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Two Cases of Tracheal Disease Misdiagnosed as Difficult-to-Treat Asthma

Running-Head: Are you sure about the diagnosis of asthma?

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Abstract

Initial management of patients with difficult-to-treat asthma must begin with confirmation of the diagnosis. Herein we present 2 cases of tracheal disease misdiagnosed as difficult-to-treat asthma. After systemic evaluation, tracheomalacia and tracheobronchial narrowing due to diffuse calcification of the cartilaginous rings was found as mimicking asthma.

Keywords: airflow limitation, asthma, difficult-to-treat asthma, severe asthma, tracheal calcification, tracheobronchomalacia

Introduction

Asthma is a serious disease with high social and economic costs that affect approximately 300 million individuals worldwide.[1, 2] The prevalence of asthma varies by country between 1% and 18% [2] and is 1%-9.4% in Turkey.[3] Proper treatment (i.e. Corticosteroids) results in a good control; however, some patients remain symptomatic despite treatment and systematic assessment of these patients must begin with confirmation of the diagnosis.[4] Herein we present 2 cases of tracheal disease misdiagnosed as difficult-to-treat asthma in order to highlight the importance of systemic assessment.

Case 1

A 46-year-old female patient was referred to allergy department with the diagnosis of difficult-to-treat asthma in 2011. Her complaints of productive cough and gradually exacerbating shortness of breath began approximately 9 years earlier. She was followed-up numerous times at several in-patient clinics with the diagnosis of acute exacerbation of asthma, particularly during winter, despite regular use of asthma medication. At the time of her referral, she was taking formoterol/budesonide 12 µg/400 µg b.i.d. She was never smoker. She underwent surgery due to chronic rhinosinusitis 9 years ago.

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Her physical examination showed bilateral expiratory rhonchi. Pulmonary function test results showed markedly diminished expiratory flow, with no reversibility (FEV1: 20%; FEV1/FVC: 42%; FVC: 41%; PEF: 84 L min^{-1}; FEF25-75: 10%) (Figure 1). Chest X-ray showed rough narrowing of the tracheae and main bronchi, and bilateral irregular infiltration in the basal segments (Figure 2). Flexible bronchoscopy was scheduled, but the patient declined the procedure. Subsequently, three-dimensional computed tomography (CT) of the thorax was performed, and reconstructed images were obtained in order to visualize the full length of the tracheae and main bronchi (Figure 3). The cartilage ring of the tracheae and main bronchi were diffusely calcified, which resulted in diffuse narrowing of the lumen by as much as 7 mm. In addition, peribronchial thickening, focal air-trapping, and peripheral reticulonodular infiltration were observed. Comparison of the images with older tomographic slides in 2007 showed progression of airway disease.

The patient was referred to the interventional bronchology and thoracic surgery departments, and both departments concluded that interventional bronchoscopy and surgical intervention would not benefit the patient. The patient refused to undergo additional diagnostic studies. With proper antibiotherapy, the patient's symptoms resolved, but there was no improvement in expiratory flow and the patient was discharged and referred to the pulmonary rehabilitation department. The final diagnosis was diffuse tracheobronchial calcification.

Case 2

A 37-year-old-female patient was referred to allergy department with the diagnosis of difficult-to-treat asthma in 2011. Episodic dyspnea began during childhood, and she was diagnosed with asthma 7 years earlier. She has been receiving systemic corticosteroid from 2009 to 2011, due to her ongoing complaints and frequent emergency room visits despite high-dose corticosteroid inhaler use and long-acting β2 agonist and leukotriene receptor antagonist treatment. She reported regular use of all this medication but remained symptomatic. She complained of wheezing and

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dyspnea during the day, and reported that during the previous month she could not go to work. The patient has never smoked and did not have any comorbidity.

Physical examination showed bilateral inspiratory and expiratory rhonchi. Pulmonary function test results showed expiratory air flow limitation (FEV1: 34%; FEV1/FVC: 66%; FVC: 45%; PEF: 238 L min^{-1}; FEF25-75: 17%) (Figure 4). Thoracic CT showed tracheoles neighboring the posterior wall of the tracheae (Figure 5). Additionally, fiberoptic bronchoscopy showed that the posterior membranous wall of the tracheae and bronchi was grossly bulging through the lumen during expiration (Figure 6). This finding was consistent with tracheobronchomalacia (TBM).

