Pulmonary manifestations of inflammatory bowel disease

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Abstract

Bronchopulmonary signs and symptoms are examples of variable extraintestinal manifestations of the inflammatory bowel diseases (IBD). These complications of Crohn's disease (CD) and ulcerative colitis (UC) seem to be underrecognized by both pulmonary physicians and gastroenterologists. The objective of the present review was to gather and summarize information on this particular matter, on the basis of available up-to-date literature. Tracheobronchial involvement is the most prevalent respiratory presentation, whereas IBD-related interstitial lung disease is less frequent. Latent and asymptomatic pulmonary involvement is not unusual. Differential diagnosis should always consider infections (mainly tuberculosis) and drug-induced lung pathology. The common link between intestinal disease and lung pathology is unknown, but many hypotheses have been proposed. It is speculated that environmental pollution, common immunological mechanisms and predisposing genetic factors may play a role.

Key words: inflammatory bowel disease, ulcerative colitis, Crohn's disease, tracheobronchitis, interstitial lung disease.

Introduction

The term inflammatory bowel disease (IBD) is frequently used to describe two distinct diseases: ulcerative colitis (UC) and Crohn's disease (CD). The incidence in developed countries is up to 24/100 000/year (for UC in Europe), with prevalence as high as 505 and 322/100 000/year for UC and CD, respectively [1]. The most widely accepted etiological concept is that IBD results from an inappropriate immune response to physiologic gut flora in a genetically susceptible host [2]. Each entity has its discriminating clinical and morphological features, but in about 10% of patients a clear differential diagnosis is not possible. The systemic character is one of the most important common clinical attributes. The best acknowledged extraintestinal manifestations of IBD, usually related to the disease exacerbations, are uveitis, conjunctivitis, arthritis and erythema nodosum. Primary sclerosing cholangitis, hemolytic anemia, Hashimoto's disease and other diseases of autoimmunologic origin are frequent co-morbidities, and may appear independently of the bowel disease activity [3]. Rankin *et al.* reported that among 569 patients with CD, 24% had a history of at least one extraintestinal manifestation, which was more frequent in patients with ileocolitis and perianal location in comparison to those with isolated small bowel disease [4]. Similar numbers were reported for UC. However, the frequency and distribution of specific manifestations seem to be different between these two diseases [5]. In

general, IBD patients report frequent respiratory symptoms [6, 7].

A PubMed database search was planned with the entries comprising compositions of the following keywords: "inflammatory bowel disease", "ulcerative colitis", "Crohn's disease", "lung", "pulmonary manifestations", "tracheobronchial disease", and "interstitial lung disease". The authors' final selection of articles directly related to the objective of the review included 135 papers (106 case reports and case series, 17 original research papers, 9 reviews, and 3 meta-analyses). Below, pulmonary manifestations of IBD are extensively discussed on the basis of available literature. The multidisciplinary approach to this topic, with special regard to clinical aspects, radiology, histopathology and treatment, was applied.

Tracheobronchial involvement

Clinical presentation

Several cases of coexistence of IBD and bronchiectasis [8–14], bronchitis, tracheobronchitis [8, 12, 15–20] and bronchiolitis [19, 21, 22] have been reported. None of these complications are specific for either UC or CD; however, the majority of cases concern abnormalities in proximal or distal conducting airways in UC. Colobronchial [23] and oesophago-pulmonary [24] fistulas have been reported in CD. Symptoms of airway involvement may precede the first symptoms of bowel disease by years [10, 21], but most often they appear in patients with a long-lasting history of IBD. Respiratory symptoms may accompany exacerbations of IBD [10, 12], but most typically they are not parallel to exacerbations, and may show up during remissions or quiescent periods [15, 18]. Such coincidence with surgical treatment of bowel disease (colectomy, proctectomy, ileostomy) has been reported [8, 12, 17, 19, 25]. Signs of tracheobronchial involvement may appear days to months after surgery.

Patients with central airway involvement usually report productive or non-productive cough, wheezing, shortness of breath, limitations of exercise, purulent expectoration, hemoptysis or chest pain. Asthma is frequently recognized, and anti-asthmatic treatment is typically started, but the control of symptoms is variable.

