Author/s:
Gurieff, G;Shivakumar, S;Lee, J;Macrae, F;Leong, TL

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Treatment-Refractory Tracheobronchitis in Crohn's Disease: A Rare Pulmonary Manifestation of Inflammatory Bowel Disease

Gabriel Gurieff[1] | Senthuran Shivakumar[1,2] | Joy Lee[1,3] | Finlay Macrae[4] | Tracy L. Leong[1,2,5]

[1]Department of Respiratory and Sleep Medicine, Austin Health, Melbourne, Australia | [2]Faculty of Medicine, Dentistry and Health Science, University of Melbourne, Melbourne, Australia | [3]School of Translational Medicine, Monash University, Melbourne, Australia | [4]Department of Colorectal Medicine and Genetics, Royal Melbourne Hospital, Melbourne, Australia | [5]Austin Health, Olivia Newton-John Cancer Research Institute, Melbourne, Australia

Correspondence: Gabriel Gurieff (gabriel.gurieff@austin.org.au)

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ABSTRACT

Large airway inflammation is a rare and under-recognised pulmonary manifestation of Crohn's disease. It is associated with significant morbidity and occurs independent of intestinal disease activity. Inflammation of the trachea and bronchi in inflammatory bowel diseases is typically responsive to corticosteroids or anti-tumour necrosis factor agents. In this report, we present a case of tracheobronchitis in Crohn's disease presenting with a chronic productive cough while on adalimumab. The diagnosis was made by bronchoscopy, which revealed inflammation of the trachea and main bronchi, with biopsies demonstrating squamous cell metaplasia consistent with pulmonary inflammatory bowel disease. The patient was unable to be weaned off steroids and, in the presence of an elevated fractional expired nitric oxide, dupilumab was trialled, which resulted in minimal improvement in his symptoms.

1 | Introduction

The inflammatory bowel diseases (IBD) are a complex and heterogeneous group of conditions with several extra-gastrointestinal manifestations. The true prevalence of pulmonary manifestations in IBD is unknown but has previously been estimated to be as low as 1%. Inflammation of the large airways is a particularly rare subset, representing just 7%–8% of all pulmonary manifestations [1]. In this report, we describe a case of tracheobronchitis in a patient with Crohn's disease (CD) who presented with intractable cough.

2 | Case Report

A 35-year-old male presented for outpatient respiratory review following nearly a year of intractable productive cough. His past medical history was significant for CD, which was diagnosed by flexible sigmoidoscopy in 2011, with previous colectomy in 2002. Since diagnosis, the patient has been treated with multiple immunomodulatory drugs, including salazopyrine, methotrexate, adalimumab and ustekinumab, with other extra-intestinal features including arthritis and skin disease. He has a minimal smoking history (less than one pack year) and no significant environmental or occupational exposures.

His cough initially developed following a lower respiratory tract infection with a viral prodrome in June 2021. He reported that while he had fevers and was systemically unwell, he did not need hospitalisation. Following this, he had a persistent cough, productive of thick tenacious sputum varying between clear and creamy yellow to green. Interventions trialled included intranasal corticosteroid sprays, treatment for gastroesophageal reflux, an eight-week course of low dose azithromycin, and

amphotericin lozenges for candidiasis, all with no material improvement in cough or sputum burden. Importantly, his work as a barrister became impacted by the persistent cough.

Computed tomography (CT) chest performed a few months following initial presentation demonstrated mild bronchial wall thickening but did not show significant parenchymal disease. His blood tests, including inflammatory markers, were not significantly abnormal. Initial (September 2022) lung function testing demonstrated normal spirometry with no significant bronchodilator response and normal gas transfer (Figure 1). However, his fractional exhaled nitric oxide (FeNO) was moderately elevated at 35 ppb. Repeat spirometry with bronchoprovocation testing showed no response to mannitol; however, it did demonstrate a significant bronchodilator response.

