CASE REPORT

Chronic cough in a patient with stable ulcerative colitis: a rare but important extraintestinal manifestation of inflammatory bowel disease

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SUMMARY

A 74-year-old woman presented to her general practitioner with cough and occasional sputum production. Having failed to respond to courses of antibiotics in the community, she was referred to the thoracic medicine clinic. High-resolution CT chest revealed cylindrical bronchiectasis predominantly in the right lower lobe. Lung function revealed preserved FEV₁ and FVC but reduced gas transfer values. Bronchiectasis secondary to ulcerative colitis was diagnosed. Inhaled corticosteroid therapy was initiated, with good clinical response noted at 6 monthly follow-up. Remission was sustained with tapering of the steroid dose. Recognition of respiratory complications in cases of inflammatory bowel disease is likely still poor among clinicians. Although rare, a working knowledge of principles of investigation and management will aid timely diagnosis and treatment, potentially preventing progression of respiratory disease.

BACKGROUND

Inflammatory bowel disease (IBD) encompasses Crohn's disease (CD) and ulcerative colitis (UC). The incidence of both is increasing over time, most notably in Europe, with a higher incidence (24.3/100 000 person years) and prevalence (505/100 000 persons) in UC.¹

In patients with UC, around 31% have at least one extraintestinal manifestation of their disease.² Many of these are well characterised in the literature and recognised clinically including involvement of musculoskeletal, ocular, dermatological and hepatobiliary systems.

Recognition of the pulmonary manifestations of IBD is likely to be poor and the true incidence underestimated.³ This is despite cases described in the literature as far back as 1962.⁴ The diagnostic challenge is compounded by heterogeneity of presentations (table 1), extreme variance in the timeframe of respiratory symptoms in relation to onset of IBD (9.3±5.3 years, range 1 week to 36 years),⁵ low prevalence of 'clinically apparent' airway involvement⁶ and uncertainty in attributing subclinical findings (physiological and radiological) to this association.

Disease affecting the larger airways is the most common in UC and includes chronic bronchitis, chronic bronchial suppuration and bronchiectasis⁷ (with anecdotal suggestions that this is a

continuum).⁸ Bronchiectasis may be the most important clinically as such permanent structural change may put patients at risk of serious recurrent respiratory infections. Unlike most causes of bronchiectasis, IBD-associated disease responds well to inhaled corticosteroid therapy.

Timely recognition of this association and effective treatment with inhaled corticosteroids may therefore prevent progression of respiratory disease and avoid unnecessary use of antibiotic therapy.

A working knowledge of this association would be beneficial for clinicians treating patients with IBD and patients with new respiratory symptoms including general practitioners (GPs), gastroenterologists, surgeons, respiratory physicians and nurse specialists.

CASE PRESENTATION

A 74-year-old woman with histologically confirmed UC was referred by her GP in January 2016 to the thoracic medicine clinic due to chronic cough. Her cough had been present for 3 years, was described as mainly 'tickly' and was occasionally productive of small amounts of mucoid phlegm. By the time of referral, the cough was 'exhausting', but she denied any associated haemoptysis or wheeze. She denied a history of night sweats or weight loss, with no change in exercise tolerance. Multiple courses of antibiotics prescribed by the GP had no effect, and a chest radiograph in 2015 was reported as normal.

This patient was hypertensive, treated with valsartan 160 mg one time a day and bendroflumethiazide 2.5 mg one time a day. She had a previously investigated thyroid adenoma, and had a normal pharyngolaryngoscopy and barium swallow when being investigated for dysphagia 1 year prior to presentation.

Her UC was diagnosed in 1999 after presentation with abdominal pain and per rectal bleeding. The diagnosis was confirmed via endoscopic biopsy, and after initial treatment with oral prednisolone she was now maintained on mesalazine 400 mg MR two times a day. She had experienced two flares of her UC: one in 2009 treated with a transient increase in mesalazine dose, and the other in 2014–2015 treated with the Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet.

She was a life-long non-smoker with no identified exposure to passive smoking, pets or possible

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Table 1 Patterns of respiratory involvement in IBD, adapted from Black *et al*⁷

Site/pattern of involvement	% of cases
Airways diseases	
Larynx/glottis	2.2
Trachea	16.6
Bronchiectasis	48.9
Chronic bronchitis	14.4
Suppurative airways disease	5.6
Bronchiolitis	11.1
Diffuse panbronchitis	1.1
Parenchymal disease (including bronchiolitis obliterans-organising pneumonia, nodules and ILD not otherwise specified)	25.8
Serositis	14.2

occupational precipitants. No family history of respiratory pathology was noted.

INVESTIGATIONS

On initial presentation to the thoracic medicine clinic, examination was unremarkable, with clear lung fields on auscultation. Preceding bloods indicated no signs of acute infection (white cell count $5.04 \times 10^9/L$, C reactive protein 2.6). There was an imbedded shrapnel fragment from the Balkan War in the right side of her neck. A plain chest radiograph at this stage revealed clear but hyperexpanded lung fields and unveiled another shrapnel fragment adjacent to the right atrium (figure 1).

