (relapsing polychondritis), exposure to toxins (mustard gas) and a complication of medical procedure (post intubation). Relapsing polychondritis frequently involves airways. In one study, the prevalence of airway involvement in relapsing polychondritis was 21% with tracheobronchomalacia the most common [11].

Dal Negro *et al*. [12] describe prevalence of tracheobronchomalacia and excessive dynamic airway collapse in asthmatics. They observed that tracheobronchomalacia in mild persistent asthma, moderate asthma and severe asthma was prevalent by 2.70%, 7.93% and 18.46%, respectively, compared with 1.61% non-obstructed subjects. However, association between tracheobronchomalacia and asthma has not been directly reported. Any patient with brittle asthma should be investigated for tracheobronchomalacia [12]. Diagnosis of tracheobronchomalacia requires computed tomography thorax and flexible bronchoscopy [13]. Empey index is a useful initial tool in predicting upper airway obstruction (UAO). It is a simple bedside calculation of ratio between forced expiratory volume in 1 s (FEV_1) (mL) and peak expiratory flow rate ($L \cdot min^{-1}$). Upper airway obstruction should be ruled out if Empey index is <10 [14]. Flow–volume loops may be normal or can show different characteristic patterns in tracheobronchomalacia. A study by Majid *et al*. [15] showed four different flow–volume loop patterns: low maximum forced expiratory flow (the most common) followed by biphasic morphology, notched expiratory loop and expiratory oscillations. A biphasic flow–volume loop in tracheobronchomalacia has also been described by Campbell and Faulks [16]. Koblet *et al*. [17] stressed on a notch in the expiratory limb of the flow–volume loop as distinctive of tracheobronchomalacia. Rapid flow oscillations pattern in tracheobronchomalacia have been outlined by Vincken and Cosio [18].

There is no known association between relapsing polychondritis and asthma but infrequently patients are wrongly diagnosed as asthma because of preliminary symptoms of airway involvement by relapsing polychondritis.

Points to ponder

Symptoms of tracheobronchomalacia and asthma maybe difficult to differentiate. Our patient presented with symptoms of asthma in 2011 and was started on inhaled corticosteroids. She continued to receive short courses of oral steroids from her general practitioner and during her inpatient stays when she had exacerbations. Her initial thorax computed tomography in 2010 did not show any evidence of tracheobronchomalacia. Tracheobronchomalacia was first apparent on computed tomography in 2018 and was further confirmed on bronchoscopy. Therefore, our patient acquired tracheobronchomalacia secondary to relapsing polychondritis.

The question arises here, did she really have asthma in 2011, or was it all due to tracheobronchomalacia or relapsing polychondritis?

The possible explanation to that question is that she did have asthma in 2011 as she improved on inhalers and there was no evidence of tracheobronchomalacia on computed tomography of the thorax. Bronchoscopy also reaffirmed the diagnosis showing thickening of basement membrane and Curschmann's spirals. We believe that the patient had both asthma and relapsing polychondritis and the latter was possibly masked due to her receiving courses of steroids and being on ICS.

Treatment of relapsing polychondritis

The rarity of the disorder has meant that few clinical trials have been performed. The choice of therapy is dependent on the severity of symptoms and the extent of disease. Corticosteroids remain the most used therapeutic measure but, despite bringing relief from symptoms and reducing the severity and duration of relapses, they do not appear to alter the disease progression. Methotrexate is often effective [19].

Treatment of tracheobronchomalacia

Treatment options for tracheobronchomalacia are internal stenting, external stenting or tracheostomy. Surgical intervention includes central airway stabilisation by posterior mesh splinting known as tracheobronchoplasty [13]. It improves symptoms, health-related quality of life, as well as function and exercise capacity [20]. Stenting can be used interim while surgery is being planned.

CPAP is also useful initial approach for symptomatic tracheobronchomalacia cases while awaiting specific treatment [21].

Learning points

- Asthma refractory to standard treatment should alert clinicians to the possibility of pathology other than asthma.
- Bedside scoring tools, *e.g*. Empey index is quite useful in suspected UAO patients.
- Any patient with tracheobronchomalacia should be investigated for relapsing polychondritis.
- A multidisciplinary approach should guide patient management.

