

## Pulmonary manifestations of inflammatory bowel disease

Xiao-Qing Ji, Li-Xia Wang, De-Gan Lu

Xiao-Qing Ji, De-Gan Lu, Department of Respiratory Medicine, Shandong Provincial Qianfoshan Hospital, Jinan 250014, Shandong Province, China

Li-Xia Wang, Division of Disinfectant and Supply, Liaocheng People's Hospital, Liaocheng 252000, Shandong Province, China  
Author contributions: Ji XQ wrote the manuscript; Wang LX and Lu DG are involved in the work; all authors have read and approved the final version to be published.

Correspondence to: De-Gan Lu, MD, Professor of Medicine, Department of Respiratory Medicine, Shandong Provincial Qianfoshan Hospital, 16766 Jingshilu, Lixia District, Jinan 250014, Shandong Province, China. [deganlu@126.com](mailto:deganlu@126.com)

Telephone: +86-531-82968368 Fax: +86-531-82963647

Received: April 1, 2014 Revised: May 4, 2014

Accepted: June 13, 2014

Published online: October 7, 2014

### Abstract

Extraintestinal manifestations of inflammatory bowel disease (IBD) are a systemic illness that may affect up to half of all patients. Among the extraintestinal manifestations of IBD, those involving the lungs are relatively rare and often overlooked. However, there is a wide array of such manifestations, spanning from airway disease to lung parenchymal disease, thromboembolic disease, pleural disease, enteric-pulmonary fistulas, pulmonary function test abnormalities, and adverse drug reactions. The spectrum of IBD manifestations in the chest is broad, and the manifestations may mimic other diseases. Although infrequent, physicians dealing with IBD must be aware of these conditions, which are sometimes life-threatening, to avoid further health impairment of the patients and to alleviate their symptoms by prompt recognition and treatment. Knowledge of these manifestations in conjunction with pertinent clinical data is essential for establishing the correct diagnosis and treatment. The treatment of IBD-related respiratory disorders depends on the specific pattern of involvement, and in most patients, steroids are required in the initial management. Corticosteroids, both systemic and aerosolized, are the mainstay therapeutic approach, while antibiotics must also be administered in

the case of infectious and suppurative processes, whose sequelae sometimes require surgical intervention.

**Key words:** Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis; Lung diseases

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The clinicopathological patterns of pulmonary involvement in inflammatory bowel disease (IBD) consist of airway disease, lung parenchymal disease, thromboembolic disease, pleural diseases, enteric-pulmonary fistulas, and pulmonary function test abnormalities. The treatment of IBD-related respiratory disorders depends on the specific pattern of involvement, and in most patients, steroids are required in the initial management. This review focuses on the pulmonary manifestations of IBD in an attempt to avoid further health impairment and to alleviate symptoms by prompt recognition and treatment.

Ji XQ, Wang LX, Lu DG. Pulmonary manifestations of inflammatory bowel disease. *World J Gastroenterol* 2014; 20(37): 13501-13511 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i37/13501.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i37.13501>

### INTRODUCTION

Inflammatory bowel diseases (IBDs) are chronic inflammatory diseases of unknown etiology that commonly involve the gastrointestinal tract<sup>[1]</sup>. Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of chronic IBD. Extraintestinal and systemic manifestations occur commonly in patients with IBD (21%-41%)<sup>[2-4]</sup>, increase with duration of intestinal disease, and affect most organ systems<sup>[5]</sup>. The extraintestinal manifestations are a significant cause of morbidity and may be particularly distressing for the patient<sup>[6]</sup>. Extraintestinal manifestations are more common in CD and may include cutaneous

ous (pyoderma gangrenosum and erythema nodosum), ocular (anterior uveitis and episcleritis), hepatic (pericholangitis and fatty liver), and articular (peripheral and axial arthropathies) diseases<sup>[7]</sup>. Mouth ulcers and venous thrombosis also occur<sup>[8]</sup>. In contrast, pulmonary involvement is rare<sup>[9,10]</sup>.

A possible link between UC and respiratory disease was described first by Turner-Warwick<sup>[11]</sup> in 1968, but it was not until the work of Kraft *et al*<sup>[12]</sup> in 1976 that respiratory involvement came to be included in the list of established complications of IBD. The authors described six adult patients with IBD who developed chronic bronchial suppuration with or without bronchiectasis. Following this report, many investigators described a similar pattern, and other manifestations of pulmonary involvement were described, including: interstitial pneumonitis, panbronchiolitis, bronchiolitis obliterans organizing pneumonia (BOOP), inflammatory tracheal stenosis, serositis, pulmonary vasculitis, apical fibrosis, Langerhan's cell histiocytosis, sarcoidosis, and conditions resembling Wegener's granulomatosis<sup>[13-23]</sup>. Respiratory diseases occurring in IBD may consist merely of a subclinical abnormal lung function or, in contrast, they may manifest as clear interstitial lung disease<sup>[15]</sup>.

Pulmonary alterations are often overlooked, especially when respiratory symptoms are already present before the diagnosis of IBD. The true prevalence of lung involvement in IBD remains unknown and it seems rather variable, because in some series only a few cases of respiratory complications have been found<sup>[24]</sup>. However, it can be difficult to establish a relationship between respiratory diseases and IBD in patients who are already affected with pulmonary disease at diagnosis of IBD, or who are current smokers.

An ongoing bowel inflammation is not a prerequisite for the onset of respiratory alterations, because broncho-pulmonary diseases that develop after colectomy have been reported<sup>[25]</sup>. Pulmonary abnormalities in IBD can present years after the onset of the bowel disease and can affect any part of the lungs. These may be overt or subclinical and do not correlate with the duration of IBD. The pulmonary manifestations are variously reported as occurring frequently during active disease, independent of disease activity, and even in post-colectomy patients<sup>[26,27]</sup>.

The pathogenesis of IBD causing lung abnormalities involves some of the following mechanisms: both the colonic and respiratory epithelia share an embryonic origin from the primitive foregut and have columnar epithelia with goblet cells and submucosal mucus glands; the lungs and gastrointestinal tract contain submucosal lymphoid tissue and play crucial roles in host mucosal defense<sup>[28,29]</sup>. The similarity in the mucosal immune system causes the same pathogenic changes that may result from epithelial exposure to common antigens by inhalation and ingestion, leading to sensitization of the lymphoid tissue and inflammation<sup>[13]</sup>. The activated inflammatory cells in the bowel tissues are capable of producing several circulating cytokines such as interleukin (IL)-1, IL-2 and IL-6 and tumor necrosis factor (TNF)- $\alpha$ . These and other media-

tors can regulate the endothelial cell adhesion molecules, alter leukocyte migration, increase production of damaging reactive oxygen metabolites, and induce damage of lung parenchyma<sup>[6,30,31]</sup>.

Although pulmonary involvement is well described in the literature, the evaluation and treatment of pulmonary disease associated with IBD remain a problem. The pulmonary associations of IBD are poorly characterized and early recognition is important<sup>[32]</sup>. Here, we review the pulmonary manifestations that are associated with IBD.

## PULMONARY DISEASES ASSOCIATED WITH IBD

### Airway diseases

Airway disease from the trachea to the bronchioles has been reported in association with IBD<sup>[29,33-50]</sup>. IBD was four times more prevalent among patients with airways disease compared with published local IBD prevalence in a retrospective analysis of outpatients over a 10-year period<sup>[51]</sup>. The pathogenesis of IBD-related airway disease is unknown, but it is clearly inflammatory in nature. Severe tracheal inflammation and obstruction are rare manifestations of IBD and correspond to the presence of irregularly friable and hemorrhagic tissue at endoscopy<sup>[52]</sup>. The tracheal epithelium is often ulcerated and is replaced by a thin layer of fibrin. The main symptoms are coughing, dyspnea, stridor and hoarseness<sup>[42]</sup>. Upper airway involvement comprises glottic/subglottic stenosis, tracheal inflammation and stenosis<sup>[13,40,42,43]</sup>. Most of this rare entity involves the trachea, presenting with shortness of breath, dysphonia, and cough<sup>[45,46,53]</sup>. It can often be identified by history, complemented by a clear X-ray film and obstructive pattern on pulmonary function testing. Laryngoscopic evaluation is necessary because airway compromise can occur. The mucosa may exhibit a cobblestone appearance similar to that seen in affected intestines<sup>[54]</sup>. Chest radiographs and computed tomography (CT) may show narrowing of any portion of the trachea, with circumferential tracheal wall thickening on CT<sup>[27]</sup>. No predilection seems to exist for specific gender or type of bowel disease.

Large airway disease, strongly associated with UC<sup>[18]</sup>, is the most common presentation of pulmonary manifestations. Bronchial inflammation and suppuration are the most common manifestations of pulmonary involvement in IBD and include chronic bronchitis and bronchiectasis in which bronchial dilatation is visualized on chest X-ray or CT scan. Bronchiectasis is the most commonly reported entity and is noted in 66% of cases of IBD involving the large airways<sup>[13,34,35,39,50]</sup>. Infrequently, in IBD patients developing new, persistent and unexplained symptoms of respiratory disease, particularly chronic productive cough, the presence of bronchiectasis may be demonstrated<sup>[18]</sup>. The majority of patients with bronchiectasis have UC. IBD is inactive in many cases and curiously, in 60% of patients, the symptoms develop a few days to a few weeks following colectomy<sup>[39,42,55]</sup>. The second most common

large airway disease in IBD is chronic bronchitis, which is distinguished from bronchiectasis only by the degree and extent of pulmonary abnormality<sup>[56]</sup>, and further abnormalities include suppurative large airway disease and acute bronchitis. The main symptom is chronic cough with purulent sputum poorly responsive to antibiotics<sup>[57]</sup>. Bronchial biopsy shows similar features: squamous cell metaplasia in the mucosa that is sometimes infiltrated by neutrophils and a dense cuff of lymphocytes and plasma cells infiltrating the submucosa<sup>[8]</sup>.

