Respiratory involvement in inflammatory bowel diseases

Interessamento respiratorio nelle malattie infiammatorie intestinali

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ABSTRACT

Inflammatory bowel diseases (IBD) include ulcerative colitis (UC) and Crohn's disease (CD) and are due to a dysregulation of the antimicrobial defense normally provided by the intestinal mucosa. This inflammatory process may extend outside the bowel to many organs and also to the respiratory tract. The respiratory involvement in IBD may be completely asymptomatic and detected only at lung function assessment, or it may present as bronchial disease or lung parenchymal alterations. Corticosteroids, both systemic and aerosolized, are the mainstay of the therapeutical approach, while antibiotics must be also administered in the case of infectious and suppurative processes, whose sequels sometimes require surgical intervention. The relatively high incidence of bronchopulmonary complications in IBD suggests the need for a careful investigation of these patients in order to detect a possible respiratory involvement, even when they are asymptomatic.

Keywords: Crohn's disease, inflammatory bowel disease, respiratory involvement, ulcerative colitis.

RIASSUNTO

Le IBD (inflammatory bowel diseases) includono la colite ulcerosa (UC) e il morbo di Crohn (CD), causate da un'alterazione della difesa antimicrobica normalmente esercitata dalla mucosa gastroenterica. Questo processo infiammatorio può estendersi al di fuori dell'intestino in altri organi e anche all'apparato respiratorio. Il coinvolgimento respiratorio nelle IBD può essere del tutto asintomatico e rilevabile solo all'esame della funzionalità respiratoria, oppure manifestarsi con sintomi di patologia delle vie aeree o del parenchima polmonare. I corticosteroidi, sia per via sistemica che inalatoria, sono il caposaldo della terapia, mentre anche gli antibiotici debbono essere somministrati nelle forme infettive e con ampia componente suppurativa, i cui reliquati talvolta richiedono un approccio chirurgico. La relativamente elevata incidenza di complicazioni broncopolmonari nelle IBD suggerisce la necessità di un'accurata valutazione di questi pazienti per rivelare un eventuale coinvolgimento respiratorio, anche in assenza di sintomi.

Parole chiave: **Coinvolgimento respiratorio, colite ulcerosa, malattie infiammatorie intestinali, morbo di Crohn.**

Definition and pathogenesis of IBD

Ulcerative colitis (UC) and Crohn's disease (CD) are usually referred to with the common label of inflammatory bowel diseases (IBD) due to their similar inflammatory nature and unknown cause. However, many differences in the clinical and pathologic features of these two chronic intestinal diseases have been found. Ulcerative colitis involves the rectum and may affect part or all of colon, and the inflammation is typically restricted to the mucosa. Crohn's disease, on the other hand, is generally limited to the ileum and colon, not rarely in a patchy manner, and the inflammation is mostly transmural, with consequent stenosis and fistulae.

IBD result from an impaired barrier function of the intestinal mucosa characterized by increased permeability and defective regulation of tight junctions [1]. The failure of this barrier, determining an exposition to fecal antigens, may induce an inappropriate activation of the acquired mucosal immune system [2]. As a matter of fact, antibodies against intestinal bacteria are frequently detected in serum of patients with IBD [3] but, although many pathogens have been incriminated, none has been demonstrated to play a causative role [4,5]. The initial fast,

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generic response to intestinal microbes is supplied by the innate immune system, while the adaptive immune system recognizes individual bacteria through antigen-specific receptors.

A number of inflammatory cells and mediators and genetic alterations involved in the pathogenesis of IBD have been identified in recent years [5]. The Th1 cytokines interleukin (IL)-12, interferon-γ, and tumor necrosis factor (TNF)-α are the main mediators of inflammation found in CD [6], whereas in UC an increased expression of Th2 cytokine IL-5 is often seen. Elevated levels of IL-23 and Th17 cytokines have been found in both CD and UC [7].