He underwent a bronchoscopy in September 2022, which revealed inflamed mucosa in the trachea and in the main bronchi with white sputum throughout (Figure 2a). Washings taken from the lung revealed increased levels of polymorphs, and the culture was positive for upper respiratory tract flora and negative for fungal, viral, acid-fast bacilli or atypical pneumonia pathogens. Endobronchial biopsies taken from areas of inflammation demonstrated a dense inflammatory infiltrate comprising of plasma cells, eosinophils and lymphocytes, as well as squamous metaplasia, which is consistent with changes associated with IBD (Figure 2b).

He was commenced on prednisolone 50 mg daily in October 2022 and had an immediate and significant (> 90%) improvement in sputum burden and reduction in cough frequency. Shortly after commencing steroids, he was switched from adalimumab to ustekinumab in the context of an undetectable adalimumab level in peripheral blood. This had no effect on the patient's symptoms independent of the prednisolone dose. Prednisolone was started at 50 mg daily for 1 week, then reduced by 10 mg reduction each month to 10 mg daily by February 2023. Once below 30 mg daily, there was a recrudescence of cough and sputum burden. The cough remitted again in May 2023 when the patient was treated with a short course of 50 mg of prednisolone for urticaria. In February 2023, at a prednisolone dose of 10 mg daily, the patient was started on inhaled corticosteroids and long-acting bronchodilators in the form of ciclesonide and budesonide combined with eformoterol (which provided a 20% improvement in his cough) and referred for chest physiotherapy, including sputum clearance techniques. Oral prednisolone was ceased in September 2023.

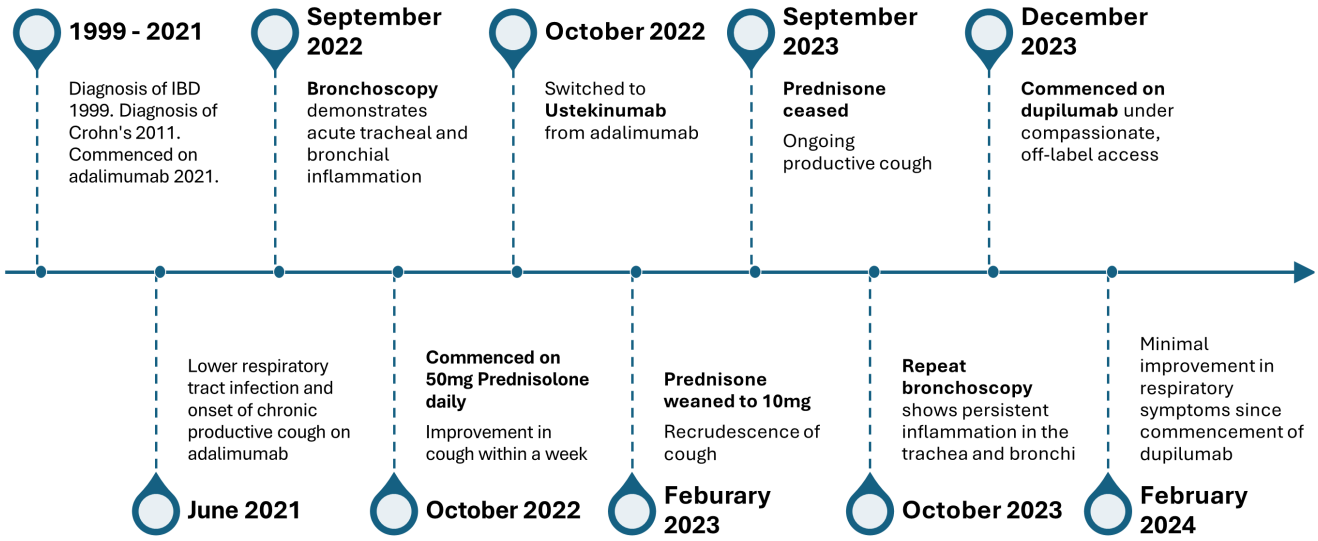

FIGURE 1 | A timeline of events during the patient's care.

