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This is the author's manuscript

Original Citation:

Availability:
This version is available http://hdl.handle.net/2318/1718009 since 2019-12-01T09:44:24Z

Published version:
DOI:10.1093/ecco-jcc/jjz165

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Original Article

Interstitial and Granulomatous Lung Disease in Inflammatory Bowel Disease Patients

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Abstract

Background: Interstitial lung [ILD] disease and granulomatous lung disease [GLD] are rare respiratory disorders that have been associated with inflammatory bowel disease [IBD]. Clinical presentation is polymorphic and aetiology is unclear.
Methods: This was an ECCO-CONFER project. Cases of concomitant ILD or GLD and IBD, or drug-induced ILD/GLD, were collected. The criteria for diagnosing ILD and GLD were based on definitions from the American Thoracic Society and the European Respiratory Society and on the discretion of reporting clinician.

Results: We identified 31 patients with ILD. The majority had ulcerative colitis [UC] \( n = 22 \). Drug-related ILD was found in 64\% of these patients, 25 patients [80.6\%] required hospitalisation, and one required non-invasive ventilation. The causative drug was stopped in all drug-related ILD, and 87\% of patients received systemic steroids. At follow-up, 16\% of patients had no respiratory symptoms, 16\% had partial improvement, 55\% had ongoing symptoms, and there were no data in 13\%. One patient was referred for lung transplantation, and one death from lung fibrosis was reported. We also identified 22 GLD patients: most had Crohn’s disease [CD] \( n = 17 \). Drug-related GLD was found in 36\% of patients and 10 patients [45.4\%] required hospitalisation. The causative drug was stopped in all drug-related GLD, and 81\% of patients received systemic steroids. Remission of both conditions was achieved in almost all patients.

Conclusions: ILD and GLD, although rare, can cause significant morbidity. In our series, over half of cases were drug-related and therefore focused pharmacovigilance is needed to identify and manage these cases.

1. Introduction

Up to 50\% of IBD patients experience at least one extra-intestinal manifestation [EIM], such as pyoderma gangrenosum, uveitis, episcleritis, polyarthritis, or thromboembolic disease. Bronchopulmonary manifestations, despite being considered rare with an unknown prevalence, are increasingly recognised. The presentation of bronchopulmonary manifestations in IBD patients is polymorphic, as all segments of the respiratory tract can be affected. Generally, pulmonary involvement in IBD may be associated with IBD medication or an EIM of the disease itself.

IBD-related lung disease can be subclassified into airway diseases, autoimmune disorder, interstitial lung disease, granulomatous disease, and fistulas [Box 1]. Particularly interstitial lung disease [ILD] and granulomatous lung disease [GLD] are rare respiratory conditions. GLD, mimicking parenchymal sarcoidosis, may be observed in CD patients. In fact, patients with CD and concomitant sarcoidosis have been reported in the literature, suggesting a link between the two diseases which share susceptibility genes. ILD is a heterogeneous group of disorders characterised by varying degrees of fibrosis and inflammation of lung parenchyma. There are estimates of more than 200 known causes of ILD leading to symptoms and radiological changes. These diseases can be classified based on the definitions from the American Thoracic society and the European Respiratory Society.

Drug-related lung disease can present with either interstitial lung disease or granulomatous disease. The diagnosis of drug-related disease can be based on several criteria:

1. a history of drug exposure with correct identification of the drugs, its duration and administration;
2. clinical imaging and histopathological patterns which are consistent with earlier observations of the same drug;
3. exclusion of other lung disease;
4. improvement after discontinuation of drug suspected;
5. recurrence of symptoms on rechallenge.

In our case series, the diagnosis was made at the discretion of different clinicians and once other causes such as infection were excluded.

We aimed to describe a series of IBD patients with a diagnosis of ILD or GLD and try to elicit the impact of the respiratory disease on IBD and outcome.

Box 1. Classification of pulmonary abnormalities in association with inflammatory bowel disease [non drug-related].

1. Upper airways
   - Epiglottitis
   - Tracheobronchitis
2. Large airways
   - Bronchiectasis
   - Acute or chronic bronchitis
3. Small airways
   - Bronchiolitis
   - Bronchiolitis obliterans
4. Interstitial disease:
   - Non-specific interstitial pneumonia
   - Acute interstitial pneumonia
   - Cryptogenic organizing pneumonia
5. Autoimmune disease:
   - Wegener’s granulomatosis
   - Pulmonary vasculitis
   - Churg Strauss syndrome
6. Vascular disease
   - Pulmonary embolism
7. Other pulmonary manifestations
   - Necrobiotic nodules
   - Pleuritis
   - Fistulae

2. Methods

2.1. Study design

This observational multicentre study retrospectively collected cases across the world through the CONFER [COllaborative Network For Exceptionally Rare case reports] project and supported by the European Crohn’s and Colitis Organisation [ECCO]. The CONFER project was initiated by ECCO in order to specifically identify and report rare IBD disease associations, which are otherwise seldom reported due to their exceptional rarity. Briefly, the CONFER methodology comprises selecting a topic worthy of investigation out of case
proposals submitted by ECCO members. The steering committee of CONFER chooses the topic, and ECCO launches a call to identify similar cases encountered by IBD physicians worldwide.