Lung function tests

Several authors have reported abnormal lung function test results in about 40–60% of asymptomatic patients, with limited airflow in peripheral airways being the most prevalent pattern [14, 26, 27]. Mild to severe bronchial obstruction has also been reported [17, 19, 21, 28]. Individual cases presenting signs and symptoms of tracheobronchial in-

volvement may have normal spirometry [12]. In the study of Louis et al. [29], 41% of patients with IBD after subtracting patients with coexisting atopy had a positive methacholine test result (compared to 5% in the control group). Peradzyńska et al. [13] reported positive methacholine challenge tests in about 15% of children suffering from IBD without pulmonary symptoms. Fractional exhaled nitric oxide (FeNO) is frequently elevated in asymptomatic IBD patients [13, 30]. The most probable explanation for these findings is latent inflammation of the bronchial tree. As indicated by Louis et al. [31], patients with CD have increased numbers of eosinophils in induced sputum. However, the intensity of eosinophilic inflammation did not correlate with the degree of forced expiratory volume in 1st of expiration (FEV$_1$) fall after methacholine inhalation, suggesting that this phenomenon is not related to eosinophilic infiltration. A positive methacholine test may cause problems in differential diagnosis between IBD-related tracheobronchial pathology and true asthma. A positive reversibility test and a very good response to inhaled steroids may indicate asthma rather than IBD-related tracheobronchitis. On the other hand, a negative methacholine test excludes asthma. The differential diagnosis may be even more problematic in view of the fact that atopy is more frequent among IBD patients than healthy controls [32].

A lung function test in patients with bronchiolitis may reveal severe bronchial obstruction non-responsive to bronchodilators [19], but in other patients mild obstruction or normal spirometry was detected [22]. Diffusing capacity for carbon monoxide (DLCO) may be reduced in more extensive and severe cases [21].

Bronchoscopy, bronchoalveolar lavage and biopsy results

Mucosal edema and hyperemia are the most typical findings [12, 16, 17]. Suppurative bronchitis is frequent, and in these instances chronic purulent expectoration is the main symptom [10, 17]. Tracheal or bronchial strictures have been described due to extensive submucosal fibrosis [17, 19], inflammatory nodules [17] or circumferential mucosal infiltration [33]. Bronchial biopsy reveals mucosal hyperplasia [17], thickening of basal membrane and angioectasia [15], cellular infiltrations composed of granulocytes [16], T and B lymphocytes [17] or non-specific chronic inflammatory infiltrates [15]. Although the most typical finding in the bronchoalveolar lavage (BAL) fluid of IBD patients is lymphocytosis, in tracheobronchial involvement BAL fluid may be dominated by neutrophils [17].

The classical form of small airway disease accompanying IBD is bronchiolitis. Non-necrotizing granulomas consisting of epithelioid, multinucle-
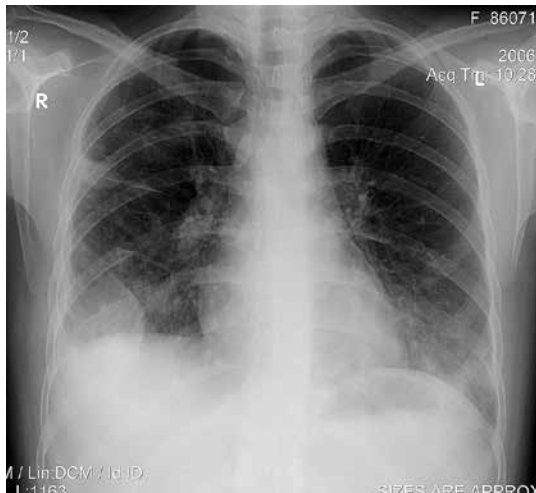
ated giant and scattered mononuclear cells surrounding small bronchioles were described in patients suffering from CD [22, 34–37]. This and other similar findings recall similarities to sarcoidosis [38]; however, the coincidence of classical sarcoidosis with CD is probably incidental. In bronchiolitis related to UC, non-granulomatous inflammation has been found [19, 21, 39]. Diffuse and fibrosing/sclerosing bronchiolitis of severe course has been described in UC [19].

