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Case report

Upper airway wheezing: Inducible laryngeal obstruction vs. excessive dynamic airway collapse

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A B S T R A C T

There are multiple causes of dyspnea upon exertion in young, healthy patients to primarily include asthma and exercise-induced bronchospasm. *Excessive dynamic airway collapse* (EDAC) describes focal collapse of the trachea or main bronchi with maintained structural integrity of the cartilaginous rings. It is commonly associated with pulmonary disorders like bronchiectasis, chronic obstructive pulmonary disease and asthma. It is believed to result secondary to airway obstruction in these conditions. While uncommon in young, healthy adults, it has recently been found as a cause of dyspnea in this population. Inducible laryngeal obstruction (ILO) is an umbrella term that describes an induced, intermittent upper airway impediment. While ILO is found in 10% of young patients with exertional dyspnea, it is primarily inspiratory in nature due to paradoxical closure of the glottis or supraglottis. This report highlights the presentation of a United States Army soldier who after a deployment was given a diagnosis of asthma, later found to have ILO and was subsequently diagnosed with concurrent EDAC. We follow up with a literature review and discussion of symptomatology, diagnosis, exercise bronchoscopy, and treatment modalities for both EDAC and ILO.

1. Introduction

Inducible laryngeal obstruction (ILO) is an umbrella term which describes episodes of breathing problems caused by recurring variable airflow obstructions in the larynx [1]. Exertional dyspnea is a common complaint in young adults and may be related to a variety of disorders to include asthma, non-specific airway hyperreactivity, exercise-induced bronchospasm (EIB), and ILO [2]. It is a challenging diagnosis in that many patients will have specific environmental triggers and symptoms may be difficult to reproduce in the pulmonary function laboratory. Nearly 25% of patients were not found to have a specific etiology based on a comprehensive evaluation [2]. Exercise-induced bronchoconstriction is reported in up to 20% of athletes and should be considered in patients with positive bronchoprovocation testing. When both spirometry is normal and bronchoprovocation testing is non-reactive, the evaluation should focus on disorders of the upper airway. ILO may be associated with psychological stressors, exercise, or airway irritants [3]. It is a common mimicker of asthma and is diagnosed on the basis of “noisy breathing,” abnormal flow volume loop (FVL), and characteristic inspiratory closure on laryngoscopy.

Excessive dynamic airway collapse (EDAC) is a clinical term used to describe localized collapse of the trachea or main bronchi. It is commonly observed as protrusion of the posterior tracheal membrane without collapse of the cartilaginous rings during expiration. If the observed collapse in the setting of symptomatic history exceeds 75% of the tracheal patency, it is deemed EDAC [4]. It is closely related to tracheobronchomalacia (TBM), characterized as a weakened or destroyed tracheal cartilage and hypotonia of the myoelastic elements. This results in anterior and posterior airway collapse causing expiratory flow limitation. Excessive dynamic airway collapse is differentiated from TBM based on its maintained mechanical integrity of the tracheal rings. Both may be associated with underlining airway disorders such as bronchiectasis, chronic obstructive pulmonary disease (COPD), and asthma. It is not uncommon for EDAC to go undiagnosed, mimicking symptoms of other pulmonary conditions and obtaining the label as “difficult to treat” lung disease [5]. Weinstein and colleagues recently demonstrated that EDAC can also be a cause of exertional dyspnea [6]. They identified six patients with exertional dyspnea and no underlining pulmonary disease who had EDAC on the basis of 1) symptoms only associated with exercise, 2) localized expiratory wheezing, 3) airway collapse on dynamic CT, and 4) localization with fiberoptic bronchoscopy. We present the case of a previously healthy thirty-one year old male with no pulmonary disease, diagnosed not only with ILO, but concordant EDAC contributing to his symptoms of dyspnea, wheezing, and exercise intolerance.