The call to physicians is made through announcements in the ECCO annual congress and in national IBD meetings across Europe and during several international IBD meetings. In addition, the call for similar cases is disseminated by direct emails to all ECCO members and affiliated physicians, on the ECCO website, and in the ECCO eNews. Physicians are then prompted to report their cases to the CONFER database using a pre-determined standardised case report form. The call for the present case series was entitled ‘Interstitial and granulomatous lung disease in IBD’.

2.2. Patients and procedures
All adult IBD patients [age >16 years] with a GLD or ILD diagnosis, according to established classifications throughout the course of IBD or prior to its diagnosis, were eligible for inclusion in this study. GLD and ILD diagnoses were made based on clinical presentation according to previous case reports and reviews. Relationship between IBD treatment and pulmonary disease was established by the physician, based on the patients’ medical history and relevant tests, when applicable. Data were collected using a case report form, which was divided into five domains. Section 1 included patient epidemiological data, past medical history, smoking habits, previous lung disease, and disease characteristics. Section 2 was focused on event description, Section 3 on event presentation and investigations, Section 4 on treatment, and Section 5 on respiratory and IBD outcomes. All the participating centres reviewed patient charts and enrolled all the patients eligible. The data were collected and analysed anonymously and handled according to local regulations. All the adverse events discussed in the text and related to any drug have been reported to pharmacovigilance according to the local regulations.

2.3. Statistics
For the statistical analysis, IBM Software SPSS Statistics Version 22.0.0 [2013 SPSS Science, Inc., Chicago, IL] was used. Depending on the number and the distribution of the data, appropriate tests were used to analyse the data.

Table 1. Clinical characteristics of inflammatory bowel disease patients.

<table>
<thead>
<tr>
<th>Patients with GLD [n = 22]</th>
<th>Patients with ILD [n = 31]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age [years]</strong></td>
<td>46.4 [range 18–86]</td>
</tr>
<tr>
<td>Sex</td>
<td>17 [77.3%] males: 5 [22.7%] females</td>
</tr>
<tr>
<td><strong>Median age at diagnosis [years]</strong></td>
<td>32.2 [range 10–74]</td>
</tr>
<tr>
<td>CD/UC/ndeterminate colitis</td>
<td>17 [77.3%]; 5 [22.7%]; 0</td>
</tr>
<tr>
<td>Montreal classification</td>
<td>8/22/1</td>
</tr>
<tr>
<td>A1/A2/A3</td>
<td>1/10/6</td>
</tr>
<tr>
<td>L1/L2/L3</td>
<td>4/8/5</td>
</tr>
<tr>
<td>B2/B2/B3</td>
<td>11/5/0</td>
</tr>
<tr>
<td>E1/E2/E3</td>
<td>0/2/3</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>5 [22.7%]</td>
</tr>
<tr>
<td>Extra-intestinal manifestations</td>
<td>8 [36.4%]</td>
</tr>
<tr>
<td>Positive family history of IBD</td>
<td>3 [13.6%]</td>
</tr>
<tr>
<td>Previous lung disease</td>
<td>3 [13.6%]</td>
</tr>
<tr>
<td>Smoking: current/past/never</td>
<td>3 [13.6%]; 7 [31.8%]; 12 [54.5%]</td>
</tr>
<tr>
<td>IBD activity at event: active/quiescent</td>
<td>4 [18.2%]; 18 [81.8%]</td>
</tr>
<tr>
<td>Drug-related lung disease</td>
<td>8 [36.4%]</td>
</tr>
<tr>
<td>5-ASA/MTX/AZA/anti-TNF/VEDO</td>
<td>0/0/1/6/1</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid; MTX, methotrexate; AZA, azathioprine; anti-TNF, anti-tumour necrosis factor; VEDO, vedolizumab.

3. Results

3.1. Interstitial lung disease patients
A total of 31 patients with ILD were identified from 14 medical centres. Patients’ characteristics are shown in Table 1. All patients had a diagnosis of IBD prior to ILD, with a median time of 10.3 years [range 0.3–51 years]. Eight [25.8%] patients had IBD disease activity at the time of ILD diagnosis; 11 [35.5%] patients had non drug-related ILD; and 20 [64.5%] had drug-related ILD [mesalazine n = 9, methotrexate n = 1, golimumab n = 1, vedolizumab n = 1, and infliximab [IFX] n = 8]. One patient had two different drug-induced ILD, related to vedolizumab and golimumab, available as Supplementary data at ECCO-JCC online and each event was analysed separately. Main characteristics and outcomes of reported ILD are shown in Figure 1.

