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REVIEW

Pulmonary involvement and allergic disorders in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) has been associated with either clinical or subclinical airway and parenchymal lung involvement and interstitial lung complications. 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. The purpose of this review is to update clinicians on recent available literature and to discuss the need for a highly suspicious approach by clinicians.

Key words: Atopy; Inflammatory bowel disease; Pulmonary involvement

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are the two major forms of chronic relapsing inflammatory bowel disease (IBD). Apart from overlapping epidemiological, clinical, radiological, endoscopic and histological characteristics[1,2] between UC and CD, there are clear differences in the extent of inflammation in the gastrointestinal tract and in several immunological parameters[3-5] suggesting that they are distinct disease processes. The pathogenesis of IBD seems to be more complex than one single cause and probably involves an interaction between genetic predisposing factors[6-8], exogenous and endogenous triggers[3,9-14], and modifying factors[3,15,16]. The outcome of these interactions is a spontaneously relapsing and remitting inflammatory process in intestinal mucosa associated with recruitment and activation of lymphocytes, macrophages and other inflammatory cells[3,17-20].

Extraintestinal and systemic manifestations occur frequently in patients with IBD[20-25]. These various disease states can be diagnosed before, concomitant with, or after the diagnosis of a specific type of IBD. Two large case studies have demonstrated that between 25% and 36% of patients with either type of idiopathic IBD will have at least one such associated disease[22-23]. Yamamoto-Furusho *et al*[8] found that extraintestinal manifestations were present in 41.5% of 848 cases with UC. More than 100 systemic complications involving almost every organ system in the body have been described[26]. The

spectrum, the frequency and the temporal relation of the complications have led to the hypothesis that IBD is a systemic disorder[22-23,26].

IBD is associated with a wide variety of extraintestinal lesions in many organs and over some decades the pattern has changed and the lung is regarded as one of these affected organs[21,26-31]. In recent years a few hundred cases with pulmonary involvement and IBD have been reported and in that way pulmonary involvement has been proved to be common. A growing number of studies in the literature have reported either clinical or latent pulmonary involvement in patients with IBD[29,31-34]. In this review we will focus on the extraintestinal manifestations that are associated with lungs and airways. In an attempt to classify the reported lung manifestations in patients with IBD in a more useful way, the manifestations were distinguished as follows: (1) involvement of airways; (2) pulmonary function testing abnormalities; and (3) diffuse or localized interstitial lung complications caused by either disease or treatment received. Finally, studies regarding the relationship between allergy and IBD will be discussed in detail.

IBD AND AIRWAYS

The manifestations of IBD in airways include, chronic bronchial suppuration particularly in patients with UC[31,34-36], bronchiectasis[32,37-40], localized obstruction of upper airways[41], bronchiolitis obliterans organizing pneumonia[32,42,43], granulomatous bronchiolitis[44], tracheobronchitis[45,46], bronchiolitis obliterans[47], tracheobronchial stenosis[48] and diffuse obstructive disease[34,49]. Obstructive disease was not confirmed in some studies[50]. An increased risk of both UC and CD in chronic obstructive pulmonary disease (COPD) patients has been reported in some studies, focusing attention on the association between airway diseases (AD) and IBD[51]. We have reported a small airway dysfunction, detected by density dependence methods, in patients with IBD[52]. In the study by Louis *et al*[53], patients with IBD, free of pulmonary symptoms, independently of the presence of atopy, showed bronchial hyperresponsiveness. This interesting finding could lead to the hypothesis that local mucosal inflammation in the intestine is responsible for the mild airway inflammation and not atopy. This hypothesis is not new. Basal cell hyperplasia, membrane thickening and submucosal inflammation have been reported in patients with UC and bronchial suppuration[36]. CD may affect the oral cavity and the colon[26,54,55] while both UC[34,41] and CD[56] have been reported to involve the larynx. There are also some morphological and developmental similarities between colonic and bronchial epithelium. Both are derived from the primitive gut, whereas the lungs arise from the laryngo-tracheal bud. Both are composed of columnar epithelium with goblet cells and submucosal mucous glands. Furthermore, there is increasing evidence that an immune system specific to the gastrointestinal tract common to all mucosal surfaces exists[57], in which lymphocytes are sensitized to antigens at one mucosal site and by circulation are localized and produce inflammation in other mucosal surfaces[53,58-61].