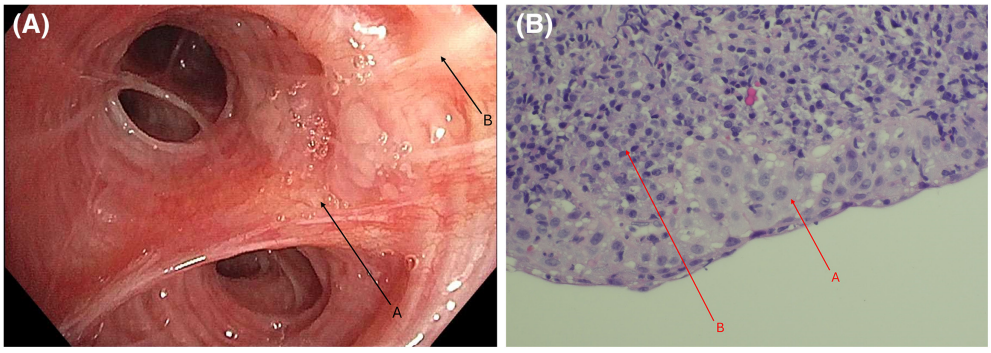

FIGURE 2 | (a) Bronchoscopy image: Demonstrates erythematous and inflamed mucosa with a nodular appearance (A) and mucopurulent secretions (B). (b) Tracheal biopsy from area denoted by arrow on (a): H&E, high power image (×40), showing inflamed and reactive metaplastic (A) squamous epithelium with underlying florid, plasma cell-rich chronic inflammatory infiltrate with eosinophils (B).

TABLE 1 | Summary of investigations.

Investigation	Findings
White cell count	7.2 (4.0–11.0)×10^9/L
Eosinophil count	0.2 (0.0–0.5)×10^9/L
CRP	9 mg/L (< 5)
ESR	8 mm/h (1–10)
ANA	Positive SSA pattern
p-ANCA	Positive
FeNO	35 ppb (elevated)
HRCT	Mild bronchial wall thickening
Spirometry (September 2022)	
FEV1	3.95 L (89% predicted), 4.15 L (94% predicted) post bronchodilator
Carbon monoxide gas transfer	119% predicted
Spirometry and mannitol bronchoprovocation (October 2022)	
FEV1	3.24 L (74% predicted), 3.35 L post mannitol, 3.81 L (87% predicted) post bronchodilator

Due to ongoing symptoms, a second bronchoscopy and endobronchial biopsy was performed in October 2023, which yielded similar findings of chronic inflammation as seen in his initial bronchoscopy in September 2022. In December 2023, given a lack of response to several treatments apart from high-dose prednisolone, he was commenced on dupilumab off-label under compassionate access following extensive multidisciplinary discussions between respiratory, gastroenterology and rheumatology. Dupilumab was commenced with a loading dose of 400 mg followed by 200 mg fortnightly. At 6 weeks post commencement, there was minimal improvement in symptoms; however, FeNO had fallen to 14 ppb (from 35 ppb). At 6 months, the patient reported no significant improvement in his symptoms, and dupilumab was ceased. There was no significant change in respiratory function tests.

3 | Discussion

CD is a multi-system disorder with a number of recognised pulmonary extra-intestinal manifestations. In this report, we outline a case of CD-associated tracheobronchitis which presented with a chronic productive cough, elevated FeNO and histological findings of squamous cell metaplasia of the biopsied epithelium. The presence of large airway inflammation despite quiescent CD treated on adalimumab (and subsequently Ustekinumab) is noteworthy, as is the lack of a durable response to inhaled and systemic corticosteroids after weaning, which are typically the mainstay of treatment [2, 3]. Furthermore, the presence of an elevated FeNO and a positive bronchodilator response on one occasion, typically seen in asthma, created some diagnostic confusion and demonstrates that a broader list of differentials is required when faced with a patient with intractable cough, unresponsive to asthma therapies.

Approximately 50% of patients with IBD exhibit lung involvement, as indicated by abnormalities in spirometry and high-resolution tomographic imaging (HRCT) [4]. However, a much smaller subset (as low as 1%) is symptomatic and will be diagnosed with a pulmonary manifestation. Involvement of the lower airways, particularly bronchiectasis followed by chronic bronchitis, is the most common site of respiratory involvement, representing ~50% of clinically significant respiratory manifestations [5]. Previous case reports that describe large airway inflammation related to IBD are typically responsive to corticosteroids and TNF inhibitors [6]. In this case, moderate doses of systemic corticosteroids resulted in only a temporary improvement in the patient's cough and had no impact on airway inflammation at follow-up bronchoscopy.