3.1.1. Non drug-related data
Eleven patients were identified, 10 [90.9%] male, with mean age at event of 51.6 years [range 20–67 years]. Mean duration of IBD was 13.3 years [range 1.3–51 years] at the time of the event. Eight [72.7%] patients had previous lung disease [asthma n = 1, previous Pneumocystis jiroveci [PJ] pneumonia n = 1, pulmonary embolus n = 1, previous perinuclear anti-neutrophil cytoplasmic antibodies [p ANCA] n = 1, not specified n = 4] [Table 1]. The main reported symptoms were cough [n = 10, 90.9%], shortness of breath [SOB] [n = 9, 81.8%], fever [n = 2, 18.1%], and lethargy [n = 3, 27.2%] with duration of symptoms varying from 12 days to 1 year.

Investigations showed that eight patients [72.2%] had abnormal chest X-ray [CXR], two had positive autoantibodies (one antinuclear antibodies [ANA] positive and one ANCA positive). All had abnormal chest high resolution computerised tomography [HRCT]. Bronchoscopy was done in seven patients [63.6%] [abnormal n = 3, normal n = 4]. Only six patients [54.5%] underwent lung biopsy. Diagnoses of ILD included cryptogenic organising pneumonia [COP] in five patients [45.4%], idiopathic pulmonary fibrosis [IPF] in three [27.3%], and three [27.3%] unclassified. Nine patients [81.8%] were hospitalised and seven [63.6%] received steroids, four of those long term. One of the patients required non-invasive ventilation with bilevel positive airway pressure [BIPAP] for 1 month.
At mean follow-up of 10 months [ranging from 4 months to 9 years] five [45.4%] patients had ongoing symptoms which included one patient with ongoing symptoms despite long-term steroids, who was then given methotrexate and referred for consideration of lung transplantation. Five [45.4%] patients had complete resolution of symptoms and respiratory data were missing for one patient. On review, two [18.2%] had abnormal CXR, five [45.4%], three [27.3%] had abnormal HRCT. Eight patients [72.7%] had active IBD, two were [18.2%] quiescent and three [27.3%] had a flare. Out of those who had a flare, one was started on adalimumab, one on IFX, and one on tacrolimus. One of the patients underwent proctocolectomy for colonic dysplasia. ILD characteristics and outcome are also summarised in Supplementary Table 1, available as Supplementary data at ECCO-JCC online.

### 3.1.2. ILD: drug related data

A total of 20 cases were identified [mesalazine n = 9, methotrexate n = 1, golimumab n = 1, vedolizumab n = 1, and IFX n = 8]. Patients’ epidemiological and IBD characteristics are summarised in Table 1 and Supplementary Table 2, available as Supplementary data at ECCO-JCC online.

#### 3.1.2.2. Biologics

There were eight cases [40% of drug-related cases] with IFX-induced interstitial lung disease. Patients were on IFX [5 mg/kg] with a mean duration of 5.4 doses [range 2–8 doses]. Main symptoms were: cough [n = 6, 75%], SOB [n = 8, 100%], fever [n = 3, 37.5%], and lethargy [n = 4, 50%] with a mean duration of symptoms of 6.3 weeks [1 day–24 weeks]. All patients had normal virology and bacterial screen. Five [62.5%] had abnormal CXR and six [75%] of them had abnormal HRCT; only one had abnormal bronchoscopy, and three [37.5%] underwent lung biopsy.

Diagnosis included three with COP [37.5%], two with IPF [25%], and three [37.5%] with unclassified interstitial lung disease [ILD unclassified]. Five patients [62.5%] were admitted, and IFX was stopped in all patients. Once infection was excluded, six patients received steroids [75%] for duration between 1–6 months.

At mean follow-up of 4.6 months [ranging from 1–14 months], five [62.5%] patients had ongoing symptoms; five [62.5%] had normal CXR; and one [12.5%] still had ongoing abnormalities. CT was normal in one patient [12%], but the majority [six] had ongoing abnormalities [75%]. Three of these patients showed improvement. With regards to IBD, four had active disease at follow-up [50%] and three had quiescent disease [37.5%]. Two required steroids to control their disease and five had new medications initiated (5-aminosalicylates [5-ASA] n = 1, azathioprine [AZA] n = 1, adalimumab n = 1, vedolizumab n = 1, ustekinumab n = 1).

There was only one case of a female patient [5% of drug-related cases] with UC E3 receiving golimumab and vedolizumab. Clinical characteristics are included in Supplementary Table 2. In this case there was previous use of IFX and vedolizumab and previous lung disease due to vedolizumab with ILD unclassified. She presented at age 24 after two doses of golimumab and active IBD at event. Symptoms included cough, SOB, fever, and lethargy. She had abnormal CXR and HRCT diagnosed as cryptogenic organising pneumonia, and was admitted to hospital and treated with steroids for 1 month. Golimumab was stopped and, despite steroid treatment, she had ongoing active IBD that required admission and subtotal colectomy and ileostomy.

