Chronic cough and inflammatory bowel disease: an under-recognised association?

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Shareable abstract (@ERSpublications)
Respiratory complications of inflammatory bowel disease (IBD) are common and may be under-recognised. Chronic cough may present many years after a colectomy for IBD, is typically productive and can be very responsive to inhaled corticosteroids. https://bit.ly/3DrHNoy

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A 51-year-old man presented with a 6-year history of chronic cough to a tertiary chronic cough clinic. The cough was productive (egg cup full of sputum daily), present day and night and associated with numerous triggers. He denied haemoptysis or breathlessness and his weight was stable. The cough was rated on a verbal cough severity scale as 9/10 in severity (where 0 is no cough and 10 is the worst possible cough), and occurred largely in bouts, which were often associated with retching and dizziness. It had worsened in severity in the 2 years prior to attending our specialist cough clinic.

His past medical history included a 15-year history of ulcerative colitis (UC), initially managed medically (combination of azathioprine and steroids), with a subsequent total colectomy (2017) and re-anastomosis (2018). He was an ex-smoker having quit in 1999, with a 5 pack-years smoking history. He worked in construction, with occasional exposure to spray paints.

He had previously been investigated for his cough between 2015 and 2019, at which point he had a normal chest radiograph, sequential blood eosinophil counts and total IgE level. His spirometry was also supranormal, with no forced expiratory volume in 1 s (FEV_1) reversibility, and a normal fractional exhaled nitric oxide (F_{ENO}). He had undergone multiple treatment trials, including azithromycin, carbocisteine, nasal sprays, proton-pump inhibitors, domperidone, baclofen, metoclopramide and gabapentin. His symptoms had not improved with any of these medications. He had not previously been treated with inhaled corticosteroids.

On examination, his body mass index was 25 $kg \cdot m^{-2}$, he was not clubbed and his chest examination was unremarkable. Further investigations were arranged, including lung function (figure 1 and table 1), blood tests, a computed tomography (CT) of the thorax (figure 2) and a bronchoscopy.

Task 1

What do the CT and spirometry investigations show?

a) Normal appearances of both CT thorax and spirometry
b) Severe airflow obstruction and emphysema
c) Mild airflow obstruction and cylindrical lower lobe bronchiectasis
d) Restrictive lung function and ground-glass opacities

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The results of the blood tests and bronchoscopy are shown in table 2.

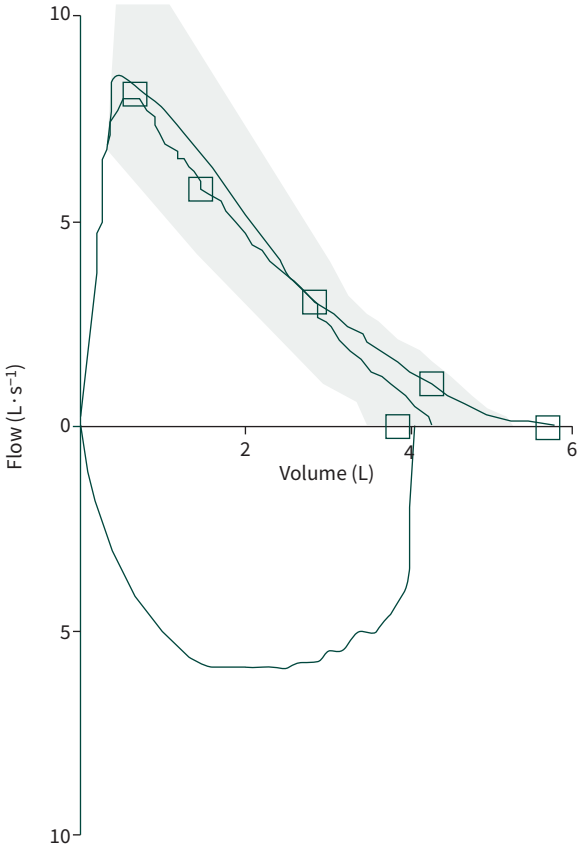

FIGURE 1 Spirometry and flow–volume loop.