As to the innate immune system, genetic factors play an important role in the development of IBD, particularly in CD. In this respect, the first identified locus is located at the chromosome position 16q12 [8,9] and the different genes included within this locus are named NOD2. The NOD2 system encodes an intracellular sensor of peptidoglycan (a component of bacterial cell wall) and activates components of the innate immune system. The stimulation of the NOD2 leads to the production of cytokines and antimicrobial peptides, and an impaired response at this level is now recognized as the likely cause of IBD [10,11]. In fact, in healthy subjects NOD2, primed by microbial peptidoglycans, activates nuclear factor(NF)-κB, which in turn enhances the production of antibacterial cytokines. However, the acute stimulation of NOD2 by bacterial peptidoglycans is also modulated by inhibitory cytokines, like transforming growth factor (TGF)-β and IL-10, which downregulate the proinflammatory cytokines, and this downregulation is impaired in subjects with IBD, who are thus exposed to a chronic intestinal inflammation. Three NOD2 polymorphisms have been seen in about 30% of European patients, each impairing responses to peptidoglycans. Carriers of a NOD2 polymorphism are more likely than non carriers to have an ileal involvement [12]. Homozygosis for a polymorphism confers a much greater risk of CD [13]. In addition, autophagy, a mechanism aimed to clear microbes, and its gene ATG16L1, are involved in CD [14], where abnormal Paneth-cell morphology has also been found [15]. The autophagy is implicated in T-cell tolerance; thus in IBD an increased susceptibility to intestinal inflammation occurs, due to defects in T-cell tolerance [16,17].

Incidence of respiratory diseases (RD) in IBD and of IBD in RD

Respiratory diseases are a possible complication of IBD, even if pulmonary alterations are often overlooked, especially when respiratory symptoms are already present before the diagnosis of IBD. The first recognition of a correlation between the diseases of the two districts is attributable to Kraft [18], who in 1976 reported a series of patients with unexplained bronchial suppuration. Since then, numerous reports have outlined the association between IBD and respiratory pathologies. The rate of extra-intestinal manifestations in patients with IBD ranges from 21 to 41% [19,20], increasing with the duration of the intestinal disease, and being greater in CD than in UC [21]. However, the true prevalence of lung involvement in IBD remains unknown and it seems rather variable, because in some series only few cases of respiratory complications have been found. In fact, in 624 patients [22] no respiratory complication was reported, and only 3/1400 cases of IBD were found by Rodgers et al. (0.4%) [23]. On the other hand, it can be difficult to establish a relationship between IBD and RD in patients who are already affected with pulmonary disease at the diagnosis of IBD, or are current smokers.

Respiratory diseases occurring in IBD may consist merely in a subclinical abnormal lung function or, in contrast, they may manifest as clear interstitial lung disease [19]. An ongoing bowel inflammation is not a prerequisite for the onset of respiratory alterations, since bronchopulmonary diseases that developed after colectomy have been reported [24]. The respiratory changes can occur at any time in the history of IBD, but they generally follow it by a time interval varying from days to decades [25].

Concerning the "respiratory dysfunction in asymptomatic patients", Mohamed-Hussein et al. [26] reported that 57.6% of their patients with UC had at least one abnormal lung function test (PFT) result: restrictive dysfunction in 30.7% and obstructive in 11.5%. The impairment of PFT was more pronounced and significant in patients with active UC than in controls or in patients with the inactive form. 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 (DL_{CO}) was the most common defect [19]. The impairment of pulmonary function has been observed also in children. Munck et al. [27] first reported a series of 26 children with CD in acute or quiescent phase, all non-smokers and asymptomatic. Ten of them were studied before the start of therapy so as to exclude possible influence of therapy itself on the respiratory abnormalities. During the remission the value of DL_{CO} resulted higher than during the acute phase ($p < 0.0001$) even if 50% of patients still presented an abnormal DL_{CO}. With the aim of investigating possible differences in respiratory function abnormalities between the two IBD identities, Tzanakis et al. [28] studied 132 patients (47 CD and 85 UC). An increased, though not significant, percentage of abnormal PFT results among both patient groups was observed compared to controls. A statistically significant difference was found only for the DL_{CO} decrease in CD patients when compared to controls ($p < 0.05$), and a slightly greater, but significant, reduction of DL_{CO} in the active compared to the inactive CD and UC. In a study of 66 IBD patients (35 CD and 31 UC), Herrlinger et al. [29] found 42% with at least one abnormal pulmonary function test compared to 3% of controls, and with no significant difference between both diseases. The forced expiratory volume in one second (FEV_1) and the inspiratory vital

capacity (IVC) resulted significantly dependent on the disease activity, whereas the DL_{CO} was not. None of the patients complained of pulmonary symptoms. Douglas et al. [30] and Bonnier et al. [31] found no correlation between DL_{CO} reduction and disease activity or severity of IBD. Dierkes-Globisch and Mohr [32] investigated 44 IBD patients without pulmonary symptoms, 20% of whom showed an obstructive or restrictive ventilatory defect compared to 5% of controls ($p < 0.05\%$), but with no correlation to activity and duration of bowel disease or to smoking habit.

