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Pulmonary abnormalities in inflammatory bowel disease

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Abstract

Extraintestinal manifestations of inflammatory bowel disease (IBD) is a common clinical problem affecting up to half of all IBD patients; pulmonary disease, however, ranks among less common extraintestinal manifestations of IBD. Pulmonary disease in patients with IBD is most frequently drug induced due to treatment with sulfasalazine or mesalamine leading to eosinophilic pneumonia and fibrosing alveolitis or due to treatment with methotrexate leading to pneumonitis. Recently, various opportunistic infections have been shown to be a further important cause of pulmonary abnormalities in those IBD patients who are treated with immunosuppressants such as anti TNF-α monoclonal antibodies, methotrexate, azathioprine or calcineurin antagonists. In not drug related pulmonary disease a wide spectrum of disease entities ranging from small and large airway dysfunction to obstructive and interstitial lung disorders exist. Patients with lung disorders and inflammatory bowel disease should be evaluated for drug-induced lung disease and opportunistic infections prior to considering pulmonary disease as an extraintestinal manifestation of inflammatory bowel disease.

Contents

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1. Introduction

Many patients with inflammatory bowel disease (IBD) suffer not only from bowel inflammation but also from extraintestinal manifestations such as pyoderma gangrenosum, erythema nodosum, dermatitis, aphtous stomatitis, uveitis, episcleritis, hepatitis, cholestatic liver disease, haemolytic anemia, arthritis, ankylosing spondylitis, pancreatitis, thyroiditis and pericarditis.[1–3] An association between pulmonary disease and IBD was recognized already about 40 years ago.[2] While the overall incidence of extraintestinal manifestations has been reported to range from 21% to 41%,[4] pulmonary disease in association with IBD seems to be uncommon.

The most frequent cause of pulmonary abnormalities in patients with IBD is drug-induced lung disease and more recently infectious forms of lung disease due to immunosuppression. Drug-induced lung disease occurs most often in patients treated with sulfasalazine or mesalamine leading to eosinophilic pneumonia and fibrosing alveolitis and methotrexate leading to pneumonitis.[4] Treatment with immunosuppressants such as anti TNF-α monoclonal antibodies, methotrexate, azathioprine or calcineurin antagonists (e.g. tacrolimus) can lead to various opportunistic infections. Therefore, drug-induced lung disease as well as opportunistic infections must be ruled out first before considering pulmonary abnormalities as extraintestinal manifestations.

In not drug-induced disease, a wide variety of pulmonary manifestations exist including small and large airway dysfunction.[5,6] In addition, obstructive and interstitial lung disorders have been described.[2] Case reports show a large spectrum of disease entities such as bronchial hyperresponsiveness,[7] bronchitis and bronchiectasis,[8] inflammatory tracheal stenosis,[9] interstitial pneumonitis[10] and bronchiolitis obliterans-organizing pneumonia.[11] Moreover, pulmonary abnormalities seem to be related to disease activity[12] and occur mainly years after the diagnosis of IBD, the incidence increasing with duration of disease.[13] Occasionally, pulmonary disease can precede the diagnosis of IBD.[3]

In this article we review the pulmonary manifestations which have been associated with IBD.

2. Drug related pulmonary abnormalities

Drug related pulmonary abnormalities occur due to treatment with sulfasalazine, mesalamine, corticosteroids, azathioprine, calcineurin antagonists, methotrexate or infliximab and can be divided into opportunistic pulmonary infections secondary to immunosuppression and drug-induced non-infectious lung disease (Table 1).

Both, sulfasalazine and mesalamine, can induce non-infectious lung disease which is not dose related and usually occurs after 2 to 6 months of therapy. Rarely, drug-induced lung disease already becomes apparent after a few days of treatment or years after starting treatment.[4] The most frequent pulmonary pathology reported is eosinophilic pneumonia with infiltration of lung tissue with eosinophils and eosinophilia in the peripheral blood.[14–20] Eosinophilic pleural effusions can also occur.[21,22] The second most common pulmonary pathology upon sulfasalazine or mesalamine treatment is fibrosing alveolitis, which is a potentially lethal drug reaction. A small number of patients with IBD and alveolar fibrosis have been reported in the literature.[23–30] Treatment with corticosteroids and withdrawal of the drug have been shown to be successful.