PULMONARY FUNCTION TESTING ABNORMALITIES

Previous reports concerning pulmonary function abnormalities in patients with IBD are conflicting. In some studies no differences in pulmonary function tests (PFTs) between patients with IBD and the control group were found[49,62]. In the study by Neilly *et al*[49] airway obstruction was the most common finding affecting patients with CD (45%). However, the indices of airway obstruction were not significantly different from those obtained in age-, sex- and smoking-matched controls. As discussed above, Louis *et al*[53] reported an increased bronchial responsiveness in IBD patients, while the baseline lung function tests were within the normal range. In the study by Mohamed-Hussein *et al*[63], fifteen out of 26 patients with UC had an important impairment in PFTs. In the study by Herrlinger *et al*[64], the impairment in PFTs was more pronounced in IBD patients with active disease than in those with inactive disease.

Pulmonary diffusion capacity (TLCO) is often impaired in IBD patients. Heatley *et al*[65] found an increased prevalence of TLCO impairment in 25% of patients with CD. Reduction of TLCO in patients with IBD has been reported in various studies[61,64,66-69]. Eade *et al*[66] and Bonniere *et al*[59] found that the reduced TLCO or other PFTs parameters were not correlated with the location and severity of IBD or with the concurrent medication mode[59,66]. We examined 132 patients, 47 (17 female, 30 male) with CD and 85 (35 female, 50 male) mean age 40 years with UC. The main finding of our study was a high prevalence of impaired TLCO in patients with CD and UC suggesting involvement of the lung parenchyma[70]. All other PFTs parameters were abnormal in a high percentage of patients, however, they did not show statistically significant differences from those in the control group. Our data suggest that the impairment of TLCO was statistically significantly higher in patients with exacerbation of disease than in remission[70]. This finding is in accordance with other studies[61,65,68-70] which reported a higher prevalence of impaired TLCO among patients with active IBD disease as compared to patients in remission. In contrast, Douglas *et al*[71] reported a reduced gas transfer factor in 16% of 44 patients with IBD but these abnormalities were not related to disease activity. The reduction in gas transfer factor indicates damage to lung parenchyma. The nature of this lung involvement remains debatable. However, some explanations will be discussed in the following section concerning the relationship between IBD and interstitial lung complications.

INTERSTITIAL LUNG COMPLICATIONS

Interstitial lung involvement has been reported to accompany both clinical IBD entities, UC[72-78] and CD[79-83]. The interstitial lung infiltrates have been proven histologically to be either pulmonary vasculitis[76,77,84] or more often granulomatous disease[74,79,80,82,83,85,86].

