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Crosstalk between the Lungs and the Gut in Inflammatory Bowel Diseases

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Abstract

Pulmonary involvement seems to be a more frequent extraintestinal manifestation of IBD than thus far supposed. In IBD, the respiratory involvement may include a wide range of pathologies. The patients with IBD are in high risk of infections. The drugs used in the treatment of IBD (sulfasalazine, mesalamine, infliximab, and methotrexate) can induce pulmonary diseases as a side effect.

Pulmonary function tests and high resolution CT are useful for detecting subclinical or clinical pulmonary involvement in IBD patients. Pulmonary function tests (PFT) and high-resolution CT (HRCT) showed abnormality in about one-quarter of patients with IBD. Corticosteroids, both systemic and aerosolized, are the main therapeutical approach, while antibiotics must also be administered in infections. Early identification is important as early treatment may improve long-term outcomes in these patients.

Key words:

Inflammatory bowel disease; Extraintestinal manifestations; Crohn's ulcerative colitis; Drugs; Lungs; Pulmonary infections; Immunosuppressant.

Abbreviations Used in the Text

IBD: Inflammatory Bowel Disease; CD: Crohn's Disease; UC: Ulcerative Colitis; HRCT: High Resolution CT; IPD: Invasive Pneumococcal Disease; PFT: Pulmonary Function Tests

Introduction

Extra-intestinal manifestations and complications are a common clinical problem in patients with inflammatory bowel diseases (IBD) and may affect almost any organ or system. Historically, lung involvement in IBD was first reported in 1976 [1]. The prevalence of lung abnormalities in IBD varies greatly among studies. Respiratory symptoms and diagnosed respiratory system disorders are more common among patients with IBD than generally expected. The spectrum of respiratory disorders occurring among patients with IBD is very broad. Diseases of the large airways are the most common form of involvement, with bronchiectasis being the most frequently reported form of IBD-associated lung disease [2].

Pulmonary disease in patients with IBD is often drug-induced due to treatment with sulfasalazine, mesalamine or due to treatment with methotrexate. Also, various opportunistic infections have been shown to be a further important cause of pulmonary abnormalities in those IBD patients who are treated with immunosuppressant, such as anti TNF-α monoclonal antibodies, methotrexate, azathioprine or calcineurin antagonists. Apart from drug-related pulmonary diseases, a wide spectrum of disease entities exists, ranging from small and large airway dysfunction to obstructive and interstitial lung disorders [3]. All those dealing with IBD patients must be aware of the possibility of the involvement of the respiratory system [4].

In this review, we provide evidence related to pulmonary manifestations in patients with IBD regarding molecular mechanisms, pulmonary infections and non-infectious diseases, drug effects to the lungs, diagnostic tests and therapeutic management.

Molecular Mechanisms-Pathogenesis

There seems to be a communication way from lung to intestine or from intestine to lung through chronic inflammatory cells such as lymphocytes, macrophages, etc. The defective respiratory burst of polymorphonuclear leukocytes in patients with inflammatory bowel disease in remission, in absence of an altered degranulation, could represent an important factor for the pathogenesis of these manifestations at the lungs [5].

Inflammatory bowel disease appears to be associated with abnormal pulmonary granulocyte accumulation. It is not apparently related to disease activity but may be the result of an associated pulmonary abnormality [6]. Pulmonary surfactant protein A is an important host defense molecule in the lung and its expression in the large intestine may reflect a close relation between the two organs in immune response towards inflammation [7].

The high prevalence of M. pneumoniae in both IBD patients and controls suggest this organism is ubiquitous and may persist in the intestinal mucosa. Epidemiological studies in IBD suggest the acquisition of some agents early in life probably during epidemics in temperate latitudes. M. pneumoniae could be one of the ubiquitous agents implicated in the pathogenesis of IBD [8].

Histamine and mast cell activity show common behaviors in both IBD and in certain allergic disorders. IgE also represents a key immunoglobulin involved in both IBD and in certain allergic pathologies, though these links require further study [9]. Also, pulmonary injury caused by increased oxidant stress in IBD may be the underlying reason of pulmonary involvement due to IBD [10].