Affiliations

Masood Ur Rasool[1], Iftikhar Nadeem[2], Usman Feroze Khatana[3], Sadiyah Hand[1]

[1]Dept of Respiratory Medicine, Norfolk and Norwich University Hospital, Norwich, UK. [2]Dept of Respiratory Medicine, Lister Hospital, Stevenage, UK. [3]Dept of Respiratory Medicine, Peterborough Hospital, Peterborough, UK.

Conflict of interest

None declared.

References

1. Robson A. Dyspnoea, hyperventilation and functional cough: a guide to which tests help sort them out. *Breathe* 2017; 13: 45–50.
2. Maricoto T, Monteiro L, Gama JMR, *et al.* Inhaler technique education and exacerbation risk in older adults with asthma or chronic obstructive pulmonary disease: a meta-analysis. *J Am Geriatr Soc* 2018; 67: 57–66.
3. Jarjour Nizar N, Peters Stephen P, Djukanovic R, *et al.* Investigative use of bronchoscopy in asthma. *Am J Respir Crit Care Med* 1998; 157: 692–697.
4. McAdam LP, O'Hanlan MA, Bluestone R, *et al.* Relapsing polychondritis: prospective study of 23 patients and a review of the literature. *Medicine* 1976; 5: 193–215.
5. Peebo BB, Peebo M, Frennesson C. Relapsing polychondritis: a rare disease with varying symptoms. *Acta Ophthalmol Scand* 2004; 82: 472–475.
6. Kent PD, Michet CJ Jr, Luthra HS. Relapsing polychondritis. *Curr Opin Rheumatol* 2004; 16: 56–61.
7. Borgia F, Giuffrida R, Guarneri F, *et al.* Relapsing polychondritis: an updated review. *Biomed* 2018; 6: 84.
8. Lang B, Rothenfusser A, Lanchbury JS, *et al.* Susceptibility to relapsing polychondritis is associated with HLA-DR4. *Arthritis Rheum* 1993; 36: 660–664.
9. Damiani JM, Levine HL. Relapsing polychondritis: report of ten cases. *Laryngoscope* 1979; 89: 929–946.
10. Carden KA, Boiselle PM, Waltz DA, *et al.* Tracheomalacia and tracheobronchomalacia in children and adults: an in-depth review. *Chest* 2005; 127: 984–1005.
11. Ernst A, Rafeq S, Boiselle P, *et al.* Relapsing polychondritis and airway involvement. *Chest* 2009; 135: 1024–1030.
12. Dal Negro RW, Tognella S, Guerriero M, *et al.* Prevalence of tracheobronchomalacia and excessive dynamic airway collapse in bronchial asthma of different severity. *Multidiscip Respir Med* 2013; 8: 32.
13. Buitrago DH, Wilson JL, Parikh M, *et al.* Current concepts in severe adult tracheobronchomalacia: evaluation and treatment. *J Thorac Dis* 2017; 9: E57–E66.
14. Empey DW. Assessment of upper airways obstruction. *BMJ* 1972; 3: 503–505.
15. Majid A, Sosa A, Ernst A, *et al.* Pulmonary function and flow-volume loop patterns in patients with tracheobronchomalacia. *Respir Care* 2013; 58: 1521–1526.
16. Campbell A, Faulks L. Bronchial pressure measurements in patients with tracheobronchial collapse. *Respiration* 1969; 26: 63–77.
17. Koblet H, Wyss F. Clinical and functional picture of genuine bronchial collapse with lung emphysema. *Helv Med Acta* 1956; 23: 553–560.
18. Vincken W, Cosio M. Flow oscillations on the flow-volume loop: clinical and physiological implications. *Eur Respir J* 1989; 2: 543–549.
19. Puéchal X, Terrier B, Mouthon L, *et al.* Relapsing polychondritis. *Joint Bone Spine* 2014; 81: 118–124.
20. Razakamanantsoa L, Chahine B, Goument L, *et al.* Portable CPAP benefits on exercise capacity in patients with excessive dynamic airway collapse (EDAC). *Eur Respir J* 2019; 54, Suppl. 63: PA672.
21. Murgu SD. Pneumatic stenting for tracheobronchomalacia. *J Bronchology Interv Pulmonol* 2014; 21: 109–112.