TABLE 1 Spirometry results

	Value	% predicted
FEV_1	3.89 L	111
FVC	5.74 L	131
FEV_1/FVC	0.67	
T_{LCO}		113
K_{CO}		101

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; T_{LCO}: transfer factor of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide.

Task 2

What do the blood test and bronchoscopy results suggest?

a) Normal findings
b) Neutrophilic inflammation in the absence of infection
c) Eosinophilic bronchitis
d) Acute bacterial infection
e) Diffuse alveolar haemorrhage

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Based on our findings, and a review of the literature, we treated this patient as a case of IBD-associated airways disease and inflammatory bronchiectasis. The patient was given a 2-week course of oral prednisolone (30 mg daily), followed by high-dose inhaled corticosteroids (beclomethasone 400 µg three times a day). The response to this was excellent, with a reduction in his verbal cough severity score from

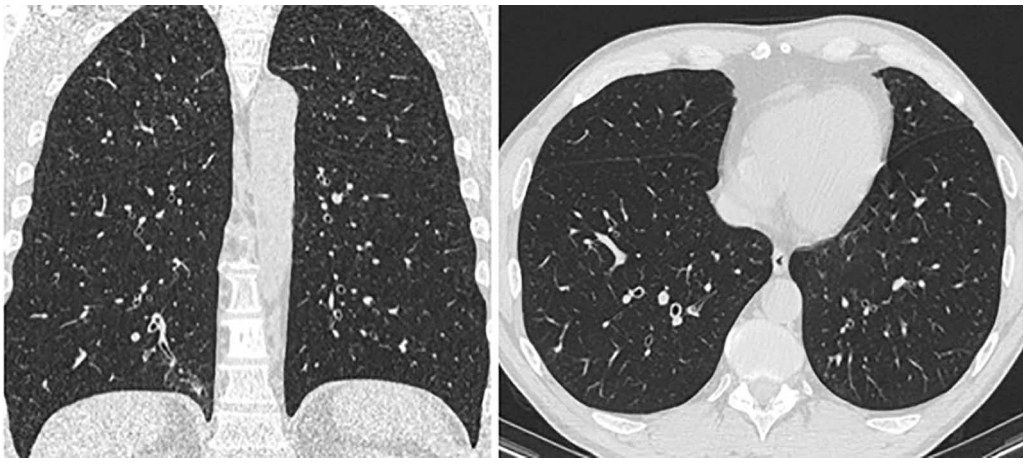

FIGURE 2 High-resolution computed tomography of the thorax.

TABLE 2 Blood test and bronchoscopy results

Test	Results	Reference range
Haemoglobin, g·L^{-1}	150	120–160
WBC, ×10^{9} cells·L^{-1}	5.6	4.0–11.0
Neutrophils, ×10^{9} cells·L^{-1}	3.90	1.8–7.5
Eosinophils, ×10^{9} cells·L^{-1}	0.20	0.0–0.4
Urea, mmol·L^{-1}	5.0	2.5–7.8
Creatinine, mmol·L^{-1}	90	59–104
CRP, mg·L^{-1}	3	<4
Plasma viscosity, mPa·s	1.72	1.50–1.72
Myeloperoxidase (MPO), AI	1.3	0–0.9
Proteinase 3 Ab (PR3), AI	>0.2	0–0.9
Total IgE, kU·L^{-1}	95.3	0–113
IgA, IgM, IgG	Normal	
Bronchoscopy findings	Marked endobronchial inflammation with a build-up of purulent sputum in both lower lobes	
BAL cell differential	Macrophages 56%, neutrophils 29%, lymphocytes 12%, eosinophils 0%, others 3%	
Bronchial wash	Low numbers of oral commensals only	

WBC: white blood cell count; CRP: C-reactive protein; AI: antibody index; BAL: bronchoalveolar lavage.