Radiology

High-resolution computed tomography (HRCT) is useful for confirming bronchiectasis. In bronchiolitis it shows irregular and patchy areas of different attenuation. The expiratory scans may help to show evidence of air-trapping in the involved areas [40].

Prognosis and treatment

Systemic steroids are the treatment of choice. Edema, cellular infiltrates and granulation typically respond to treatment [10, 16, 17, 21], but high doses are frequently needed. Inhaled steroids are worth trying, especially in milder cases [20, 31]. Bronchiectasis, strictures caused by fibrosis of the bronchial or tracheal wall, and deposits of fibrous material do not respond to pharmacological treatment [9, 19], although symptoms of bronchiectasis, e.g. productive cough, may improve [9].
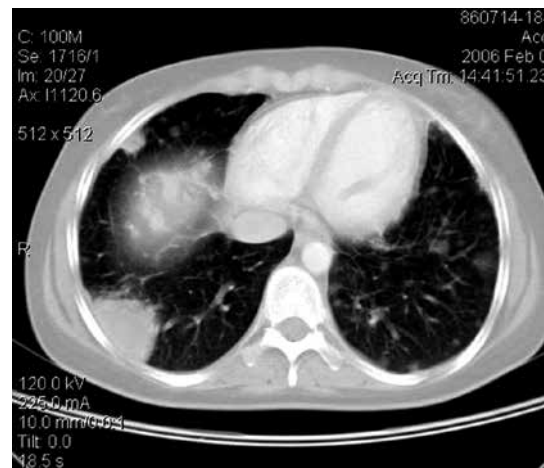
Interstitial lung disease

Clinical presentation

Similarly to tracheobronchial signs and symptoms, interstitial disease may precede the first symptoms of bowel disease by years [41], but most commonly it appears in patients with long-lasting IBD. In addition, interstitial disease signs and symptoms are not related to bowel disease activity and may be present in patients with inactive IBD [42–45]. The clinical course is not characteristic. Asymptomatic lung involvement is possible [46]. General symptoms are frequently reported, and may include malaise, fever or sub-febrile state, loss of weight and arthralgias [42, 47, 48]. The general symptoms seem to be especially frequent in patients with organizing pneumonia (OP) [42, 47] and resemble those described in the course of cryptogenic organizing pneumonia (COP) [49]. Respiratory symptoms include dry cough, breathlessness on exertion or at rest and chest tightness. Expectoration of blood-stained sputum is rare.

Radiology

Radiological presentations of interstitial lung involvement are quite diverse. Pneumonia-like opacities are very frequent [15, 21, 37, 50], especially in patients with OP [42, 47, 51] (Figure 1). Multiple pulmonary nodules of different size and location may be present (Figure 2). The bigger coin lesions may resemble metastatic lung disease [42, 43]. The nodes and small nodules may be located subpleurally [34, 42] (Figure 2). Small cavitations reflecting central necrosis may be present [34]. Tumors with

Figure 1. Chest X-ray of a 19-year-old woman with long standing CD treated with mesalazine. Pulmonary infiltrations and right sided pleural effusion are visible. Due to the presence of fever, dry cough and pleural chest pain, pleuropneumonia was diagnosed and antibiotics were introduced. Because of lack of response to antimicrobial treatment she was referred to a pulmonary physician, who recommended withdrawal of mesalazine. After initial improvement, the general and radiological symptoms relapsed (see Figure 2), suggesting the possibility of IBD-related pathology