Table 1 Studies on the relationship between IBD and atopic features

Group	Protocol	Atopy history	Skin prick tests	IgE	Ref.
CD: 11 UC: 19 Normals: 16	Skin prick tests SIgE Atopy history	Allergic symptoms were more prevalent in IBD *vs* controls $P < 0.007$ (in UC $P < 0.004$)	IBD *vs* control $P < 0.02$	No statistically significant differences	[109]
UC: 14 CD: 20 Controls: 72	IgA, IgG, IgM IgE	-	-	Increased IgG, IgM and IgE in patients *vs* controls ($P < 0.01$)	[114]
UC: 300 CD: 200 Controls: 254	Questionnaire	Asthma, hay fever, allergic rhinitis; UC *vs* Controls: $P < 0.02$; CD *vs* Controls: NS; Eczema-Any atopy-Family history; Both UC & CD *vs* controls: $P < 0.001$	-	-	[117]
UC: 39 CD: 35 Healthy: 37	Skin prick tests to various common allergens	23.1% in UC; 22.9% in CD; 21.4% in disease controls; 20% among healthy subjects	14/39 in UC and 12/35 in CD in food allergens ($P < 0.001$)	No differences	[119]
UC: 39 CD: 19 Normals: 20	Skin prick tests to milk proteins	Positive: 15.7% of UC and 13.3% of CD; Significant difference between patients and healthy subjects	No differences	No differences	[120]
UC: 63 CD: 59 Controls: 103	Skin prick tests to various common allergens	No difference between patients and healthy subjects	No difference between patients and healthy subjects	No difference between patients and healthy subjects	[121]
CD: 308 Normals: 930	Questionnaire	Atopic disease was more common in CD *vs* normal ($P = 0.001$); Atopic eczema was twice as common in CD *vs* normal ($P = 0.001$)	-	-	[124]
UC: 50 Healthy: 50	Skin prick/patch tests to airborne, food, contact allergens SIgE Atopy history and family history	Allergic symptoms were more prevalent in UC and first degree relatives than in controls ($P < 0.0001$, $P = 0.008$)	UC *vs* controls; Immediate type hypersensitivity $P = 0.01$; Delayed type hypersensitivity $P = 0.03$	IgE levels were higher in UC than in controls $P = 0.02$	[125]

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis.

Treatment with corticosteroids[75,78] or with appropriate medication such as sulfasalazine or mesalamine for the basic gastrointestinal disease[74] appeared to be satisfactory for both diseases. Pneumonitis, in contrast, due either to sulphasalazine or mesalamine is a well-recognized adverse drug reaction in these patients[50,87-95].

The above observations and the histological similarities between CD and sarcoidosis in particular, have led several groups to investigate the number and types of cells recovered by bronchoalveolar lavage (BAL)[58,59,96]. An increased percentage of alveolar lymphocytes was reported in the study by Wallaert *et al*[58] in patients with CD. In the same study, a correlation between BAL differential cell count and PFTs abnormalities, drug treatment or CD site and activity was not reported[58]. The same group reported an increased level of IgG and IgM in BAL recovered from patients with alveolitis but not in those with normal BAL[97]. This observation of subclinical alveolitis was confirmed in the study by Bonniere and associates in 22 patients with CD[59]. In the same study, a significant increase in superoxide anion production by alveolar macrophages related to spontaneous activation and alteration of pulmonary function was observed[59,98]. Bartholo *et al*[99] found lymphocytosis in induced sputum of patients with CD even without pulmonary symptoms. Raj *et al*[100] reported a trend for higher lymphocyte counts in the sputum of patients with CD compared with UC. Smiéjan *et al*[96] reported lymphocytosis alveolitis in patients with CD but not in patients with other inflammatory bowel disorders including UC. In the same study, an increase in the CD4 lymphocyte subset (increased ratio of CD4/CD8) was found in patients with an active stage of CD similar to patients with sarcoidosis[96]. Yamaguchi *et al*[101] reported increased BAL lymphocytes with an elevated CD4/CD8 ratio and enhanced expression of CD2 antigen in lung T cells in 8 patients with CD. Ussov *et al*[102] found a significant increase in the pulmonary vascular granulocyte pool in patients with CD. The meaning of this subclinical alveolitis and alterations in lung parenchyma is unclear. A subclinical inflammatory alveolitis as assessed by BAL cell analysis may be present in asymptomatic patients with immunological systemic disorders and with normal chest X-ray[103]. The fact that pulmonary involvement is not as common during extrathoracic granulomatosis as CD, whereas subclinical alveolitis is frequent, suggests that the lung possibly downregulates, in some way, alveolar inflammation due to the systemic immune disorder. The alveolitis observed in IBD patients does not necessarily precede the development of pulmonary granulomatosis and fibrosis[97,103]. Increased pulmonary permeability to diethylenetriaminepenta-acetate radiolabelled with 99m-technetium (^{99m}Tc-DTPA) related to abnormal BAL findings has also been reported in patients with CD[104]. The reduction in diffusing capacity of the lungs (DLCO) is common and early manifestations of interstitial lung diseases[64,68,97] and latent lymphocytosis alveolitis could explain, in part, the reduction in DLCO observed in patients with CD[60].