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2. Case presentation

The patient is a 31 year-old male with eight years of active duty service with the United States Army. He presented initially in August 2012 with complaints of difficulty breathing and transient hand numbness after running a mile and was no longer able to pass his required Army physical fitness test 2-mile run. His dyspnea symptoms usually abated quickly after reducing his speed or stopping exercise. He was deployed to Iraq for a nine month period in 2010 but did not report any significant exposures or symptoms. Initial spirometry was within normal limits with a forced expiratory volume at 1 s (FEV_1) of 3.96 (98% predicted), forced vital capacity (FVC) of 4.86 (100% predicted) and normal FEV_1/FVC ratio of 81%. Methacholine challenge testing was non-reactive with a 9% reduction of FEV_1 at a maximum dose of 16 mg/ml. Exercise testing with laryngoscopy demonstrated paradoxical inspiratory vocal cord adduction post exertion and he was diagnosed with inducible laryngeal obstruction (ILO). He was placed on nasal fluticasone, cetirizine and omeprazole while undergoing speech pathology training that utilized vocal cord relaxation techniques to improve his symptoms.

He continued to have intermittent exertional symptoms over the next two years, with ongoing complaints of audible wheezing and difficulty taking a full breath. He also began to develop intermittent hoarseness which worsened after dyspneic episodes. His symptoms progressed to dyspnea at rest, with symptomatic resolution after treatment with bronchodilators and noninvasive positive pressure ventilation (NIPPV). After transferring to San Antonio, he was referred for a formal laryngology evaluation where repeat exercise laryngoscopy showed no ILO, but the patient was heard to have audible expiratory wheezing. The laryngoscope was passed through the vocal cords and 50% collapse of the lower trachea and mainstem bronchi were visualized. After minute ventilation reduced post exercise, the collapse resolved with full return of normal tracheal patency.

Because of this large airway finding, he was referred to the pulmonary service for further evaluation and enrolled in a post-deployment dyspnea study. Pulmonary function tests again demonstrated normal lung function with normal flow volume loop morphology. Resting impulse oscillometry showed no increase in resistance or reactance while methacholine testing was again non-reactive. High resolution chest computed tomography (CT) showed 50% expiratory narrowing of the trachea at the carina. Transthoracic echocardiography was normal with a left ventricular ejection fraction of 65%, and normal size and function of the right atrium and ventricle. During cardiopulmonary exercise testing (CPET) on a treadmill, he demonstrated limited exercise based on a maximum oxygen consumption (VO_2 max) of 77% predicted without elevation of ventilatory parameters. The patient noted profound dyspnea and was heard to have significant audible expiratory wheezing during exercise. The loudest ausculatory sound was noted over the mid-trachea and was expiratory in nature. Repeat exercise laryngoscopy demonstrated a widely patent upper airway during inspiration.

He next underwent fiberoptic bronchoscopy (FOB) with minimal sedation with normal findings during tidal breathing. During bronchoscopy the patient performed multiple forceful expiratory maneuvers that revealed diffuse EDAC with 50–60% collapse of the distal trachea, complete collapse of the right upper lobe (RUL) posterior segment and 70–80% collapse of the left upper lobe (LUL) takeoff (Fig. 1). With repeated forced expiratory maneuvers, the findings were reproducible with localized expiratory wheezing heard on auscultation. Because of persistent symptoms of hoarseness and ausculatory findings, bronchoscopy with the patient actively exercising on a cycle ergometer one month later found that the patient still had no ILO, but now had a subglottic protuberation (and corresponding expiratory wheezing) believed to be the primary limiting segment of his previously diagnosed EDAC in addition to continued EDAC of distal trachea, RUL and LUL as described above. (Fig. 2).