From all these reports it seems clear that the pulmonary involvement in IBD is more frequent than believed, has no clear relationship with the activity of the intestinal disease and often is asymptomatic and detectable only at the lung function investigation. This is further supported by the finding by Wallaert et al. of a high proportion of latent lymphocytic pulmonary alveolitis in the bronchoalveolar lavage (BAL) of 18 consecutive patients with CD, all free from respiratory symptoms and showing a normal chest X-ray [33]. In fact, an abnormal percentage of alveolar lymphocytes was observed in 11 of 18 patients (61%) with a T-lymphocyte prevalence. The same was found by Sarioglou et al. at the BAL fluid examination, where a lymphocytic alveolitis was evident in 46.6% of IBD cases [34].

A number of clinical lung diseases can be found in the course of IBD, but the true frequency of these conditions is unknown [19], although it has been shown that the incidence is higher in patients with UC than in those with CD (35). Respiratory diseases in patients affected by IBD can be classified as "airways disease": tracheobronchial stenosis, bronchiectasis, chronic bronchial suppuration, chronic bronchitis, COPD, asthma and bronchiolitis; "parenchymal disease": cryptogenic organizing pneumonia (COP), interstitial lung disease, localized interstitial fibrosis, necrotic nodule and eosinophilic pneumonitis; "pleural effusions" are uncommon as a manifestation of IBD (Table I).

According to Black et al. [36], who report 171 respiratory pathologies in 155 patients, the "large airways" are the most common site of involvement in IBD, accounting for 39% of all cases, and bronchiectasis was present in 66% of these cases. The second most frequently reported respiratory disease in IBD patients is chronic bronchitis [37], detected in a surprisingly high proportion (81%) of nonsmoker patients [36]. This led the authors [36] to affirm that in these patients the bronchial inflammation is mainly caused by a diffusion of the bowel inflammatory condition to the bronchial tree. These results confirm the previous findings of Camus et al. [35] where 15/33 patients (45.4%) with IBD had large airways involvement, six of them (40%) in the form of bronchiectasis; 9 of the 15 cases were post-colectomy. Bronchiectasis was also the predominant finding in the report of Spira et al. [38] regarding 7 patients with IBD and large airways involvement, where three of them developed respiratory symptoms in 1-4 months after colectomy. Finally, Kelly et al. [39], in a retrospective analysis of patients with IBD and respiratory manifestations, identified 10 patients with bronchiectasis, 8 of whom post colectomy. These authors also reported that bronchiectasis in IBD patients is more severe, more rapidly progressive and more responsive to steroids than in non IBD patients. Moreover, since colectomy has no effect on the respiratory involvement, they formulated the hypothesis that the discontinuation of anti-inflammatory drugs after the surgical resection of an intestinal tract is probably able to uncover or worsen the pulmonary manifestations.

The involvement of the "small airways" in IBD, considered rare in both entities, has proved more frequent than was supposed in the days before expiratory high resolution computed tomography (HRCT) of the chest was introduced. This imaging tool has allowed the detection of the small airways involvement in these patients, some of whom also with normal PFT results. In like manner, Songur et al. [40] examined with PFT and inspiratory and expiratory HRCT 36 patients with IBD (23 UC and 13 CD, only one with CD a current smoker), and 14 healthy non-smokers, free from respiratory symptoms. Nineteen (53%) patients had HRCT abnormalities, with features suggestive of air trapping in expiratory CT scan in 12 (33%) patients, 6 of whom were symptomatic. No significant correlation was found between HRCT abnormalities and PFT results, whereas there was a difference between the two

