EDITORIAL

The lung in inflammatory bowel disease

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Attention has long been devoted to the respiratory manifestations that may be associated with systemic diseases, or with diseases of distant organs. Although many such associations have been known for a long time [1], a few have escaped detection until recently. Examples of this include bronchiolitis obliterans-organizing pneumonia (BOOP) [2–6] and bronchiectasis [7] as markers of connective tissue diseases, and the constellation of respiratory changes that may be seen in patients with inflammatory bowel disease (IBD) [8–13]. The latter manifestations are now considered part of the spectrum of extraintestinal manifestations of IBDs, and it is important that they are recognized, labelled and treated early. Otherwise, they tend to generate persistent and annoying symptoms, and may lead to destructive and irreversible changes in the airway wall, or to the "end-stage lung".

Historically, the respiratory manifestations associated with IBD were first recognized by KRAFT *et al.* [8], who reported on six patients with (five with ulcerative colitis (UC)) with otherwise unexplained copious bronchial suppuration, with or without bronchiectasis. Following this report, several cases and case series have expanded the number of patterns of respiratory involvement that can be seen in IBD [9, 10, 12, 14, 15]. The latest addition in this field by MAHADEVA *et al.* [16] in this issue of the Journal has in no way a feel of *déjà vu*. Instead, it is an important further addition in the field, because it is the first to describe the merits of expiratory computed tomography results as an indicator of small airways disease, and to attempt to correlate radiographic changes and lung function.

All these studies, along with the data accrued in the authors' ongoing international Registry of Bowel and Lung Disease, which now harbours >100 case histories [12], currently allow a more refined description of the various possible respiratory changes in IBD (table 1). Although some overlap does exist, the patterns of respiratory change seen in patients with UC and Crohn's disease (CD), respectively, is distinctive [12, 17, 18] (table 1). Also, the

incidence of respiratory changes is greater in UC, as opposed to CD [8, 12]. In the majority of patients, the pattern and site of respiratory involvement remains approximately the same over time, although the severity may change under the influence of disease activity on the one hand, and of steroid treatment on the other. In that respect, the patients described by MAHADEVA *et al.* [16] who developed interstitial lung disease (ILD) followed by bronchial disease is atypical.

Overall, the respiratory manifestations seen in patients with IBD remain unusual. Also, they are puzzling, especially since they may develop in patients whose IBD is controlled by medical treatment or, even more disturbing, in whom coloproctectomy has been performed earlier, sometimes in the very remote past. Although these respiratory changes can develop at any time in the history of the IBD, most do so following the onset of the bowel disease (by days to decades). The reason(s) for the wide range of time-to-onset of the respiratory disease is unknown, as are the reasons why only a few patients develop the disease, and the factors that govern flares and aggressiveness. Occasionally, the respiratory symptoms develop very early (from a few days to a few weeks) after coloproctectomy [12, 14, 19]. This intriguing shift of the inflammatory process from the bowel to the lung is often taken as evidence of a causal link between the two processes [9], possibly because of the common ancestry of the bowel and the bronchial tree [15]. It has even been speculated that colonic surgery may promote the onset of respiratory disease, as suggested by illustrative case histories [12, 19]. Additional evidence for a causal or common link between colonic and bronchial inflammation includes the parallel flares of bowel and lung symptoms seen in some patients [9, 12, 16], the exquisite steroid sensitivity of the airways disease seen in many patients, and the fact that the biliary tract, which also originates from the primitive gut, can also be involved in IBD. In rare instances, the respiratory symptoms predate the IBD [12, 20]. In no case has colectomy been shown to improve the classic respiratory manifestations of IBD [12]. Withdrawal of bowel disease-modifying drugs has not been shown to improve the airways disease in IBD, but may be useful in patients with ILD in the context of IBD (see below).