Pulmonary symptoms in patients with eosinophilic pneumonia or fibrosing alveolitis are non-specific, the most common symptoms being dyspnea, cough, chest pain and fever.[4] Eosinophilia was reported in about 50% of patients.[31] Diffusion capacity is reduced in most patients and infiltrates can be seen on chest X-rays. Treatment consists in drug withdrawal and therapy with corticosteroids.[4]

Azathioprine and probably also 6-mercaptopurine rarely cause interstitial pneumonitis or bronchiolitis obliterans.[32–34] However, interstitial pneumonia can also be caused by infection with *Pneumocystis jiroveci* or *Mycobacterium xenopi* although this seems to be as rare as non-infectious lung disease with only three patients reported worldwide.[35–37]

Methotrexate can lead to a potentially lethal pneumonitis.[38] Pulmonary symptoms include dyspnea, fever and cough as well as hypoxemia and tachypnea. Chest X-rays usually show diffuse interstitial or mixed interstitial and alveolar infiltrates, pulmonary function tests reveal restrictive disease. Pneumonitis due to methotrexate therapy has not been reported in patients with Crohn disease, however over

Table 1 Drug-induced pulmonary abnormalities in inflammatory bowel disease (IBD) due to treatment with sulfasalazine, mesalamine, methotrexate or infliximab

Non-infectious cause	Eosinophilic pneumonia
	Eosinophilic pleura effusion
	Fibrosing alveolitis
	Pneumonitis
Opportunistic infections	*Mycobacterium tuberculosis*
	Pneumocystis jiroveci (carinii)
	Listeria monocytogenes
	Aspergillus fumigatus
	Histoplasma capsulatum
	Coccidioides immitis
	Overwhelming infection with *Plasmodium falciparum*
	Cryptococcus neoformans
	Cytomegalovirus
	Nocardia asteroides

100 cases with this side effect of methotrexate treatment have been described in patients with rheumatoid arthritis.[38] Immunosuppression using methotrexate – similar to azathioprine – can also lead to opportunistic lung infections caused by Cytomegalovirus, *Cryptococcus*, *Nocardia*, *P. jiroveci* or *Mycobacterium tuberculosis*.[39–42] Even Ebstein–Bar-virus-induced pulmonary lymphoma have been described.[43]

Infliximab, an anti-TNF-α monoclonal antibody (mAb), is increasingly used in patients with IBD. Recent data investigating the use of infliximab in patients with rheumatoid arthritis showed an increased risk of infection.[44,45] The incidence of infections was reported to be highest within 6 months after initiation of anti-TNF-α mAb therapy. Keane et al. report 70 cases of tuberculosis in patients treated with infliximab, 31% of which had pulmonary involvement.[46] Screening for tuberculosis prior to treatment initiation is mandatory and prophylactic tuberculostatic treatment is recommended if latent infection is found and anti-TNF-α mAb therapy is the only treatment option.[47] Further infections found in patients treated with TNF blockade include *Pneumocystis jiroveci* pneumonia,[48,49] histoplasmosis due to *Histoplasma capsulatum*[50–52] and coccidioidomycosis due to *Coccidioides immitis*.[53] For diagnosis of *P. jiroveci* pneumonia bronchoscopy with broncho-alveolar lavage is necessary early in the course of the disease. The onset of symptoms of pneumonia has been described to be early after initiation of infliximab therapy with a mean of 21 days, moreover, the mortality rate has been reported to be high (27%).[49] Prophylaxis for *P. jiroveci* infection must be considered in all patients with double or triple immunosuppression as well as in those patients who have already had this infection. Importantly, also treatment with systemic corticosteroids have been reported to have more common infections with *P. jiroveci*, *Aspergillus*, and Mycobacteria.[40]

