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Bronchiolitis Obliterans in Immunocompromised Males

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Abstract

Introduction

Bronchiolitis obliterans (BO) is the worst outcome from bronchiolitis and is characterized by fibrosis constricting or obliterating the bronchiolar lumen. It has multiple causes and is difficult to treat.

Cases

Case 1 developed BO secondary to prolonged Haemophilus Influenzae infection as a result of chronic hypogammaglobulinemia from Rituximab therapy for a prior diagnosis of lymphoma.

Case 2 developed BO secondary to HIV infection which has only been rarely reported.

Outcome

Case one received Co-Amoxyclav followed by long term macrolide therapy and prednisone but unfortunately failed to improve significantly.

Case two was commenced on anti-retroviral therapy, prolonged macrolide therapy, prednisone, Co-Trimoxazole prophylaxis and an ICS/LABA inhaler. He showed some symptomatic improvement but never recovered to his pre-morbid baseline.

Discussion/Conclusion

BO is a rare entity and has rarely been described in such scenarios. We provide an overview of bronchiolitis and its rare subtype BO. We review its aetiologies, presentation and current evidence for management.

Introduction

Bronchiolitis is a term used to describe inflammation of the bronchioles which are less than 2 mm in diameter. Bronchioles are normally invisible on CT scan unless there is inflammation of the wall of these airways or the airways become fluid-filled. Bronchiolitis is usually diagnosed on thin-section CT scan where it appears as characteristic "tree-in-bud (TIB)" inflammation[1]. It has a number of aetiologies and outcomes ranging from full resolution of the inciting process to severe scarring and obliteration of the bronchioles most often seen post lung transplantation[1-2]. We present here two interesting cases of bronchiolitis obliterans (BO), also known as obliterative bronchiolitis, in immunosuppressed males followed by a review of the topic focusing on aetiology, investigation and treatment.

Case 1

A 45 year old male smoker presented to clinic in February 2021 with a six week history of severe dyspnoea, wheeze and purulent cough. He had a 10 pack year history of smoking and did not use vaping devices. His past medical history was significant for Diffuse Large B Cell Lymphoma (DLBCL) which had presented with spinal cord compression requiring emergency decompression of T3-T9 in 2019. He subsequently received 6 cycles of Rituximab-CHOP and high dose methotrexate and was in complete remission by December 2019. Unfortunately his treatment was complicated by Doxorubicin induced cardiomyopathy resulting in an ejection fraction of 30%. One year later he noted severe progressive dyspnoea on exertion. He was not taking any pneumotoxic medication and he had no significant environmental exposures. Physical examination revealed O2 saturations of 92% on room air and bibasal inspiratory squawks. There were no signs of heart failure. His BMI was 17.8.

PFTs revealed marked obstruction with an FEV1 of 0.83L (22% predicted), an FVC of 2.9L (62% predicted). He had a bronchodilator response of only 3%. Mid-expiratory phase of forced expiratory flow (MEF) was reduced at 12%. Diffusion capacity was severely reduced at 31% predicted. Chest radiography revealed hyperinflation only. CT showed peribronchial nodularity and TIB changes in the lower lobes. (Fig. 1) The patient could not comply with expiratory HRCT images. Bronchoscopy revealed marked bilateral purulent secretions and washings cultured a pan-sensitive *Haemophilus Influenzae*. This was negative for *Pneumocystis jiroveci,* fungi, mycobacteria and COVID-19. Blood investigations were significant for pan hypogammaglobulinemia with an undetectable IgG level, Ig M 0.22 g/L and IgA 0.09g/L. Retrospectively his IgG was only 3.34 g/L 18 months prior in May 2019.

Despite acute co-amoxiclav, long-term macrolides and prednisolone his symptoms, radiological and spirometric parameters failed to improve significantly. He was also commenced on immunoglobulin replacement therapy but his best recorded FEV1 over the last 12 months showed only marginal improvement to 1.18 L or 31% predicted. His symptom burden remains much the same. His last cardiac echo in January 2022 still showed an ejection fraction of only 30%. His diagnosis is Bronchiolitis obliterans (BO) secondary to severe airway infection with *Haemophilus influenzae* due to prolonged hypogammaglobulinemia following rituximab therapy.