Despite being placed on continuous positive airway pressure at night and during episodes of dyspnea and limiting exercise, he continued to have intermittent exacerbations to include at rest that required multiple emergency room visits each month. He was referred to interventional bronchoscopy and a Y-stent was placed from the upper trachea to the mainstem bronchi. Two weeks after placement, he was briefly hospitalized for a secondary pneumonia. He received intravenous antibiotics and airway clearance therapy. On the day of discharge, he returned to the emergency department after a coughing spasm. Imaging demonstrated dislodgement of the stent which was protruding through the vocal cords (Fig. 3). The stent was removed via bronchoscope and later the patient underwent tracheobronchoplasty. During this surgery, mesh was sutured to the trachea and both left and right mainstem bronchi, extending from the thoracic inlet to the secondary carina of each mainstem bronchi. This procedure completely relieved his symptoms. Cardiopulmonary exercise testing pre and post intervention is shown in Table 1. It was noted that after tracheobronchoplasty the patient had a deeper voice, which he reported had been consistent with the tone of his voice two years previously. During subsequent follow ups the patient was without further episodes of dyspnea upon exertion nor at rest and he had not required NIPPV for symptomatic management.

3. Discussion

Excessive dynamic airway collapse is a known cause of dyspnea, wheezing, and exercise intolerance. It refers to the collapse of the airway lumen greater than 75% (primarily the posterior membrane) while still maintaining the cartilaginous structural integrity of the trachea [7]. This entity is commonly seen in patients with bronchiectasis, chronic obstructive pulmonary disease (COPD), or asthma and may be the result of chronic inflammation. It has been postulated to be caused by recurrent coughing, gastric content aspiration in the setting of reflux, recurrent infection, or cigarette smoking which leads to atrophy of the elastic fibers of the posterior membrane of the trachea [7]. During forced expiration, smooth muscle tension opposes hyperbolic invagination of the posterior tracheal membrane and stabilizes the airway structure. However, absent smooth muscle tension may allow for a negative transmural pressure gradient to drive an invagination of the posterior trachea. The point of airway collapse is commonly referred to as the “choke point.” Ultimately, the collapse of the airway lumen in EDAC is thought to be a cumulative interaction between airway resistance, airway compliance, pleural pressures, and elastic recoil [8].

Inducible laryngeal obstruction describes various glottic conditions resulting in paradoxical inspiratory laryngeal closure [1]. First described in 1983, Christopher et al. published a comprehensive description of five patients with a syndrome of inspiratory vocal cord adduction with a posterior chink (glottic opening) presenting as asthma with symptoms of dyspnea and noisy breathing [9]. Dyspnea is the predominant symptom in 73% of patients followed by wheeze (36%) and stridor (28%), cough (25%), chest tightness (25%), throat tightness (22%), and changes in voice (12%) [3]. Differentiation between wheezing (suggesting lower airway disease) and stridor (suggesting upper airway disease) and the phase of respiration is poorly described in most reported cases. Etiologies related to this episodic phenomenon of intermittent glottic closure include exercise, airway irritants, reflux, and psychologic stressors. However, a direct physical irritant effect and laryngeal hypersensitivity has never been documented [10]. Poorly understood mechanisms secondary to emotional distress and exertion have previously been postulated and up to 25% of patients with exercise-induced ILO have underlining psychiatric conditions [11–13].

3.1. Diagnostic studies

Initial diagnostic studies in the workup of exertional dyspnea should include spirometry with bronchodilator response, bronchoprovocation