Several cases of *Listeria monocytogenes* infections associated with infliximab therapy in patients with Crohn's disease have been reported.[54,55] A further rare complication of infliximab treatment is overwhelming parasitemia with *Plasmodium falciparum*, which has been reported in one case.[56] Other infections associated with infliximab treatment include invasive aspergillosis.[57,58] Furthermore, a case of pneumonia due to *Cryptococcus neoformans* in a patient receiving infliximab has been reported.[59] Because of the

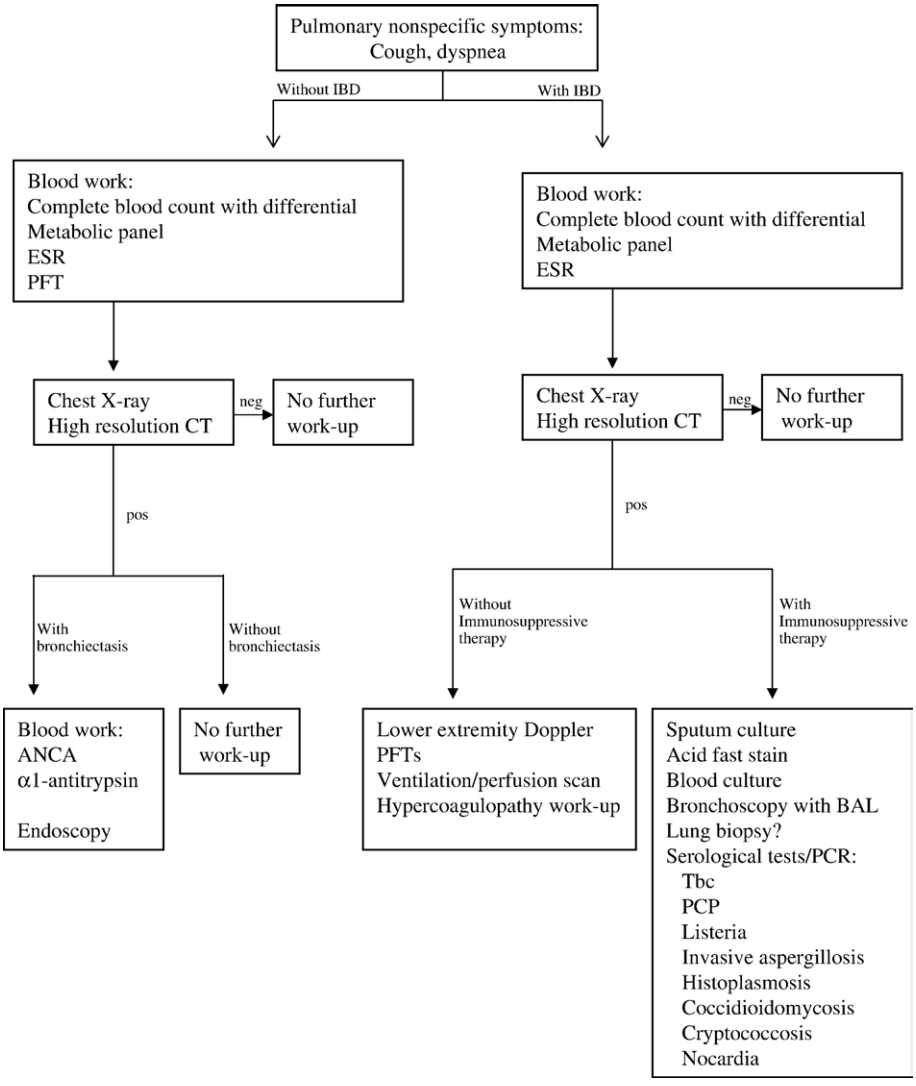

Figure 1 Flow chart for work-up of patients with pulmonary abnormalities in IBD.

multitude of case reports upon opportunistic infections in patients treated with infliximab one might think that most patients on infliximab might develop a lung infection at some point. This is clearly not the case and we can only assume at present that anti-TNF-α mAB seem to lead to a more severe immunosuppression particularly when used together with steroids and other immunosuppressants.