The most prevalent and distinctive pattern of respiratory involvement in IBD is airway inflammation, which results in airway narrowing and, if left untreated, puts the patient at risk of developing irreversible destruction of the air passages with tracheal stenosis, bronchiectasis or bronchiolitis obliterans syndrome as a result (depending on the localization of the process in the bronchial tree). ILDs [12,

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A checklist for cases of IBD-related lung disease is available on request from one of the authors (philippe.camus@chu-dijon.fr).

Table 1. – The lung in inflammatory bowel disease: patterns of involvement, clinical/endoscopic/radiographic/pathological correlates and therapeutic modalities

Site of involvement	Pattern	UC	CD	Presenting symptoms	Imaging	Endoscopy	BAL	Recommended treatment	Long-term outcome
Upper airway									
Larynx/glottis	Glottic/subglottic stenoses	++	+	Cough, dyspnoea, hoarseness, stridor	Narrowing	Glottic/subglottic oedema and inflammation, granulomatous in CD	ND	Intravenous steroids±laser resection	Favourable
Trachea	Tracheal inflammation and stenoses	++	+	Cough, dyspnoea, hoarseness, stridor, haemoptysis	Narrowing	Tracheal stenosis/inflammation	ND	Intravenous/oral steroids±laser ablation	Favourable
Bronchi	Simple chronic bronchitis	++	±	Slightly productive cough, wheeze	Normal	Mild inflammation of large airways	PMN	Inhaled steroids	Favourable
	Bronchial distension*,#	±	-	Cough, asymptomatic	Bronchial distension on CT	ND	ND	Inhaled steroids	Favourable
	Isolated mucoid impaction*	+	-	Asymptomatic	Branched shadow on CT	ND	ND	Simple follow-up, surgery	Favourable
	Scarred bronchial granulomas	-	+	Cough, hoarseness	Normal	Scarred granulomas	ND	Oral±inhaled steroids	Favourable
	Chronic bronchial suppuration	++	±	Cough, wheeze, copious sputum	Thickened bronchi	Large airways inflammation, often severe	PMN	Inhaled/nebulized/oral steroids	Variable residual impairment common
	Bronchiectasis	++	+	Cough, wheeze, abundant sputum	Thickened/dilated bronchi	Extensive airway inflammation and narrowing	PMN	Inhaled/nebulized/oral steroids, serial bronchial lavage with steroids, surgery rarely advocated	Variable residual impairment common
Small airways+	Granulomatous bronchiolitis*	-	+	Nonproductive cough	Mosaic on CT	Normal	Lym	Oral steroids	Favourable
	Necrotizing bronchiolitis#	+	-	Dyspnoea	ND	ND	ND	ND	ND
	Diffuse pan-bronchiolitis+	+	-	Dyspnoea±sputum	Tree-in-bud/mosaic on CT	Normal-to-mild inflammation	ND	Inhaled/oral steroids	Usually severe
	Bronchiolitis obliterans	+	-	Dyspnoea, airflow obstruction	Mosaic on CT	Normal	ND	Inhaled/oral steroids	Usually severe
Parenchyma of the lung	BOOP	++	±	Dyspnoea/fever/ARF	Bilateral foci or diffuse	Normal	Variable	Oral/intravenous steroids	Favourable
	NSIP cellular	+	+	Dyspnoea	Basilar opacities	Normal	Lym	Oral steroids	Favourable
	Granulomatous ILD	±	++	Dyspnoea	Diffuse shadows	Normal	Lym	Oral steroids	Favourable
	DIP	+	-	Dyspnoea	Bilateral	Normal	ND	Oral steroids	Favourable
	PIE	+	±	Dyspnoea±fever	Bilateral opacities	Normal	EO	Oral steroids	Favourable
	Sterile necrobiotic nodules	+	+	Dyspnoea, chest pain, sometimes pyoderma in skin present	Multiple lung nodules/cavities	Normal	ND	Oral/intravenous steroids	Favourable