The patient was referred to the interventional pulmonology department for stent placement and the thoracic surgery department for surgical intervention, but the respective departments concluded that stent placement and surgery were inappropriate for the patient due to diffuse involvement of the tracheae and large bronchi.

Discussion

Difficult-to-treat asthma patients remain symptomatic despite the high-dose use of ≥2 asthma control drugs.[2] Such patients usually undergo systemic corticosteroid treatment for many years and therefore, experience the systemic side effects of such medication. Treatment of difficult-to-treat asthma patients must be systematically based and begin with confirmation of the diagnosis.[2] Cough, wheezing and dyspnea are common respiratory symptoms that potentially have an extensive differential diagnosis. Although asthma is the most common cause of cough, wheeze, and dyspnea in all ages, asthma is often attributed inappropriately to symptoms from other causes.[5]

Differential diagnosis in adults includes the presence of chronic obstructive pulmonary disease, vocal cord dysfunction, and benign or malignant diseases of the tracheobronchial tree (Table).[6]

The presented cases of benign tracheal disease that were misdiagnosed as asthma were using >2 asthma control medications had frequent hospitalizations and took systemic corticosteroids for many years. Both patients were housewives and did not have any environmental and occupational

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exposure. Case 1 had diffuse narrowing of the tracheobronchial system due to diffuse calcification of the cartilaginous rings. Tracheal calcification can be observed in relapsing polychondritis, tracheobronchopathia osteochondroplastica, amyloidosis, rhinoscleroma, and Keutel syndrome.

Relapsing polychondritis is a rare autoimmune syndrome characterized by recurrent cartilaginous inflammation, with destruction and fibrosis.[7] Various cartilaginous structures, such as the ear, nose, joints, larynx, and tracheobronchial tree, may be involved.[8] Thickening of the tracheal wall and destruction of the cartilaginous rings are key findings, whereas the posterior membranous region is spared.[9] Diagnosis is based on the presence of ≥3 of the following: bilateral auricular chondritis, non-erosive seronegative inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory tract chondritis, and audio vestibular damage. The tracheobronchial tree in case 1 was diffusely involved. The disease progressed during the previous 4 years. The patient's tracheobronchial cartilaginous rings were diffusely calcified, but not destroyed. Deformation of nasal cartilage was evident, and she complained of difficulty hearing, thought there were no signs of auricular chondritis. She reported no history of ocular inflammation or polyarthritis, and as such, relapsing polychondritis was considered a possible diagnosis.

Tracheobronchopathia osteochondroplastica and amyloidosis are diseases of submucosal tissue.[7] The former is characterized by multiple submucosal osteocartilaginous nodules that spare the posterior membrane of airways. The latter is deposition of abnormal proteinaceous material in extracellular tissue. There are 3 forms of amyloidosis: diffuse interstitial deposits, single or multiple pulmonary nodules, and, most commonly, submucosal tracheobronchial deposits.[10] Submucosal tracheobronchial deposits usually exhibit calcification.[11] Amyloidosis is differentiated from tracheobronchopathia osteochondroplastica by involvement of the posterior membrane. Case 1 had calcified cartilaginous rings and the submucosal area was spared.

Rhinoscleroma is a chronic, progressive granulomatous *Klebsiella rhinoscleromatis* infection that affects the upper and lower respiratory tract.[12] Tracheobronchial disease is not common.[13] Thickening of the tracheal wall, nodular deformity of mucosa, subglottic stricture, and

concentric narrowing of the tracheae and central bronchi are the main radiologic findings.[14] A positive *Klebsiella rhinoscleromatis* culture is diagnostic but is observed in <60% of cases.[15] Radiologic features in case 1 were consistent with the disease, but we could not obtain a specimen for microbiological investigations because the patient did not consent.

Keutel syndrome is a rare syndrome characterized by brachytelephalangism, abnormal cartilage calcification, neural hearing loss, and peripheral pulmonary stenosis.[16] Most Keutel syndrome patients are children and young adults. Case 1 was 46 years old, and onset of the disease occurred when the patient was 9 years old; the disease radiologically progressed during the previous 4 years in the absence of other systemic features.