Lung function tests (table 2 and figure 2) showed normal FEV₁ and FVC, with a ratio of 0.8 but a reduction in the gas transfer (TLco and transfer coefficient (KCO) 74% and 75% predicted, respectively). Immunoglobulin levels indicated IgA 13.26, IgG 2.52, IgM 0.68 and IgE 31 g/L, respectively (all within normal limits). Further immunological assessment was not deemed necessary at this stage.

Routine annual surveillance colonoscopies (most recently in January 2017) consistently indicated no increase in colonic

Table 2 Lung function results from the patient prior to commencing treatment

Spirometry	Measured	% Predicted
PEF L/s	6.36	106
FEV ₁ (L)	2.83	126
FVC (L)	3.56	132
FEV ₁ /FVC	79.6	106
Transfer factor		
TLco (SI)	5.57	74
KCO (SI)	1.05	75

disease, with the original diagnostic colonoscopy reporting a pancolitis.

Owing to the patient's variable sputum production, and response to first-line therapy in the outpatient setting, no sputum samples for microscopy, culture and sensitivities or cell differential were analysed. As such, more invasive diagnostic procedures such as bronchoscopy/lung biopsy were not pursued.

A high-resolution CT chest demonstrated cylindrical bronchiectasis with moderate thickening and dilatation of the segmental, subsegmental and more peripheral bronchi in the posterior basal segment of the right lower lobe (figures 3 and 4). There was more diffuse dilatation of the central airways suggesting early bronchiectatic change (figure 5).

DIFFERENTIAL DIAGNOSIS

In the absence of a positive chest radiograph or systemic symptoms, a chronic lung infection such as pulmonary tuberculosis or chronic aspergillosis could be ruled out. Failure of response from courses indicated a chronic bacterial bronchitis was less likely.

Figure 1 Plain chest radiograph taken prior to first clinic appointment indicating hyperexpanded lung fields and a shrapnel fragment adjacent to right atrium.

Figure 2 Flow-volume loop from the patient prior to starting treatment.

Figure 3 Bronchiectatic change in the right lower lobe.

A resistant organism (eg, methicillin resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*) could be possible but should be identified by sputum culture.

Given an 18-year history of mesalazine use, a drug-induced toxicity in the lung could be considered. Although less 'pneumotoxic' than other medications used in IBD (methotrexate and sulfasalazine), there are reports of induced pulmonary eosinophilia and organising pneumonia.⁹ However, these will both show abnormalities on the chest radiograph.

Very rare conditions that affect central airways should be considered including granulomatosis with polyangiitis, sarcoidosis and tracheal amyloidosis⁸ but should cause corresponding abnormalities in the lung function or radiology.

The most common causes of chronic cough with normal radiology are cough-variant asthma, postnasal drip or gastro-oesophageal reflux. However, there were no specific symptoms suggestive of these, and the CT scan demonstrated bronchiectasis, a recognised association with UC, suggesting her clinical condition was secondary to its presence.⁸ There was no clinical or biochemical evidence for an alternative cause of bronchiectasis independent of UC.

TREATMENT

Inhaled corticosteroid therapy was initiated with QVAR (beclometasone dipropionate) 100 µg two puffs two times a day.

Figure 4 Bronchiectatic change in the right lower lobe.

Figure 5 Diffuse dilatation of central airways presenting early bronchiectatic change.

This was altered to a Fostair preparation containing the equivalent steroid dose plus the long acting β_2 agonist salmeterol. No change to her mesalazine dose was necessary.

OUTCOME AND FOLLOW-UP

Six months after initial presentation, a good clinical response was noted with remission of cough and no ongoing sputum production. Treatment was maintained then downtitrated to a daily dose from 400 µg to 200 µg when her improvement had been sustained for a further 6 months. This did not lead to relapse in her symptoms, and her inhaled steroid therapy may be withdrawn in the future.

DISCUSSION

The pathophysiological mechanism for this association has not been fully elucidated. Histological changes seen in respiratory tissues appear to mirror those seen in the gut and include neutrophilic infiltrates, epithelial changes and subepithelial gland destruction.¹⁰ In 'typical' bronchiectasis, such cellular infiltrates may be less, and appearance more follicular.⁸

The common embryological origin of both lung and gut tissue has led to the suggestion that sensitisation to antigens in the gut evokes an inflammatory response in similar tissues.^{7,8} Alternatively, a common antigen that is both inhaled and ingested could sensitise lymphoid tissue in both lung and gut leading to inflammation.¹¹