Figure 2. Computed tomography of the same patient performed a few weeks after the presented chest X-ray (Figure 1). Subpleural nodes and nodules are visible. Video-assisted thoracoscopic examination was performed and lung biopsy revealed organizing pneumonia. Clinical and radiological symptoms responded very well to oral steroids and did not relapse until renewed introduction of mesalazine

central necrosis may resemble granulomatosis with polyangitis (GPA) and may require thorough differentiation with this disease, especially in cases of UC with positive anti-neutrophil cytoplasmic antibodies (ANCA) in the serum [52–57]. Overlapping of UC with GPA in such cases should be considered [58]. Solitary nodules presenting as primary lung tumors may be found [56]. Interstitial pneumonitis may be another radiological presentation. The HRCT scans in these cases reveal ground-glass opacities, alveolar filling or a reticular pattern [40, 59–61]. Extensive fibrosis is rare [62]. Upper lobe fibrosis may resemble TB infection [63]. Some authors report vanishing patterns of radiological lesions not related to treatment or IBD activity [42]. Spontaneous migration of lung opacities has been reported [64]. In the study of Mahadeva et al. [40], which was designed to detect latent respiratory abnormalities in patients with IBD, abnormal HRCT findings were reported in almost all studied patients. The majority had bronchiectasis, air-trapping and "tree-in-bud" patterns. The HRCT findings consistent with alveolitis were present only in 3 patients. It reflects the low frequency of interstitial lung disease (ILD) and high frequency of tracheobronchial pathology in patients with IBD [59, 65]. More recent reports present similar results [14]. These studies and many case reports show the possibility of coexistence of different forms of lung involvement. It is especially interesting that a high proportion of patients with HRCT abnormality are respiratory-symptom-free [26, 65].

Lung function tests

These may be normal [43, 64] or show a mild [11, 66] to severe restrictive ventilatory defect [47, 51, 67]. Diffusion capacity may be decreased [47,

but normal values are also frequently reported [43, 64, 66]. Hypoxemia at rest or on exertion may be present [67]. Munck et al. [68] found that pediatric patients with CD, with no signs of pulmonary involvement, have decreased DLCO during exacerbations of the bowel disease. Other authors found DLCO significantly decreased during periods of IBD exacerbations in respiratory-symptom-free adults [27]. About 20% of patients with pulmonary involvement have inactive bowel disease [65]. This suggests the possibility of a latent asymptomatic lung inflammation in the course of IBD.

Bronchoscopy, BAL and biopsy results

The BAL cellular pattern is usually abnormal, but changes are not specific. Increased total cell count and mild lymphocytosis are the most typical findings [43, 47, 67]. Some authors reported an increased percentage of BAL eosinophils [64]. Patients without clinical evidence of pulmonary involvement may have alveolar lymphocytosis [69]. Diagnosis is usually confirmed by surgical lung biopsy, but transbronchial peripheral lung biopsy may be sufficient [11, 43, 64, 67]. Therefore it is always worth trying as a less invasive method.

The possible pathological patterns are listed in Table I [70–80].

Aseptic lung abscesses [81] and lung bullae [9] may represent destructive forms of pulmonary involvement in patients suffering from IBD.

Inflammatory bowel disease in childhood

The age of onset of pulmonary involvement may vary in a wide range. The incidence of symptomatic bronchopulmonary involvement in children suffering from IBD seems to be much lower than in

Table I. Possible pathological patterns of IBD-related pulmonary interstitial lung disease. The frequency was estimated arbitrarily on the basis of published case reports and personal expert opinions expressed in review papers [59, 75]. A systematic study on the real frequency of various patterns has not been performed so far, probably due to the low frequency of IBD-related lung disease

Pathological pattern	IBD	Frequency	References
Non-specific lymphocytic infiltrations	CD and UC	High	[21, 51, 64, 67]
Organizing pneumonia (OP)	CD and UC	High	[47, 70–72]
Non-caseating granulomas	CD	High	[38, 43, 50, 73]
Eosinophilic pneumonia	CD and UC	Moderate	[64, 74]
Necrobiotic pulmonary nodules	CD	Moderate	[34, 75]
Vasculitis	UC	Moderate	[76–78]
Amyloid nodules	CD	Incidental	[79]
Diffuse alveolar hemorrhage	UC	Incidental	[76]
Usual interstitial pneumonia-like pattern	UC	Incidental	[60, 62]
Desquamative interstitial pneumonitis (DIP)	UC	Incidental	[80]
Necrotizing granuloma	CD	Incidental	[41]
Non-specific interstitial pneumonitis (NSIP)	UC	Incidental	[61]

adults [13]. The spectrum of lung pathologies is quite similar, and available reports comprise nodules consisting of non-caseating granulomas [36, 51], cavitating lesions [82], pleuritis [82], lymphocytic infiltrations [15] and organizing pneumonia (OP) in patients with CD [51] and UC [72].