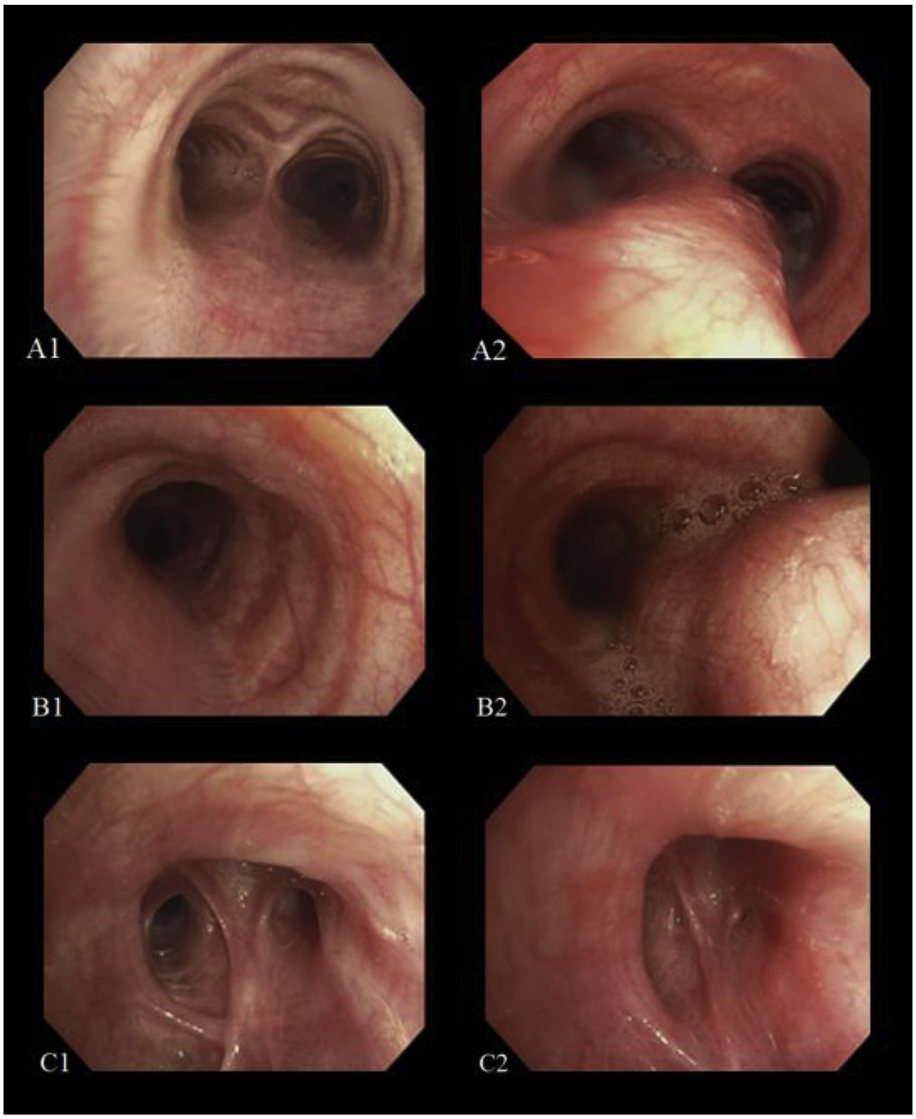

Fig. 1. Bronchoscopic findings at rest with their corresponding changes during forced expiration revealing diffuse EDAC. The carina at rest showed normal patency (A1) with subsequent collapse greater than 50% during forced expiration (A2). The left mainstem bronchus at rest (B1) showed significant invagination during forced expiration (B2), while the right upper lobar bronchus (C1) showed complete collapse of the posterior segment (C2).

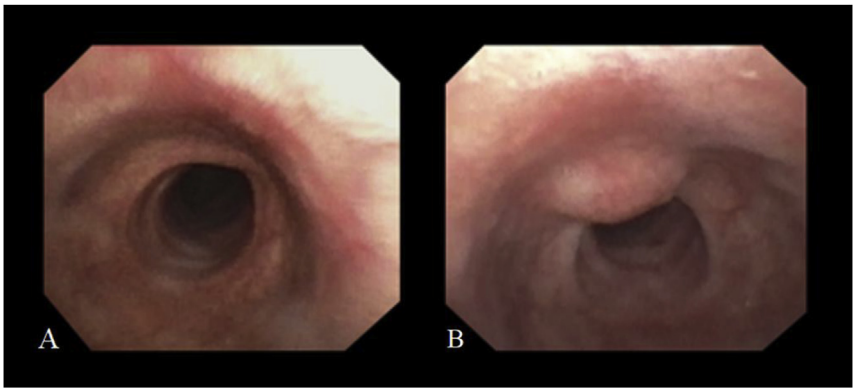

Fig. 2. Proximal trachea without evidence of collapse during inspiratory phase of respiration (A). Subglottic mucosal protuberation manifesting during expiratory phase (B).