9/10 to 1/10. He was followed up with a telephone call at 6 months and reported a sustained improvement in his symptoms.

Task 3

Which of following respiratory conditions can be associated with IBD?

a) Bronchiectasis
b) ILD
c) Inflammation, scarring and stenosis of the central airways
d) Single or multiple pulmonary nodules
e) All of the above

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Discussion

IBD is common, with an estimated prevalence of 84 per 100 000 population globally [7]. There are a variety of well-documented respiratory manifestations of IBD, which can range from mild nonspecific

respiratory symptoms through to severe, debilitating sequelae. The prevalence of respiratory symptoms in this group is high (25–63%) [8, 9], and even in the absence of these symptoms, lung function is diminished in up to 45% of patients [10].

The diagnosis is frequently delayed given symptoms are nonspecific, can precede the diagnosis of IBD or may manifest many years after colectomy [11]. In this case, the cough pre-dated the patient's colectomy, but continued despite definitive intervention for IBD, worsening in severity in the 2 years prior to presentation at our clinic. Interestingly, there are a number of case reports of cough manifesting for the first time after definitive treatment of IBD, occurring as early as months after surgery, to over a decade later, in both Crohn's disease and UC [12, 13].

The underlying mechanisms linking respiratory disease with IBD are not fully established, but could lie in their common embryonic pathway, with the respiratory system developing from the ventral wall of the foregut at 3–4 weeks gestation [14].

Pulmonary manifestations may occur at any location in the respiratory tract (see table 3). Airway inflammation is most common, and results in cough, often with expectoration of copious amounts of mucopurulent secretions [16]. At the severe end of the spectrum, widespread inflammation can occur, with extensive mucosal involvement of the large airways, in some cases leading to stenosis and a "cobble-stone" appearance (interestingly, similar to luminal findings seen in active bowel disease). The most common association is bronchiectasis, which has been reported in nearly 10% of patients [17]. The incidence of this is higher in females and nonsmokers [9, 18], and usually occurs in the lower lobes. Smaller airways are less commonly involved but should be considered where wheeze and breathlessness accompany cough, with case series describing both pan-bronchiolitis and granulomatous bronchiolitis [19, 20].

The incidence of interstitial lung disease (ILD) in IBD is thought to be low, but evidence is largely limited to case reports. In a 2020 review of 31 cases of IBD-related ILD across 14 European centres, the incidence was higher in UC compared with Crohn's disease and most frequently related to medications (64.5%) [21]. In this group the most common medications causing respiratory disease were infliximab and aminosalicylates. The most commonly cited non-drug related ILD in this group was organising pneumonia and usual interstitial pneumonia, but there have also been case reports of lymphocytic interstitial pneumonia, eosinophilic pneumonia and desquamative interstitial pneumonia [22].

Studies have suggested genetic similarities between sarcoidosis and Crohn's disease, in which CD4 lymphocyte activation drives the formation of non-caseating granulomas [23]. It is therefore not surprising that both mimicry and overlap can occur with up to 10% of patients with sarcoidosis having

TABLE 3 Respiratory manifestations of inflammatory bowel disease

Site	Cross-sectional imaging	Lung function	Bronchoscopic findings	Treatment options
Glottis/upper trachea	Narrowing and stenosis	Flow–volume loop may demonstrate fixed upper airway obstruction	Narrowing and stenosis	Treat as severe disease: intravenous steroids Laser therapy ablation has been used [15]
Bronchi	Bronchial wall thickening Dilated bronchi and bronchiectasis	Normal Airflow obstruction with reduced FEV_1/FVC ratio	Airway inflammation Mucopurulent secretions	Inhaled corticosteroids Oral steroids (severe) and nebulised (if refractory to inhaled) also used
Small airways	Mosaic attenuation/gas trapping Tree-in-bud changes	Reduced $FEF_{25–75}$	Normal/mild inflammation	Oral or inhaled steroids
Parenchyma	Nodules +/- cavitations Bilateral ground-glass opacities (usually basal predominant)	Normal Reduction in FVC and T_{LCO} in more severe cases	Normal	Intravenous or oral steroids

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75}$: forced expiratory flow at 25–75% of FVC; T_{LCO}: transfer factor of the lung for carbon monoxide.

gastrointestinal involvement [24]. A definitive link between UC and sarcoidosis is less clear, but has been reported [25].