Case 2

A 55 year old male presented to clinic in May 2021 with a 4 month history of severe dyspnoea following a febrile illness, purulent cough and 7 kg weight loss. His symptoms were refractory to several courses of antibiotics. Prior to this he could walk 8 km. His past medical history was significant for myocardial infarction 10 years previously and a recent coronary stent for a 70% LAD stenosis. He stopped smoking 10 years ago with a 10 pack year history. He did not vape. He worked as a farmer but denied exposure to mouldy hay.

Examination revealed fine bi-basal crepitations and inspiratory squawks. Oxygen saturations were 96% on room air desaturating to 90% after an 80 metre walk. Chest radiograph showed bilateral infiltrates. Lung function revealed marked obstruction with an FEV1 of 0.95L (27% predicted), an FVC of 2.53L (58% predicted). MEF was severely reduced at 10%. There was no bronchodilator response. Diffusion capacity was moderately reduced at 53% predicted. HRCT thorax revealed TIB, emphysema in the upper zones, pneumonia, ground glass opacities and bronchial wall thickening. (Fig. 2)

A HIV test was sent, because of the persistent antibiotic-refractory bronchorrhoea. This returned positive, with a viral load of 2653 copies/ml and a preserved CD4 count of 385. Due to concern for *Pneumocystis jiroveci* (PJP)infection an urgent bronchoscopy was performed and this was negative for PJP, bacteria, fungi, mycobacteria and Covid-19.

The patient was commenced on prednisolone, azithromycin, co-trimoxazole 480mg od as PJP prophylaxis and an ICS/LABA inhaler. He was also started on anti-retroviral treatment. Over the following months his exercise tolerance improved to 2 kilometres although he remained breathless on strenuous exertion. His FEV1 improved to 1.69L (50%) but at present is only 38% predicted. His HRCT thorax now reveals only mild emphysema with air trapping on expiratory images. The diagnosis is BO secondary to HIV infection. We cannot determine if there was any COPD prior to diagnosis as he had no previous lung function tests.

Results

Our case of severe immunoglobulin deficiency with completely unrecordable IgG was due to his anti-CD20 treatment i.e. Rituximab, which his last dose was 14 months previously. The effects of the drug on B cells can last from 6-12 months if used as monotherapy and up to 24 months if used in combination with other chemotherapeutics as in our case[5-6]. He may also have had a low baseline due to lymphoma. Of note, however, BO, has rarely been described in association with R-CHOP therapy[7]. His gas transfer of only 31% predicted and his low oxygen saturations, in the absence of obvious infiltrates on chest radiograph, was perhaps an early clue that a lot of his peripheral bronchioles had already become fibrosed. Presumably with such compromised innate immunity, *Haemophilus influenzae* damaged his airways irreversibly despite the aggressive, attempted salvage therapy[8-9].

HIV has been reported as a cause of bronchiolitis in only a few cases. The mechanism is thought to be due to development of follicular bronchiolitis which is characterised by hyperplasia of the bronchiolar lymphoid tissue secondary to an antigenic trigger leading to narrowing of the endobronchial lumen[2,10]. As in our case, HRCT findings consisted of centrilobular and peribronchial nodules that have a ground glass attenuation[4]. (**Fig. 2)** Evidence for treatment is based predominantly on case reports but consists of addressing the underlying HIV infection with anti-retroviral treatment[10]. Steroids and macrolide therapy have also been trialled to varying effect[8,11-13].

Discussion

Bronchiolitis in children is mostly an acute infectious process caused by viral infections such as RSV[2]. In adults it is a much more heterogeneous disease and often chronic. Bronchiolitis is frequently due to infection and often complicates airway conditions including asthma, COPD and bronchiectasis. It can also be associated with connective tissue disease (particularly rheumatoid arthritis), gastro-oesophageal reflux disease (GORD), immunosuppression, inhalational injuries, drug reactions, and lung transplantation[2-4]. It is often classified according to clinical, radiological, histopathologic or aetiological features. However no universally accepted consensus exists on how best to classify bronchiolitis[2-3].

