CASE REPORT

Constrictive bronchiolitis presenting with a mixed obstructive and restrictive pattern, associated with acid reflux

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SUMMARY

A previously healthy 55-year-old woman presented with worsening dyspnoea on exertion. The patient lived at altitude, did not smoke and had no exposure to occupational or environmental toxins. Her physical examination, including pulmonary, was unremarkable. Pulmonary function tests showed forced expiratory volume in 1 s/forced vital capacity ratio 74% predicted, diffusing capacity for carbon monoxide (DLCO) 92% predicted and residual volume 213% predicted. Rheumatological workup was negative. Chest radiograph showed hyperinflation without consolidation, and high-resolution chest CT showed mosaic attenuation with air trapping on expiratory imaging. A decreasing DLCO lead to transbronchial biopsies that were inconclusive. A video-assisted thoracic surgery lung biopsy showed small airway disease suggestive of constrictive bronchiolitis. Oesophagram and a barium swallow showed a hiatal hernia with large volume gastro-oesophageal reflux to the level of the clavicles. The development of constrictive bronchiolitis in this patient was possibly secondary to hiatal hernia and silent gastroesophageal reflux disease (GERD). In the face of presumably idiopathic lung disease, clinicians should perform a GERD workup even in the absence of GERD symptoms.

BACKGROUND

Constrictive bronchiolitis (CB) is a small airway disease in which inflammation and fibrosis develop within the submucosa of respiratory bronchioles. This external, peribronchial fibrosis constricts the airway in a concentric manner leading to eventual obliteration of the lumen.[1] This disease entity is most commonly associated with lung transplantation rejection or inhalation of diacetyl associated with popcorn manufacturing or vaping e-cigarettes.[2]

CB typically presents as an obstructive lung disease and less commonly as a restrictive lung disease.[3] However, in a few rare reports CB has presented in a mixed obstructive/restrictive pattern.[3 4] In these unusual cases, there has usually been an association with a known risk factor for CB. This report documents a mixed obstructive/restrictive case of CB without a known recognised cause of CB in association with a history of acid reflux.

This case illustrates that the traditional categories of obstructive and restrictive lung diseases are not mutually exclusive and can coexist in rare instances, as well as presenting possible support for an association between GERD and CB in the absence of all other known risk factors.

CASE PRESENTATION

A 55-year-old woman experiencing gradual worsening of dyspnoea on exertion presented for initial medical evaluation in 2009. The patient lived at altitude in Denver, CO, did not smoke (including e-cigarettes) or drink alcohol. She had no history of lung transplantation or exposure to occupational or environmental toxins and had only travelled once outside the USA to Ethiopia 16 years ago. She was adopted and her limited family history was significant for a father who was a heavy smoker with emphysema. Her physical examination, including pulmonary, was unremarkable.

Vitals signs were: blood pressure 142/85 mm Hg, temperature 98.5 °C, pulse 66 per minute, respirations 16 per minute, body mass index (BMI) 40.1 and SpO_2 on room air was 93%.

INVESTIGATIONS

Pulmonary function tests showed forced expiratory volume in 1 s (FEV_1) of 59% predicted, forced expiratory volume in 1 s/forced vital capacity ratio (FEV_1/FVC) 74% predicted, FVC of 64% predicted, diffusing capacity for carbon monoxide (DLCO) of 92% predicted, residual volume (RV) of 213% predicted and total lung capacity (TLC) of 95% predicted.

Alpha-1 antitrypsin levels showed negative results.

Chest X-ray showed hyperinflation. Both inspiratory and expiratory CT scans revealed findings consistent with significant airway disease including bronchial wall thickening, mosaic attenuation and expiratory gas trapping. There was no significant bronchiectasis seen.

Her initial impression was interstitial pneumonia disease and she was treated with supplemental oxygen during activity and a short course of prednisone. In addition, the patient changed her diet in an attempt to lose weight. Subsequently, she was able to reduce her BMI from 40.1 to 36 and along with initiation of the medical therapy reported significant improvement in her symptoms.

Over the next year she had exacerbations of worsening dyspnoea and several episodes of home measurements of pulse oximetry as low as 72% lasting 10–15 min. Because of these symptoms, she

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was treated with a continuous course of prednisone and 24-hour supplemental oxygen. A course of azithromycin was halted due to urticaria. Inhaled bronchodilators did not appear to improve her clinical course.

Because the patient moved to a farm, a hypersensitivity pneumonitis panel for mould and animals was conducted, including chicken, turkey, pine, trees, goat and horses, with no positive results. In addition, the patient was administered a course of oral *N*-acetylcysteine (900 mg two times per day) with little improvement in her symptoms.

In 2011, bronchoscopy with biopsy was performed. Bronchoalveolar lavage was notable for a 16% lymphocytosis. Her cultures were positive for *Mycobacterium avium* complex. She underwent transbronchial biopsies at that time, which showed chronic bronchitis and some mild non-specific interstitial disease.

Pulmonary function tests remained stable with a slight decrease in DLCO from 92% to 89%. In 2012, the patient moved off the farm with no apparent improvement in her symptoms. New onset peripheral oedema and crackles on lung auscultation revealed WHO type III pulmonary hypertension with a severe haemodynamic phenotype based on an elevated mean pulmonary artery pressure (34 mm Hg), transpulmonary gradient (19 mm Hg) and diastolic pressure gradient (11 mm Hg). However, there was no evidence of right heart failure.

Several months later, the patient returned again for dyspnoea, this time citing dry mouth and dry eyes. Her rheumatological workup was non-contributory. Her erythrocyte sedimentation rate was normal but C-reactive protein was elevated at 1.58 mg/dL.