The pathophysiological basis of the link between the IBDs and airways disease is still largely unknown [7]. However, some similarities have been reported at genetic, anatomical and histological levels. Genetic studies highlight several loci that are associated with CD and airway inflammation in COPD and asthma, such as NOD2 single-nucleotide polymorphisms which regulate inflammatory responses to bacterial cell wall components [8] and ORMDL2 which regulates T helper 2 cell activity [7]. Intestinal and airway epithelium act as the interface between the immune system and the resident flora inhabiting the lumen [9], and develop from a common embryological origin within the foregut. It is postulated that the similarities in the immune structures of these organs underlie the overlap in pathology seen in intestinal and mucosal disease. For example, one study demonstrated increased epithelial permeability of the intestinal mucosa in asthma patients [10]. Finally, the histological features of both gut and airway disease are similar and are characterised by inflammatory cell infiltrates in the submucosa, with infiltrates of lymphocytes, plasma

cells, neutrophils, squamous cell metaplasia, mucosal ulceration and occasionally necrosis [9, 11–13].

Overall, the role of biologics in the management of pulmonary manifestations of IBD is yet to be determined, and the literature on this subject is limited to case reports. Hayek et al. summarised the use of infliximab in the management of eight cases of IBD-associated pulmonary disease, including only one patient with tracheal inflammation, where all patients were responsive to infliximab [2]. This reinforces the importance of this case, demonstrating a possible patient cohort who will develop significant large airway inflammation despite quiescent intestinal disease and will fail to achieve a durable response with steroids and anti-TNF biologics. To date, there have been no case reports outlining the use of ustekinumab or dupilumab in this condition. Dupilumab use has been associated with a protective odds ratio (0.26) for the development of CD [14] and is currently being investigated for treatment of UC with an eosinophilic phenotype [15]. A 2023 case series demonstrated dupilumab was likely to be a safe and effective treatment for atopic dermatitis in the IBD cohort; however, dupilumab had no effect on IBD disease activity scores [16]. In this case, despite evidence of eosinophilic inflammation and a marked FeNO reduction with dupilumab, the drug had no meaningful or sustained effect on cough independent of prednisolone, and thus does not support its use for this extra-intestinal manifestation of IBD. This case does reinforce the efficacy of steroids in this condition, although the response was limited to high (> 30 mg) doses. Further research is needed to delineate the role of biologics in IBD-associated pulmonary disease, particularly in the management of large airway inflammation (Table 1).

Author Contributions

Gabriel Gurieff is a primary author. Senthuran Shivakumar is author and clinician who provided care for this patient. Joy Lee is author and consulting clinician. Finlay Macrae is author and consulting clinician; professor Macrae is the patient's gastroenterologist who was involved in multidisciplinary discussions regarding the diagnosis and treatment in this case. Tracy L. Leong is author and primary respiratory physician in this case.

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Dupilumab was provided free of charge, accessed via the Sanofi Australia Medicines Access Program for a non-TGA approved indication. Sanofi was not involved in the design, collection, analysis, interpretation or reporting of the data, but was provided the opportunity to review the publication prior to submission. The decision to submit for publication was made independently by the authors.

Ethics Statement

The off-label prescription of Dupilumab complied with all local regulations and verbal consent was obtained from the patient prior to the commencement of the treatment.

Consent

The authors declare that written informed consent was obtained for the publication of this manuscript and accompanying images and attest that the form used to obtain consent from the patient complies with the Journal requirements as outlined in the author guidelines.

Conflicts of Interest

Unrelated to this article, Joy Lee has received speaker asnd travel honoraria from Sanofi, AstraZeneca and GlaxoSmithKline, and has served on an advisory board for AstraZeneca. Tracey L. Leong is an Editorial Board member of Respirology Case Reports and a co-author of this article. She was excluded from all editorial decision-making related to the acceptance of this article for publication. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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