Clinically, small airway disease is less frequently reported and is described as occurring in isolation from large airway disease. However, the recent advent of high-resolution CT has increased the detection of small airway involvement in these patients. These abnormalities seem to occur earlier in the course of the disease and at a younger age than large airway disease<sup>[41,47-49,58-60]</sup>. Moreover, small airway disease is more frequently apparent before the onset of IBD than other airway diseases<sup>[48]</sup>. CT shows bronchiolar wall thickening, mucoid impaction, centrilobular ground-glass nodules, and mosaic attenuation because of air trapping, and some patients have normal pulmonary function test (PFT) findings<sup>[32]</sup>.

Bronchiolitis is an inflammatory and potentially fibrosing condition affecting mainly the intralobular conducting and transitional small airways<sup>[61]</sup>. Among small airway diseases are associated with IBD, bronchiolitis is the most frequently detected<sup>[62,63]</sup>. Chronic bronchiolitis contributes to morbidity and/or mortality if it persists and/or progresses to diffuse airway narrowing and distortion or complete obliteration. Bronchiolitis in specific settings leads to bronchiolectasis, resulting in bronchiectasis. The main symptoms of bronchiolitis associated with IBD include mild productive cough and chronic bronchorrhea; wheezes are heard at auscultation. Small airway involvement can precipitate abnormalities on PFTs. Histological samples show varied patterns ranging from nonspecific fibrosing and stenosing bronchiolitis to an inflammatory lesion indistinguishable from the original description of panbronchiolitis<sup>[8]</sup>. The CT appearances coupled with the evaluation of pulmonary function parameters usually lead to the diagnosis.

In IBD-related large airways disease, steroid drugs are effective, but recommendations for their use including dosage, duration and route of administration remain empirical. Steroids are the major therapy although some patients do not require systemic therapy. Clinical improvement with inhaled steroids alone or in combination with systemic steroids has been reported<sup>[18,29,43,64]</sup>. Ineffectiveness of inhaled corticosteroids may be due to airways filled with inspissated secretions, in which case either topical corticosteroids via bronchoalveolar lavage (BAL) or systemic corticosteroids are recommended<sup>[57]</sup>. Broadly speaking, inhaled steroids seem more effective and are better tolerated than oral steroids. Rarely, other forms of immunomodulation have been used to treat IBD-related airway disease<sup>[65]</sup>. Small airway disease is usually refractory to inhaled steroids, and the improvement brought about by oral steroids ranges from slight to modest<sup>[8]</sup>. Lung

transplantation has been required in some cases. Surgery of the colon, which may aggravate prior airway disease<sup>[37]</sup>, is not recommended for treatment of airway disease.

### Lung parenchymal diseases

Lung parenchymal disease associated with IBD is relatively uncommon. Analysis of diffuse lung disease in IBD patients is further confounded by documented pulmonary sequelae to various medical therapies used to treat IBD. In contrast to other extraintestinal manifestations, lung parenchymal disease associated with IBD is seen more commonly with UC than CD<sup>[8]</sup>. Age of onset varies, and there is a slight female predominance.

BOOP is the most commonly reported parenchymal manifestation of IBD<sup>[63,66-69]</sup>. BOOP is often caused by inhalation injury, or results from a post-infection origin or drugs and may present acutely or subacutely with fever, cough, dyspnea and pleuritic chest pain<sup>[15,70,71]</sup>. Chest radiography shows focal to diffuse peripheral predominant airspace opacities. CT shows scattered, nonsegmental, unilateral, or bilateral foci of consolidation, ill-defined centrilobular nodules, and large irregular nodules. It can be associated with other autoimmune diseases such as rheumatoid arthritis, lupus and Wegener's granulomatosis. Dyspnea and cough are the most common presenting symptoms. Systemic steroids are recommended for treatment but BOOP may also remit without treatment in a minority of cases<sup>[13]</sup>.

Other forms of parenchymal disease that may be related to IBD or drug toxicity are eosinophilic pneumonia and nonspecific interstitial pneumonitis. Although interstitial disease most commonly involves drug-induced reactions with mesalamine and sulfasalazine, a small number of unrelated cases of fibrosing alveolitis and eosinophilic pneumonia have been reported<sup>[72-77]</sup>. On CT, peripheral consolidation predominates in cases of eosinophilic pneumonia, whereas nonspecific interstitial pneumonitis shows ground-glass opacities, interlobular septal thickening, and irregular linear opacities<sup>[78]</sup>. The interstitial lung infiltrates have been proven histologically to be either pulmonary vasculitis<sup>[79-81]</sup> or more often granulomatous disease<sup>[82-85]</sup>.

Pulmonary nodules have been infrequently reported in patients with IBD. Histologically, these lesions have been reported to be necrobiotic, granulomatous, or otherwise<sup>[86]</sup>. Necrobiotic nodules, composed of sterile aggregates of neutrophils with necrosis, may also be seen in rheumatoid arthritis, Wegener's granulomatosis, or septic pulmonary emboli, and should be differentiated from malignancy and infection. An infectious origin should be excluded because necrobiotic nodules will respond to steroids but not to antibiotics. Sarcoidosis and CD are both granulomatous diseases, of the lung and bowel, respectively. It is not surprising that these two diseases may simultaneously appear in the same patient, with pulmonary involvement<sup>[87]</sup>, even though this happens rarely and the two diseases usually follow an independent clinical course<sup>[88]</sup>. An infectious cause, specifically atypical *Mycobacterium* has been postulated to contribute to granuloma

formation in both sarcoidosis and CD, and has even been detected in tissues from patients with both diseases<sup>[89]</sup>.

The manifestations of lung parenchymal disease in IBD usually respond dramatically to inhaled and/or systemic steroids. Steroids administered orally lead to marked improvement in patients with interstitial lung disease, BOOP, pulmonary infiltrates with eosinophilia, and necrotic nodules. Intravenous steroids are required in the initial management of life-threatening complications such as extensive interstitial lung disease. The addition of cyclophosphamide or infliximab may show rapid clinical and radiological response and are well tolerated in some cases<sup>[90,91]</sup>.

### Thromboembolic diseases

IBD is a chronic inflammatory condition, characterized by microvascular and macrovascular involvement. Inflammation and immune response could lead to endothelial dysfunction, which is the earliest stage of the atherosclerotic process<sup>[92]</sup>. Chronically inflamed intestinal microvessels of IBD patients have demonstrated significant alterations in their physiology and function compared with vessels from healthy and uninvolved IBD intestine<sup>[93]</sup>. Thromboembolism is an extraintestinal manifestation and an important cause of mortality in IBD<sup>[94]</sup>. The incidence of thromboembolic events in IBD patients is three to four times higher than in age-matched control subjects<sup>[95,96]</sup>. It happens at an earlier age than in non-IBD patients. The majority of thromboembolic events among IBD patients are venous thromboembolism, manifested as either deep venous thrombosis or pulmonary embolism, but arterial thromboembolism and venous thrombosis at unusual sites have also been reported<sup>[97]</sup>. Prothrombotic risk factors in IBD patients could be distinguished as acquired, such as active inflammation, immobility, surgery, steroid therapy, and use of central venous catheters, and inherited<sup>[93]</sup>.

The risk of thromboembolism appears to be multifactorial and related to mucosal inflammatory activity in most patients. Pulmonary embolism should be always considered in IBD patients with breathing difficulties. However, the diagnosis of venous and arterial thromboembolism is extremely challenging and requires a high degree of vigilance. Deep vein thrombosis and pulmonary embolism may be clinically silent or manifest with only a few specific symptoms. Up to one-third of thromboembolic events in this population occur while IBD is quiescent, suggesting an unknown risk factor that is unrelated to treatment or disease activity<sup>[13]</sup>. The pathogenesis of increased thrombotic risk among patients with IBD is unclear. About 80% of IBD patients have active disease when pulmonary embolism occurs<sup>[98]</sup>. Early diagnosis plays a central role in optimizing the therapeutic intervention and reducing the risk of short-term and long-term thrombosis-associated complications. The decision regarding the duration of systemic anticoagulation must take into account the individual risk of intestinal bleeding<sup>[99]</sup>.

### Pleural diseases

Rarely, IBD involves the pleural space and pericardium,

causing inflammatory exudative pleural and/or pericardial effusions<sup>[100,101]</sup>. This is a relatively rare presentation of the uncommon and probably under-reported and under-recognized pulmonary extraintestinal manifestations of IBD<sup>[102]</sup>. Pleuropericardial inflammatory disease and effusion can be directly related to IBD, its complications, associated infections, or the medications used to treat it<sup>[103]</sup>. Most patients are young, male, and have UC during the quiescent phase of the disease. The manifestations of pleural disease can be classified as: pneumothorax<sup>[104]</sup>, pleural thickening<sup>[105]</sup>, pleuritis, and pleural effusion<sup>[106]</sup>. Pleural fluid directly related to IBD is usually unilateral, an exudate with neutrophils, and may be hemorrhagic. Mesalazine may also induce lupus-like symptoms, such as arthralgia, pericarditis, tamponade, and/or pleural effusion, with positive antinuclear antibody<sup>[107]</sup>. It is important to evaluate pleural effusion and rule out other etiologies before making this diagnosis. Pleural or pericardial biopsies are rarely necessary, and probably show nonspecific acute and chronic inflammatory changes<sup>[103]</sup>. Although the specific pathophysiology of pleuropericardial disease in patients with IBD remains unclear, the response to systemic steroids is usually adequate. However, pleural drainage may be required occasionally.