Prognosis and treatment

Overall prognosis is good. The ILD in patients with IBD responds well to treatment with systemic steroids. Moderate doses of 0.5 mg/kg of prednisone daily with gradual dose reduction are usually sufficient. However, relapses may occur when the steroid dose is tapered down or withdrawn [21, 67]. Rare severe interstitial lung fibrosing pneumonitis may be steroid-resistant and fatal [60, 62, 83]. In more severe cases the addition of cyclophosphamide to a high dose of steroid treatment was shown to improve the outcome [67]. An anti-TNF treatment such as infliximab may be an effective alternative to steroids [51, 84]. Spontaneous remission of lung granulomas has also been described [74].

Other forms of respiratory involvement

Exudative pleuritis, usually eosinophilic, may accompany other lung pathologies [64, 82, 85–89]. Exudative pericarditis with possible life-threatening tamponade may also be present in these patients [87–89]. Pachypleuritis with extensive pleural fibrosis was described in a CD patient [64]. Good responses to steroids have been reported in all cases of pleuritis or pleuropericarditis. Pneumothorax is a rare complication, and was described in a patient suffering from CD-related granulomatous lung disease [90]. An air-leak syndrome (pneumothorax, pneumomediastinum and subcutaneous emphysema) associated with organizing pneumonia pattern was described as an unusual presentation of UC-related bronchopulmonary involvement [91].

Patients with IBD are at increased risk of pulmonary embolism. The risk of thromboembolic complications is 3–4 times higher compared to the general population [92]; therefore thromboembolism should always be considered in cases of acute and unexplained pulmonary symptoms in IBD patients.

Drug-related lung pathology in inflammatory bowel disease patients

5-Aminosalicylate agents (5-ASA), sulfasalazine and mesalazine, are the mainstay of treatment of IBD. The possibility of pulmonary lesions being induced by these drugs has been acknowledged for decades [93]. However, the incidence of adverse effects in general is low, and in some trials respiratory symptoms have not even been reported [94].

There is a variety of pulmonary changes induced by 5-ASA, all of them practically indistinguishable from IBD-related lung pathology [95]. The most commonly reported clinico-pathological entities include eosinophilic exudative pleuritis [96–98] and interstitial pneumonitis with the predominance of lymphocytes or eosinophils [93, 97–106]. Poorly formed non-necrotizing granulomas may be found in the lung biopsy [101]. The OP is another possible, albeit less frequent, pathological pattern [107]. Acute phase reaction and peripheral blood eosinophilia may be present [99, 104, 106, 108]. Infiltrations may be asymptomatic [109], but non-productive cough, shortness of breath and general symptoms, most commonly fever, are frequently present. Drug-related lung changes may appear days to years after the start of the treatment. Although 5-ASA- induced lung toxicity is not very common, such a possibility should always be considered at the beginning of the diagnostic process. Withdrawal of the suspected drug may result in a spectacular remission [105, 110, 111]. Severe symptoms, functional impairment, or respiratory insufficiency justify treatment with steroids [91, 102] or, in more problematic cases, immunosuppressive agents [50]. There is one report suggesting dose dependence of mesalamine-induced pulmonary hypersensitivity, based on resolution of lung manifestation after dose reduction [103]. Although 5-ASA-induced lung pathology seems to be group-specific, incidental reports exist showing improvement after shifting from one drug to another [112].

Azathioprine is used for the treatment of more difficult cases of IBD. Interstitial infiltrations due to azathioprine are rare but may be extensive and of severe course. The pathological pattern described in the context of IBD treatment includes interstitial pneumonitis [113, 114] and OP [113]. Methotrexate (MTX) is indicated in IBD cases resistant to steroids and purine analogs [115]. It is a drug of acknowledged lung toxicity, which is rare but may be severe and irreversible. Although the risk of interstitial pneumonitis increases with cumulative MTX dose, symptoms may appear even after the first dose, which suggests that immunological mechanisms are involved. In a meta-analysis summarizing the incidence of adverse events in 465 IBD patients treated with MTX, the incidence of interstitial pneumonitis was 0.5% [116].