Cyclosporine may be used for treatment of steroid resistant ulcerative colitis. A case of *Nocardia asteroides* lung abscess in patient with ulcerative colitis treated with cyclosporine has been described.[60]

Since opportunistic infections of the lung and non-infectious pulmonary manifestations due to treatment with sulfasalzine, mesalamine or methotrexate are the most frequent cause of the pulmonary abnormalities in IBD, drug-induced lung disease and particularly opportunistic lung infections must always be ruled out first in these patients. For patients with IBD presenting with non-specific pulmonary symptoms we propose the diagnostic work up as demonstrated in Fig. 1.

3. Pulmonary abnormalities not related to drug treatment

When pulmonary abnormalities are not related to drug treatment various forms have been described in patients with IBD and in one single patient multiple sites in the lung can be involved. In this section we will discuss pulmonary function abnormalities first, thereafter various pulmonary manifestations according to their thoracic localisation (see Table 2), and finally autoimmune and other pulmonary diseases associated with IBD which cannot be classified according to their localisation.

Table 2 Pulmonary abnormalities reported in association with IBD without drug-induced disease

Pulmonary function abnormalities	Restrictive
	Obstructive
	Diffusion abnormalities
	Bronchial hyperresponsiveness
	Hyperinflation
Upper airways	Epiglotitis
	Tracheobronchitis
Large airways	Bronchiectasis
	Acute/chronic bronchitis
	Chronic bronchial suppuration
Small airways	Bronchiolitis
	Bronchiolitis obliterans
	Bronchiolitis obliterans organizing pneumonia
Interstitial disease	Nonspecific interstitial pneumonia
	Fibrosing alveolitis
	Eosinophilic pneumonia
Autoimmune disease	Wegener granulomatosis
	Pulmonary vasculitis
	Churg–Strauss syndrome
	Microscopic polyangitis
Other pulmonary manifestations	Necrobiotic nodules
	Pleuritis
	Fistulae (colobronchial, esophagopulmonary)

3.1. Pulmonary function abnormalities

Various studies testing pulmonary function in patients with IBD have revealed a spectrum of abnormalities including restrictive disease, obstructive disease, bronchial hyperresponsiveness and hyperinflation as well as a decreased diffusion capacity of the lung. There is evidence that more than 50% of patients with ulcerative colitis have pulmonary function impairment without clinical or radiologic findings.[61] Only few studies have shown no difference in pulmonary function test between patients with and without IBD[62] and obstructive pulmonary disease has also been reported in patients with ulcerative colitis as compared to control subjects.[63] More frequently a decrease in diffusion capacity of the lung has been described in patients with IBD as compared to control subjects.[64] This phenomenon has been reported to be more accentuated during periods of active disease as compared to periods of remission.[5] Herrlinger et al. also found an influence of disease activity but did not emphasize measurement of diffusion capacity as a specific marker for disease activity since values for forced expiratory volume in 1 sec and inspiratory vital capacity were also decreased during periods of active disease.[65] Studies assessing functional residual capacity in patients with Crohn disease have shown evidence of hyperinflation[66,67] and were also able to show an association between active disease and hyperinflation. Other investigations have revealed bronchial hyperresponsiveness in patients with IBD, although further studies were not able to confirm these results.[68,69]

