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REVIEW

Pulmonary manifestations of Crohn's disease

De-Gan Lu, Xiao-Qing Ji, Xun Liu, Hong-Jia Li, Cai-Qing Zhang

De-Gan Lu, Xiao-Qing Ji, Hong-Jia Li, Cai-Qing Zhang, Department of Respiratory Medicine, Shandong Provincial Qianfoshan Hospital, Jinan 250014, Shandong Province, China
Xun Liu, Department of ENT, Central Hospital of Taian City, Taian 271000, Shandong Province, China
Author contributions: Lu DG wrote the manuscript; Ji XQ, Li HJ, Zhang CQ and Liu X are involved in the work; all authors have read and approved the final version to be published.
Correspondence to: Cai-Qing Zhang, MD, Professor, Department of Respiratory Medicine, Shandong Provincial Qianfoshan Hospital, No. 16766 Jingshi Road, Lixia District, Jinan 250014, Shandong Province, China. deganlu@126.com
Telephone: +86-531-82968368 Fax: +86-531-82963647
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Abstract

Crohn's disease (CD) is a systemic illness with a constellation of extraintestinal manifestations affecting various organs. Of these extraintestinal manifestations of CD, those involving the lung are relatively rare. However, there is a wide array of lung manifestations, ranging from subclinical alterations, airway diseases and lung parenchymal diseases to pleural diseases and drug-related diseases. The most frequent manifestation is bronchial inflammation and suppuration with or without bronchiectasis. Bronchoalveolar lavage findings show an increased percentage of neutrophils. Drug-related pulmonary abnormalities include disorders which are directly induced by sulfasalazine, mesalamine and methotrexate, and opportunistic lung infections due to immunosuppressive treatment. In most patients, the development of pulmonary disease parallels that of intestinal disease activity. Although infrequent, clinicians dealing with CD must be aware of these, sometimes life-threatening, conditions to avoid further impairment of health status and to alleviate patient symptoms by prompt recognition and treatment. The treatment of CD-related respiratory disorders depends on the specific pattern of involvement, and in most patients, steroids are required in the initial management.

Key words: Crohn's disease; Inflammatory bowel disease; Lung; Extracolonic involvement

Core tip: The clinicopathological patterns of pulmonary involvement consist of subclinical alterations, airway diseases, lung parenchymal diseases, pleural diseases and drug-related diseases in Crohn's disease (CD). The treatment of CD-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 CD in an attempt to avoid further impairment of health status and to alleviate patient symptoms by prompt recognition and treatment.

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INTRODUCTION

Crohn's disease (CD) is a granulomatous systemic disorder of unknown etiology commonly involving the gastrointestinal tract. However, CD may also have extraintestinal manifestations, which occur in at least 25% of CD patients[1]. Of these extraintestinal manifestations, arthritis, erythema nodosum, pyoderma gangrenosum, and primary sclerosing cholangitis are the most common. The lungs are not classically thought to be affected, although there is growing evidence for pulmonary involvement in CD[2-11]. CD can involve the tracheobronchial tree, the lung parenchyma and the pleura[12]. Although obvious pulmonary involvement is exceptional, latent pulmonary impairment and subclinical alveolitis as evidenced by lymphocytosis in bronchopulmonary lavage (BAL) have been

described and are well recognized[13,14].

There are a number of mechanisms by which the lungs may become involved in CD. These include the same embryological origin of the lung and gastrointestinal tract by ancestral intestine[15], similar immune systems in the pulmonary and intestinal mucosa[16], the presence of circulating immune complexes and auto-antibodies[17], and the adverse pulmonary effects of some drugs.

CD is characterized by an exaggerated immune response to the luminal flora, suggesting that deficiencies in barrier function of intestinal flora may be involved[18,19]. The epithelial layer of the intestines must meet two opposing requirements: on one hand it must allow for efficient uptake of nutrients and fluids, and on the other hand it is a vital defense barrier between the milieu interior and the milieu exterior. Airway epithelia contain a cell-autonomous system in which motile cilia both sense noxious substances entering airways and initiate a defensive mechanical mechanism to eliminate the offending compound[20]. In contrast to the lung which by virtue of ciliary movement is kept virtually sterile, the gut epithelium is confronted by a large microbiological load and a substantial xenobiotic challenge[21]. This may explain why lung involvement is quite rare in CD.

The clinicopathological patterns of pulmonary involvement consist of subclinical alterations, airway diseases, lung parenchymal diseases, pleural diseases and drug-related diseases. The present article examines pulmonary manifestations of CD.