Chest radiography is insensitive for the detection of bronchiolitis. High Resolution CT (HRCT) is the gold standard for detecting Bronchiolitis[2-3]. Direct signs of bronchiolitis appreciable on HRCT include: bronchiolar wall thickening due to inflammation or fibrosis, bronchiolectasis and luminal impaction (due to secretions/fibrosis). Luminal impaction makes the peripheral airways become visible in the form of nodules, linear branches, and TIB opacities. Indirect signs of bronchiolitis include air trapping and atelectasis which can combine to cause mosaic attenuation[4].

BO is the worst outcome from bronchiolitis and is characterised by fibrosis obliterating the bronchiolar lumen. There are a myriad of causes and it is postulated to be the final common pathway of the bronchiolar response to many small airway insults[3,14]. BO may have no direct CT signs of bronchiolitis but indirect findings of air trapping and mosaic attenuation on CT expiratory images provides a strong clue to its presence[3-4]. Clinical criteria for a diagnosis of BO include severe irreversible airflow obstruction measured by spirometry, with an FEV 1 of <60% in the absence of other pathologic causes for airway obstruction as was seen in both our cases. A mid-expiratory phase of forced expiratory flow (MEF) of <30% is a sensitive indicator of BO as it is a measure of small airways disease[3,15,16].

The biggest threat to lung transplant recipients 6 months post-surgery is development of BO. The main driver of this is thought to be micro-aspiration. This is due to vagal nerve damage by the surgery, calcineurin inhibitors also have an inhibitory effect on oesophageal peristalsis and some patients have a pre-existing hiatus hernia before transplant. For those with BO, inhaled steroids,

azithromycin, montelukast +/- short burst high dose corticosteroids have been shown to stabilize or increase FEV1 in some cases[16].

In summary, we present 2 cases of bronchiolitis obliterans in immunosuppressed males. The aetiology appears to be quite rare in both cases. They have both severe obstructive lung physiology with limited response to treatment. In patients receiving R- CHOP it is important to monitor their immunoglobulin levels on a 3 to 6 monthly basis and all adults with bronchiolitis should have a HIV test[6].