3.2. Upper airway abnormalities

Only few studies report involvement of the upper airways in overall 15 patients with IBD.[3,4] Symptoms described in these patients include shortness of breath, cough and dysphonia. The diagnosis of upper airway stenosis can be made by radiologic examinations, pulmonary functions testing showing evidence of pulmonary obstruction and laryngoscopic examination. In all patients with upper airway involvement there was evidence of tracheal disease, but laryngeal and glottic involvement was also reported. Rickli et al. describes a case of severe inflammatory upper airway stenosis due to pseudotumorous swelling of the larynx, trachea and main bronchi.[70]

3.3. Large airway abnormalities

Bronchiectasis is the most common pulmonary disease found in IBD patients. Bronchiectasis is an irreversible dilation of bronchioles which leads to coughing and abnormal amounts of sputum. This pulmonary abnormality has been reported in up to 66% of patients with IBD and pulmonary disease.[3] The second most common large airway disease in IBD patients is chronic bronchitis, further abnormalities include suppurative large airway disease and acute bronchitis.

Though an association between IBD and bronchiectasis has been reported in various studies, the pathogenesis still remains unclear. Histological examination of bronchial and colonic tissue shows similar changes with non-specific inflammation. Butland et al. propose an autoimmune process

since most of their patients had a positive family history of autoimmune disease, positive antinuclear antibodies and anti-smooth-muscle antibodies.[71] Kirsner et al. propose that common antigens synthesize both the lung and gut associated lymphoid tissue and that this can lead to a similar inflammatory response in both.[72,73]

Therapy of pulmonary abnormalities in patients with IBD has been described in case reports. Surgery of the colon is not recommended for treatment of airway disease, however, inhaled or systemic corticosteroids are recommended as first line therapy.[2,70,74] Ineffectiveness of inhaled corticosteroids may be due to airways filled with inspissated secretions in which case either topical corticosteroids via BAL or systemic corticosteroids are recommended.[73]

3.4. Small airway abnormalities

Involvement of the small airways in patients with IBD has been detected by high-resolution computed tomography.[8] These abnormalities seem to occur earlier in the course of the disease and at a younger age than large airway disease.[75] Moreover, small airway disease is more frequently apparent before the onset of IBD than other airway diseases.[76] Bronchiolitis is the most frequently detected disease among small airway diseases.[2,75–79] Histological examination of pulmonary tissue shows peribronchiolar granuloma formation and, less frequently, peribronchiolar inflammation with neutrophils or lymphocytes and plasma cells, concentric small airway fibrosis and diffuse panbronchiolitis.[3]

Bronchiolitis obliterans organizing pneumonia (BOOP) has also been described in patients with IBD.[64,80,81] BOOP can be associated with other autoimmune diseases e.g. rheumatoid arthritis, lupus and Wegener granulomatosis. Presenting symptoms with cough and dyspnea are non-specific. Systemic steroids are recommended for treatment but BOOP may also remit without treatment in a minority of cases.[3,4]

3.5. Interstitial disease

Interstitial lung disease in patients with IBD is usually due to drug therapy with mesalamine and sulfasalzine, less common azathioprine or methotrexate. A small number of cases with interstitial lung disease have been described which were not related to drug therapy. The pathology described in these cases include nongranulomatous interstitial diffuse lung disease, mild to severe interstitial fibrosis and desquamative interstitial pneumonitis.[82–87] Patients with IBD and interstitial lung disease were treated with steroids or immunosuppressive agents such as cyclosporine and azathioprine. In one case where no response could be achieved with these drugs mycophenolate was used successfully.[88]

3.6. Autoimmune disease

A small number of cases with IBD and pulmonary vasculitis have been reported.[2,89–95] Pulmonary disease in these patients was not due to drug reactions. Symptoms with cough and dyspnea were non-specific and chest X-ray films showed bilateral infiltrates or nodules. Other entities include Churg–Strauss syndrome,[96] microscopic polyangitis and Wegener granulomatosis.[97] In most cases corticosteroids were administered for treatment. On the other hand, intestinal involvement of Wegener granulomatosis, a pulmonary vasulitis, has been reported in few cases.[98–106] Symptoms such as bloody diarrhea, abdominal pain and intestinal perforation have been described, and biopsy is essential for diagnosis.