*: very few data are available for these patterns; + : may associate with pneumothorax or pneumomediastinum; # : some patterns have been seen in patients submitted to the authors' International Registry for Bowel and Lung disease but have not yet been validated by peer review and publication. - : not described; ± : unusual-to-very unusual; + : occasionally observed; ++ : typical/relatively common. UC: ulcerative colitis; CD: Crohn's disease; BAL: bronchoalveolar lavage; BOOP: bronchiolitis obliterans-organizing pneumonia; NSIP: nonspecific interstitial pneumonitis; ILD: interstitial lung disease; DIP: desquamative interstitial pneumonitis; PIE: pulmonary infiltrates and eosinophilia (note: some of these patterns of ILD (NSIP, BOOP and PIE) may also be induced by the bowel disease-modifying drugs sulfasalazine and mesalazine); ARF: acute respiratory failure; CT: computed tomography; ND: not determined; PMN: polymorphonuclear neutrophil; Lym: lymphocyte; EO: eosinophil.

21], sterile necrotic lung nodules [12, 22, 23] and serositis [12] are less common, and usually more amenable to treatment (table 1).

Pulmonologists may face several clinical situations in the IBD patient.

1) The most common aggregate of symptoms includes cough and expectoration of variable amounts of muco-purulent sputum (up to several hundred millilitres in some cases, which impacts markedly upon social life), along with breathlessness and a physiology of obstructive lung disease of variable severity. These symptoms correspond to inflammation of the airways. Surprisingly, bronchial reactivity to methacholine remains normal, at least in cases with mild airways involvement, and the bronchomotor response to β_2-agonists is usually slight or inconsistent. Against the symptomatic background of cough and phlegm, common to all forms of airways disease in IBD, the predominant site of involvement of the IBD-related inflammatory process dictates additional symptoms, such as stridor and hoarseness in cases with upper airway involvement [12, 24, 25], pneumothorax/pneumomediastinum [12, 26] or severe obstruction to airflow in cases with involvement of diminutive airways [12, 20]. Endoscopy shows variable degrees of inflammation in nearly all cases with major airways involvement and, in the most florid ones, exuberant pseudotumoral changes are seen, which severely restrict airway patency. The bronchoalveolar lavage cell profile is generally neutrophilic. Interestingly, patients with IBD (even Caucasian ones) can develop a pattern of diffuse panbronchioiltis, a distinctive disease of the small airways originally described, and most prevalent, in people of Asian ascent [20, 27–29]. In all cases with airways disease, a steroid trial is necessary (see below and table 1).

2) Patients with IBD, even though they are not exposed to drugs, may develop various forms of ILD (table 1), the most common being BOOP, or what would now be termed nonspecific intersitial pneumonitis (NSIP), cellular. In many cases, lung biopsy is still required to establish an accurate diagnosis, and to guide treatment. In the setting of IBD, BOOP typically localizes in both lung apices [12, 30], in the form of elliptic foci abutting the pleural surface, and is associated with fevers and chest pain. Occasionally, patients with BOOP present with diffuse opacities and this results in life-threatening respiratory failure [12]. Little is known about bronchoalveolar lavage results in this setting. All other patterns of ILD remain unusual, and chance associations cannot be ruled out. Except in the colectomized patient who is taking no drugs, any discussion regarding ILD in IBD should include the background of exposure to bowel disease-modifying drugs. The issue is complex, because sulphasalazine and mesalazine can induce problems in the lung (BOOP, NSIP and pulmonary eosinophilia), some of them similar to those seen in IBD patients unexposed to drugs [12, 31, 32], and also because opportunistic infections of the lung have been reported in IBD patients treated with immunosuppressive agents [33]. In the setting of ILD in IBD patients exposed to these drugs, stopping the drug has resulted in definite improvement of constitutional symptoms and of the lung disease in some cases [34, 35]. However, physicians should be aware that stopping IBD-modifying drugs exposes the patient to the risk of recurrence of the bowel disease a few weeks later.