Case 2 was diagnosed as TBM, which is characterized by a weak tracheae and main stem bronchi.[17] Normal intrathoracic airways dilate during inspiration and narrow during expiration, according to changes in intrathoracic pressure during the respiratory cycle. TMB can be congenital but is more commonly acquired. Prolonged intubation, tracheostomy, external trauma, emphysema, and chronic infections are the most common etiological factors in adult TBM.[17] Many of these conditions create segmental involvement of the airway, whereas chronic infections and emphysema are usually related to diffuse disease. The most common symptoms of TBM are dyspnea, wheezing, cough, and sputum production. Diagnosis is usually based on fiberoptic bronchoscopic visualization of >50% tracheal narrowing during expiration.[17] Treatment is usually conservative, and in severe cases continuous positive airway pressure (CPAP), stent placement, or surgical interventions are indicated.

Congenital TBM was considered as diagnosis in case 2 because her complaints began in childhood; however, it was rejected because diffuse disease is usually related to congenital anomalies and syndromes associated with other systems that are diagnosed during infancy, and to some cartilage abnormalities with involvement of other cartilaginous structures.[17]

Asthma is the most common disease in the differential diagnosis of limited expiratory flow. Many TBM patients receive asthma medications prior to the definitive diagnosis. Case 2 had

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received almost all available asthma medications for 3 years. As the tracheae and main stem bronchi were diffusely involved, we concluded that chronic infections were the cause of the patient's symptoms.

Conclusion

Difficult-to-treat asthma patients must be systematically evaluated via differential diagnosis. Many diverse conditions must be responsible from expiratory airflow limitation. Definitive diagnosis of underlying disease is crucial in order to avoid unnecessary long-term high-dose corticosteroid treatment, which can have severe systemic side effects rather than therapeutic action.

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Figure Legends

Figure 1. Case 1 flow-volume curve. Pulmonary function test results showed severe fixed airflow limitation.

Figure 2. Case 1 chest X-ray shows diffuse narrowing of the airways and bilateral infiltration in the basal segments.

Figure 3. Case 1 transverse sections from the upper (A) and lower levels of the tracheae (B), and reconstructed images of the thorax (C: coronal view; D: sagittally view) show diffuse calcification of the tracheobronchial cartilaginous rings and narrowing of the tracheobronchial tree.

Figure 4. Case 2 flow-volume curve. Pulmonary function test results showed severe expiratory airflow limitation.

Figure 5. Case 2 thoracic CT shows an increase in the diameter of the airway at the level of tracheae (A) and main bronchi (B).

Figure 6. Case 2 fiberoptic bronchoscopic images. Airways increased in size during inspirium (A) and collapsed during expiration (B).

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Table. Common Diagnoses That May Mimic Severe Treatment-Resistant Asthma (7)
(Adapted from the British Thoracic Society SIGN Asthma Guidelines 2011)

Without Airflow Obstruction	**With Airflow Obstruction**	**In Association with Asthma**
Chronic cough syndromes (eg, nonasthmatic eosinophilic bronchitis, reflux-associated cough)	COPD	Allergic bronchopulmonary aspergillosis
Rhinitis	Bronchiectasis	Pulmonary eosinophilic syndromes (eg, Churg-Strauss syndrome)
Vocal cord dysfunction	Sarcoidosis	
Cardiac failure	Lung cancer	
Pulmonary fibrosis	Central airway stenosis	
Dysfunctional breathing/hyperventilation syndrome	Obliterative bronchiolitis	
	Inhaled foreign body	