### Enteric-pulmonary fistulas

Fistula formation is frequent in CD and occurs in 33% of patients<sup>[107]</sup>. Most of the fistulas appear in the perineal area<sup>[108]</sup>; to date, only a few reports (mostly as single cases) are available on the occurrence of enteric-pulmonary fistulas in IBD, such as colobronchial<sup>[109-112]</sup>, ileobronchial<sup>[113]</sup>, and esophagobronchial<sup>[114,115]</sup> fistulas. In most cases, colobronchial fistulas extend from the splenic flexure in the colon to the lower lobe of the left lung. This is likely due to the anatomical proximity between the two structures. However, Mercadal *et al.*<sup>[116]</sup> reported a rare case of right-sided colobronchial fistula in a 47-year-old, severely malnourished man with a history of regional enteritis and recurrent right lower and middle lobe pneumonia, medically managed with the addition of the immunomodulator infliximab prior to surgery.

Diagnosis of fecopneumothorax is based on meticulous clinical examination and additional diagnostic procedures. Recurrent pneumonia with feculent sputum in patients with CD should raise suspicion of colobronchial fistula. Once the abnormal connections between the bowel and respiratory tract are suspected, an enema using water-soluble contrast medium certainly helps to confirm the presence of fistulas<sup>[110]</sup>. Abdominal and thoracic CT scan or magnetic resonance imaging could provide additional information about the stage of the disease and exclude the presence of abscess or fluid collection in the abdominal cavity. Colopleural fistula and fecopneumothorax are rare but life-threatening complications of CD<sup>[117]</sup>. Surgical treatment is mandatory as soon as the diagnosis is established<sup>[118]</sup>.

### Pulmonary function test abnormalities

PFT abnormalities are found frequently in patients with

IBD without presence of any respiratory symptoms and lung radiograph findings<sup>[20]</sup>. IBD patients show significantly decreased lung function tests in comparison to healthy controls. In a review including over 600 patients with UC, more than 50% of patients showed abnormal PFT results when compared to healthy controls, and the decrease in diffusion capacity of the lung for carbon monoxide (DLCO) was the most common defect<sup>[15]</sup>. 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<sup>[119-133]</sup>. The severity and frequency of these PFT abnormalities that are detected even in the remission periods increase with disease activity. There is no difference between UC and CD in PFTs<sup>[51]</sup>, and smoking status is not predictive of these abnormalities.

The most commonly described abnormality is a decrease in lung diffusion capacity<sup>[66]</sup>. In most studies, this alteration could not be predicted by current or past smoking status, occupational history, or current medication use. Lung transfer factor for carbon monoxide abnormalities is related to the degree of disease activity<sup>[122]</sup>. Pulmonary involvement in IBD is often asymptomatic and detectable only at the time of lung function investigation. This is further supported by the finding of Wallaert *et al.*<sup>[134]</sup> of a high proportion of latent lymphocytic pulmonary alveolitis in the BAL of 18 consecutive patients with CD; all free from respiratory symptoms and showing normal chest X-ray. Therefore, PFT may be used as a noninvasive diagnostic procedure in determining the activation of IBD and might aid early diagnosis of latent respiratory involvement<sup>[135]</sup>. Early recognition is important, because PFT abnormalities can be steroid responsive<sup>[136]</sup>.

PFT studies in IBD suggest that subclinical pulmonary disease may be present in a large subpopulation of patients. A high degree of suspicion is necessary to detect the pulmonary abnormalities in IBD, because a large proportion of symptom-free patients have abnormal findings on pulmonary function testing. Although the mechanism of these abnormalities remains unclear, it may be a result of the increased capacity of alveolar macrophages to produce superoxide anions, which has been shown in some patients with CD<sup>[137]</sup>.

## DRUG-RELATED LUNG DISEASES

Although drug-related diseases are not “proper” IBD-associated diseases, because IBD patients use several drugs for prolonged periods of time, it is not surprising that some of these may also cause problems to the lungs. Therefore, this type of pathology must be kept in mind for patients taking azathioprine (AZA), 6-mercaptopurine (6-MP), sulfasalazine, mesalamine, methotrexate, and anti-TNF- $\alpha$ .

### AZA and 6-MP

AZA and 6-MP are therapeutic options for patients with moderate to severe IBD<sup>[138]</sup>. However, between 10% and

29% of patients treated with these drugs are forced to stop therapy due to side effects. Pulmonary toxicity due to these drugs has been reported infrequently in the literature, although interstitial pneumonitis<sup>[139]</sup>, BOOP<sup>[140]</sup>, chronic pneumonitis/fibrosis and pulmonary edema<sup>[141]</sup> have been described after use of AZA and 6-MP. Although rare, AZA and 6-MP can cause direct, dose-dependent and serious pulmonary toxicity<sup>[140,142]</sup>. The largest number of cases of lung toxicity related to AZA was described in seven patients undergoing renal allograft transplant immunosuppression with AZA<sup>[142]</sup>. Lung biopsies revealed interstitial pneumonitis in 5 patients and diffuse alveolar damage in 2; 3 patients died and the other 4 improved after stopping AZA, and in 2 of these patients, cyclophosphamide therapy was needed to resolve this side effect completely. Thus, it is important for clinicians to have a high index of suspicion for this adverse reaction, which occurs within 1 mo after purine analog use in IBD.

### Sulfasalazine and mesalamine

Sulfasalazine and mesalamine are commonly used medications for the long-term treatment of IBD, and their side effects may be dose-related or idiosyncratic and should be differentiated from the respiratory involvement occurring in IBD and due to the underlying disease, although this is challenging because they share similar pathological features<sup>[47]</sup>. Commonly reported lung pathology related to the use of these compounds is mostly due to interstitial disease<sup>[54,128,143-145]</sup>, although eosinophilic pleuritis<sup>[146]</sup>, eosinophilic pneumonia<sup>[71,147-150]</sup>, and bronchiolitis obliterans<sup>[67]</sup> have also been described. Patients present with progressive respiratory symptoms such as dyspnea, chest pain and cough, and radiographic abnormalities. Alternatively, sulfasalazine and mesalamine may induce asymptomatic lung injury more commonly than is presently suspected<sup>[151]</sup>. Although sulfasalazine or mesalamine-induced lung injury is a rare entity, its possibility should be fully considered in patients developing unexplained respiratory symptoms while on sulfasalazine or mesalamine therapy<sup>[150]</sup>. In most cases, symptoms appear after 2-6 mo of drug use, whereas in a few cases they appear after a few days or after many years. These pulmonary toxicities appear reversible after withdrawal of the drug, and in some cases, with the use of systemic corticosteroids<sup>[152,153]</sup>.

### Methotrexate

Methotrexate (MTX) may be useful in the treatment of IBD<sup>[154]</sup>, but can cause adverse effects in the lungs, which in some cases are lethal<sup>[155]</sup>. The mechanism of MTX-induced lung pathology remains unclear. A hypersensitivity reaction was suggested by lung biopsy findings: interstitial pneumonitis, granuloma formation and bronchiolitis<sup>[156]</sup>, and by BAL findings: lymphocytic alveolitis, increased eosinophils and reversed CD4/CD8 ratio<sup>[157]</sup>, together with the clinical findings of fever, peripheral eosinophilia and response to corticosteroids. MTX may also cause pneumonitis<sup>[158]</sup>, and abnormal ventilation is an early sign and should lead to further investigation<sup>[159]</sup>. The diagnosis of

MTX-induced lung disease is difficult because there are no pathognomonic findings and this condition may mimic other pulmonary diseases. The most frequent complaints include dyspnea, fever and nonproductive cough. PFTs show a restrictive picture with low CO diffusion capacity. MTX-related lung toxicity is potentially fatal, thus, regular monitoring of the status of the respiratory system in MTX-treated patients is necessary and patients should be instructed to report any new pulmonary symptoms without delay<sup>[160]</sup>. Besides supportive therapy, withdrawal of MTX seems to be a logical approach.

### Biological therapy

Biological therapy with anti-TNF drugs such as infliximab, adalimumab and certolizumab has represented a significant advance in the treatment of IBD over the past few years<sup>[161-163]</sup>. However, serious side effects do occur, necessitating careful monitoring of therapy<sup>[164]</sup>. Several associated opportunistic infections have been observed as a result of suppression of T-cell-mediated immunity; the most frequent being tuberculosis<sup>[165-167]</sup>. Physicians should be aware of the increased risk of reactivation of tuberculosis in patients treated with anti-TNF agents and regularly look for usual and unusual symptoms of tuberculosis. Moreover, the use of biological therapy has been associated with *Pneumocystis carinii* pneumonia<sup>[168]</sup>, as well as with other pulmonary infections (coccidiomycosis, histoplasmosis, aspergillosis, nocardia asteroides, actinomycosis and listeriosis)<sup>[169-173]</sup>, especially in older patients<sup>[174]</sup>.

Although infective complications are the most feared after the use of biological agents, these may induce other uncommon effects in the lung, such as acute respiratory distress syndrome<sup>[175]</sup>, diffuse alveolar hemorrhage<sup>[176]</sup>, non-bronchiolitis inflammatory nodular pattern of the lung<sup>[177]</sup>, and interstitial lung disease<sup>[178-180]</sup>. Close observation of patients undergoing treatment with TNF inhibitors for evolving signs and symptoms of autoimmunity is required. Organ involvement is unpredictable, which makes correct diagnosis and management extremely challenging.

### CONCLUSION

Pulmonary manifestations of IBD are being increasingly recognized. The involvement of the respiratory system in IBD, which can range from a simple defect of pulmonary function without symptoms, to fibrosing alveolitis with a greater risk of mortality, is relatively rare but sometimes potentially harmful. Early identification of latent pulmonary involvement is important to prevent future and more severe respiratory impairment and can be life-saving. The manifestations in the lung vary and often represent a confounding diagnostic problem. It is imperative for clinicians to maintain a high index of suspicion for the development of pulmonary disease in the setting of IBD in order to institute appropriate treatment early and avoid further complications and morbidity in IBD patients, and to recognize prompt treatment for these events. Steroids are effective in the majority of cases.