TABLE I: RESPIRATORY ALTERATIONS IN IBD

Respiratory function defects
• Restrictive
• Obstructive
• Hyperinflation
• BHR
• DL_{CO} abnormality
Airways disease
• Glottic or subglottic stenosis
• Tracheal stenosis
• Chronic bronchitis
• COPD
• Bronchiectasis
• Bronchiolitis
• Asthma
Parenchymal disease
• Diffuse interstitial lung disease
• COP
• Pulmonary granulomatosis
• Pulmonary vasculitis
• Necrobiotic pulmonary nodules
Drug-induced pneumonitis

Definition of abbreviations: BHR, bronchial hyperresponsiveness; COP, cryptogenic organizing pneumonia; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity of the lung for carbon monoxide; IBD, inflammatory bowel diseases.

types of IBD as to the incidence of CT abnormalities, that was 92% in CD and 39% in UC. Tzakanis et al. [41] investigated the function of small airways using the density dependence of airflow technique in 30 patients with IBD (18 UC and 12 CD) and 16 healthy subjects. They found that both groups of patients with IBD had an increased volume of isoflow (Viso $\dot{V}$) despite their normal baseline spirometric values. The average Viso $\dot{V}$ was lower in active vs. inactive UC ($p < 0.05$), while there was no difference between the two forms of IBD. The mean value of Viso $\dot{V}$ in untreated patients was significantly greater than in control subjects ($p < 0.05$).

"Bronchiolitis" is the most commonly reported disease involving the small airways in patients with IBD, and it is frequently associated with peribronchiolar granuloma [36,42-46]. Camus et al. [35] reported two cases diagnosed with this pathological manifestation among 33 patients. They were young men affected by UC, in an inactive phase in one case, who complained of productive cough, and showed diffuse small opacities at chest x-ray and an obstructive pattern at PFT. In this patient the open lung biopsy revealed fibrosing and stenosing bronchiolitis and inflammatory lesions. Both Vandenplas et al. [43] and Trow et al. [47] reported one case each of granulomatous bronchiolitis in women with CD who had undergone bowel resection. The respiratory alteration presented with nonproductive cough and progressive dyspnea, and chest pain was also reported by Vandenplas' patient. In both cases the CT of the chest demonstrated irregularly dispersed micronodular densities, and the lung biopsy revealed an infiltrate of mononuclear cells associated with non-necrotizing epithelioid granulomas and giant cells in the bronchiolar walls. A $CD4^+$:$CD8^+$ cell ratio of 3:1 in BAL was found in the first patient, whereas in the second patient there was a peribronchial lymphocytic infiltrate and poorly organized granuloma with a normal BAL $CD4^+$:$CD8^+$ ratio.

Sometimes patients complaining of symptoms due to bronchiolitis may erroneously be thought to be affected with asthma, as reported by Bentur et al. [48] in a 13-year-old girl with CD since 8 years of age. The repeated episodes of shortness of breath, which started at age 9 years in this patient, had been interpreted as asthma. CT scan of the chest revealed irregularly diffused ground glass, and lung biopsy showed bronchiolitis obliterans and mononuclear inflammation with noncaseating granulomas, not related to sulfasalazine, because the pulmonary status did not improve when sulfasalazine was stopped.

Also the incidence of "asthma" is far more frequent than previously considered and the disease has a more severe course in IBD patients. A prevalence of 7.1-7.8% is reported by Bernstein et al. [49], with a higher percentage in women [19].