Thus, gastroenterological advice is warranted in all cases. Although oral or intravenous corticosteroids usually improve any form of ILD, they ultimately complicate the analysis of drug dechallenge. Thus, to the extent to which it is possible, they should be restricted to cases with noticeable pulmonary symptoms.

3) Other patterns are rare but, again, early recognition is necessary. Serositis may be associated with intense chest pain. Associated myocarditis is a possibility, with attending left heart failure and/or conduction disturbances (for review, see [12]). Necrotic nodules are sterile spherical aggregates of neutrophils in the lung, which tend to cavitate quickly [12]. Sometimes overt pyoderma gangrenosum is present in addition [12, 22]. The response to corticosteroids is excellent, but careful exclusion of an infectious cause is mandatory.

The treatment of IBD-related respiratory involvement depends on the specific pattern of involvement. First, neither coloproctectomy nor classic nonsteroidal IBD-modifying drugs including immunosuppressants have demonstrated any effect in controlling the respiratory manifestations of IBD, except in rare instances. Further, colonic surgery may aggravate prior airways disease, a clinical observation made by several groups [11, 12, 14]. Although most of the respiratory changes associated with IBD respond to steroids, it is the airway disease that is more difficult to treat than any other form.

Most cases of ILD, necrotic nodules and serositis are very responsive to steroids, Overall, the duration of steroid treatment is similar to that of ILD, necrotic nodules or serositis of other causes. As far as ILD is concerned, the duration of treatment is guided by the initial histological findings. For instance, pulmonary infiltrates and eosinophilia will require shorter treatment periods than other ILDs. In any event, careful follow-up is required, to titrate steroid dosage and duration.

In IBD-related large airways disease, steroid drugs are effective, but recommendations for their use including dosage, duration and route of administration remain empirical. They are based only on clinical experience, and are in no way sacrosanct. No randomized study is available yet, and probably none will be in the foreseeable future. With these limitations in mind, the authors recommend a graded approach (table 1): the inhaled steroids beclomethasone and budesonide, at rather elevated dosages (in the order of 2,500 and 2,000 $\mu g \cdot day^{-1}$, respectively), are the two drugs that have been used to date with benefit in this setting. They are the first line and mainstay of therapy. They are able to durably control symptoms, and to improve or even normalize lung function in IBD-related chronic bronchitis. They may also offer substantial symptomatic improvement in patients with IBD-related chronic bronchial suppuration with or without bronchiectasis [12].

Broadly speaking, inhaled steroids seem far more effective and better tolerated than are oral steroids. In cases with mild involvement and an appropriate response to treatment, inhaled steroids may prudently be tapered, and some patients may be weaned completely without undergoing recurrence of their symptoms before months or even years have elapsed [12]. The handling of inhaled steroids in IBD is similar to that in mild asthma. More aggressive airway inflammation will often require nebulized steroids (e.g. budesonide 2–4 $mg \cdot day^{-1}$ in three or four doses), in

conjunction with oral steroids, the latter being given at least for a few weeks, and sometimes indefinitely. The dosage and duration of treatment with oral steroids are guided by the symptomatic response, and by pulmonary function test results, which rarely normalize in patients with aggressive airway inflammation. In a fraction of IBD patients with airway involvement, inhaled and oral steroids do not prove capable of controlling the disease, and/or induce unacceptable adverse effects dictating a reduction in their dosage. In such refractory cases regardless of the reason, serial bronchial lavage *via* a fibreoptic bronchoscope have been proposed [12], in an attempt to deliver higher steroid dosages locally. The technique was inferred from that employed by gastroenterologists for enemas. A 40–80-mg dose of methylprednisolone (budesonide was not effective in the authors' hands) in normal saline is instilled alternately into the right or left bronchial tree every 2–3 days. Later, the time interval between instillations can be increased to 3–4 days, as definite improvement in broncial inflammation is visualized and some symptomatic relief is obtained. The authors know of patients who have been lavaged in this way three times a week for several years, with long-lasting symptomatic benefit, and no undue adverse effects. The fine-tuning of all aspects of steroid treatment in IBD-related airways disease is, more often than not, carried out in close association with the patients, who are astute observers of their own illness. To what extent the endoscopic, as compared to systemic, administration minimizes the impact of steroids upon adrenal function remains unclear. Also, whether and in whom steroids prevent the development of irreversible changes in airways structure is not known.