### REFERENCES

- 1 Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine* (Baltimore) 1976; **55**: 401-412 [PMID: 957999]
- 2 Rankin GB. Extraintestinal and systemic manifestations of inflammatory bowel disease. *Med Clin North Am* 1990; **74**: 39-50 [PMID: 2404180]
- 3 Su CG, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; **31**: 307-327 [PMID: 12122740 DOI: 10.1016/S0889-8553(01)00019-X]
- 4 Rankin GB, Watts HD, Melnyk CS, Kelley ML. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. *Gastroenterology* 1979; **77**: 914-920 [PMID: 467943]
- 5 Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. *Ann Med* 2010; **42**: 97-114 [PMID: 20166813 DOI: 10.3109/07853890903559724]
- 6 Williams H, Walker D, Orchard TR. Extraintestinal manifestations of inflammatory bowel disease. *Curr Gastroenterol Rep* 2008; **10**: 597-605 [PMID: 19006617 DOI: 10.1007/s11894-008-0108-6]
- 7 Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. *J Clin Gastroenterol* 1996; **23**: 29-34 [PMID: 8835896 DOI: 10.1097/00004836-199607000-00009]
- 8 Camus P, Piard F, Ashcroft T, Gal AA, Colby TV. The lung in inflammatory bowel disease. *Medicine* (Baltimore) 1993; **72**: 151-183 [PMID: 8502168 DOI: 10.1097/00005792-199372030-00003]
- 9 Loftus EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; **126**: 1504-1517 [PMID: 15168363 DOI: 10.1053/j.gastro.2004.01.063]
- 10 Hoffmann RM, Kruis W. Rare extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 140-147 [PMID: 15168815 DOI: 10.1097/00054725-200403000-00013]
- 11 Turner-Warwick M. Fibrosing alveolitis and chronic liver disease. *Q J Med* 1968; **37**: 133-149 [PMID: 4872529]
- 12 Kraft SC, Earle RH, Roesler M, Esterly JR. Unexplained bronchopulmonary disease with inflammatory bowel disease. *Arch Intern Med* 1976; **136**: 454-459 [PMID: 1267553 DOI: 10.1001/archinte.136.4.454]
- 13 Black H, Mendoza M, Murin S. Thoracic manifestations of inflammatory bowel disease. *Chest* 2007; **131**: 524-532 [PMID: 17296657]
- 14 Tzanakis NE, Tsiligianni IG, Sifakas NM. Pulmonary involvement and allergic disorders in inflammatory bowel disease. *World J Gastroenterol* 2010; **16**: 299-305 [PMID: 20082474 DOI: 10.3748/wjg.v16.i3.299]
- 15 Storch J, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2003; **9**: 104-115 [PMID: 12769444 DOI: 10.1097/00054725-200303000-00004]
- 16 Casey MB, Tazelaar HD, Myers JL, Hunninghake GW, Kakar S, Kalra SX, Ashton R, Colby TV. Noninfectious lung pathology in patients with Crohn's disease. *Am J Surg Pathol* 2003; **27**: 213-219 [PMID: 12548168 DOI: 10.1097/00000478-200302000-00010]
- 17 Camus P, Colby TV. The lung in inflammatory bowel disease. *Eur Respir J* 2000; **15**: 5-10 [PMID: 10678613 DOI: 10.1183/09031936.00.15100500]
- 18 Spira A, Grossman R, Balter M. Large airway disease associated with inflammatory bowel disease. *Chest* 1998; **113**: 1723-1726 [PMID: 9631822 DOI: 10.1378/chest.113.6.1723]
- 19 Douglas JG, McDonald CF, Leslie MJ, Gillon J, Crompton GK, McHardy GJ. Respiratory impairment in inflamma-

- tory bowel disease: does it vary with disease activity? *Respir Med* 1989; **83**: 389-394 [PMID: 2616823 DOI: 10.1016/S0954-6111(89)80070-8]
- 20 **Kuzela L**, Vavrecka A, Prikazska M, Drugda B, Hronec J, Senkova A, Drugdova M, Oltman M, Novotna T, Brezina M, Kratky A, Kristufek P. Pulmonary complications in patients with inflammatory bowel disease. *Hepatogastroenterology* 1999; **46**: 1714-1719 [PMID: 10430329]
- 21 **Marvisi M**, Bassi E, Civardi G. Pulmonary involvement in inflammatory bowel disease. *Curr Drug Targets Inflamm Allergy* 2004; **3**: 437-439 [PMID: 15584891 DOI: 10.2174/1568010042634514]
- 22 **Calder CJ**, Lacy D, Raafat F, Weller PH, Booth IW. Crohn's disease with pulmonary involvement in a 3 year old boy. *Gut* 1993; **34**: 1636-1638 [PMID: 8244155 DOI: 10.1136/gut.34.11.1636]
- 23 **Betancourt SL**, Palacio D, Jimenez CA, Martinez S, Marom EM. Thoracic manifestations of inflammatory bowel disease. *AJR Am J Roentgenol* 2011; **197**: W452-W456 [PMID: 21862772 DOI: 10.2214/AJR.10.5353]
- 24 **Rogers BH**, Clark LM, Kirsner JB. The epidemiologic and demographic characteristics of inflammatory bowel disease: an analysis of a computerized file of 1400 patients. *J Chronic Dis* 1971; **24**: 743-773 [PMID: 5146188 DOI: 10.1016/0021-9681(71)90087-7]
- 25 **Weatherhead M**, Masson S, Bourke SJ, Gunn MC, Burns GP. Interstitial pneumonitis after infliximab therapy for Crohn's disease. *Inflamm Bowel Dis* 2006; **12**: 427-428 [PMID: 16670533]
- 26 **Rothfuss KS**, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. *World J Gastroenterol* 2006; **12**: 4819-4831 [PMID: 16937463]
- 27 **Songür N**, Songür Y, Tüzün M, Doğan I, Tüzün D, Ensari A, Hekimoglu B. Pulmonary function tests and high-resolution CT in the detection of pulmonary involvement in inflammatory bowel disease. *J Clin Gastroenterol* 2003; **37**: 292-298 [PMID: 14506385]
- 28 **van Lierop PP**, Samsom JN, Escher JC, Nieuwenhuis EE. Role of the innate immune system in the pathogenesis of inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2009; **48**: 142-151 [PMID: 19179875 DOI: 10.1097/MPG.0b013e3181821964]
- 29 **Higenbottam T**, Cochrane GM, Clark TJ, Turner D, Millis R, Seymour W. Bronchial disease in ulcerative colitis. *Thorax* 1980; **35**: 581-585 [PMID: 7444824 DOI: 10.1136/thx.35.8.581]
- 30 **Marvisi M**, Fornasari G. [Is the lung a target organ in inflammatory bowel disease?]. *Recenti Prog Med* 2001; **92**: 774-777 [PMID: 11822102]
- 31 **MacDermott RP**, Schloemann SR, Bertovich MJ, Nash GS, Peters M, Stenson WF. Inhibition of antibody secretion by 5-aminosalicylic acid. *Gastroenterology* 1989; **96**: 442-448 [PMID: 2562949]
- 32 **Mahadeva R**, Walsh G, Flower CD, Shneerson JM. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. *Eur Respir J* 2000; **15**: 41-48 [PMID: 10678619 DOI: 10.1183/09031936.00.15104100]
- 33 **Butland RJ**, Cole P, Citron KM, Turner-Warwick M. Chronic bronchial suppuration and inflammatory bowel disease. *Q J Med* 1981; **50**: 63-75 [PMID: 7267968]
- 34 **Gibb WR**, Dhillon DP, Zilkha KJ, Cole PJ. Bronchiectasis with ulcerative colitis and myelopathy. *Thorax* 1987; **42**: 155-156 [PMID: 3433242 DOI: 10.1136/thx.42.2.155]
- 35 **Pang JA**, Vicary FR. Carcinoma of the colon, sclerosing cholangitis, pericholangitis, and bronchiectasis in a patient with chronic ulcerative colitis. *J Clin Gastroenterol* 1984; **6**: 361-363 [PMID: 6481120]
- 36 **Moles KW**, Varghese G, Hayes JR. Pulmonary involvement in ulcerative colitis. *Br J Dis Chest* 1988; **82**: 79-83 [PMID: 3048360 DOI: 10.1016/0007-0971(88)90012-5]
- 37 **Gionchetti P**, Schiavina M, Campieri M, Fabiani A, Cornia BM, Belluzzi A, Brignola C, Iannone P, Miglioli M, Barbara L. Bronchopulmonary involvement in ulcerative colitis. *J Clin Gastroenterol* 1990; **12**: 647-650 [PMID: 2266241 DOI: 10.1097/00004836-199012000-00010]
- 38 **Lamblin C**, Copin MC, Billaut C, Marti R, Tacq V, Riviere O, Wallaert B. Acute respiratory failure due to tracheobronchial involvement in Crohn's disease. *Eur Respir J* 1996; **9**: 2176-2178 [PMID: 8902486 DOI: 10.1183/09031936.96.09102176]
- 39 **Eaton TE**, Lambie N, Wells AU. Bronchiectasis following colectomy for Crohn's disease. *Thorax* 1998; **53**: 529-531 [PMID: 9713458 DOI: 10.1136/thx.53.6.529]
- 40 **Garg K**, Lynch DA, Newell JD. Inflammatory airways disease in ulcerative colitis: CT and high-resolution CT features. *J Thorac Imaging* 1993; **8**: 159-163 [PMID: 8315712 DOI: 10.1097/00005382-199321000-00010]
- 41 **Wilcox P**, Miller R, Miller G, Heath J, Nelems B, Muller N, Ostrow D. Airway involvement in ulcerative colitis. *Chest* 1987; **92**: 18-22 [PMID: 3595232 DOI: 10.1378/chest.92.1.18]
- 42 **Vasishta S**, Wood JB, McGinty F. Ulcerative tracheobronchitis years after colectomy for ulcerative colitis. *Chest* 1994; **106**: 1279-1281 [PMID: 7924516 DOI: 10.1378/chest.106.4.1279]
- 43 **Rickli H**, Fretz C, Hoffman M, Walser A, Knoblauch A. Severe inflammatory upper airway stenosis in ulcerative colitis. *Eur Respir J* 1994; **7**: 1899-1902 [PMID: 7828702 DOI: 10.1183/09031936.94.07101899]
- 44 **Kuzniar T**, Sleiman C, Brugière O, Groussard O, Mal H, Mellot F, Pariente R, Malolepszy J, Fournier M. Severe tracheobronchial stenosis in a patient with Crohn's disease. *Eur Respir J* 2000; **15**: 209-212 [PMID: 10678648]
- 45 **Shad JA**, Sharieff GQ. Tracheobronchitis as an initial presentation of ulcerative colitis. *J Clin Gastroenterol* 2001; **33**: 161-163 [PMID: 11468448 DOI: 10.1097/00004836-200108000-00016]
- 46 **Lemann M**, Messing B, D'Agay F, Modigliani R. Crohn's disease with respiratory tract involvement. *Gut* 1987; **28**: 1669-1672 [PMID: 3428695 DOI: 10.1136/gut.28.12.1669]
- 47 **Vandenplas O**, Casel S, Delos M, Trigaux JP, Melange M, Marchand E. Granulomatous bronchiolitis associated with Crohn's disease. *Am J Respir Crit Care Med* 1998; **158**: 1676-1679 [PMID: 9817724 DOI: 10.1164/ajrccm.158.5.9801070]
- 48 **Desai SJ**, Gephardt GN, Stoller JK. Diffuse panbronchiolitis preceding ulcerative colitis. *Chest* 1989; **95**: 1342-1344 [PMID: 2721273 DOI: 10.1378/chest.95.6.1342]
- 49 **Hilling GA**, Robertson DA, Chalmers AH, Rigby HS. Unusual pulmonary complication of ulcerative colitis with a rapid response to corticosteroids: case report. *Gut* 1994; **35**: 847-848 [PMID: 8020818 DOI: 10.1136/gut.35.6.847]
- 50 **Shneerson JM**. Lung bullae, bronchiectasis, and Hashimoto's disease associated with ulcerative colitis treated by colectomy. *Thorax* 1981; **36**: 313-314 [PMID: 6895127 DOI: 10.1136/thx.36.4.313]
- 51 **Raj AA**, Birring SS, Green R, Grant A, de Caestecker J, Pavord ID. Prevalence of inflammatory bowel disease in patients with airways disease. *Respir Med* 2008; **102**: 780-785 [PMID: 18321696 DOI: 10.1016/j.rmed.2007.08.014]
- 52 **Karasalihoğlu A**, Kutlu K, Yilmaz T. Laryngotracheal obstruction in ulcerative colitis (apropos of a case). *Rev Laryngol Otol Rhinol (Bord)* 1988; **109**: 469-471 [PMID: 3073480]
- 53 **Janssen WJ**, Bierig LN, Beuther DA, Miller YE. Stridor in a 47-year-old man with inflammatory bowel disease. *Chest* 2006; **129**: 1100-1106 [PMID: 16608963 DOI: 10.1378/chest.129.4.1100]
- 54 **Foster RA**, Zander DS, Mergo PJ, Valentine JF. Mesalamine-related lung disease: clinical, radiographic, and pathologic manifestations. *Inflamm Bowel Dis* 2003; **9**: 308-315 [PMID: 14555914 DOI: 10.1097/00054725-200309000-00004]
- 55 **Alcázar Navarrete B**, Quiles Ruiz-Rico N, González Vargas F, Cabrera Torres L. [Bronchiectasis following colectomy in a