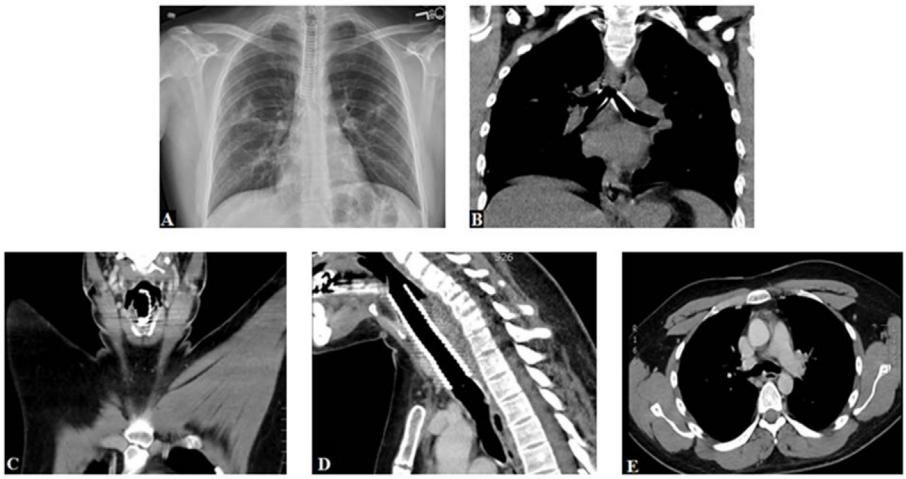

Fig. 3. (A) Chest x-ray on presentation displaying multi-focal pneumonia with endotracheal stent with Y-arms extending into the left and right mainstem bronchi. (B) Coronal chest CT displaying both arms of the stent in the left and right mainstem bronchi. Three days later CT imaging showed superior stent migration with proximal aspect of the stent erupting through the vocal cords (C), confined solely to the trachea and abutting the epiglottis (D). Stent arms were no longer deployed into the right and left mainstem bronchi (E).

Table 1
Cardiopulmonary exercise testing before and after tracheoplexy.

	Jan 2017	Jan 2018
Exercise time (min)	7	8
VO_2 max (L/min)	2.57 (77%)	2.54 (79%)
Anaerobic threshold (L/min)	1.74 (52%)	2.07 (64%)
Heart rate (maximum)	188	167
Heart rate response (beats/min)	44	40
O_2 pulse	13.67 (77.5% pred)	15.21 (89.1% pred)
Respiratory rate	43	32
VE max (L/min)	95.1	81.4
VT (L)	2.48	2.57
VE/MVV	0.64	0.61
VT/IC	0.74	0.68
VE/VCO_2 (max)	34	22

VO_2 – oxygen consumption: VE – minute ventilation; VT – tidal volume; MVV-mandatory minute ventilation; IC – inspiratory capacity; VE/VCO_2 – ventilatory equivalent for carbon dioxide.

testing, allergy testing, and chest imaging. Both ILO and EDAC may have characteristic PFT findings which may indicate these airway disorders. Inspiratory flow volume loop flattening or truncation may be highly suggestive of a variable extrathoracic obstruction such as ILO but is only reported in 25% of patients and may only be present during symptomatic periods [14]. Further evaluation of the upper airway is warranted when present to rule out anatomic abnormalities. PFTs may show subtle patterns associated with EDAC to include diminished expiratory flow with notching (which expresses a sudden decrease in flow at the initiation of exhalation as the airway collapses), and a biphasic flow-volume loop or saw-tooth appearing loops [5]. In both ILO and EDAC, PFT findings are not diagnostic and are more likely to be normal in patients with exertional dyspnea as the primary complaint. However, an initial series of 95 ILO patients found that 56% also had airway hyperreactivity based on reactive bronchoprovocation testing or bronchodilator response [15]. Additionally, many obstructive lung diseases to include asthma, COPD and bronchiectasis can be associated with EDAC and often PFTs only reflect the underlying lung disorder.