Pulmonary Infections in IBD

Inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic diseases characterized by an inappropriate immune response, which may also increase the risk of infections. In addition, the immunosuppression from the related drugs plays an important factor in opportunistic pulmonary infections. The Nationwide Danish Cohort Study (from 1977 to 2013) shows that the risk of Invasive Pneumococcal Disease (IPD) is significantly increased both before and after the diagnosis of IBD, with limited impact of IBD medications. This suggests that the risk of IPD in patients with IBD is related to the underlying altered immune response in these patients [11].

Also, lowest income UC patients were shown to have higher adjusted odds for influenza virus infection, and additionally H. influenzae may be another cause for pneumonia among IBD patients [12]. CMV pneumonia should always be suspected in IBD patients who present fever and tachypnea, especially if the latter is worsening and/or is associated with dyspnea. Treatment must be early and specific [13]. Although the overall incidence of Pneumonocystic Carinii/jiroveci Pneumonia is low, patients with IBD are at increased risk [14].

Pulmonary Non-infectious Diseases in IBD

Camus and Colby provided an exhaustive description of all pulmonary manifestations. In general, the most notable symptoms are cough, expectoration and dyspnea, to which dysphonia or stridor can be added if the lesion is found in the upper airways, or pneumothorax, pneumomediastinum, or significant obstruction if it occurs in the small airway. In a very small number of cases hemoptysis has also been reported [15].

In not drug-related pulmonary disease a wide spectrum of disease entities ranging from small and large airway dysfunction to obstructive and interstitial lung disorders exists. Patients with lung disorders and inflammatory bowel disease should be evaluated for drug-induced lung disease and opportunistic infections prior to considering pulmonary disease as an extra-intestinal manifestation of inflammatory bowel disease [3] (**Table 1**).

Table 1: Pulmonary abnormalities reported in association with IBD.

A. Pulmonary abnormalities reported in association with IBD without drug-induced disease	
Pulmonary function abnormalities	Restrictive
	Obstructive
	Diffusion abnormalities
	Bronchial hyperresponsiveness
	Hyperinflation
Upper airways	Epiglotitis
	Tracheobronchitis
Large airways	Bronchiectasis
	Acute/chronic bronchitis
	Chronic bronchial suppuration
Small airways	Bronchiolitis
	Bronchiolitis obliterans
	Bronchiolitis obliterans organizing pneumonia
Interstitial disease	Nonspecific interstitial pneumonia
	Fibrosing alveolitis
	Eosinophilic pneumonia
Autoimmune disease	Wegener granulomatosis
	Pulmonary vasculitis
	Churg–Strauss syndrome
	Microscopic polyangitis
Other pulmonary manifestations	Necrobiotic nodules
	Pleuritis

	Fistulae (colobronchial, esophagopulmonary)
B. Drug-induced pulmonary abnormalities in inflammatory bowel disease (IBD) due to treatment with sulfasalazine, mesalamine, methotrexate or infliximab	
Non-infectious cause	Eosinophilic pneumonia
	Eosinophilic pleura effusion
	Fibrosing alveolitis
	Pneumonitis
Opportunistic infections	Mycobacterium tuberculosis
	Pneumocystis jiroveci (carinii)
	Listeria monocytogenes
	Aspergillus fumigatus
	Histoplasma capsulatum
	Coccidioides immitis
	Overwhelming infection with Plasmodium falciparum
	Cryptococcus neoformans
	Cytomegalovirus
	Nocardia asteroides

Bronchiectasis is the most common pulmonary disease found in IBD patients. Bronchiolitis is the most frequently detected disease from the small airway diseases. Several studies have reported that atopy has a high prevalence in IBD patients. Overlapping allergic disorders seem to be present in both the respiratory and gastrointestinal systems [16].

Thromboembolism is an extraintestinal manifestation and an important cause of mortality in IBD [17]. The incidence of thromboembolic events in IBD patients is three to four times higher than in age-matched control subjects [18,19]. 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.