ATOPY AND IBD

The gastrointestinal tract comes into direct contact with a great variety of foreign substances and under certain conditions these may act as antigens causing allergic reactions[105]. On the other hand, atopic subjects are possibly susceptible to several inhalants or food allergens[106], while clinical features of atopic disorders include many organs among them both the pulmonary and gastrointestinal systems. Hippocrates reported that milk could cause gastric upset and urticaria and was probably the first to relate general atopy with gastrointestinal allergy. Hammer *et al*[107] found an increased prevalence of all atopic features. Asthma was also documented as being highly prevalent in a large study by Bernstein *et al*[108]. Studies on the relation between IBD and atopy are listed in Table 1. Ceyhan *et al*[109] reported that allergic symptoms and skin prick test positivity were more common in IBD patients (Table 1). Fireman *et al*[110] reported a higher percentage of eosinophils in induced sputum in patients with UC. Several studies have tried to investigate the attractive hypothesis that IBD, in particular UC, may be an allergic response to food[111,112] especially in individuals susceptible to various allergens. This hypothesis is supported by certain evidence that eosinophils and eosinophil-derived mediators contribute to the histopathology and pathophysiology of IBD[19,113-116]. Most studies confirmed the observation that atopic features are more frequent in patients with IBD than in the general population[114,117-120] (Table 1). This may be an explanation for the overlapping allergic disorders in both the respiratory and gastrointestinal systems. However, the frequency of bronchial hyperresponsiveness was significantly higher in IBD patients than in normal subjects (41% *vs* 5%), even when non-atopic subjects were considered[53]. This finding is consistent with the hypothesis that another immune system common to both exists and may be responsible for the inflammation in both systems[36]. Only one study by Troncone *et al*[121] showed that there was no correlation between atopy and IBD.

Engkilde *et al*[122] found an inverse association between a contact allergy and IBD. In this study although there was a chronic contact allergic dermatitis which was considered by the authors to have a Th2 profile, contact allergy has a Th1 profile. Engkilde *et al*[122] suggested that this may be due to shared genetic factors, common environmental determinants or skewness of the immune system. Medoff *et al*[123] suggested that T cell trafficking takes place in peripheral tissue in allergic asthma. It is suggested that this trafficking may involve several interactions between innate immune cells and T cells[123]. Several explanations for this phenomenon have been given over the years, however, no definite conclusions have been reached. Hammer *et al*[107] suggested a genetic predisposition, Myrelid *et al*[124] implicated TNF mast cells and D'Arienzo *et al*[125] suggested a Th2 or Th1 helper response. The mechanisms of atopy in IBD merit further investigation.

CONCLUSION

Three patterns of pulmonary involvement have been reported to accompany IBD: (1) airway disease including large airway stenosis, chronic bronchitis, small airway dysfunction, severe bronchial suppuration and bronchiectasis; (2) parenchymal lung involvement either as subclinical lymphocytic alveolitis or several types of pulmonary infiltrate such as granulomatous bronchiolitis and bronchiolitis obliterans; and (3) a reduction in the diffusing capacity of the lung is a well established abnormality of pulmonary function testing in some patients with IBD.

We propose that patients suffering from IBD should undergo pulmonary evaluation which should include physical examination, chest X-ray and pulmonary function testing with DLCO measurement. This pulmonary evaluation may be useful in detecting subclinical or clinical pulmonary involvement in IBD patients or as a baseline evaluation. In clinical cases with pulmonary manifestations, inhaled or systemically administered steroids appear to be an effective treatment. With regard to atopy, routine investigations should be considered, at least in patients with IBD who also present with airway dysfunction.

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