CD-RELATED LUNG DISEASES

Subclinical alterations

Although the overall prevalence of concomitant bronchopulmonary manifestations is only 0.4%[22], subclinical alterations in at least half of adults with CD have been demonstrated[23-25], suggesting the underlying bronchial inflammation. Patients with CD present with a subclinical inflammatory process despite the absence of pulmonary symptoms[26]. This pulmonary involvement can be reflected by an increased lymphocyte count in the BAL fluid[27,28] and/or lung function abnormalities[29,30].

BAL has provided a fresh dimension in the investigation of pulmonary and multisystem disorders. BAL fluid may be analyzed for cells and chemical mediators in the diagnosis and serially in the management of granulomatous disorders such as CD[31]. BAL studies in asymptomatic CD subjects have demonstrated the presence of persistently elevated alveolar lymphocytosis, suggesting latent pulmonary involvement[23,32]. There is no correlation between BAL differential cell count and drug treatment or CD site, and activity[27].

Pulmonary function test abnormalities are frequently found in patients with CD without the presence of respiratory symptoms or lung radiograph findings[33]. The severity and frequency of these pulmonary function test abnormalities which are detected even in remission periods increase with activation of the disease[34]. Pulmonary inflammation may correlate with bowel inflammation, as shown in the studies[23,35,36] which demonstrated a reduction in diffusing capacity and other pulmonary function abnormalities during CD exacerbations. Moreover, lung transfer factor for carbon monoxide (TLCO) abnormalities are related to the degree of disease activity[35]. Therefore, pulmonary function tests may be used as a non-invasive diagnostic procedure to determine the activation of CD and might aid the early diagnosis of latent respiratory involvement.

Nitric oxide (NO) can be detected non-invasively in exhaled air (eNO) and is considered a surrogate marker of airway inflammation. Fractional eNO values were found to be significantly higher in CD patients and correlated positively with CD activity. eNO measurement may be of clinical value in the follow-up of CD patients[37]. An increased eNO level may be used to identify patients with CD who need further pulmonary evaluation[38]. It is important to be alert to this clinical disorder and to try to detect it as early as possible in order to prevent future respiratory disturbances.

Airway diseases

CD is an inflammatory bowel disease associated with a variety of systemic manifestations, including large and small airway involvement. Major patterns of airway diseases associated with CD are upper-airway obstruction[39-41], tracheobronchitis[42,43], chronic bronchitis[44], granulomatous bronchiolitis[45], bronchiectasis[41], asthma[46] and acute respiratory failure due to tracheobronchial involvement[47]. In cases with large airway involvement, marked tracheobronchial inflammation and narrowing of the tracheal and/or bronchial lumen are typically observed at bronchoscopy as erythematous and edematous tracheal mucosa with diffuse scattered whitish lesions, while biopsy reveals metaplastic changes in the epithelium, granulomatous infiltration by inflammatory cells and mucosal ulcerations[7,42,47]. The latter is most often a subclinical condition, and requires expensive and invasive diagnostic approaches. Bronchial hyperresponsiveness may be the expression of subclinical inflammation of the airways by several inflammatory cell types and their products, epithelial damage, microvascular leakage, and autonomic neural mechanisms[48], a phenomenon which can be responsible for the development of various pulmonary manifestations in CD[49].

The most commonly reported airway disease is bronchiectasis[50,51], which is defined as an abnormal and irreversible dilation of the medium-sized bronchioles. It most frequently presents with cough and copious amounts of sputum production. In some patients, the manifestations of bronchiectasis may only become clinically significant after surgery and the withdrawal of medical treatment[52]. Bronchiectasis is commonly associated with childhood pneumonia, necrotizing pneumonia, bronchial obstruction, and diseases that cause abnormal host immunity.

Tracheobronchitis associated with CD has several very

specific clinical findings[42,53]. A productive dry cough is typically the chief symptom, occasionally associated with shortness of breath or fever. It can often be identified by history, complemented by a clear X-ray film and obstructive pattern on pulmonary function testing. Although X-ray films of the chest field are usually normal, inflammation of the peripheral airways may present as infiltrates. Bronchoscopy shows diffuse inflammation of the trachea and bronchi with diffuse scattered whitish lesions, while biopsy reveals metaplastic changes in the epithelium and granulomatous infiltration by inflammatory cells.