Antineutrophil cytoplasmatic antibodies are found in many forms of vasculitis. Whereas p-ANCA is present in patients with microscopic polyarteritis and other autoimmune diseases, ANCA with a snowdrift pattern has been detected in patients with ulcerative colitis.[107,108] This points towards a common autoimmune component in both diseases.

3.7. Other pulmonary manifestations

Necrobiotic nodules are a very rare pulmonary abnormality in patients with IBD and have been reported in two cases.[109,110]

A small number of cases with pleuritis, i.e. pleural effusion, have been described in patients with IBD.[2,111–113] Symptoms in these patients, who are usually young, male and have ulcerative colitis, included dyspnea and chest pain.[3] Mostly pleural effusions are unilateral and, when examined, prove to be exudates. Treatment with corticosteroids was reported to be successful. Pericardial involvement has also been reported, and in an even smaller number of cases both pleural and pericardial involvement has been described.

Patients with Crohn disease can develop fistulae to any neighbouring structure. Patients with colobronchial fistulae and ileobronchial fistulae have been reported.[114–119] These patients present with pneumonia and pleural effusions. Sputum culture with evidence of enteric pathogens points towards the diagnosis of fistulae. Usually lung surgery is necessary for treatment. In very rare cases of esophageal involvement in patients with Crohn disease pulmonary fistulae have been reported.[120–122] In these patients surgical treatment is also necessary. When patients with Crohn disease develop chronic pneumonia and sputum culture shows enteric pathogens pulmonary fistulas can be the underlying cause.

Sarcoidosis and Crohn disease are both idiopathic granulomatous diseases which have similar ocular, dermatologic and joint manifestations in common. An increased CD4:CD8 ratio has been found in alveolar lavage from patients with sarcoidosis and in patients with Crohn disease.[123,124] These findings point towards a possible common pathogenesis of both diseases. 53 cases of patients with sarcoidosis and Crohn disease have been reported in a review of the literature of 2007.[3] Most of these cases were treated with corticosteroids, but recent reports show that treatment with infliximab (anti-TNF-α) can be successful in the treatment of Crohn disease and sarcoidosis as well.[125,126] This finding further supports a common pathogenesis of both diseases.

Alpha-1-antitrypsin deficiency leads to pulmonary emphysema and hepatic dysfunction. A small number of patients with α_1-antitrypsin deficiency and IBD have been reported,[127] and studies analysing abnormal α_1-antitrypsin alleles in patients with IBD have shown a higher prevalence of PiZ carriers among patients with IBD as compared to the general population.[128] PiZ carrier status was associated with increased severities of colitis and an effect of smoking with local tissue damage in the gastrointestinal tract via changed neutrophil elastase regulation in α_1-antitrypsin deficiency was suggested.[3]

Patients with IBD have an increased risk of thrombembolic disease. Both arterial and venous thrombosis have been described with an incidence between 1 and 8%.[129–135] Deep venous thrombosis and pulmonary emboli (see Fig. 2) have been observed in patients with IBD, but IBD itself has also been associated with a hypercoagulable state since deep venous thrombosis has been described in patients with inactive IBD. This finding points towards a thrombotic risk in patients with IBD which is not related to disease activity or therapy. However, the pathogenesis of this increased thrombotic risk in patients with IBD remains unclear. The prevalence of activated protein C resistance or factor V Leiden mutation is not higher in patients with IBD than in the general population.[131] Anticardiolipin antibody levels were shown to be elevated in patients with IBD, but seem to play no role in the pathogenesis of thromboembolic disease in this setting.[136] Hyperhomocysteinemia as a risk factor for thrombosis which can be due to genetic factors, medications such as corticosteroids, methotrexate and sulfasalazine and nutritional deficiencies has been described in patients with IBD.[137] Other laboratory markers indicating an activation of the coagulation system have been found in some patients with IBD, but the significance of these findings is not clear. An exact molecular mechanism for the hypercoagulable state in patients with IBD, however, needs further investigations.