Several key points about the clinical presentation of ILO should be emphasized. Patients have increased medical utilization with recurrent emergency department visits or hospitalizations [16]. Patients take numerous asthma medications without effect on symptoms and may be diagnosed as “refractory to asthma.” Episodes may be abrupt in onset and resolve without typical worsening symptoms over several hours to days compared to asthmatic symptoms. Careful evaluation of patients will demonstrate high-pitched inspiratory sound (stridor) commonly mistaken for wheezing. Physical examination will disclose the sound to be primarily inspiratory with tracheal localization and not peripheral airway expiratory wheezing. Commonly, patients will have a normal examination when they are asymptomatic. There are no definitive radiological or laboratory studies that can currently confirm the diagnosis of and must be done by direct laryngeal visualization. While there are variations in protocol for laryngoscopy during exercise or immediately post exercise, real-time visualization of the larynx throughout exercise is attainable when a headset with an attached laryngoscope is worn [17]. This permits continuous visualization throughout the time of physical exertion as exercise ILO typically occurs at high levels of ventilation [18]. It is noteworthy that as the speed by which ventilator volume decreases after exercise, there is potential that the ILO may resolve prior to visualization with the laryngoscope post exercise cessation. As in this case, the patient underwent exercise laryngoscopy on three occasions, the last two finding no evidence of ILO, further confirmed during continuous exercise bronchoscopy.

In the evaluation of EDAC, high resolution computed tomography (HRCT) with expiratory prone and inspiratory supine phases may allow for specific gradation on the degree of collapse of the trachea. Obtaining dynamic CT images during an end-inspiratory state reveals the greatest degree of collapse and should be routinely used [19]. Dynamic expiratory imaging is advised because the forced expiratory maneuvers create more transtracheal pressure than low lung volumes without flow [20]. Additionally, findings on HRCT have been found to show a similar degree of airway collapse identified during fiberoptic bronchoscopy [21]. It is advised to pursue CT imagining initially due to its non-invasiveness, ability to evaluate the peritracheal structures that may be inducing the airway collapse, and to specifically measure the degree of airway collapse.

Direct visualization of airway collapse with bronchoscopy during forceful exhalation allows for determination of the choke point location and ultimately distinguishes EDAC from TBM. Bronchoscopic evaluation is limited by the subjective nature in quantifying airway collapse, optical effects such as distortion and magnification on imagining, the effect of instrumentation upon the airway, and limited ability to perform the investigation while the patient is dyspneic [7]. Exercise bronchoscopy allows for real time visualization of the upper tracheobronchial tree during elevated minute ventilation. It provides further evaluation of exertional symptoms and localized expiratory wheezing. Prior to exercise, the airway is anesthetized using nebulized lidocaine followed by direct application of lidocaine to the larynx and upper airway to level of the carina with an ultra-slim bronchoscope (Olympus BF-XP190). The patient then begins exercising on a cycle ergometer and the bronchoscope is reinserted at the beginning of symptoms. Direct visualization of the tracheobronchial tree mechanics during exercise permits close attention to anatomical areas correlating to the generalized location of the audible expiratory wheezing heard with

stethoscope. The advantages of bronchoscopy over laryngoscopy during exercise are improved visualization of abnormalities in the upper tracheobronchial tree, and improved views due to ability to clear secretions which are often abundant during exercise.

Murgu and Colt proposed a classification for the degree of EDAC and TBM based on bronchoscopic findings for expiratory tracheal narrowing. They proposed ranking the degree of occlusion as: normal, mild (50–75%), moderate (75–100%) and severe (100% with airway wall contact) [22]. This classification scheme additionally takes into account the choke-point location, patient function, and underlining etiology. Results of dynamic CT studies have shown that 70%–80% of normal individuals may meet the 50% criteria for collapse [20,23,24]. It is only in the presence of symptoms, localized expiratory wheezing and identification of collapse (either by CT or bronchoscopy) that EDAC can reasonably be diagnosed.