- patient with ulcerative colitis and factor V Leiden mutation]. *Arch Bronconeumol* 2005; **41**: 230-232 [PMID: 15826533 DOI: 10.1016/S1579-2129(06)60428-X]
- 56 **Basseri B**, Enayati P, Marchevsky A, Papadakis KA. Pulmonary manifestations of inflammatory bowel disease: case presentations and review. *J Crohns Colitis* 2010; **4**: 390-397 [PMID: 21122534 DOI: 10.1016/j.crohns.2010.03.008]
- 57 **Cohen M**, Sahn SA. Bronchiectasis in systemic diseases. *Chest* 1999; **116**: 1063-1074 [PMID: 10531174]
- 58 **Ward H**, Fisher KL, Waghray R, Wright JL, Card SE, Cockcroft DW. Constrictive bronchiolitis and ulcerative colitis. *Can Respir J* 1999; **6**: 197-200 [PMID: 10322103]
- 59 **Veloso FT**, Rodrigues H, Aguiar MM. Bronchiolitis obliterans in ulcerative colitis. *J Clin Gastroenterol* 1994; **19**: 339-341 [PMID: 7876520 DOI: 10.1097/00004836-199412000-00019]
- 60 **Bentur L**, Lachter J, Koren I, Ben-Izhak O, Lavy A, Bentur Y, Rosenthal E. Severe pulmonary disease in association with Crohn's disease in a 13-year-old girl. *Pediatr Pulmonol* 2000; **29**: 151-154 [PMID: 10639206]
- 61 **Papiris SA**, Malagari K, Manali ED, Kolilekas L, Triantafyllidou C, Baou K, Rontogianni D, Bouros D, Kagouridis K. Bronchiolitis: adopting a unifying definition and a comprehensive etiological classification. *Expert Rev Respir Med* 2013; **7**: 289-306 [PMID: 23734650 DOI: 10.1586/ers.13.21]
- 62 **Serrano J**, Plaza V, Franquet T, Giménez A, Rubio J. [Bronchiolitis associated with ulcerative colitis]. *Arch Bronconeumol* 1996; **32**: 151-154 [PMID: 8634796]
- 63 **Kubota Y**, Hosogi S, Iwasaki Y. [A case of Crohn's disease with broncho-bronchiolitis]. *Nihon Kokyuki Gakkai Zasshi* 2004; **42**: 655-659 [PMID: 15357269]
- 64 **Trow TK**, Morris DG, Miller CR, Homer RJ. Granulomatous bronchiolitis of Crohn's disease successfully treated with inhaled budesonide. *Thorax* 2009; **64**: 546-547 [PMID: 19478123 DOI: 10.1136/thx.2008.107185]
- 65 **Alrashid AI**, Brown RD, Mihalov ML, Sekosan M, Pastika BJ, Venu RP. Crohn's disease involving the lung: resolution with infliximab. *Dig Dis Sci* 2001; **46**: 1736-1739 [PMID: 11508676]
- 66 **Heatley RV**, Thomas P, Prokipchuk EJ, Gauldie J, Sieniewicz DJ, Bienenstock J. Pulmonary function abnormalities in patients with inflammatory bowel disease. *Q J Med* 1982; **51**: 241-250 [PMID: 7146309]
- 67 **Haralambou G**, Teirstein AS, Gil J, Present DH. Bronchiolitis obliterans in a patient with ulcerative colitis receiving mesalamine. *Mt Sinai J Med* 2001; **68**: 384-388 [PMID: 11687866]
- 68 **Gil-Simón P**, Barrio Andrés J, Atienza Sánchez R, Julián Gómez L, López Represa C, Caro-Patón A. [Bronchiolitis obliterans organizing pneumonia and Crohn's disease]. *Rev Esp Enferm Dig* 2008; **100**: 175-177 [PMID: 18416645]
- 69 **Aydoğdu M**, Gürsel G, Özyilmaz E, Akyürek N, Memiş L. A case of ulcerative colitis complicated with bronchiolitis obliterans organizing pneumonia (BOOP) and air leak syndrome. *Turk J Gastroenterol* 2012; **23**: 590-595 [PMID: 23161307]
- 70 **Carratú P**, Dragonieri S, Nocerino MC, Trabucco SM, Lacedonia D, Parisi G, Resta O. A case of cryptogenic organizing pneumonia occurring in Crohn's disease. *Can Respir J* 2005; **12**: 437-439 [PMID: 16331316]
- 71 **Kim JH**, Lee JH, Koh ES, Park SW, Jang AS, Kim D, Park CS. Acute eosinophilic pneumonia related to a mesalazine suppository. *Asia Pac Allergy* 2013; **3**: 136-139 [PMID: 23667838 DOI: 10.5415/apallergy.2013.3.2.136]
- 72 **Hotermans G**, Benard A, Guenanen H, Demarcq-Delerue G, Malart T, Wallaert B. Nongranulomatous interstitial lung disease in Crohn's disease. *Eur Respir J* 1996; **9**: 380-382 [PMID: 8777981 DOI: 10.1183/09031936.96.09020380]
- 73 **Meadway J**. Ulcerative colitis, colitic spondylitis and associated apical pulmonary fibrosis. *Proc R Soc Med* 1974; **67**: 324-325 [PMID: 4835275]
- 74 **McKee AL**, Rajapaksa A, Kalish PE, Pitchumoni CS. Severe interstitial pulmonary fibrosis in a patient with chronic ulcerative colitis. *Am J Gastroenterol* 1983; **78**: 86-89 [PMID: 6130700]
- 75 **Teague WG**, Sutphen JL, Fechner RE. Desquamative interstitial pneumonitis complicating inflammatory bowel disease of childhood. *J Pediatr Gastroenterol Nutr* 1985; **4**: 663-667 [PMID: 2863342 DOI: 10.1097/00005176-198508000-00030]
- 76 **Balestra DJ**, Balestra ST, Wasson JH. Ulcerative colitis and steroid-responsive, diffuse interstitial lung disease. A trial of N = 1. *JAMA* 1988; **260**: 62-64 [PMID: 3379724 DOI: 10.1001/jama.260.1.62]
- 77 **Chikano S**, Sawada K, Ohnishi K, Fukunaga K, Tanaka J, Shimoyama T. Interstitial pneumonia accompanying ulcerative colitis. *Intern Med* 2001; **40**: 883-886 [PMID: 11579949 DOI: 10.2169/internalmedicine.40.883]
- 78 **Katzenstein AL**, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med* 1998; **157**: 1301-1315 [PMID: 9563754 DOI: 10.1164/ajrccm.157.4.9707039]
- 79 **Isenberg JI**, Goldstein H, Korn AR, Ozeran RS, Rosen V. Pulmonary vasculitis--an uncommon complication of ulcerative colitis. Report of a case. *N Engl J Med* 1968; **279**: 1376-1377 [PMID: 5697529 DOI: 10.1056/NEJM196812192792506]
- 80 **Forrest JA**, Shearman DJ. Pulmonary vasculitis and ulcerative colitis. *Am J Dig Dis* 1975; **20**: 482-486 [PMID: 1130374 DOI: 10.1007/BF01070795]
- 81 **Collins WJ**, Bendig DW, Taylor WF. Pulmonary vasculitis complicating childhood ulcerative colitis. *Gastroenterology* 1979; **77**: 1091-1093 [PMID: 582812]
- 82 **Mazer BD**, Eigen H, Gelfand EW, Brugman SM. Remission of interstitial lung disease following therapy of associated ulcerative colitis. *Pediatr Pulmonol* 1993; **15**: 55-59 [PMID: 8093553]
- 83 **Beer TW**, Edwards CW. Pulmonary nodules due to reactive systemic amyloidosis (AA) in Crohn's disease. *Thorax* 1993; **48**: 1287-1288 [PMID: 8303644 DOI: 10.1136/thx.48.12.1287]
- 84 **Puntis JW**, Tarlow MJ, Raafat F, Booth IW. Crohn's disease of the lung. *Arch Dis Child* 1990; **65**: 1270-1271 [PMID: 2248544 DOI: 10.1136/adc.65.11.1270]
- 85 **Kayser K**, Probst F, Gabius HJ, Müller KM. Are there characteristic alterations in lung tissue associated with Crohn's disease? *Pathol Res Pract* 1990; **186**: 485-490 [PMID: 2247378 DOI: 10.1016/S0344-0338(11)80468-1]
- 86 **Hardaron S**, Labrecque DR, Mitros FA, Neil GA, Goeken JA. Antineutrophil cytoplasmic antibody in inflammatory bowel and hepatobiliary diseases. High prevalence in ulcerative colitis, primary sclerosing cholangitis, and autoimmune hepatitis. *Am J Clin Pathol* 1993; **99**: 277-281 [PMID: 8447289]
- 87 **Fellermann K**, Stahl M, Dahlhoff K, Amthor M, Ludwig D, Stange EF. Crohn's disease and sarcoidosis: systemic granulomatosis? *Eur J Gastroenterol Hepatol* 1997; **9**: 1121-1124 [PMID: 9431906]
- 88 **Fries W**, Grassi SA, Leone L, Giacomini D, Galeazzi F, Naccarato R, Martin A. Association between inflammatory bowel disease and sarcoidosis. Report of two cases and review of the literature. *Scand J Gastroenterol* 1995; **30**: 1221-1223 [PMID: 9053978]
- 89 **Storch I**, Rosoff L, Katz S. Sarcoidosis and inflammatory bowel disease. *J Clin Gastroenterol* 2001; **33**: 345 [PMID: 11588558 DOI: 10.1097/00004836-200110000-00023]
- 90 **Krishnan S**, Banquet A, Newman L, Katta U, Patil A, Dozor AJ. Lung lesions in children with Crohn's disease presenting as nonresolving pneumonias and response to infliximab therapy. *Pediatrics* 2006; **117**: 1440-1443 [PMID: 16585347 DOI: 10.1542/peds.2005-1559]
- 91 **Freeman HJ**, Davis JE, Prest ME, Lawson EJ. Granulomatous bronchiolitis with necrobiotic pulmonary nodules in Crohn's disease. *Can J Gastroenterol* 2004; **18**: 687-690 [PMID: 15565210]
- 92 **Principi M**, Mastrodonato M, Scicchitano P, Gesualdo M, Sassara M, Guida P, Bucci A, Zito A, Caputo P, Albano F,