Anti-tumor necrosis factor (anti-TNF) agents have become widely used for the treatment of IBD in recent years [117]. Infections and malignancies may occur in patients during such treatment [118]. A number of pulmonary infections have been reported in patients treated with anti-TNF agents, the most important being tuberculosis [119] (Figures 3 A and B). Less frequent ones include lung actinomycosis [120] and invasive aspergillosis

[121]. Diffuse alveolar hemorrhage has been described after infusion of infliximab in patients with CD [122]. The number of reports on infliximab-induced lung complications may be growing, with the increasing acceptance of this therapeutic option for the treatment of IBD [123]. In the context of both UC and CD, non-specific interstitial pneumonia (NSIP) was described recently [124, 125].

## Possible links between bowel and lung disease

Both the colonic and the respiratory epithelia provide the first barrier against microbial agents, antigens and toxins. Exposure to air pollutants, especially to particulate matter (PM), was shown to increase morbidity and mortality related to respiratory and cardiovascular diseases. This effect may be related to the induction of systemic inflammation, which is an important element in the pathogenesis of these diseases. Various pollutants may be swallowed and absorbed from the intestines, potentially inducing systemic and local inflammation. The incidence of IBD has significantly increased in the last five decades, probably reflecting changes in the industrialized environment [126]. The idea of the impact of air pollution on the pathogenesis of IBD is intriguing, but evidence is scarce yet [127].

There are several papers documenting higher frequency of IgE-related and delayed-type hypersensitivity in IBD patients [128–130]. Interestingly, colonic tissue eosinophilia was higher in patients with positive skin prick tests for food allergens [130, 131]. Based on such data, it may be suggested that atopy could be a common link between IBD and airway disease (asthma) in some patients. Unfortunately, other data do not support this concept. For instance, asthma and atopy are Th2-mediated diseases, whereas CD is a Th1-mediated pathology [132, 133].

In epidemiological studies, there is a strong association between chronic obstructive pulmonary disease (COPD) and IBD. The risk of COPD in CD patients is 2.7 times, and in UC 1.8 times higher, than in healthy controls [134]. On the other hand, COPD is a strong mortality factor for CD patients (standardized mortality ratio above 2.5) [135]. Smoking, a major risk factor for COPD, increases the risk of CD three-fold [1]. Although the situation is reversed in UC, as active smoking protects against this disease, the risk of UC outbreaks increases in ex-smokers and is higher compared to subjects who have never smoked [1]. An interesting concept of a common origin of these diseases was proposed by a group of Australian authors [136], who speculate on the role of common genetic risk factors (e.g. NOD2), pulmonary and intestinal epithelial barrier disruption due to loss of tight-junctional integrity, similar cytokine profile (TNF, IL-6, IL-13, IL-17) and disruption of the microbiome.