The airway inflammation sometimes may not be detectable by routine PFT and only an asymptomatic increase in bronchial hyperresponsiveness (BHR) [50] together with high IgE levels may be found during the chronic bowel inflammation despite the absence of atopic symptoms [51,52]. Mansi et al. [53] studied 14 CD children without extraintestinal manifestations, 5 of whom in a phase of clinical remission, with the aim to evaluate the bronchial responsiveness to methacholine in comparison with 10 healthy nonatopic subjects and 10 with mild bronchial asthma. In patients with CD, BHR was present in a very high proportion (71% of cases) even in the absence of clinical and functional evidence of airways disease. The dose of bronchoconstrictor agent causing a 20% reduction of FEV_1 compared to baseline (PD_{20}) was not related either to the baseline FEV_1 or to total blood eosinophil count or serum IgE levels; however the PD_{20} values found in these patients were higher than those seen in asthmatic individuals. BHR was evident both in atopic patients with CD and in 7 of the 10 nonatopic CD subjects. The higher prevalence of BHR reported in this study than in others [50] may likely depend on the different mean age of the study group and this accords with the observation that BHR progressively decreases with age [54]. BHR was found in several studies with an incidence ranging from 17 to 45% [50,55]. In a study comparing 30 IBD patients with 16 controls without gastrointestinal disease the respiratory and allergic symptoms were more prevalent in IBD patients ($p < 0.04$ and $p < 0.007$ respectively) than in the controls, and particularly in UC patients ($p < 0.004$). Abnormal PFTs were present in 27% of patients ($p < 0.04$ vs. controls) and BHR in 17%. Skin prick tests were positive in 50% IBD but no difference was found between the two IBD subgroups. In 4 of the patients the PD_{20} value of methacholine (MCh) test was < 16 mg/ml, while negative in all control subjects, and this hyperreactivity index was unrelated to the activity of the intestinal disease [55]. Bartholo et al. [56] found a greater ($p = 0.026$) positivity with methacholine challenge in 15 patients with CD than in 20 healthy controls, and a higher ($p = 0.011$) level of lymphocytes in induced sputum. These results strengthen the possibility that a subclinical inflammation in absence of pulmonary symptoms can occur. Ceyan et al. [55] demonstrated a higher prevalence of positive skin-prick tests ($p < 0.02$) and increased allergic symptoms ($p < 0.007$) among 30 patients with IBD (19 UC and 11 CD) compared to 16 controls without gastrointestinal disease.

Alterations affecting the "lung parenchyma" are relatively rare in IBD patients, and cryptogenic organizing pneumonia (COP) is the most common reported manifestation [35].

Pathogenesis of respiratory complications in IBD

The current pathogenetic hypothesis of IBD is an impairment of the mucosal immune regulation of the gastrointestinal system concerning intraluminal bacterial antigens in genetically predisposed persons [57]. As a matter of fact, antibodies against intestinal bacteria are frequently detected in serum of patients with IBD (2), and increased titers of anti-

Saccharomyces cerevisiae antibodies to baker's yeast have been seen in CD patients [58]. One hypothesis to explain the respiratory involvement in IBD is that these products cross-react with common antigens outside the bowel in the human body. Furthermore, a common embryologic origin of both gastrointestinal and bronchial tree may support the onset of inflammation at two different sites with common embryological origin. Respiratory symptoms may also be due to an aberrant homing of inflammatory cells to the lungs from the primary site of chronic inflammation [59], and this might also explain why the large airways disease is frequently not cured by colectomy [38]. Thus, according to this hypothesis, the inflammatory process would shift from the gastrointestinal tract to the airways [60].
A recent study has shown that patients with CD have increased pulmonary permeability which appears unrelated to the disease activity [61]. The same conclusions were reached by Gursoy et al. [62] in their study on UC patients without respiratory symptoms, who underwent technetium-99m aerosol scintigraphy. The increase in permeability might even provide a satisfactory explanation for the occurrence of bronchial hyperresponsiveness (BHR) [53].
It should also be taken into account that not rarely the side effects of treatments may be a cause of pulmonary disease in IBD patients [63], in the form of hypersensitivity reactions and pulmonary edema [64-66]. Usually, most reactions related to sulfasalazine and 5-ASA are seen between 2 and 6 months after commencement of drug administration [19]. Also a relapse or onset of pulmonary tuberculosis may be caused by the immunosuppressant monoclonal antibodies and other anti-inflammatory drugs used to control the chronic intestinal inflammatory process [67-69].