Rarely patients can present with a serositis, which can manifest as pleuritic chest pain [26]. A higher frequency of pulmonary nodules are also observed, thought to be related to aggregation of neutrophils. These can be numerous and tend to cavitate [27].

Small vessel vasculitides, including EGPA, MPA and granulomatosis with polyangiitis (GPA), are multisystem conditions that can present with diffuse alveolar haemorrhage [28]. Affiliation with IBD is rare, with a recent retrospective of 1697 vasculitis patients reporting a co-prevalence of 0.78% between EGPA and UC and 0.71% between Crohn's disease and GPA. No cases were associated with MPA. A raised MPO antibody level is not specific for vasculitis in patients with IBD, with 62% of patients testing positive despite no evidence of vasculitis [29]. MPO antibodies do however correlate with IBD activity and treatment responses [30].

It is important to consider a broad differential diagnosis in any patient presenting with cough on the background of current or pre-existing IBD. An initial history should focus on the nature of symptoms (cough with or without sputum), dyspnoea and previous or current use of disease-modifying drugs or biologic treatments.

Treatment

Treatment of IBD-related respiratory disease depends on the site of involvement, nature and severity of symptoms. In the case presented, cough was the main symptom, which had been chronic, refractory to previous treatment and very troublesome. The response to inhaled corticosteroids was pronounced. This is in keeping with reports from case series, where either high-dose inhaled or oral corticosteroids have been used with success in IBD-related respiratory disease [9]. Expert consensus suggests longer courses of oral steroids should be reserved for patients with parenchymal disease or resistant airways disease [22]. In this case an improvement in cough was achieved with inhaled corticosteroids alone, but given the associated bronchiectasis, the patient will also be treated according to guidelines, with microbiological surveillance of sputum and chest physiotherapy for airway sputum clearance [31, 32].

Durable clinical responses have been reported, with the two most cited inhaled corticosteroids in IBD related-airways disease being beclomethasone (up to 2500 μg daily) and budesonide (up to 2000 μg daily) [16]. Nebulised steroids (budesonide 2–4 mg per day) can be used in conjunction with oral steroids in refractory cases [16]. Sequential and repeated endobronchial delivery of methylprednisolone (40–80 mg to the left or right bronchial tree) has been utilised to good effect in cases refractory to standard treatment [33].

There is paucity of data on the role of anti-tumour necrosis factor therapy in IBD-related respiratory disease, aside from isolated case reports in Crohn's disease [34]. The risks of infection with this treatment, particularly in patients with bronchiectasis, would have to be carefully be considered [35].

Treatment of IBD-ILD is not empiric and will depend on the site and severity and cause of the disease.

Conclusion

Chronic cough is a debilitating condition, which left untreated has severe physical and psychological consequences. Large airways disease and bronchiectasis should be strongly considered in patients presenting with a cough on the background of IBD (even if this is quiescent or definitively treated with a colectomy in the past). Cross-sectional imaging and bronchoscopy are of value in this group, followed by early treatment with high-dose inhaled corticosteroids, which are often highly effective. Respiratory manifestations of IBD are common, and cover the breadth of the respiratory tract, from upper airway problems to large and small airways and parenchymal disease.