- Ierardi E, Di Leo A, Ciccone MM. Endothelial function and cardiovascular risk in active inflammatory bowel diseases. *J Crohns Colitis* 2013; **7**: e427-e433 [PMID: 23473915 DOI: 10.1016/j.crohns.2013.02.001]
- 93 **Papa A**, Scaldaferrri F, Danese S, Guglielmo S, Roberto I, Bonizzi M, Mocchi G, Felice C, Ricci C, Andrisani G, Fedeli G, Gasbarrini G, Gasbarrini A. Vascular involvement in inflammatory bowel disease: pathogenesis and clinical aspects. *Dig Dis* 2008; **26**: 149-155 [PMID: 18431065 DOI: 10.1159/000116773]
- 94 **Bernstein CN**, Nabalamba A. Hospitalization-based major comorbidity of inflammatory bowel disease in Canada. *Can J Gastroenterol* 2007; **21**: 507-511 [PMID: 17703250]
- 95 **Miehsler W**, Reinisch W, Valic E, Osterode W, Tillinger W, Feichtenschlager T, Grisar J, Machold K, Scholz S, Vogelsang H, Novacek G. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* 2004; **53**: 542-548 [PMID: 15016749 DOI: 10.1136/gut.2003.025411]
- 96 **Bernstein CN**, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thromb Haemost* 2001; **85**: 430-434 [PMID: 11307809]
- 97 **Quera R**, Shanahan F. Thromboembolism--an important manifestation of inflammatory bowel disease. *Am J Gastroenterol* 2004; **99**: 1971-1973 [PMID: 15447758 DOI: 10.1111/j.1572-0241.2004.40923.x]
- 98 **Solem CA**, Loftus EV, Tremaine WJ, Sandborn WJ. Venous thromboembolism in inflammatory bowel disease. *Am J Gastroenterol* 2004; **99**: 97-101 [PMID: 14687149 DOI: 10.1046/j.1572-0241.2003.04026.x]
- 99 **Di Fabio F**, Lykoudis P, Gordon PH. Thromboembolism in inflammatory bowel disease: an insidious association requiring a high degree of vigilance. *Semin Thromb Hemost* 2011; **37**: 220-225 [PMID: 21455856 DOI: 10.1055/s-0031-1273086]
- 100 **Faller M**, Gasser B, Massard G, Pauli G, Quoix E. Pulmonary migratory infiltrates and pachypleuritis in a patient with Crohn's disease. *Respiration* 2000; **67**: 459-463 [PMID: 10940806 DOI: 10.1159/000029550]
- 101 **Patwardhan RV**, Heilpern RJ, Brewster AC, Darrah JJ. Pleuropericarditis: an extraintestinal complication of inflammatory bowel disease. Report of three cases and review of literature. *Arch Intern Med* 1983; **143**: 94-96 [PMID: 6849612 DOI: 10.1001/archinte.1983.00350010098017]
- 102 **Orii S**, Chiba T, Nakadate I, Fujiwara T, Ito N, Ishii M, Oana S, Chida T, Kudara N, Terui T, Yamaguchi T, Suzuki K. Pleuropericarditis and disseminated intravascular coagulation in ulcerative colitis. *J Clin Gastroenterol* 2001; **32**: 251-254 [PMID: 11246357 DOI: 10.1097/00004836-200103000-00017]
- 103 **Abu-Hijleh M**, Evans S, Aswad B. Pleuropericarditis in a patient with inflammatory bowel disease: a case presentation and review of the literature. *Lung* 2010; **188**: 505-510 [PMID: 20827555 DOI: 10.1007/s00408-010-9259-y]
- 104 **Smith PA**, Crampton JR, Pritchard S, Li C. Pneumothorax as a presenting feature of granulomatous disease of the lung in a patient with Crohn's disease. *Eur J Gastroenterol Hepatol* 2009; **21**: 237-240 [PMID: 19212215]
- 105 **Desai D**, Patil S, Udawadia Z, Maheshwari S, Abraham P, Joshi A. Pulmonary manifestations in inflammatory bowel disease: a prospective study. *Indian J Gastroenterol* 2011; **30**: 225-228 [PMID: 21935713 DOI: 10.1007/s12664-011-0129-1]
- 106 **Mukhopadhyay D**, Nasr K, Grossman BJ, Kirsner JB. Pericarditis associated with inflammatory bowel disease. *JAMA* 1970; **211**: 1540-1542 [PMID: 5467054 DOI: 10.1001/jama.211.9.1540]
- 107 **Singh D**, Cole JC, Cali RL, Finical EJ, Proctor DD. Colobronchial fistula: an unusual complication of Crohn's disease. *Am J Gastroenterol* 1994; **89**: 2250-2252 [PMID: 7977257]
- 108 **Nielsen OH**, Rogler G, Hahnloser D, Thomsen OØ. Diagnosis and management of fistulizing Crohn's disease. *Nat Clin Pract Gastroenterol Hepatol* 2009; **6**: 92-106 [PMID: 19153563 DOI: 10.1038/ncpgasthep1340]
- 109 **Karmy-Jones R**, Chagpar A, Vallieres E, Hamilton S. Colobronchial fistula due to Crohn's disease. *Ann Thorac Surg* 1995; **60**: 446-448 [PMID: 7646116 DOI: 10.1016/0003-4975(95)00207-2]
- 110 **Domej W**, Kullnig P, Petritsch W, Melisch B, Schaflinger E, Smolle-Jüttner FM, Schalk V, Ratschek M. Colobronchial fistula: a rare complication of Crohn's colitis. *Am Rev Respir Dis* 1990; **142**: 1225-1227 [PMID: 2240849]
- 111 **Flueckiger F**, Kullnig P, Melzer G, Posch E. Colobronchial and gastrocolic fistulas: rare complication of Crohn's disease. *Gastrointest Radiol* 1990; **15**: 288-290 [PMID: 2210196 DOI: 10.1007/BF01888799]
- 112 **Mera A**, Sugimoto M, Fukuda K, Tanaka F, Imamura F, Matsuda M, Ando M, Shima K. Crohn's disease associated with colobronchial fistula. *Intern Med* 1996; **35**: 957-960 [PMID: 9030994 DOI: 10.2169/internalmedicine.35.957]
- 113 **Gumbo T**, Rice TW, Mawhorter S. Recurrent pneumonia from an ileobronchial fistula complicating Crohn's disease. *J Clin Gastroenterol* 2001; **32**: 365-367 [PMID: 11276288]
- 114 **Ho IK**, Guarino DP, Pertsovskiy Y, Cerulli MA. Infliximab treatment of an esophagobronchial fistula in a patient with extensive Crohn's disease of the esophagus. *J Clin Gastroenterol* 2002; **34**: 488-489 [PMID: 11907371]
- 115 **Rieder F**, Hamer O, Gelbmann C, Schölmerich J, Gross V, Feuerbach S, Herfarth H, Rogler G. Crohn's disease of the esophagus: treatment of an esophagobronchial fistula with the novel liquid embolic polymer "onyx". *Z Gastroenterol* 2006; **44**: 599-602 [PMID: 16823701 DOI: 10.1055/s-2006-926644]
- 116 **Mercadal NR**, Wiebke EA. Recurrent pneumonia and colobronchial fistula from Crohn's disease: Infliximab alters and simplifies surgical management. *Ann Gastroenterol* 2012; **25**: 361-364 [PMID: 24714263]
- 117 **Alameel T**, Maclean DA, Macdougall R. Colobronchial fistula presenting with persistent pneumonia in a patient with Crohn's disease: a case report. *Cases J* 2009; **2**: 9114 [PMID: 20062691 DOI: 10.1186/1757-1626-2-9114]
- 118 **Barisiae G**, Krivokapiae Z, Adziae T, Pavloviae A, Popoviae M, Gojniae M. Fecopneumothorax and colopleural fistula - uncommon complications of Crohn's disease. *BMC Gastroenterol* 2006; **6**: 17 [PMID: 16756646]
- 119 **Pasquis P**, Colin R, Denis P, Baptiste P, Galmiche JP, Hecketsweiler P. Transient pulmonary impairment during attacks of Crohn's disease. *Respiration* 1981; **41**: 56-59 [PMID: 7244392 DOI: 10.1159/000194359]
- 120 **Godet PG**, Cowie R, Woodman RC, Sutherland LR. Pulmonary function abnormalities in patients with ulcerative colitis. *Am J Gastroenterol* 1997; **92**: 1154-1156 [PMID: 9219789]
- 121 **Tiwary RS**, Pruthi HS, Lakhera SC, Kain TC. Pulmonary functions in ulcerative colitis. *J Assoc Physicians India* 1989; **37**: 773-774 [PMID: 2636583]
- 122 **Tzanakis N**, Bouros D, Siamiou M, Panagou P, Mouzas J, Manousos O, Siafakas N. Lung function in patients with inflammatory bowel disease. *Respir Med* 1998; **92**: 516-522 [PMID: 9692115 DOI: 10.1016/S0954-6111(98)90301-8]
- 123 **Munck A**, Murciano D, Pariente R, Cezard JP, Navarro J. Latent pulmonary function abnormalities in children with Crohn's disease. *Eur Respir J* 1995; **8**: 377-380 [PMID: 7789480 DOI: 10.1183/09031936.95.08030377]
- 124 **Eade OE**, Smith CL, Alexander JR, Whorwell PJ. Pulmonary function in patients with inflammatory bowel disease. *Am J Gastroenterol* 1980; **73**: 154-156 [PMID: 6104919]
- 125 **Louis E**, Louis R, Drion V, Bonnet P, Lamproye A, Radermecker M, Belaiche J. Increased frequency of bronchial hyperresponsiveness in patients with inflammatory bowel disease. *Allergy* 1995; **50**: 729-733 [PMID: 8546267 DOI: 10.1111/j.1398-9995.1995.tb01214.x]