3.2. Treatment options

The therapeutic approach in treating the patient with ILO requires a multidisciplinary approach and there are currently no specified treatment guidelines for this condition [10]. Behavioral modifications and psychotherapy remain the cornerstones of therapy. Speech language pathologists are integral in assisting patients with vocal cord relaxation techniques and behavioral therapies to assist with decreasing the frequency of breath holding maneuvers and upper body tension. Several of these techniques are believed to assist with vocal cord abduction during exercise. As there is a well-known association between stress invoking factors, anxiety disorders and ILO, use of various psychotherapies remain an important treatment modality. Its use along with treatment of concordant depression and anxiety may not only assist in providing therapeutic benefit for these primary conditions, but may also promote alleviation of ILO as a secondary psychologic manifestation of them. Other treatment options such as treatment of acid reflux, direct airway interventions with botulinum toxin, or use of resistance valves are less frequently used [14].

Primary treatment modalities for EDAC includes treatment of the underlying pulmonary disorder and NIPPV. NIPPV is believed to serve as a pneumatic stent, improving airway lumen rigidity and expiratory flow while decreasing pulmonary resistance. Less transpulmonary pressure is required to maintain an adequate expiratory flow as elevated transpulmonary pressures increase the work of breathing, potentially underlining the dyspnea experienced in EDAC [4].

Some patients have experienced improved quality of life after their central airways have been stabilized through invasive therapies such as stent deployment. Endoluminal stents maintain airway patency, and studies have shown improvement in ventilatory function after stent insertion for various causes of central airway obstruction [25]. While the patient's symptomatic improvement is not explained by lack of increased FEV_1, it is believed that central airway solidity decreases turbulent flow with improved exercise capacity [26]. Murgu and Colt found that silicon stent insertion at choke points immediately improved functional status [27]. The patient in this case underwent dynamic Y-stent placement; a single-piece bifurcated tube designed to secure the trachea, left, and right mainstem bronchi and he had initial symptomatic improvement. While stenting can be used in patients with tracheobronchomalacia, it is also commonly used to maintain airway patency in tracheal stenosis or seal tracheoesophageal fistulas. However, stent placement is not without complication, which includes: obstruction by mucus, infection, fracture, perforation and hemorrhage, relocation of the choke point, or as in this case, migration [26]. While there are no contraindications for stent deployment in emergency situations, there are warnings not to use in patients with operable stenosis, open tracheostomas or compression of airways by vascular anomalies. As described in several studies of patients with severe tracheobronchomalacia, improvement of respiratory symptoms, quality of life, and functional status all resulted after airway stenting or surgical intervention in selected candidates [26,28]. As in this patient, surgical intervention primarily involves suturing of mesh to the exterior aspects of the airways to maintain patency, providing the trachea and mainstem bronchi a lattice to cling to that would otherwise collapse.

4. Conclusion

There are limited causes of dyspnea upon exertion in young, healthy patients. With normal spirometry and negative bronchoprovocation testing, consideration should be given for potential functional airway disorders. Both ILO, which may manifest as inspiratory closure of the vocal cords, and EDAC, expiratory collapse of the large airways, should be considered in a patient with reported “wheezing.” Although initially diagnosed and treated for ILO, EDAC was a consideration for this patient due to the exertional component of his wheezing and location based on ausculatory findings. While laryngoscopy should be the primary technique for evaluating upper airway “wheezing,” consideration should be given for additional radiographic and/or endoscopic imaging of the large airways if the larynx is functionally normal. Due to multiple foci of collapse in the tracheobronchial tree and progressive symptoms, he underwent stenting and eventually tracheobronchoplasty with complete symptomatic resolution.

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Appendix A. Supplementary data

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