The same patient [as above] presented with ILD [unclassified]: disease duration at event was 12 years and age at presentation was 24 years. She had previous use of infliximab and was switched to vedolizumab due to ongoing active IBD. Lung disease presented with SOB after two doses of vedolizumab, with cough, SOB, fever, and lethargy. She had abnormal CXR, HRCT, and bronchoscopy. She was diagnosed with ILD [unclassified], treated with steroids, and admitted to hospital. Vedolizumab was stopped, but she had ongoing active IBD at review 4 months later and was admitted with a flare that required steroids and initiation of golimumab.

#### 3.1.2.3. 5-ASA

There were nine patients [45% of drug-related cases], six of them male [66.7%]. Two [22.2%] patients had previous lung disease [asthma n = 1, Sjögren’s syndrome n = 1]. Patients’ ILD characteristics...
and outcomes are summarised in Supplementary Table 3, available as Supplementary data at ECCO-JCC online. Mean age at time of event was 32 years [range 18–85 years] with mean duration of IBD 6.6 years [range 0.8–14 years]. At the time of event, two [22.2%] patients had active disease and seven [77.8%] had quiescent disease.

5-ASA mean dose at event was 2.3 g [range 0.8–3 g] and mean duration of 5-ASA use was 5.11 years [range 0.8–14 years]. Presenting symptoms were: cough [n = 7], SOB [n = 8], fever [n = 6], and lethargy [n = 1], with mean duration of 7.5 weeks [ranging 1.5–12 weeks]. All patients had abnormal CXR and CT. One had abnormal bronchoscopy [11.1%] and only two had lung biopsy [22.2%]. Diagnosis included two patients with COP [22.2%]; five had ILD unclassified [55.5%], one with idiopathic interstitial disease [3.3%] and one with eosinophilic pneumonia [3.3%]. The drug was stopped in all patients. Eight [88.9%] patients were admitted to hospital and treated with steroids [88.9%] with mean duration of 6.47 months [0.3–24 months]: two needed long-term use. Any infection was excluded before commencing steroids.

At mean follow-up of 11.6 months, [ranging 3–24], five patients [55.5%] had ongoing symptoms, four had abnormal CXR [44.4%], and two [50%] experienced improvement. Three [33.3%] had abnormal HRCT. One [11%] became steroid dependent and died 5 years later, due to progressive lung disease. After treatment, one patient [11%] had a flare that required steroids, three [33.3%] started new medications [AZA, steroids, one restarted 5-ASA]. 5-ASA induced ILD characteristics and outcome are also summarised in Supplementary Table 3.

3.1.2.4. Methotrexate

Only one patient [5%] was identified, a female with CD L2. Age at event was 44 years, and at presentation she had received methotrexate [MTX] for 2 years at 15 mg every week, and her IBD was in remission. She presented with cough, SOB, fever, and lethargy; that lasted a few days. Abnormal CXR and spirometry [mixed restrictive and obstructive pattern] and also abnormal HRCT were reported. She was treated with steroids for 1 month after being admitted to hospital. A diagnosis of ILD [unclassified] was made. At review 1 month later, she had lethargy and normal CXR. Subsequently she had a flare of her CD, and adalimumab was started 3 years later.

3.2. Granulomatous lung disease patients

We identified 22 GLD patients from 18 university hospitals, most of them with CD [77.3%]. Patients’ characteristics are shown in Table 1. In 17 patients, IBD diagnosis preceded lung disease diagnosis after a median time of 10.6 years [range 0.5–27 years]; only four patients had active disease at the time of GLD diagnosis. In four patients, lung disease was diagnosed at a median time of 14 months [range 8–24 months] before IBD and, in one patient, IBD and lung disease diagnoses were established simultaneously.

A total of 14 cases [63.6%] were considered non drug-related GLD [primary sarcoidosis n = 7, fungal infection n = 2, and unspecified n = 5]. Eight cases [36.4%] were considered drug-related GLD [IFX n = 4, certolizumab n = 1, adalimumab n = 1, vedolizumab n = 1, and azathioprine [AZA] n = 1], among whom five had sarcoidosis. Characteristics of GLD and outcomes are shown in Figure 2.

3.2.1. Non drug-related GLD

We identified 14 patients [63.6%] with non drug-related GLD and IBD, 11 male [78.6%], with mean age at event of 44.5 years [range 18–85 years]. At event only four patients had active IBD disease. Nine patients presented with cough [64.3%], four with SOB [28.6%], two with fever [14.3%], and two with weight loss [14.3%]. Investigations showed that 12 patients had abnormal CT scan [85.7%], 11 [78.6%] had abnormal CXR, and four had abnormal spirometry [28.6%, restrictive pattern n = 2, obstructive pattern n = 2]. Three had abnormal bronchoscopy, and 12 patients [85.7%] had a lung biopsy compatible with granulomatous non-necrotising disease.