The treatment of CD-related airway diseases depends on the specific pattern of involvement, and if left untreated, the patient will be put at risk of developing irreversible destruction of the air passage[54]. In the majority of patients with airway diseases, marked and long-lasting responses are seen following systemic or inhaled steroids. Bronchial lavages with methylprednisolone are effective in some patients with severe airway inflammation.

Lung parenchymal diseases

Several forms of lung parenchyma involvement in CD are recognized, including interstitial lung diseases such as bronchiolitis obliterans with organizing pneumonia (BOOP)[55,56], unspecified interstitial lung disease[57-59] non-caseating granulomatous inflammation and fibrosis[60], parenchymal nodules and granulomata[61-63], alveolitis[64] and alveolar consolidation[65]. *Mycobacterium xenopi* infection[66], noninfectious lung pathology[67], colopleural fistula and fecopneumothorax[68,69] have also been described in CD.

Cryptogenic organizing pneumonia, formerly known as BOOP, often caused by inhalation injury, or from a post-infection origin or drugs, has been described in about a dozen cases of CD, and may present acutely or sub-acutely with fever, cough, dyspnea and pleuritic chest pain[70]. Radiographic findings may range from patchy focal opacities to diffuse infiltrates on plain films, to pleural opacities and air bronchograms on chest computed tomography (CT) scans.

Although interstitial diseases most commonly involve drug-induced reactions with mesalamine and sulfasalazine, a small number of unrelated cases of fibrosing alveolitis and eosinophilic pneumonia have been reported[59]. In patients with an interstitial lung disease, most require open or thoracoscopic lung biopsy for diagnosis and clarification of the disease. The latter technique may be useful for precise diagnosis with minimal invasion. The alterations are similar, showing acute alveolitis, granulomatous lymphocytic infiltration of the interstitium and of the walls of small arteries, with slight interstitial fibrosis. Sarcoidosis is included in the differential diagnosis of these lesions in some cases.

CD and sarcoidosis are chronic inflammatory barrier diseases that share several common clinical, genetic and immunological features[70], including the occurrence of granulomas. Since these two conditions also share common susceptibility loci[71], it is not surprising that these two diseases may simultaneously appear in the same patient, with pulmonary involvement[72], although this happens quite rarely and the two diseases usually follow an independent clinical course[73]. The clinical pictures of these two diseases are usually easy to differentiate, due to the topography of the lesions: while both diseases may be disseminated, sarcoidosis mainly involves mediastinal lymph nodes and lungs, while CD is essentially a digestive disease.

Multiple pulmonary nodules are an infrequent finding in patients with CD. When they are found, the nodules are composed of sterile aggregates of neutrophils with necrosis, and histology usually shows sterile necrobiotic nodules, which are spherical, and aggregates of neutrophils, which frequently cavitate[62].

Fistula formation is frequent in CD and occurs in approximately 33% of patients[74]. However, fistulous communication between the pleural cavity and adjacent organs below the diaphragm is an extremely rare complication of CD. Recurrent pneumonia with feculent sputum in patients with CD should raise suspicion of colobronchial fistula. The diagnosis of fecopneumothorax is based on meticulous clinical examination and additional diagnostic procedures. Abdominal and thoracic CT scans or magnetic resonance imaging (MRI) may provide additional information on the stage of the disease and can exclude the presence of abscess or fluid collection in the abdominal cavity. Colopleural fistula and fecopneumothorax are rare, but life-threatening complications of CD[75]. Surgical treatment is mandatory as soon as the diagnosis is established[76].

The manifestations of lung parenchyma in CD usually respond markedly to inhaled and/or systemic steroids. Steroids administered orally lead to marked improvement in patients with interstitial lung disease and necrotic nodules, and 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 result in a rapid clinical and radiologic response and is well tolerated in some cases[77,78].

Pleural diseases

Few cases of pleural involvement in CD have been reported in the literature. Pleural involvement can be classified as: pneumothorax[79], pleural thickening[80], pleuritis and pleural effusion[81,82]. Pleural effusion alone is a rare manifestation and is more often associated with pericarditis[45]. Pleural fluid is an exudate containing neutrophils and may be hemorrhagic. The pleural complications of CD may run an independent course and may be present at the time of inactive bowel disease. Mesalamine may also induce lupus-like symptoms, such as arthralgia, pericarditis, tamponade, and/or pleural effusion, with positive antinuclear antibodies[83]. Therefore, pleural diseases induced by drugs need to be ruled out. Prednisone is administered for pleural complications if the patient is not already on a regimen of this drug or an increased dosage of prednisone is given, which usually results in resolution

of the pleural effusions. However, pleural drainage may occasionally be required.