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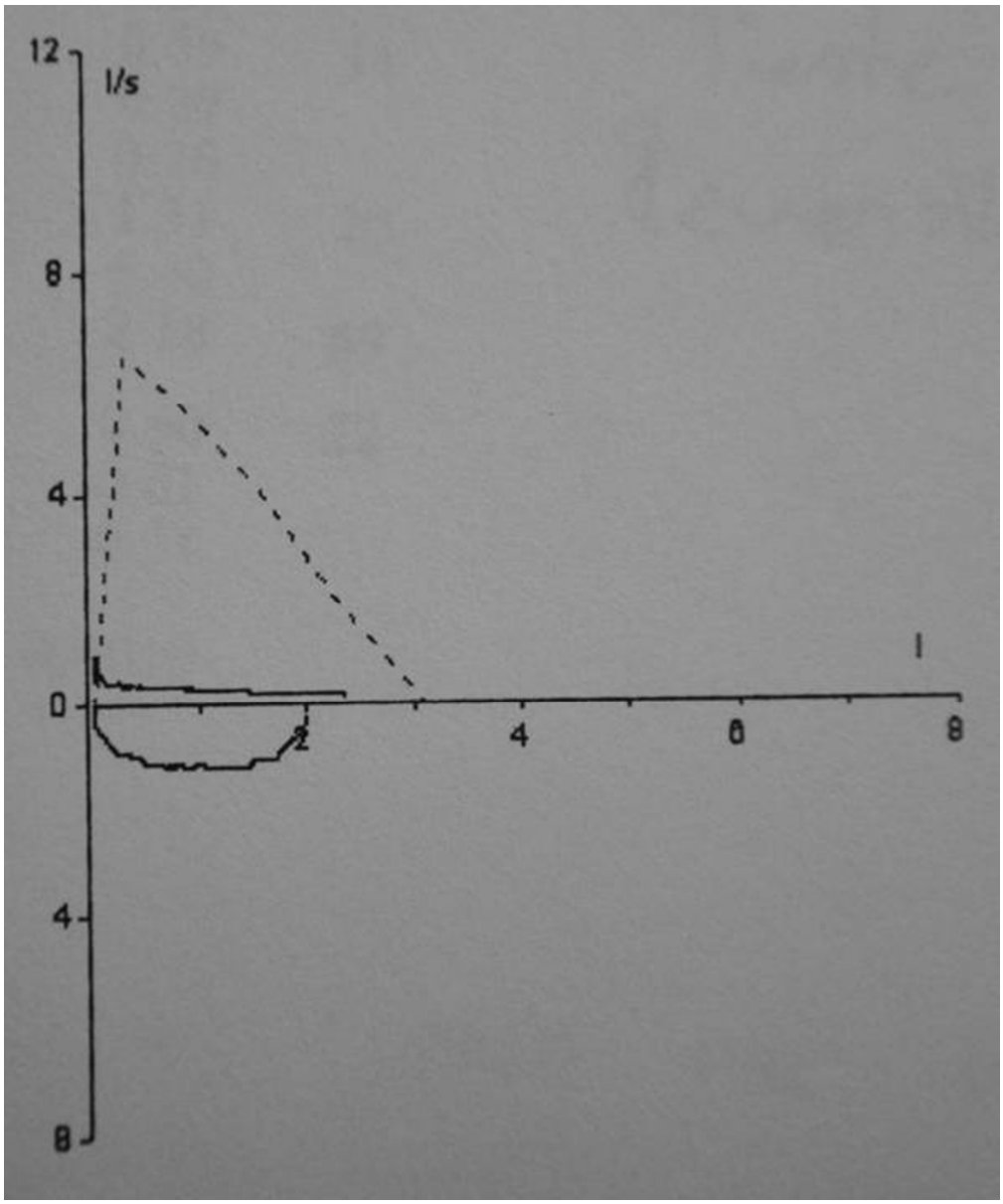