Diagnosis was primary sarcoidosis in seven patients [50%] [six males; four patients with CD and three with UC]. One patient was receiving anti-tumour necrosis factor [TNF] therapy [adalimumab], one immunosuppressive therapy [AZA], and two 5-ASA therapy; three were without therapy. The first patient had

![Figure 2](https://academic.oup.com/ecco-jcc/advance-article-abstract/doi/10.1093/ecco-jcc/jjz165/5585570) Characteristics and respiratory outcomes of GLD related to IBD [non- and drug-related] in our cohort. GLD, granulomatous lung disease; IBD, inflammatory bowel disease.
received adalimumab therapy for just only 1 month when the diagnosis of sarcoidosis was established. Due to progressive deterioration with weight loss, fatigue, and arthralgia, further investigation was made which revealed systemic granulomatosis with skin, lung, spleen, bone, heart, bone marrow, joint [right knee], and gastro-intestinal involvement. Due to severe lung deterioration and cardiac involvement, a high dose of steroids was initiated. In the remaining six patients, diagnoses of both IBD [CD \( n = 3 \), UC \( n = 3 \)] and sarcoidosis were made. Initially all patients received steroids, and during the follow-up two patients started on immunosuppression with AZA, achieving remission of both conditions, whereas one UC patient, who had already been submitted to protococleotomy, was started on immunosuppression with MTX due to ongoing respiratory symptoms.

Five patients [36%] were considered to have an unspecified GLD [three males; all of the five with CD]: two patients had no IBD medication [lung disease was established before or at the same time as IBD], two patients were under 5-ASA, and one under MTX. All patients initially received steroids. Additionally, during the follow-up, four patients started anti-TNF therapy [adalimumab], of whom three achieved steroid-free remission of both conditions.

We identified two patients [14%] [two males; one patient with CD and one with UC] with a GLD caused by a fungal infection: one patient was under systemic steroid therapy and the other patient had the diagnosis of pulmonary histoplasmosis made before IBD diagnosis. At follow-up, neither patient had ongoing pulmonary symptoms. With regards to IBD, the first patient had pancolitis and during the follow-up was submitted to surgery [ileal pouch-anal anastomosis: IPAA] to control IBD, and the other still had disease activity despite the introduction of budesonide therapy.

Among patients with non drug-related GLD, hospital admission was needed in eight patients [57.1%], but none needed invasive ventilation. Remission of both conditions was achieved in almost all patients.

3.2.2. Drug-related GLD

We identified eight patients [36.4%] with drug-related GLD [IFX \( n = 4 \), certolizumab \( n = 1 \), adalimumab \( n = 1 \), vedolizumab \( n = 1 \), and AZA \( n = 1 \)] and IBD, six males [75.0%], with mean age at event of 48.1 years [35–76 years]. At event presentation, only one patient had active IBD disease. Six patients presented with cough [75.0%], five with SOB [62.5%], five with lethargy [62.5%], three with fever [37.5%], and two with weight loss [25.0%]. Investigations showed that all patients had abnormal thorax CT scan and three had abnormal spirometry [37.5%, restrictive pattern \( n = 2 \), mixed pattern \( n = 1 \)]. Bronchoscopy was done in seven patients [abnormal \( n = 2 \), normal \( n = 5 \)]. Most patients [\( n = 5 \), 62.5%] had lung biopsy, all of them compatible with granulomatous non-necrotising disease.

3.2.2.1. Biologics

There was a total of six cases [75.0% of drug-related cases] with anti-TNF induced GLD. Diagnosis included five patients with sarcoidosis [83.3%] and one with GLD unspecified [16.7%]. In the sarcoidosis group [\( n = 5 \); three males, four with CD; mean age of 41.4 years] all were under anti-TNF therapy [IFX \( n = 3 \), adalimumab \( n = 1 \), certolizumab \( n = 1 \)] for a mean time of 55 months [range 10–108 months]. The causative drug was stopped in all patients and two also received steroids. At mean follow-up of 33 months [range 12–84 months] there were no patients with ongoing respiratory or IBD symptoms. Three patients were started on vedolizumab therapy, and one patient treated with IFX was successfully switched to adalimumab [data not available for one patient]. One male patient with CD, who was on IFX for 72 months, had a diagnosis of GLD [non-sarcoidosis] related to anti-TNF. The anti-TNF was stopped and he was given steroids, with resolution of respiratory symptoms. When reviewed at 3 months, AZA was started for maintenance of his IBD.