Drug Side-effects to the Lungs

Drug related pulmonary abnormalities include disorders which are directly induced by sulfasalzine, mesalamine, methotrexate or rarely azathioprine, and opportunistic lung infections with pulmonary manifestations due to immunosuppressive treatment with anti TNF-α monoclonal antibodies, methotrexate, azathioprine or calcineurin antagonists [3](**Table 1**).

Sulfasalazine and mesalamine are commonly used medications for the long-term treatment of IBD. The lung pathology, related to the use of these medicines includes interstitial disease [20-23], eosinophilic pleuritis [24], eosinophilic pneumonia [25-27], and bronchiolitis obliterans [28]. Biological therapy, with anti-TNF drugs such as infliximab, adalimumab and certolizumab, has been associated with several opportunistic infections, as a result of suppression of T-cell-mediated immunity, the most frequent being tuberculosis [29,30].

Diagnosis of Pulmonary Involvement in IBD-Diagnostic tests

A study found that respiratory pathology was most often detected by pulmonary function tests (44.1%), with a targeted detection of respiratory symptoms (32.9%), especially during High Definition Computed Tomography (HDCT). Much less marked physical (8.6%) and radiological (12.3%) signs of pulmonary disease, which indicates the low sensitivity of standard X-ray. Airflow obstruction in the majority (78.3%) of the patients was represented mainly by obstruction of small bronchus, while 51.6% of the patients with impaired respiratory functions had no respiratory complaints, and 79.4% of them had no radiographic signs [31].

In the context of investigation for pulmonary abnormalities in the lung function the following can be used: forced expiratory volume in 1 sec (FEV1), FEV1/forced vital capacity (FVC), forced expiratory flow (FEF) 25%-75%, transfer coefficient for carbon monoxide (DLCO), DLCO/alveolar volume [32,33].

Pulmonary function tests and high resolution computed tomography abnormalities did not differ significantly between Crohn's disease and ulcerative colitis. No significant difference related to inflammatory bowel disease activity was found ($P>0.05$) [34].

Highly significant differences were found in Fractional exhaled nitric oxide (FeNO) between CD, UC and control patients, notably more common in adult patients. An increased FeNO level may be used for identifying patients with IBD who need further pulmonary evaluation [35]. The carbon monoxide transfer factor was found to be significantly reduced in patients with IBD [36].

Therapy

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 main therapeutic approach. The route of administration, dosage, titration and duration of treatment with corticosteroid varies with the patient and is largely empirical. The addition of oral corticosteroids (e.g. 25–60 mg oral prednisolone or equivalent depending on sex, weight and severity) is normally indicated when there has been no or very slow clinical improvement after a few weeks of inhaled corticosteroid therapy. Oral steroids are more readily efficacious, enabling quicker control of the symptoms and are indicated in patients with moderate or severe airway involvement. It is important to reach the normal clinical state as quickly as possible, in order to ensure the best possible quality of remission. Antibiotics must also be administered in the case of infectious and suppurative processes, whose sequelae sometimes require surgical intervention [14,37].

Gastroenterology providers should continue to evaluate the need for prophylaxis on a case-by-case basis to recognize patients who may benefit from primary Pneumonocystic Carinii/jiroveci Pneumonia prophylaxis. In particular, older patients on corticosteroids, multiple immunosuppressive agents, and patients with lymphopenia should be considered for prophylaxis [38].

Patients with IBD are at increased risk for pneumonia. Medications such as corticosteroids and narcotics are particularly associated with pneumonia in this population. An emphasis upon primary prevention of pneumonia through vaccination (influenza, H.influenzae, pneumococcus) and reduction of risk factors is warranted [11,39,40].

Conclusions

The pulmonary involvement in IBD is more frequent than believed and often is asymptomatic and detectable only at the lung function investigation. So, a high index of suspicion for respiratory disorders is warranted in patients with IBD. Early identification of respiratory manifestations of IBD is important as early therapy may improve long-term outcomes in these patients.

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-Conception and design of the review.

-Drafting the article and revising it critically for intellectual content.

-Final approval of the version to be submitted.

Conflict of Interest

None

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