- 126 **Marvisi M**, Borrello PD, Brianti M, Fornarsari G, Marani G, Guariglia A. Changes in the carbon monoxide diffusing capacity of the lung in ulcerative colitis. *Eur Respir J* 2000; **16**: 965-968 [PMID: 11153600 DOI: 10.1183/09031936.00.16596500]
- 127 **Mansi A**, Cucchiara S, Greco L, Sarnelli P, Pisanti C, Franco MT, Santamaria F. Bronchial hyperresponsiveness in children and adolescents with Crohn's disease. *Am J Respir Crit Care Med* 2000; **161**: 1051-1054 [PMID: 10712362 DOI: 10.1164/ajrccm.161.3.9906013]
- 128 **Herrlinger KR**, Nofzt MK, Dalhoff K, Ludwig D, Stange EF, Fellermann K. Alterations in pulmonary function in inflammatory bowel disease are frequent and persist during remission. *Am J Gastroenterol* 2002; **97**: 377-381 [PMID: 11866276 DOI: 10.1111/j.1572-0241.2002.05473.x]
- 129 **Welsh L**, Haller W, King LE, Soto-Martinez M, Oliver M, Catto-Smith A, Robinson PJ. Pulmonary function abnormalities in children with active Crohn's disease. *Am J Respir Crit Care Med* 2012; **186**: 1060-1061 [PMID: 23155218 DOI: 10.1164/ajrccm.186.10.1060]
- 130 **Mikhailova ZF**, Parfenov AI, Ruchkina IN, Rogozina VA. [External respiratory function in patients with Crohn's disease]. *Eksp Klin Gastroenterol* 2011; (2): 82-85 [PMID: 21560645]
- 131 **Tzanakis N**, Samiou M, Bouros D, Mouzas J, Kouroumalis E, Siafakas NM. Small airways function in patients with inflammatory bowel disease. *Am J Respir Crit Care Med* 1998; **157**: 382-386 [PMID: 9476847 DOI: 10.1164/ajrccm.157.2.97-04075]
- 132 **Neilly JB**, Main AN, McSharry C, Murray J, Russell RI, Moran F. Pulmonary abnormalities in Crohn's disease. *Respir Med* 1989; **83**: 487-491 [PMID: 2623217 DOI: 10.1016/S0954-6111(89)80132-5]
- 133 **Sommer H**, Schmidt M, Gruber KD. [Pulmonary functional disorders in ulcerative colitis and Crohn's disease]. *Dtsch Med Wochenschr* 1986; **111**: 812-815 [PMID: 3698863]
- 134 **Wallaert B**, Colombel JF, Tonnel AB, Bonniere P, Cortot A, Paris JC, Voisin C. Evidence of lymphocyte alveolitis in Crohn's disease. *Chest* 1985; **87**: 363-367 [PMID: 3971763 DOI: 10.1378/chest.87.3.363]
- 135 **Ateş F**, Karıncaoğlu M, Hacıevliyagıl SS, Yalınz M, Seçkin Y. Alterations in the pulmonary function tests of inflammatory bowel diseases. *Turk J Gastroenterol* 2011; **22**: 293-299 [PMID: 21805420]
- 136 **Mohamed-Hussein AA**, Mohamed NA, Ibrahim ME. Changes in pulmonary function in patients with ulcerative colitis. *Respir Med* 2007; **101**: 977-982 [PMID: 17049827 DOI: 10.1016/j.rmed.2006.09.005]
- 137 **Wallaert B**, Aerts C, Bonniere P, Cortot A, Tonnel AB, Paris JC, Voisin C. Superoxide anion generation by alveolar macrophages in Crohn's disease. *N Engl J Med* 1985; **312**: 444-445 [PMID: 2982094]
- 138 **Present DH**, Meltzer SJ, Krumholz MP, Wolke A, Korelitz BI. 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 1989; **111**: 641-649 [PMID: 2802419 DOI: 10.7326/0003-4819-111-8-641]
- 139 **Nagy F**, Molnar T, Makula E, Kiss I, Milassin P, Zollei E, Tiszlavicz L, Lonovics J. A case of interstitial pneumonitis in a patient with ulcerative colitis treated with azathioprine. *World J Gastroenterol* 2007; **13**: 316-319 [PMID: 17226917]
- 140 **Ananthakrishnan AN**, Attila T, Otterson MF, Lipchik RJ, Massey BT, Komorowski RA, Binion DG. Severe pulmonary toxicity after azathioprine/6-mercaptopurine initiation for the treatment of inflammatory bowel disease. *J Clin Gastroenterol* 2007; **41**: 682-688 [PMID: 17667053 DOI: 10.1097/01.mcg.0000225577.81008.ee]
- 141 **Fauroux B**, Meyer-Milsztain A, Boccon-Gibod L, Levenger G, Clément A, Biour M, Tournier G. Cytotoxic drug-induced pulmonary disease in infants and children. *Pediatr Pulmonol* 1994; **18**: 347-355 [PMID: 7892068 DOI: 10.1002/ppul.1950180602]
- 142 **Bedrossian CW**, Sussman J, Conklin RH, Kahan B. Azathioprine-associated interstitial pneumonitis. *Am J Clin Pathol* 1984; **82**: 148-154 [PMID: 6380265]
- 143 **Bitton A**, Peppercorn MA, Hanrahan JP, Upton MP. Mesalamine-induced lung toxicity. *Am J Gastroenterol* 1996; **91**: 1039-1040 [PMID: 8633548]
- 144 **Alskaf E**, Aljoudeh A, Edenborough F. Mesalazine-induced lung fibrosis. *BMJ Case Rep* 2013; **2013**: [PMID: 23576654 DOI: 10.1136/bcr-2013-008724]
- 145 **Pascual-Lledó JF**, Calvo-Bonachera J, Carrasco-Miras F, Sanchez-Martínez H. Interstitial pneumonitis due to mesalamine. *Ann Pharmacother* 1997; **31**: 499 [PMID: 9101017]
- 146 **Trisolini R**, Dore R, Biagi F, Luinetti O, Pochetti P, Carrabino N, Luisetti M. Eosinophilic pleural effusion due to mesalamine. Report of a rare occurrence. *Sarcoidosis Vasc Diffuse Lung Dis* 2000; **17**: 288-291 [PMID: 11033846]
- 147 **Saltzman K**, Rossoff LJ, Gouda H, Tongia S. Mesalamine-induced unilateral eosinophilic pneumonia. *AJR Am J Roentgenol* 2001; **177**: 257 [PMID: 11418451 DOI: 10.2214/ajr.177.1.1770257]
- 148 **Yaffe BH**, Korelitz BI. Sulfasalazine pneumonitis. *Am J Gastroenterol* 1983; **78**: 493-494 [PMID: 6136183]
- 149 **Park JE**, Hwangbo Y, Chang R, Chang YW, Jang JY, Kim BH, Dong SH, Kim HJ. [Mesalazine-induced eosinophilic pneumonia in a patient with Crohn's disease]. *Korean J Gastroenterol* 2009; **53**: 116-120 [PMID: 19237838]
- 150 **Tanigawa K**, Sugiyama K, Matsuyama H, Nakao H, Kohno K, Komuro Y, Iwanaga Y, Eguchi K, Kitaichi M, Takagi H. Mesalazine-induced eosinophilic pneumonia. *Respiration* 1999; **66**: 69-72 [PMID: 9973695 DOI: 10.1159/000029341]
- 151 **Cilloniz R**, Chesrown SE, Gonzalez-Peralta RP. Asymptomatic presentation of mesalamine-induced lung injury in an adolescent with Crohn disease. *BMJ Case Rep* 2009; **2009**: [PMID: 21686567 DOI: 10.1136/bcr.09.2008.0908]
- 152 **Sossai P**, Cappellato MG, Stefani S. Can a drug-induced pulmonary hypersensitivity reaction be dose-dependent? A case with mesalamine. *Mt Sinai J Med* 2001; **68**: 389-395 [PMID: 11687867]
- 153 **Parry SD**, Barbatzas C, Peel ET, Barton JR. Sulphasalazine and lung toxicity. *Eur Respir J* 2002; **19**: 756-764 [PMID: 11999006 DOI: 10.1183/09031936.02.00267402]
- 154 **Kozarek RA**, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med* 1989; **110**: 353-356 [PMID: 2492786 DOI: 10.7326/0003-4819-110-5-353]
- 155 **Imokawa S**, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J* 2000; **15**: 373-381 [PMID: 10706507 DOI: 10.1034/j.1399-3003.2000.15b25.x]
- 156 **Sostman HD**, Matthay RA, Putman CE, Smith GJ. Methotrexate-induced pneumonitis. *Medicine (Baltimore)* 1976; **55**: 371-388 [PMID: 957997 DOI: 10.1097/00005792-197609000-00002]
- 157 **White DA**, Rankin JA, Stover DE, Gellene RA, Gupta S. Methotrexate pneumonitis. Bronchoalveolar lavage findings suggest an immunologic disorder. *Am Rev Respir Dis* 1989; **139**: 18-21 [PMID: 2521438 DOI: 10.1164/ajrccm/139.1.18]
- 158 **Margagnoni G**, Papi V, Aratari A, Triolo L, Papi C. Methotrexate-induced pneumonitis in a patient with Crohn's disease. *J Crohns Colitis* 2010; **4**: 211-214 [PMID: 21122509 DOI: 10.1016/j.crohns.2009.11.007]
- 159 **Brechmann T**, Heyer C, Schmiegel W. [Methotrexate-induced pneumonitis in a woman with Crohn's disease]. *Dtsch Med Wochenschr* 2007; **132**: 1759-1762 [PMID: 17713885 DOI: 10.1055/s-2007-984962]
- 160 **Karoli NA**, Rebrov AP, Roshchina AA, Steshenko RN, Bukia AS. [Iatrogenic lung diseases]. *Klin Med (Mosk)* 2012; **90**: 70-72 [PMID: 22896987]
- 161 **Rutgeerts P**, Vermeire S, Van Assche G. Biological therapies