One male patient with CD [12.5% of drug-related cases] had the diagnosis of CD established 7 years before and had already been treated with AZA and golimumab. After 4 months of vedolizumab therapy [300 mg q4w], he developed cough, SOB, and lethargy. He had a diagnosis of GLD secondary to vedolizumab. Vedolizumab was stopped and he was treated with steroids, with resolution of respiratory symptoms. Due to active IBD, 15 months later he was started on anti-TNF therapy.

3.2.2.2. Azathioprine [AZA]

There was only one such case, of male patient with CD [12.5% of drug-related cases]. This patient had the diagnosis of CD established 7 years before and was in remission under AZA [2.5 mg/kg]. After 24 months of AZA he developed cough, SOB, and lethargy, and the diagnosis of unspecified GLD was established. The patient was admitted, AZA was stopped, and he was treated with steroids. Four years later the patient still needed steroids [10 mg/day] to control respiratory symptoms and still had abnormal CT chest and spirometry. There was no need for new IBD therapy.

Among patients with drug-related GLD, hospital admission was needed in two patients [25%] but none needed invasive ventilation. Remission of both conditions was achieved in all patients, with only one patient still needing steroid to control lung disease.

4. Discussion

Even though pulmonary manifestations in IBD are rare they are increasingly recognised. The true prevalence in IBD remains unknown. Our retrospective study describes a series of IBD patients affected by ILD [\( n = 31 \)] and GL [\( n = 22 \)]. Most cases were reported to be drug-related [\( n = 28 \)] and 25 were non drug-related cases. Most of the current data in literature comes from rheumatological patients and also small case series; our study provides insight into the IBD population.

Establishing an accurate diagnosis of ILD can be challenging for clinicians, as there are more than 200 different subtypes and over the past decade ILD has been reclassified in comprehensive international consensus statements. Determination of disease subtypes requires consideration of patients’ clinical features, radiological pattern, serology, and in some cases lung biopsy.

Making a diagnosis of granulomatous lung disease can also be challenging. Even with histology, it can be difficult to distinguish between sarcoidosis and Crohn’s disease. In fact, both entities are barrier disorders of unknown aetiology, with several aspects in common [non-necrotising granulomas, an increased intestinal permeability, local and peripheral T cell activation, and an increased proinflammatory cytokine release]. Moreover, the patterns of possible organ involvement outside the primary manifestations in the lung and gut are similar and include eye, skin, joints, and liver. Sarcoidosis manifestations in the gut, CD manifestations in the lung, and manifestations of both diseases in the same patient, have been reported in rare cases, which may impose considerable diagnostic difficulties.

In our case series, 11 patients had non drug-induced ILD with male predominance, 73% with pre-existing lung disease and concomitant
UC. None of the pre-existing lung disease included previous ILD. Only six patients had lung biopsy, making classification difficult, with three cases unclassified. Three cases were diagnosed as IPF which is a progressive lung disease; two of these had ongoing respiratory symptoms and radiological changes, but for one no respiratory data exist. One of the ILD unclassified cases had progressive deterioration of his respiratory symptoms requiring referral for consideration of lung transplantation, despite ongoing steroid treatment. A high proportion of the cases were admitted and treated with steroids, with resolution of symptoms in 45% of patients, which possibly is related to the ILD subtype of COP which has a good prognosis and responds to steroid treatment.

We also identified 14 patients with non-drug-related GLD, and 12 patients had lung biopsy. Seven patients were diagnosed with sarcoidosis and five had GLD unclassified, which again demonstrates the difficulty in diagnosis; two cases were due to fungal infection. Almost all cases recovered with the use of steroids and AZA [sarcoidosis] or IFX [unspecified GLD].

The most common pulmonary manifestations of IBD are drug-induced lung disease. Most IBD drugs have been implicated, and definitive diagnosis of drug-induced lung disease can be difficult. Clinical presentation and exclusion of other causes play important roles in making the diagnosis, but sometimes invasive procedures such as bronchoscopy and lung biopsy may be necessary. 22–27

Patients can present with virtually all histopathological patterns of either ILD or GLD. Moreover, some drugs can produce more than one pattern of respiratory involvement. There have been identified some risk factors for developing drug-related lung disease, including: extremes of age, sex, ethnicity, dose of medication, concomitant use of oxygen, drug interaction, and underlying lung disease. 31 Diagnostic criteria exist as mentioned earlier, but despite that it can still be a difficult diagnosis. 4

Side effects of sulphasalazine and mesalazine are rare and can be dose-related or idiosyncratic. Mesalazine-induced lung injury is rare and usually presents as interstitial and eosinophilic pneumonia, bronchiolitis obliterans, and eosinophilic pleural effusion. 32