The frequently quoted similarities of granulomatous bowel inflammation in CD and lung sarcoidosis may go beyond simple coincidence. Bowel granulomas in the course of CD may have identical histological composition as lung sarcoid granulomas
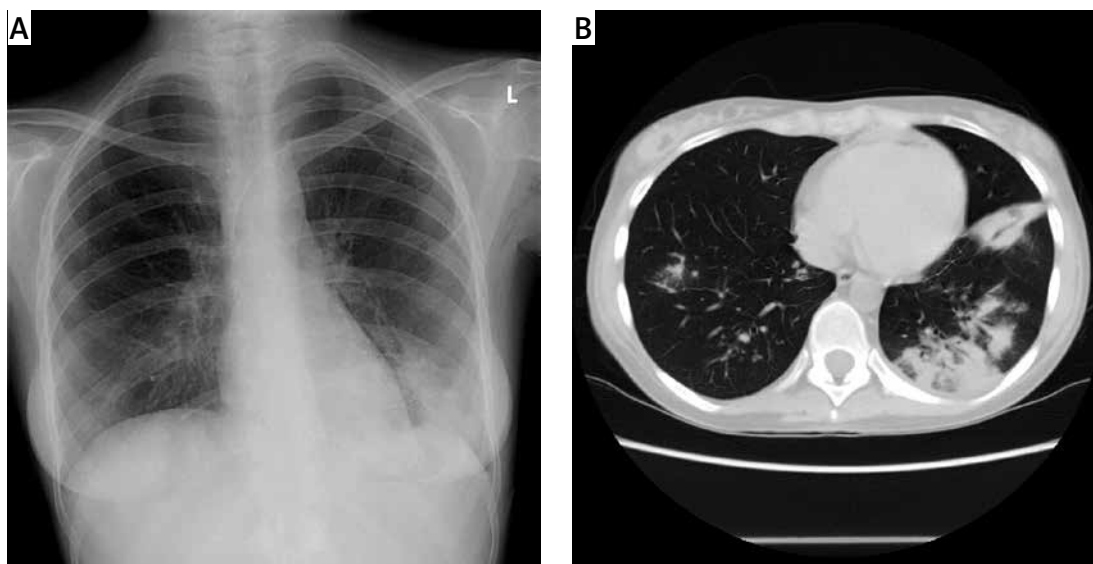
Figure 3. Chest X-ray of a young woman treated for CD with infliximab, showing consolidation in the left lower lobe (**A**) and a CT scan showing bilateral opacities predominantly in the left basal segments (**B**). She presented with productive cough and fever, non-responsive to empirical antibiotic treatment. The radiological picture and clinical context suggested IBD-related lung disease. Transbronchial lung biopsy was non-diagnostic and the patient refused surgical biopsy. Steroids were introduced but were withdrawn shortly after the bronchoalveolar aspirate appeared positive for *Mycobacterium tuberculosis*. Note the atypical location of TB lung infiltrations

[38, 43, 50, 74]. BAL fluid of patients with CD-related lung infiltrations shows the predominance of CD4+ over CD8+ cells, similarly to sarcoidosis [133]. Neither IBD nor sarcoidosis is a result of defects in a single major gene or chemical pathway; instead, multiple genes, each contributing a relatively minor effect, are likely to be involved. Recent findings of Fischer *et al.* [137], who investigated the association of IBD risk loci with sarcoidosis, add further evidence to the postulated common genetic basis of both disorders. In the above context, CD-related bowel inflammation may be a chronic reaction to an unknown environmental antigen (the postulated "sarcoid agent"), which enters the body through the digestive tract. A good example of a common genetic factor is a mutation (single nucleotide polymorphism, SNP) in a gene encoding for nucleotide-binding oligomerization domain containing 2 (NOD2/CARD15). NOD2 is a pattern recognition receptor (PRR), which recognizes a component of the bacterial cell wall (a muramyl dipeptide). This interaction is crucial for a control response to infection at the intestinal mucosa and to regulate autophagy [136]. The defective polymorphic variant (R702W) occurs in about 15% of CD patients, and is a risk factor of a more severe course [123]. The same functional polymorphic variant was linked to severe chronic sarcoidosis [138].

Overlapping pulmonary and intestinal symptoms in UC and WG and high incidence of various ANCA autoantibodies in IBD patients may suggest the presence of a common autoantigen.

All these possible links gain more value in view of the common ancestry of the digestive tract and tracheobronchial tree, which both originate from the primitive gut. Simultaneous involvement of the biliary duct (which also originates from the primitive gut) in the course of UC with lung and airway involvement is an additional argument for the importance of the above-mentioned relationship [19, 80].

Concluding remarks

Tracheobronchial and pulmonary lesions are relatively rare, but recently more and more frequently recognized extraintestinal manifestations of IBD. Such a possibility should always be kept in mind in the case of unusual clinical symptoms and radiological signs. The spectrum of pathological and radiological patterns is vast. First of all, infection, especially TB, and drug-related changes should be considered in the differential diagnosis. Greater awareness of possible pulmonary manifestations of IBD among both gastroenterologists and pulmonologists may enable better clinical vigilance and form a platform for future research on the common pathological pathways and mutual connections in this area of interest.

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