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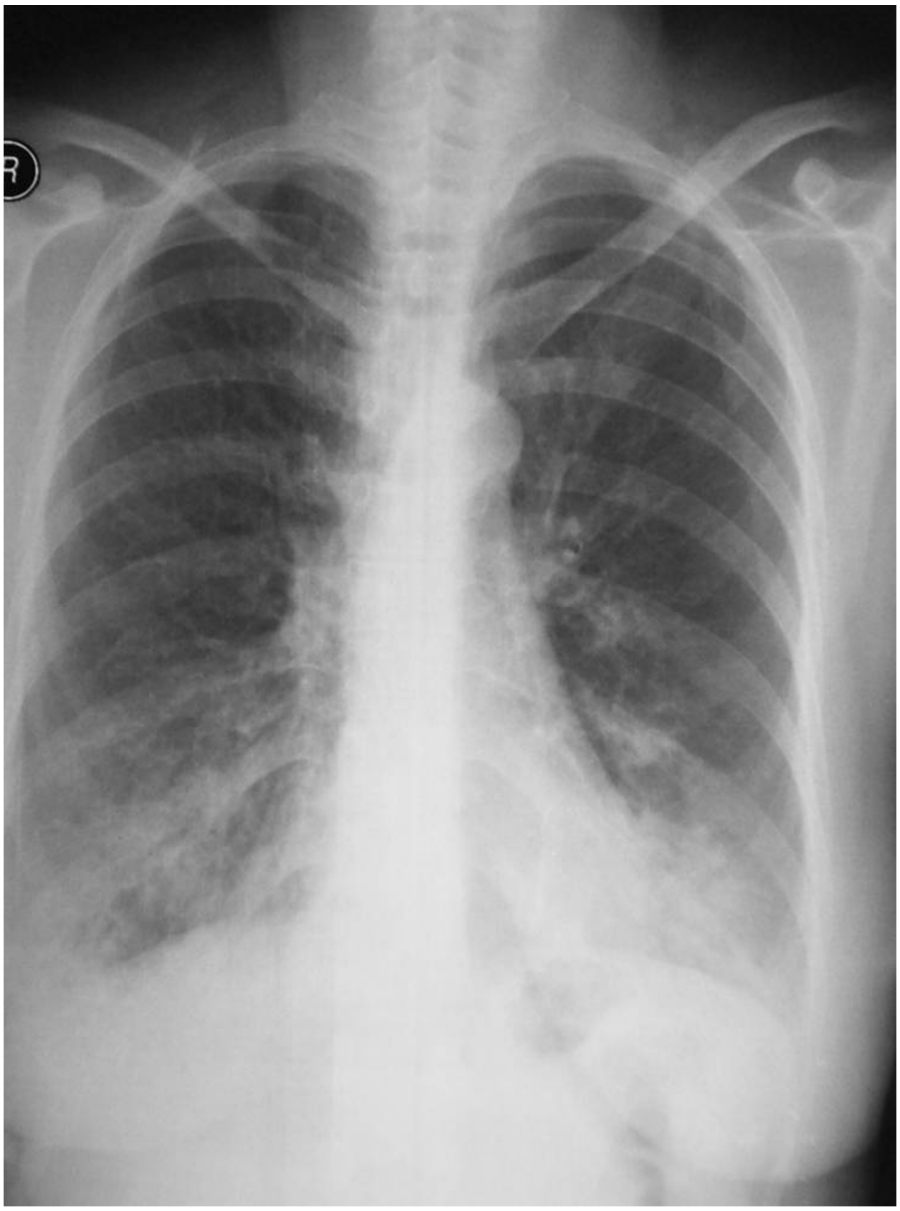

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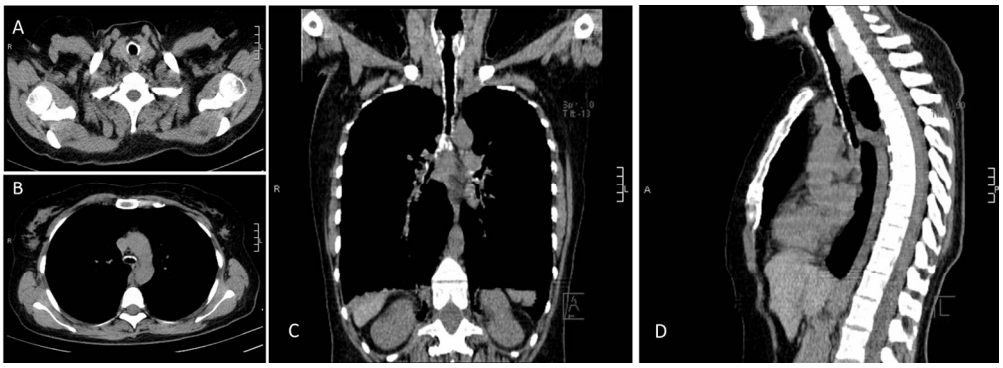