- for inflammatory bowel diseases. *Gastroenterology* 2009; **136**: 1182-1197 [PMID: 19249397 DOI: 10.1053/j.gastro.2009.02.001]
- 162 **Ghosh S.** Anti-TNF therapy in Crohn's disease. *Novartis Found Symp* 2004; **263**: 193-205; discussion 205-218 [PMID: 15669643 DOI: 10.1002/0470090480.ch14]
- 163 **Cheifetz AS.** Management of active Crohn disease. *JAMA* 2013; **309**: 2150-2158 [PMID: 23695484 DOI: 10.1001/jama.2013.4466]
- 164 **Hoentjen F, van Bodegraven AA.** Safety of anti-tumor necrosis factor therapy in inflammatory bowel disease. *World J Gastroenterol* 2009; **15**: 2067-2073 [PMID: 19418577 DOI: 10.3748/wjg.15.2067]
- 165 **Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM.** Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; **345**: 1098-1104 [PMID: 11596589 DOI: 10.1056/NEJMoa011110]
- 166 **Mayordomo L, Marengo JL, Gomez-Mateos J, Rejon E.** Pulmonary miliary tuberculosis in a patient with anti-TNF-alpha treatment. *Scand J Rheumatol* 2002; **31**: 44-45 [PMID: 11922200 DOI: 10.1080/030097402317255372]
- 167 **Milenković B, Dudvarski-Ilić A, Janković G, Martinović L, Mijac D.** Anti-TNF treatment and miliary tuberculosis in Crohn's disease. *Srp Arh Celok Lek* 2007; **139**: 514-517 [PMID: 21980664 DOI: 10.2298/SARH1108514M]
- 168 **Kaur N, Mahl TC.** Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases. *Dig Dis Sci* 2007; **52**: 1481-1484 [PMID: 17429728 DOI: 10.1007/s10620-006-9250-x]
- 169 **Colombel JF, Loftus EV, Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, Zinsmeister AR, Sandborn WJ.** The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004; **126**: 19-31 [PMID: 14699483 DOI: 10.1053/j.gastro.2003.10.047]
- 170 **Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP.** Fungal infections complicating tumor necrosis factor alpha blockade therapy. *Mayo Clin Proc* 2008; **83**: 181-194 [PMID: 18241628 DOI: 10.1016/S0025-6196(11)60839-2]
- 171 **Cohen RD, Bowie WR, Enns R, Flint J, Fitzgerald JM.** Pulmonary actinomycosis complicating infliximab therapy for Crohn's disease. *Thorax* 2007; **62**: 1013-1014 [PMID: 17965080 DOI: 10.1136/thx.2006.075150]
- 172 **Kasai S, Tokuda H, Otsuka Y, Ookohchi Y, Handa H, Emoto N, Yoshikawa M.** [Two cases of respiratory infection complicating treatment with infliximab]. *Nihon Kokyuki Gakkai Zasshi* 2007; **45**: 366-371 [PMID: 17491318]
- 173 **Stratakos G, Kalomenidis I, Papas V, Malagari K, Kollintza A, Roussos C, Anagnostopoulou M, Paniara O, Zakyntinos S, Papiris SA.** Cough and fever in a female with Crohn's disease receiving infliximab. *Eur Respir J* 2005; **26**: 354-357 [PMID: 16055885 DOI: 10.1183/09031936.05.00005205]
- 174 **Toruner M, Loftus EV, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ.** Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008; **134**: 929-936 [PMID: 18294633 DOI: 10.1053/j.gastro.2008.01.012]
- 175 **Riegert-Johnson DL, Godfrey JA, Myers JL, Hubmayr RD, Sandborn WJ, Loftus EV.** Delayed hypersensitivity reaction and acute respiratory distress syndrome following infliximab infusion. *Inflamm Bowel Dis* 2002; **8**: 186-191 [PMID: 11979139 DOI: 10.1097/00054725-200205000-00005]
- 176 **Panagi S, Palka W, Korelitz BI, Taskin M, Lessnau KD.** Diffuse alveolar hemorrhage after infliximab treatment of Crohn's disease. *Inflamm Bowel Dis* 2004; **10**: 274-277 [PMID: 15290924]
- 177 **Reid JD, Bressler B, English J.** A case of adalimumab-induced pneumonitis in a 45-year-old man with Crohn's disease. *Can Respir J* 2011; **18**: 262-264 [PMID: 21969926]
- 178 **Ostör AJ, Chilvers ER, Somerville MF, Lim AY, Lane SE, Crisp AJ, Scott DG.** Pulmonary complications of infliximab therapy in patients with rheumatoid arthritis. *J Rheumatol* 2006; **33**: 622-628 [PMID: 16511933]
- 179 **Ramos-Casals M, Brito-Zerón P, Muñoz S, Soria N, Galiana D, Bertolaccini L, Cuadrado MJ, Khamashta MA.** Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore)* 2007; **86**: 242-251 [PMID: 17632266 DOI: 10.1097/MD.0b013e3181441a68]
- 180 **Villeneuve E, St-Pierre A, Haraoui B.** Interstitial pneumonitis associated with infliximab therapy. *J Rheumatol* 2006; **33**: 1189-1193 [PMID: 16622902]

**P- Reviewer:** Ierardi E, Mendall MA **S- Editor:** Ma YJ

**L- Editor:** O'Neill M **E- Editor:** Du P





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgooffice@wjgnet.com](mailto:bpgooffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327