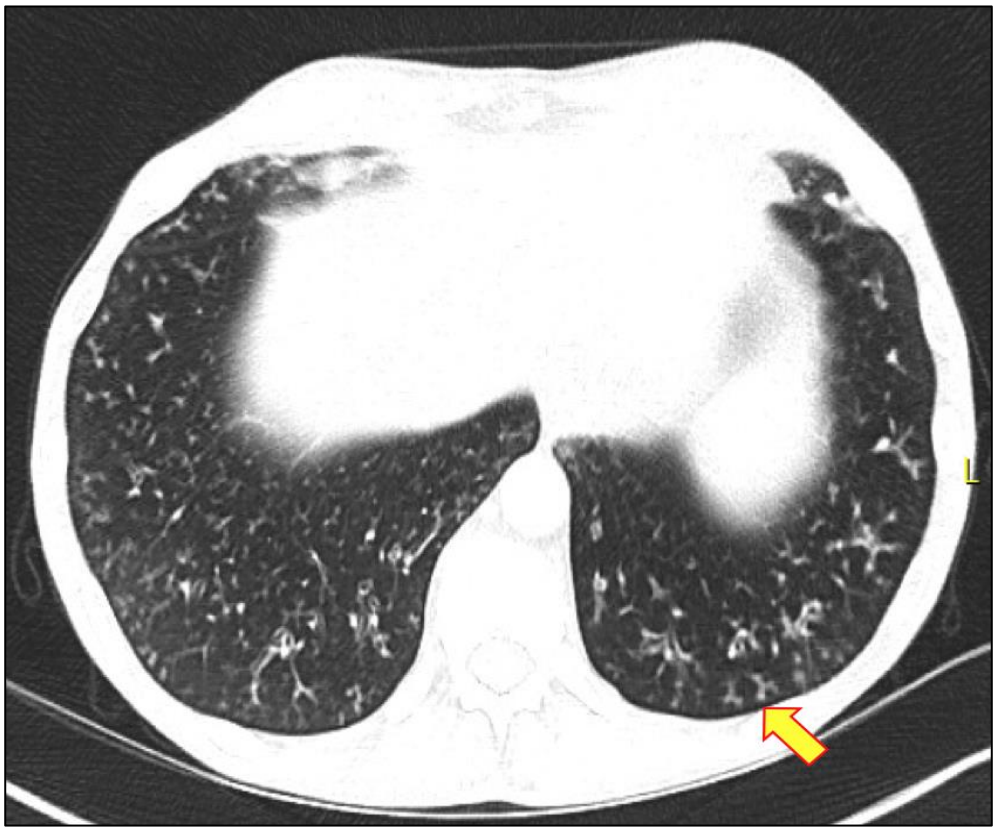

Fig 1: Computed Tomography: Bronchial wall thickening. Diffuse peribronchial nodularity and tree in bud changes worse in the lower zones than upper (arrow)

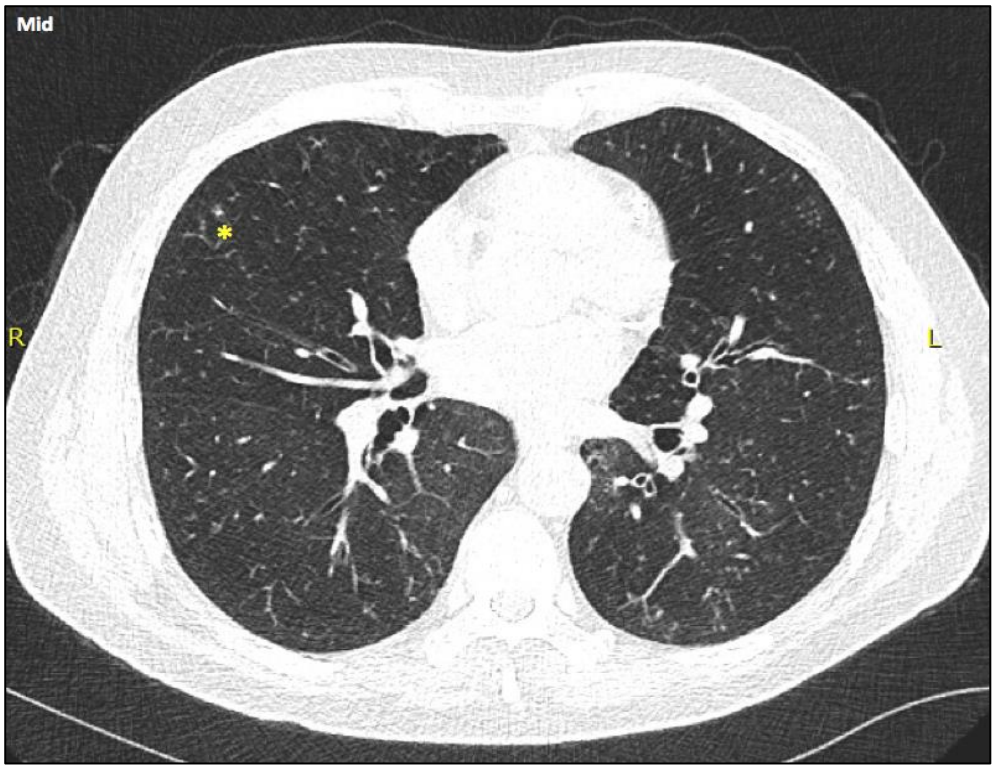

Fig 2: Computed tomography: Diffuse nodularity particularly in the right middle lobe with sparse tree in bud (*). Patchy ground glass changes

Conflict of interests:

The authors of this article have no conflict of interests to declare.

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