Answer 1

c. This patient's lung volumes are supranormal, but the FEV_1/forced vital capacity (FVC) is <0.70 suggesting mild airflow obstruction. The gas transfers are normal. The CT thorax shows mild lower lobe bronchiectasis, which is more marked on the right side. Radiologically bronchiectasis is defined by abnormally widened and thickened airways (airway diameter larger than corresponding blood vessel – "signet ring sign") that fail to taper as they extend to the lung parenchyma [1]. There is no evidence of emphysema, ground-glass changes or cavitation.

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Answer 2

b. The American Thoracic Society (ATS) reference range for normal bronchoalveolar lavage (BAL) cell differential in non-smoking adults is eosinophil count <1%, lymphocytes 10–15%, neutrophils <3%, macrophages >85% and others <5% [2].
The BAL differential cell count is consistent with neutrophilic inflammation in the absence of an identified infection. This supports the macroscopic findings of inflamed airways and excessive purulent secretions.
The blood tests are unremarkable aside from the mildly raised myeloperoxidase (MPO) titre on the enzyme-linked immunosorbent assay (ELISA). The perinuclear anti-neutrophil cytoplasmic antibodies pattern observed here can be associated with microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [3, 4]. Neither the history nor clinical examination were in keeping with these. There was no evidence of diffuse alveolar haemorrhage at bronchoscopy. Renal function was also normal, with no evidence of microscopic proteinuria or haematuria. MPO is an enzyme stored within cytoplasmic granules of neutrophils. Described as "friend and foe", it plays an important role in innate defence against infections, but may also be a marker (and contribute to the pathogenesis) of inflammatory conditions, such as inflammatory bowel disease (IBD), vasculitis and atherosclerosis [5, 6].

<< Go to Task 2

Answer 3

e. These conditions are all associated with IBD and will be discussed in more detail in the Discussion section.

<< Go to Task 3

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References

1 Hansell DM, Bankier AA, MacMahon H, *et al.* Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; 246: 697–722.
2 Meyer KC, Raghu G, Baughman RP, *et al.* An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med* 2012; 185: 1004–1014.
3 Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. *Allergol Int* 2019; 68: 430–436.
4 Chung SA, Seo P. Microscopic polyangiitis. *Rheum Dis Clin North Am* 2010; 36: 545–558.
5 Khan AA, Alsahli MA, Rahmani AH. Myeloperoxidase as an active disease biomarker: recent biochemical and pathological perspectives. *Med Sci (Basel)* 2018; 6: 33.
6 Klebanoff SJ. Myeloperoxidase: friend and foe. *J Leukoc Biol* 2005; 77: 598–625.
7 Alatab S, Sepanlou SG, Ikuta K, *et al.* The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; 5: 17–30.
8 Yilmaz A, Yilmaz Demirci N, Hoşgün D, *et al.* Pulmonary involvement in inflammatory bowel disease. *World J Gastroenterol* 2010; 16: 4952–4957.
9 Mahadeva R, Walsh G, Flower CD, *et al.* Clinical and radiological characteristics of lung disease in inflammatory bowel disease. *Eur Respir J* 2000; 15: 41–48.
10 Herrlinger KR, Noftz MK, Dalhoff K, *et al.* Alterations in pulmonary function in inflammatory bowel disease are frequent and persist during remission. *Am J Gastroenterol* 2002; 97: 377–381.
11 Raj AA, Birring SS, Green R, *et al.* Prevalence of inflammatory bowel disease in patients with airways disease. *Respir Med* 2008; 102: 780–785.
12 Eaton TE, Lambie N, Wells AU. Bronchiectasis following colectomy for Crohn's disease. *Thorax* 1998; 53: 529–531.
13 Ocak I, Bollino G, Fuhrman C. Delayed recurrence of ulcerative colitis manifested by tracheobronchitis, bronchiolitis, and bronchiolectasis. *Radiol Case Rep* 2017; 12: 686–689.