Kraft *et al*⁶ estimated prevalence of clinically apparent respiratory involvement in patients with IBD to be 0.21%. A later retrospective analysis of patients with confirmed respiratory disease found a prevalence of IBD to be around approximately four times higher than local baseline rates expected (OR 4.21, 95% CI 1.71 to 10.41, $p=0.001$),¹² with the OR for the presence of bronchiectasis in UC versus background data was of 7.88 (95% CI 2.71 to 22.91, $p<0.001$). Overall 4% of IBD cases had bronchiectasis. In another study investigating the aetiology of bronchiectasis, 3% had IBD (all UC).¹³

Physiological changes

Tzanakis *et al*¹⁴ reported no significant differences in spirometry (FEV1, FVC, FEV1/FVC) between patients with UC ($n=85$) and controls, with no relation to disease severity. Mahadeva *et al*³ found neither FEV1 nor FVC was associated with severity of respiratory symptoms or bronchiectasis.

Decrements in transfer factor have been identified previously in patients with UC (TLco % predicted 73.87 ± 14.27 vs 87.31 ± 11.23 , $p=0.003$ and KCO % predicted 77.50 ± 15.05 vs 87.62 ± 13.25 , $p=0.05$).¹⁵ This is in agreement with Tzanakis *et al*, who found TLco % predicted values of 78 ± 16.2 $p=0.05$ in active UC.¹⁴ However, these defects in transfer factor were found only in patients with active UC unlike this case patient who had stable colonic disease. Mahadeva *et al*³ did not correlate KCO with respiratory symptom severity or bronchiectasis severity.

Radiological changes

The plain chest radiograph is frequently normal in patients with bronchiectasis or UC (73%).¹⁶ If changes are present on chest radiograph, these tend to be non-specific.⁸

High-resolution CT is more sensitive in identifying bronchiectasis. In those with UC recruited by Mahadeva *et al*, 11/14 had bronchiectasis.³ Sputum production was associated with more extensive bronchiectasis, and a 'tree bud' appearance associated with the presence of cough.

Aside from bronchiectatic change, air trapping can also be seen in a high proportion of patients with IBD and was the most frequently reported abnormality in a mixed cohort of symptomatic and asymptomatic patients (no correlation to lung function).¹⁶

Treatment

Inhaled steroid treatment is the initial treatment of choice in IBD-related airways disease.

Mahadeva *et al*³ recorded a response to steroids in 8/11 patients with UC and bronchiectasis. Of these, three responded to oral prednisolone of doses up to 60 mg daily, three responded to inhaled beclomethasone of up to 2000 mg daily, one responded to an unspecified steroid and only one case did not respond to steroid treatment. The duration of treatment was around 2–4 weeks for oral therapy and 1–3 months for inhaled therapy.

An initial dose of equivalent fluticasone 500 µg daily (1000 µg beclomethasone) was suggested by Weinberger and Peppercorn¹⁷; however, they acknowledged the evidence base for this is weak, and our case had a good clinical response to a significantly lower inhaled steroid dose.

A recent European Crohn's and Colitis Organisation guideline¹⁸ suggests inhaled corticosteroids as first-line agents in large airways disease, with oral therapy reserved for parenchymal involvement or inhaled steroid resistant large airways disease. Nebulised steroids could be considered in disease where diffusion may be limited by secretions, and immunomodulating/biological therapy for refractory disease (however, evidence for the latter is taken from a single

trial of anti-Tumour necrosis factor therapy in CD-related respiratory disease). Here, the need to rule out drug-induced respiratory disease by considering withdrawing salicylates and methotrexate is emphasised.

Successful treatment is associated with improved symptomology, pulmonary function (if initially decreased) and cellular reduction in neutrophilia. Imaging may show improvements in the degree of air trapping,¹⁹ but no follow-up studies of patients with early bronchiectasis have been performed.

This case illustrates key aspects of the diagnostic challenge in such patients, with specific regard to insidious onset of symptoms, and disassociation between first presentation of colonic and airways disease symptoms. It also provides evidence that lower dose inhaled corticosteroid treatment was effective in inducing remission of symptoms in early bronchiectasis.

Contributors TC planned and wrote the case report. This included gathering images and contacting the patient regarding the submission. JB oversaw the writing process by reviewing the case report regularly and providing ongoing editorial support to ensure accuracy of content. He was responsible for the identification of the patient, who remains under his clinical care.

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Learning points

- ▶ Respiratory symptoms may emerge years after the diagnosis of inflammatory bowel disease, with no relation to bowel disease activity.
- ▶ Drug-related causes should always be considered
- ▶ Investigation should include high-resolution CT chest and transfer factor.
- ▶ Instigating a lower dose of inhaled corticosteroid treatment than has previously been described (400 µg daily) showed good clinical efficacy in this case, and should be considered in those presenting as an outpatient.
- ▶ Large airway involvement in ulcerative colitis is one of the more common (although still rare) associations and can serve as an illustrative case in remembering this group of associations.

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