Case report data suggest that mesalazine-induced lung toxicity follows a milder course; however, there have been case reports with more severe presentation requiring intubation. 33 In a recent review of 50 cases of sulphasalazine lung toxicity, most patients presented with cough, breathlessness, fever, and weight loss. Most cases demonstrated chronic interstitial pneumonia, desquamative interstitial pneumonia, eosinophilic pneumonia, or acute interstitial pneumonia. Clinical improvement occurred in majority of cases, with resolution occurring on average 6.5 weeks after initiation of therapy. There were five deaths due to pulmonary pathology, and all cases had UC as underlying condition. 34 In another review of case reports of 5-ASA-induced lung toxicity, mean age of presentation was 46 years, with most cases being female and having UC as underlying disease. The time for appearance of symptoms ranged from 2 days to 8 years. 35 5-ASA lung toxicity usually responds to discontinuation of drug, and some may require a course of steroids. 36 In our case series we identified nine cases and, unlike the literature, most of them were male [67%] and 89% had ulcerative colitis. The mean duration use of 5-ASA was 5.1 years [range 0.8–14 years] which is similar to the previous review. Only two patients had lung biopsy and most cases were ILD unclassified. At follow-up, 55% of them had ongoing respiratory symptoms. There was one death due to progressive fibrosis. This was an 81 year-old male patient who was diagnosed with idiopathic pulmonary fibrosis and became steroid-dependent.

The use of anti-TNF drugs [IFX, adalimumab, golimumab, certolizumab] in IBD has increased and improved the outcomes of IBD patients. 37,38 The most important side effects include increased risk of opportunistic infections. 39 There has been some evidence that anti-TNF therapy can cause acute respiratory distress syndrome, diffuse alveolar haemorrhage, 40 and ILD. 41–44 A large-scale post-marketing surveillance study in Japan, on safety of IFX in rheumatology patients, revealed that the development of ILD was a rare event at 0.5% [23/5000]. Mean age of those patients was 62.9 years and pneumonitis occurred after a mean dose of 2.8 infusions of IFX. 45 Another case-control study from Nakashita investigated the potential risk of TNF inhibitors on progression of ILD in patients with rheumatoid arthritis [RA] revealed increased risk of ILD events and also progression of pre-existing ILD disease. 46 Patients presented mostly with dyspnoea and cough with IFX use of 6–14 weeks preceding presentation. Diagnosis included: non-specific interstitial pneumonitis, drug-related alveolitis, and drug-induced interstitial lymphocytic pneumonitis; all had discontinuation of IFX with complete resolution of symptoms with steroids. 46–49 There has been one case report of fatal acute interstitial pneumonia after an accelerated dose of IFX for acute severe UC. 50 In our case series, we identified eight IFX-induced ILD cases with male predominance. Only two patients had lung biopsy. One young male was diagnosed with idiopathic pulmonary fibrosis, but he responded to steroids and it was therefore unclear whether that diagnosis was the correct one. Most of our patients had ongoing symptoms and radiological changes despite steroid treatment and discontinuation of the drug. The different outcome might be due to the diversity of the subtype of ILD, as different subtypes have different outcomes.

Another uncommon pulmonary adverse event associated with anti-TNF therapy is the development of sarcoid-like lesions. The estimated frequency is 1:28 000 [0.04%] which comes from case reports published from rheumatological data. 51–53 Symptoms are non-specific, including dyspnoea, non-productive cough, erythema nodosum, parotid enlargement, and neuro-ocular manifestations. Radiologically, the most common findings are mediastinal and hilar adenopathy, and less frequently, upper lobe opacities. The diagnosis is confirmed histologically by the presence of well-formed non-necrotising granulomas. Ultimately, sarcoidosis is a diagnosis of exclusion, once all infectious causes have been ruled out. 54 In a recent review of the available literature, the authors evaluated the published cases of sarcoidosis associated with anti-TNF therapy and found a total of 90 patients with median age of 43 years [7–72] and a female predominance [61%]. The underlying anti-TNF therapy was etanercept [n = 53, 59%], adalimumab [n = 21, 23%], and IFX [n = 16, 18%], and the median duration between initiation of anti-TNF therapy and diagnosis was 22.5 months [1–84]. Regarding treatment options, in 43 cases, the anti-TNF therapy was discontinued and steroids were started, with an improvement or resolution in 41 cases [95%]; in 37 cases, anti-TNF discontinuation was the only intervention, giving improvement in 32 cases [86%]; in five cases, addition of steroid therapy alone gave improvement in four cases [80%]; and in one out of three cases, improvement was observed without any intervention [33%]. In 20 cases, the anti-TNF therapy was restarted: in six cases the same drug was used, which resulted in recurrence in four; and in 14 cases, another anti-TNF was initiated, with relapse in three. 55 In our series we found a male predominance, but the other characteristics and outcomes are similar to those previously reported. All patients fully recovered by stopping anti-TNF therapy and receiving steroids.