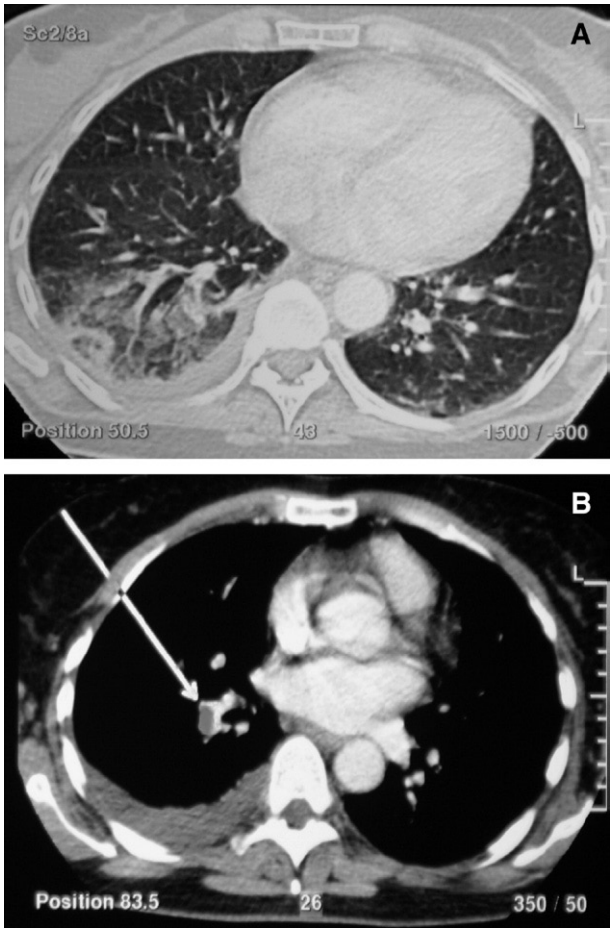

Figure 2 Thromboembolism in IBD. Shown is TC scan images of a patient with a history of ulcerative colitis presenting with a dorsolateral pneumonia (A) due to pulmonary emboli as shown in (B).

Asthma has been shown to have a higher prevalence among patients with IBD as compared to control subjects.[138] Furthermore, a more severe course of asthma has been described in patients with IBD. This was shown in a study by Kanazawa et al., where patients with ulcerative colitis and asthma had increased airway obstruction and a 20% decrease of FEV1 on metacholine challenge as compared to patients with asthma and without ulcerative colitis.[139] Increased inflammation, increased vascular endothelial growth activity and vascular permeability in patients with asthma and ulcerative colitis was proposed.

4. Conclusions

Pulmonary abnormalities in patients with inflammatory bowel disease can be divided into frequent drug related and not drug related disorders.

Drug related pulmonary abnormalities include disorders which are directly induced by sulfasalzine, mesalamine, methotrexate or rarely azathioprine and opportunistic lung infections with pulmonary manifestations due to immunosuppressive treatment with anti TNF-α monoclonal antibodies, methotrexate, azathioprine or calcineurin antagonists. In patients with IBD, screening for tuberculosis prior to treatment is mandatory and prophylactic tuberculostatic treatment is recommended if anti TNF-α monoclonal antibodies are the only treatment option. Prophylactic treatment of *P. jiroveci* must be considered in patients with double or triple immunosuppression and in those patients who have already had this infection.

Not drug related pulmonary abnormalities may be considered as true extraintestinal manifestations of inflammatory bowel disease and include a wide variety of disease entities. The most common abnormality of these is bronchiectasis.

Non-infectious lung disorders due to treatment with sulfasalazine, mesalamine or methotrexate and opportunistic infections of the lung must be ruled out first before extraintestinal manifestations of inflammatory bowel disease are considered.

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