One year later, the patient developed acute-onset mid-chest pain radiating to her back, which was associated with sweating, flushing, heart palpitations and nausea. She went to the emergency department where she underwent a full cardiac workup which was negative. Endoscopy and a proximal oesophageal biopsy showed squamous mucosa with mild chronic inflammation. Oesophagram and a tailored barium swallow showed a small sliding hiatal hernia with large volume gastro-oesophageal reflux to the level of the clavicles. However, no tracheal aspiration was observed. No mucosal lesions, strictures or obstructive lesions were identified in the oesophagus. Oesophageal manometry with a pH/impedance study was performed. The pH impedance study showed no evidence of abnormal acid or non-acid reflux, but proximal extent of reflux was higher than normal. Greater than 50% of the reflux episodes extended into the proximal oesophagus suggesting oesophageal spasm or oesophagitis as a result of reflux. She was started on omeprazole 40 mg two times per day and a laparoscopic fundoplication was considered.

As the transbronchial biopsy performed earlier had been inconclusive, a video-assisted thoracic surgery (VATS) lung biopsy was performed. Histopathology showed evidence of small airway disease suggestive of CB without lung parenchyma abnormalities. There was evidence of significant air trapping and hyperinflation when attempting to deflate the lung for the VATS. Tissue culture from the biopsy was negative for AFB implying a colonisation rather than an infection.

Pulmonary function tests revealed a decrease in TLC from 95% 7 years earlier to 77%, a decrease in RV to 106%, FEV_1 stable at 54% and FEV_1/FVC stable at 74%.

OUTCOME AND FOLLOW-UP

The patient subsequently moved from altitude in Colorado to sea level and reported a significant improvement in her breathing. She continued taking prednisone and tapered down to 5 mg daily. She was considering a trial of mycophenolate mofetil to replace the prednisone as she had developed cataracts and severe weight gain from its use. She continued to require supplemental oxygen on exertion and while sleeping. She had also started pulmonary rehabilitation and reported benefit.

DISCUSSION

A thorough search of the literature revealed few cases of mixed CB.[3 4] Most were associated with a known CB risk factor, however one was idiopathic without a history of GERD.[4]

The cases of CB reported in the literature show that it can result from several known and well-documented causes. Published case reports show it is the primary cause of post lung transplant rejection and thus the main obstacle to long-term survival in these patients.[1] It can also be caused by the inhalation of noxious fumes, notably the popcorn flavouring chemical diacetyl, leading

Learning points

- Constrictive bronchiolitis (CB) is also known as bronchiolitis obliterans or obliterative bronchiolitis. CB should not be confused with bronchiolitis obliterans organising pneumonia in which inflammatory polyps and granulation tissue develop internally from the airway wall, occluding the lumen.[1]
- CB has a pleomorphic presentation. Chest radiography can often be normal and chest CT may or may not show air trapping, bronchial wall thickening or mosaic attenuation.[6] Due to the sporadic nature of the inflammation and fibrosis in CB, a transbronchial biopsy is insufficiently sensitive to make the diagnosis.[10] Thus, an open lung biopsy is the only way to definitively diagnose CB.[3]
- CB typically presents as an obstructive lung disease. However, rarely it can present in a mixed obstructive/restrictive pattern. The patient's total lung capacity is 77% predicted, indicating a restrictive aetiology but all other findings support an obstructive pattern: hyperinflation on chest X-ray, the difficulty in deflating the lung for the video-assisted thoracic surgery, a residual volume of 106% predicted, FEV_1/FVC of 77% and CT scans showing air trapping. It is thought that this restrictive pattern component is due to dynamic compression of the lungs during exhalation.[1]
- A possible causative relationship exists between GERD and CB. A study in 2013 published in The Society for Surgery of the Alimentary Tract suggests that the triad of obesity, hiatal hernia and GERD, as found in this patient, puts one at higher risk for GERD-associated pulmonary fibrosis.[11] Over the past 40 years, numerous studies have reported high rates of GERD in patients with advanced lung disease including interstitial pulmonary fibrosis, chronic bronchitis and chronic obstructive pulmonary disease.[12] However, several recent studies have shown an additional association between GERD and CB.[13] Two studies published in 2012 and 2016 suggest that gastric acid reflux can promote the development of aspiration-induced CB in rat lung allografts, offering the first evidence of causality and not just association between GERD and CB.[14 15] It is possible that an aetiology of GERD could account for some of the cases of CB previously diagnosed as idiopathic. In our case, the patient presents with an extremely unusual form of CB: obstructive and restrictive pulmonary pattern. In addition, she has no known risk factors for CB. A possible causative relationship between GERD and CB is a potential hypothesis for her presentation.

to CB in popcorn factory workers, coined 'popcorn lung'.[2] This association has recently been further examined due to the use of diacetyl in e-cigarettes and vaping. A recent study by Harvard School of Public Health published in June of 2016 reports that of the 51 e-cigarette flavours tested, more than 75% of them contain diacetyl.[5]

CB has gained additional recent attention from the military due to cases presenting in soldiers returning from Afghanistan and Iraq.[6] The unique fumes the soldiers inhale have been questioned as possible causes in these cases. These include burning jet fuel, combustion of trash pits, sand from sandstorms, aerosolised metal from detonated Improvised Explosive Devices (IEDs) and mustard gas.[7] Normal, everyday environmental exposures such as inhaling animal feed and cigarette smoke have also been reported to cause CB.[8] Less commonly, CB can be a result of viral or atypical mycoplasma infection and has been linked to rheumatoid arthritis.[1] Idiopathic CB outside of these risk factors is very rare and mainly occurs in middle-aged women.[9]

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