IBD-related small airways disease [12, 19, 36] is clearly the most difficult pattern regarding management and prognosis. Small airways disease is usually refractory to inhaled steroids, and the improvement brought about by oral steroids ranges from slight to modest. There are no data on therapeutic lavage with steroids in this setting. It is fortunate that this pattern is rare. The possible beneficial role of macrolide antibiotics in IBD-associated small airways disease has not yet been sufficiently evaluated. Lung transplantation has been required in some cases [12].

Additional treatment measures include the following. 1) Antibiotics, since bouts of infection may repeatedly complicate the course of the airways disease in IBD in some, but not all, patients. 2) The authors also advocate regular bronchial toilet (daily, if possible), and regular physical exercise with the aim of dislodging secretions and strengthening bony structures, especially if systemic steroids are employed. The authors also recommend the inhalation of the nebulized steroid in various body positions (prone, supine, upright). These measures are of unproven efficacy; at least, it is felt that they are harmless.

Now that a coherent catalogue of IBD-related respiratory disease has emerged, it is necessary to look ahead with several questions in mind. 1) Although the aforementioned patterns are well delineated, an awareness of IBD-mimics is necessary. The main diagnostic concern is Wegener's granulomatosis. Indeed, Wegener's granulomatosis can manifest with active colitis mimicking UC [37] or CD [38]. Also patients with Wegener's granulomatosis may develop tracheal ulceration/stenosis or cavitating lung nodules, and IBD-patients may do so as well [12, 22]. To further complicate the issue, antibodies directed against neutrophil constituents (perinuclear antineutrophil cytoplasm antibody (ANCA) (pANCA)) may be found with a high prevalence in patients with IBD, mainly UC [23, 39]. However, both histopathology and ANCA-specificity differ in Wegener's granulomatosis as opposed to IBD (typically antiproteinase 3 cytoplasmic ANCAs *versus* variegated pANCAs, in Wegener's granulomatosis and IBD, respectively) [39]. This has been misleading in some cases [23]. 2) Are there ways to detect IBD-related respiratory disease early? Several studies have addressed this question and examined pulmonary physiology in UC patients with no respiratory complaints [40–46]. Only small and inconsistent changes have been detected, which are unlikely to be clinically helpful. Accordingly, IBD-related respiratory disease seems an all-or-none phenomenon, and, in that respect, resembles IBD itself. A distinctive lymphocytic aveolitis has been described in patients with CD and not in UC [47, 48]; long-term follow-up of these CD patients has not shown the development of overt ILD (B. Wallaert, personal communication). 3) Almost nothing is known about the cytokine profile, adhesion molecules, cellular infiltrate and changes thereof under the influence of treatment in IBD-related airways disease. The precise pathophysiological mechanisms are unclear. Studies in this unique spontaneous human model may improve the understanding of bronchial inflammation and reactivity, as well as steroid refractoriness. 4) Finally, although most studies of combined bowel and lung disease have focused on IBD, clinical data indicate that patients with coeliac [49–57] or Whipple's disease [58–62] are not immune to the development of, sometimes devastating, lung disease. It is thus important to maintain a watchful interest in all aspects of lung illnesses in association with any form of bowel disease.

To conclude, in the light of this unique bipolar association, it is pleasant that pulmonology is expanding its fields of interest toward others. It is also pleasant that unusual but treatable diseases are becoming better appreciated. This will result is a means of shrinking the unduly wide territory occupied by "idiopathic disease".

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