No data exist in the IBD population regarding golimumab-induced ILD. According to the European Medicines Agency [EMA]
2009 Assessment report, serious non-infectious pulmonary adverse events were observed in five Phase 3 trials of golimumab for the treatment of rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis: one case of interstitial disease, two of pneumonitis, and one of fibrosing alveolitis.\textsuperscript{36-41} Most of patients were also on methotrexate, and it was therefore not possible to make a definite association between ILD and golimumab. We reported a case of a young woman with previous use of IFX and previous lung disease due to vedolizumab, who had golimumab-induced COP and required steroids. The golimumab was stopped and she was given steroids and, due to ongoing active UC, she had subtotal colectomy and ileostomy.

Vedolizumab, unlike other drugs used for IBD, has not been associated with the development of serious opportunistic infections and malignancies.\textsuperscript{62} However, clinical observations indicate an increased risk for extra-intestinal autoimmune events under this therapy.\textsuperscript{63} There have been two case reports of ILD in the literature.\textsuperscript{64,65} The only case of vedolizumab-related ILD [unclassified subtype] reported in our cohort responded to steroids, but had further admissions due to flare of her disease and required golimumab therapy.

We also reported a case of a CD male patient who developed cough, shortness of breath, and lethargy 4 months after starting vedolizumab. He was diagnosed as GLD associated with vedolizumab therapy but, as the similar case recently published,\textsuperscript{66} this patient can be reclassified as a patient with a newly developed pulmonary manifestation of CD under vedolizumab.

Methotrexate [MTX] may be useful in IBD treatment but can cause adverse events in lungs which can be lethal.\textsuperscript{67} The mechanism is unclear and thought to be an idiosyncratic reaction that can cause interstitial pneumonitis and bronchiolitis.\textsuperscript{68} MTX pneumonitis is a rare complication, with only 123 case reports in the literature. Most cases have a subacute onset and it is most common within the first year of treatment, with a reported incidence that varies from 0.8\% to 6.9\%.\textsuperscript{68,70} Treatment of MTX pneumonitis includes withdrawal of MTX, high-dose corticosteroids, and supportive therapy.\textsuperscript{70} We identified one case that presented with ILD unclassified after 2 years of weekly MTX use due to CD; this patient was treated with 1 month of steroids, with resolution of symptoms.

Pulmonary toxicity due to AZA/6-MP [6-mercaptopurine] has been reported infrequently in the literature, although interstitial pneumonitis, restrictive lung disease, Goodpasture-like syndrome, and pulmonary haemorrhage have been described after use of these drugs.\textsuperscript{71} The largest series of lung toxicity related to AZA, with description of seven cases on AZA therapy, was reported in patients undergoing renal allograft transplantation immunosuppression. Lung biopsies revealed interstitial pneumonitis in five patients and diffuse alveolar damage in two patients: three patients died. The other four improved after stopping AZA, and in two of these patients cyclophosphamide therapy to resolve completely this side effect was needed.\textsuperscript{71} There are no cases of GLD due to AZA/6-MP in the literature. Here we described a case of a CD male patient in remission who developed cough, shortness of breath, and lethargy 24 months after AZA initiation. He was diagnosed with AZA-related GLD and was admitted to hospital. He responded to steroids and became steroid-dependent to control his respiratory symptoms, with ongoing radiological and spirometry changes 4 years later.

Our study has several limitations: it was a retrospective case report data collection, and it relied on voluntary submission of cases by physicians who responded to the ECCO calls and therefore might be subject to geographical and selection biases. Only 12 ILD cases [38.7\%] had lung biopsy and 17 GLD cases [77\%], which resulted in a lot of cases having ILD unclassified. The classification of ILD and whether a drug was the caveat depended on the clinician submitting the relevant information and, as cases were collected from 2000–17, the classification might have not been the correct one—as classification of ILD has been revised over 2013–15.

Due to the low sample size, the correlation between IBD therapies and lung disease is challenging to assess. Also no risk factors or predictors can be investigated, due to the very low sample size and the heterogeneity of cases. In conclusion, ILD and GLD although rare can cause significant morbidity. About half of our cases were drug-related, and therefore clinicians should be more vigilant regarding IBD medications, especially when infectious causes have been excluded. Early recognition and treatment is important, as most respond to withdrawal of medication and use of steroids.

**Funding**

No funding has been received for this project.

**Conflict of Interest**

None declared.

**Author contributions**

EE and JM initiated the study: EE analysed and interpreted ILD data and drafted and revised the manuscript. JM was responsible for analysis and interpretation of data and drafting the GLD part of manuscript. GF participated in study design and critically revised the manuscript. All the authors contributed the cases and were responsible for revision of the manuscript as well as for the treatment of the patients. All other collaborating authors contributed with at least one case and critically revised the manuscript.

**Supplementary Data**

Supplementary data are available at ECCO-JCC online.

**References**