14 Berrocal T, Madrid C, Novo S, *et al.* Congenital anomalies of the tracheobronchial tree, lung, and mediastinum: embryology, radiology, and pathology. *RadioGraphics* 2004; 24: e17.
15 Rickli H, Fretz C, Hoffman M, *et al.* Severe inflammatory upper airway stenosis in ulcerative colitis. *Eur Respir J* 1994; 7: 1899–1902.
16 Camus P, Colby T. The lung in inflammatory bowel disease. *Eur Respir J* 2000; 15: 5–10.
17 Desai D, Patil S, Udwadia Z, *et al.* Pulmonary manifestations in inflammatory bowel disease: a prospective study. *Indian J Gastroenterol* 2011; 30: 225–228.
18 Black H, Mendoza M, Murin S. Thoracic manifestations of inflammatory bowel disease. *Chest* 2007; 131: 524–532.
19 Desai SJ, Gephardt GN, Stoller JK. Diffuse panbronchiolitis preceding ulcerative colitis. *Chest* 1989; 95: 1342–1344.
20 Casey MB, Tazelaar HD, Myers JL, *et al.* Noninfectious lung pathology in patients with Crohn's disease. *Am J Surg Pathol* 2003; 27: 213–219.
21 Eliadou E, Moleiro J, Ribaldone DG, *et al.* Interstitial and granulomatous lung disease in inflammatory bowel disease patients. *J Crohns Colitis* 2019; 14: 480–489.
22 Harbord M, Annese V, Vavricka SR, *et al.* The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2015; 10: 239–254.
23 Cerri S, du Bois RM, Spagnolo P. Genetic commonality between inflammatory bowel disease and sarcoidosis: the beginning of the end or the end of the beginning? *Eur Respir J* 2011; 37: 489–491.
24 Alqdah M, Lenox R. Gastric sarcoidosis. *South Med J* 2007; 100: 237–238.
25 Sumi T, Yamada G, Yorozuya T, *et al.* Sarcoidosis development during ulcerative colitis remission in a patient with a susceptible human leukocyte antigen serotype. *Sarcoidosis Vasc Diffuse Lung Dis* 2021; 38: e2021010.
26 Lu S, Wang L, Zhang W, *et al.* Ulcerative colitis with acute pleurisy: a case report and review of the literature. *Medicine (Baltimore)* 2017; 96: e7630.
27 Myer AS, Shah K, Patel KM. An infrequent extraintestinal manifestation of ulcerative colitis: pulmonary necrobiotic nodules. *Cureus* 2020; 12: e9774.
28 Okazaki T, Shinagawa S, Mikage H. Vasculitis syndrome-diagnosis and therapy. *J Gen Fam Med* 2017; 18: 72–78.
29 Bornstein G, Ben-Zvi I, Furie N, *et al.* Clinical significance of positive anti-neutrophil cytoplasmic antibodies without evidence of anti-neutrophil cytoplasmic antibodies-associated vasculitis. *Int J Rheum Dis* 2019; 22: 940–945.
30 Hansberry DR, Shah K, Agarwal P, *et al.* Fecal myeloperoxidase as a biomarker for inflammatory bowel disease. *Cureus* 2017; 9: e1004.
31 Hill AT, Welham SA, Sullivan AL, *et al.* Updated BTS adult bronchiectasis guideline 2018: a multidisciplinary approach to comprehensive care. *Thorax* 2019; 74: 1–3.
32 Polverino E, Goeminne PC, McDonnell MJ, *et al.* European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; 50: 1700629.
33 Camus P, Piard F, Ashcroft T, *et al.* The lung in inflammatory bowel disease. *Medicine (Baltimore)* 1993; 72: 151–183.
34 Alrashid AI, Brown RD, Mihalov ML, *et al.* Crohn's disease involving the lung: resolution with infliximab. *Dig Dis Sci* 2001; 46: 1736–1739.
35 Blanchard E, Truchetet ME, Machelart I, *et al.* Respiratory infections associated with anti-TNFα agents. *Med Mal Infect* 2017; 47: 375–381.