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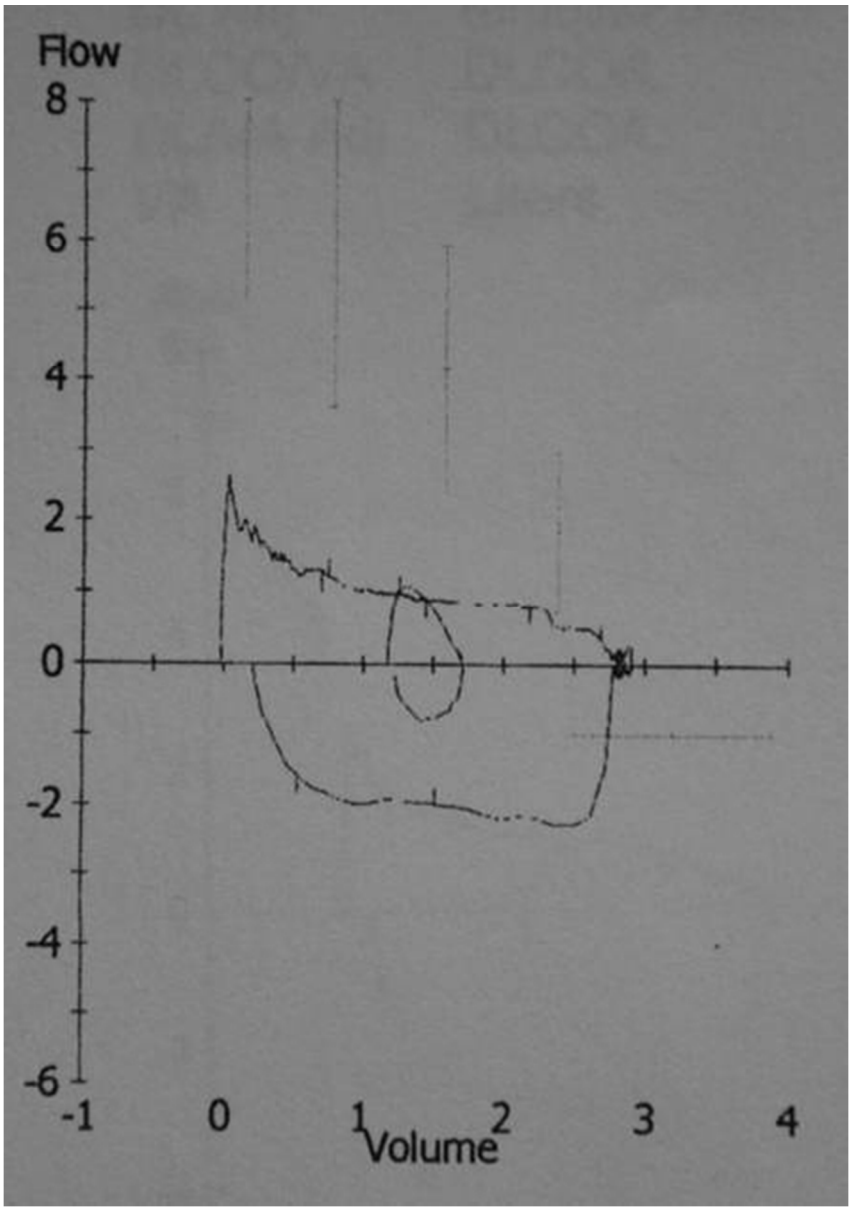