DRUG-RELATED LUNG DISEASES

Although drug-related diseases are not "proper" CD-associated diseases, as CD 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 in patients taking sulfasalazine, mesalamine, methotrexate, and anti-tumor necrosis factor (TNF)-alpha.

Sulfasalazine and mesalamine

Sulfasalazine and mesalamine are commonly used medications for the long-term treatment of CD, and their side effects may be dose-related or idiosyncratic and should be differentiated from the respiratory involvement occurring in CD and due to the underlying disease, although this is challenging because they share similar pathological features[45]. Commonly reported lung pathology related to the use of these compounds is mostly due to interstitial disease[84-88], although eosinophilic pleuritis[89] and eosinophilic pneumonia[13,90,91] 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[92]. In most cases, symptoms appear after 2-6 mo of drug use, whereas in a few cases they appear after some days or after many years[93]. Interestingly, these pulmonary toxicities appear reversible after withdrawal of the drug, and in some cases, with the use of systemic corticosteroids[14].

Azathioprine and 6-Mercaptopurine

Azathioprine (AZA) and 6-Mercaptopurine (6-MP) are therapeutic options for patients with moderate to severe CD[94]. Pulmonary toxicity due to these drugs has been reported infrequently in the literature, although interstitial pneumonitis, BOOP[95], chronic pneumonitis/fibrosis and pulmonary edema[96] 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[95,97]. The largest series of lung toxicity related to AZA was described in 7 cases undergoing renal allograft transplant immunosuppression with AZA[97]. Lung biopsies revealed interstitial pneumonitis in 5 patients and diffuse alveolar damage in 2 patients; 3 patients died and the other 4 improved after stopping AZA and in 2 of these patients cyclophosphamide therapy was needed to completely resolve this side effect. 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 CD.

Methotrexate

Methotrexate (MTX) may be useful in the treatment of CD[98], but can cause adverse effects in the lungs, which in some cases are lethal[99]. The mechanism of MTX-induced lung pathology remains unclear. A hypersensitivity reaction was suggested by lung biopsy findings: interstitial pneumonitis, granuloma formation and bronchiolitis[100], and by BAL findings: lymphocytic alveolitis, increased eosinophils and reversed CD4/CD8 ratio[101], together with the clinical findings of fever, peripheral eosinophilia and response to corticosteroids. MTX may also cause pneumonitis[102] and abnormal ventilation is an early sign and should lead to further investigation[103]. The diagnosis of MTX-induced lung disease is difficult as there are no pathognomonic findings and this condition may mimic other pulmonary diseases. The most frequent complaints include dyspnea, fever and nonproductive cough. Lung function tests show a restrictive picture with low carbon monoxide diffusion capacity. As MTX-related lung toxicity is potentially fatal, 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[104]. Besides supportive therapy, withdrawal of MTX seems 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 CD over the past few years[105-108]. However, serious side effects do occur, necessitating careful monitoring of therapy[109]. A number of associated opportunistic infections have been observed as a result of suppression of T cell-mediated immunity, the most frequent being tuberculosis[110-112]. 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[113], as well as with other pulmonary infections (coccidiomycosis, histoplasmosis, aspergillosis, nocardia asteroids, actinomycosis and listeriosis)[114-118], especially in older patients[119].

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[120], diffuse alveolar hemorrhage[121], nonbronchiolitis inflammatory nodular pattern of the lung[122] and interstitial lung disease[123-126]. 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[127].

CONCLUSION

In conclusion, CD is a systemic disorder and not restricted to the intestine. Pulmonary manifestations of

CD are being increasingly recognized. The involvement of the respiratory system is relatively rare, but sometimes potentially harmful. The lung manifestations of CD vary and often represent a confounding diagnostic problem necessitating a complex work-up. As far as possible, extraintestinal manifestations need to be distinguished from the complications of intestinal inflammation and from the side effects of drugs used in its treatment. Patients suffering from CD should undergo pulmonary evaluation which should include physical examination, chest X-ray and pulmonary function tests with measurement of diffusing capacity of carbon monoxide. Invasive measures, such as bronchoscopy and thoracoscopy, are typically required to reach a final diagnosis and steroids are the most frequently reported treatment. It is imperative to maintain a high index of suspicion for the development of pulmonary disease in the setting of CD in order to initiate appropriate early treatment and avoid complications.

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