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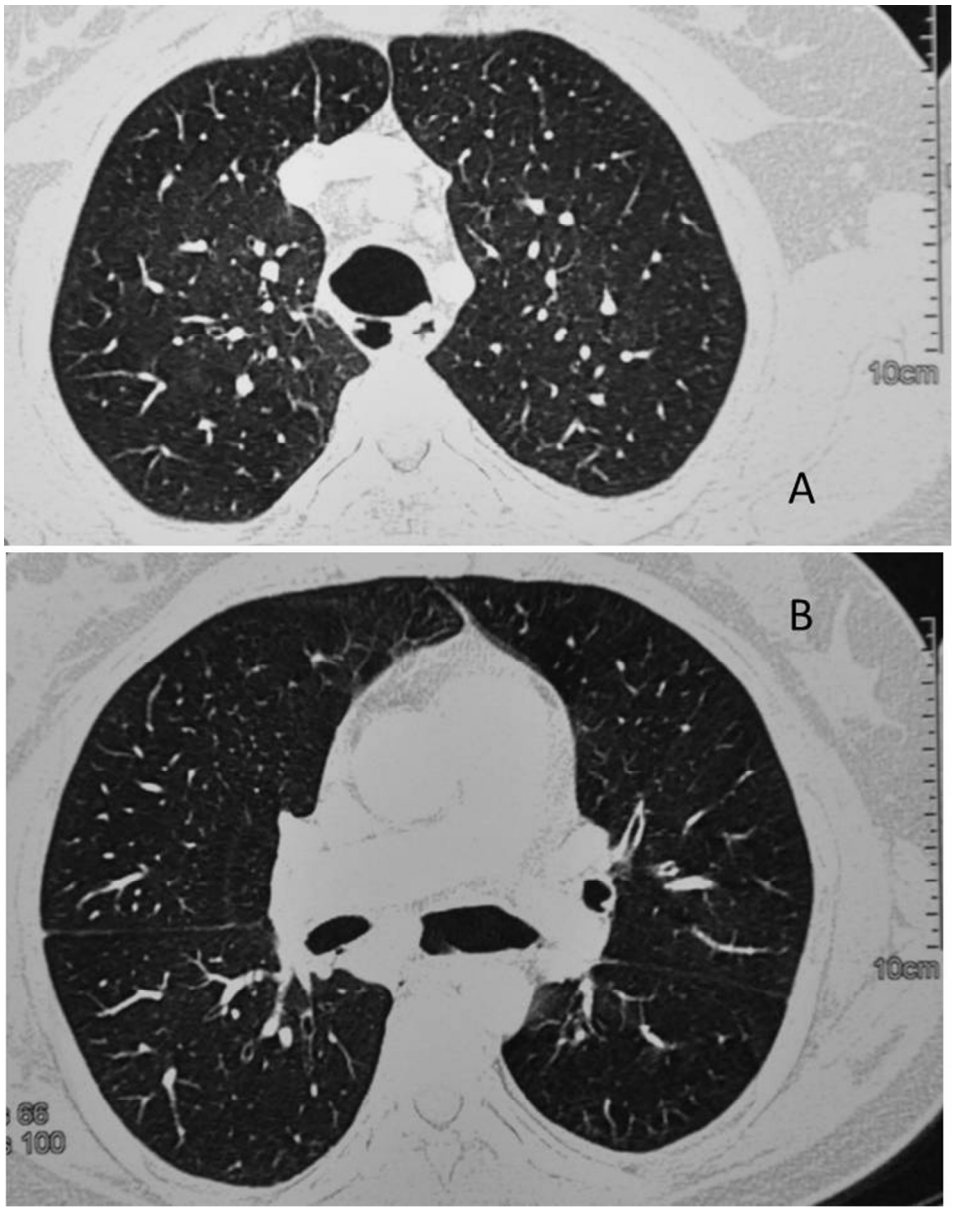

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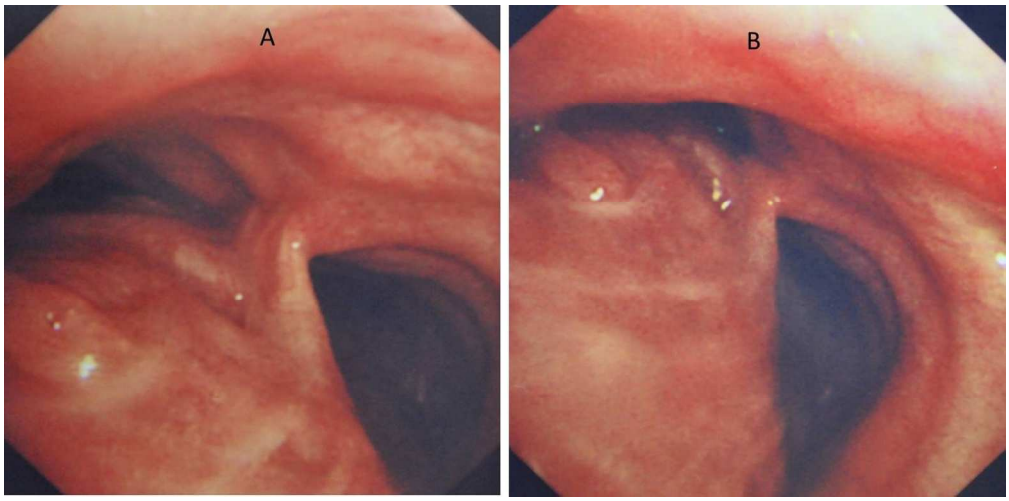

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