Clinical manifestations and treatment of RD in IBD
The involvement of the airways in the course of IBD may manifest itself with persistent productive cough, exertional dyspnea, obstructive and/or restrictive ventilatory deficit with or without abnormal chest radiograph. Interestingly, a severe tracheobronchial stenosis has been reported [70] in a young patient with CD. His respiratory symptoms developed two years after colectomy, with a productive cough initially controlled by beclomethasone. However, ten years later there was an increase in the volume of sputum with purulent features and fever, and a CT scan of the chest showed a marked distortion of the large bronchi with mucoid impaction in the small bronchi and alveolar micronodules. Fiberoptic bronchoscopy (FOB) revealed mucosal inflammation, purulent secretions and tracheal and bronchial deformities, with a severe stenosis of both mainstem bronchi, and marked airflow obstruction at the PFT. The patient was initially treated with antibiotics and oral steroids, tapered over a period of 13 months. After 12 months CT and FOB appeared unchanged, but no mucosal inflammation was present, and symptoms had disappeared at six weeks following the start of therapy; an improvement on PFT was measured at 28 months of switch therapy with inhaled budesonide. This case probably represents an advanced stage of tracheo-bronchial involvement which had developed over a long period of time.
Symptoms due to bronchiectasis and chronic bronchitis are the most frequent clinical presentation of airways pathology in IBD, generally following the onset of bowel disease and sometimes after the colectomy (71). Also in the series reported by Kelly et al. [39], 80% of IBD patients with bronchiectasis developed their symptoms after surgery for IBD, supporting Kinnear's and Higenbottam's hypothesis that inflammatory process may shift from the bowel to the airway [60] and manifest or increase after the bowel inflammation has been eliminated [39]. In a series collected by Higenbottam et al. [72], ten patients with UC, all non smokers, presented productive cough. Six out of these had normal chest radiograph and three a minor obstructive ventilatory defect on PFT. In one of these patients bronchography revealed the presence of bronchiectasis. The remaining 4 patients developed a marked exertional dyspnea and bilateral pulmonary shadows on the chest X-ray with a mixed ventilatory defect. There was no correlation with sulfasalazine therapy and in 3 patients the symptoms began after colectomy. In 7 patients the symptoms were relieved by inhaled beclomethasone.
However the presence of respiratory symptoms may be highly variable in IBD patients and completely absent in those with milder disease. In fact, HRCT performed in 17 IBD patients (3 out of 17 were CD patients) revealed bronchiectasis in 13 (76%), in the absence of sputum production in those with a lesser extent of bronchial alteration, while 9 patients presented signs of air trapping, and 5 a "tree in bud" pattern at CT [73].
As regards asthma symptoms, Bernstein et al. [74] report an increased risk for this disease in either form of IBD in a population-based study screening for a number of other chronic inflammations. Asthma was the second most common extraintestinal comorbidity, after arthritis, without significant differences in relation to the type of IBD and gender, although a slightly greater prevalence in women was present [19].
Sometimes patients complain of dyspnea on exertion or even at rest, nonproductive cough, fever and general malaise due to the involvement of lung parenchyma in the form of interstitial and alveolar diffuse changes. In these cases it is necessary to distinguish the alterations directly consequent to the bowel disease from those caused by adverse reactions to the drugs used for IBD. Alterations of the lung parenchyma are more frequent in UC and in females, cryptogenic organizing pneumonia (COP) being the most reported single case [36]. In most patients [21,35,75-78] COP generally follows the onset of IBD, and it presents with fever, dyspnea, dry cough, pleuritic chest pain and weight loss.

Areas of peribronchiolar inflammation and fibrosis and/or fibrosis of the peribronchial region [24] or subpleural opacities [78] have been seen on CT scan, with a tendency to migrate and consolidate [77]. At physical examination of the chest, inspiratory crackles are found on both sides of the chest, and pulmonary function tests show a restrictive pattern. The culture of bronchoalveolar lavage fluid generally does not lead to the growth of bacteria, acid-fast bacilli or fungi, and the cytologic study shows an increased percentage of lymphocytes with a variable, although usually normal, CD4/CD8 ratio. A normal CD4/CD8 ratio is reported by Simon [77], whereas Carratù [78] found it increased. In this case an open-lung biopsy revealed isolated foci of non-specific chronic inflammation, myofibroblastic proliferation and peripheral endoalveolar foamy macrophages. Rarely, cases of pulmonary infiltrates and eosinophilia have been reported both before and during or after the diagnosis of IBD [35]. Dry cough was the only symptom referred by a 38-year-old woman affected by CD and treated with mesalazine [79]. Chest x-ray showed some alveolar opacities in the right middle lobe, that were interpreted as pneumonitis and successfully treated with antimicrobial drugs. However the pulmonary infiltrates relapsed despite the intense antibiotic therapy previously adopted. BAL was performed and the cellular examination revealed a marked increase (30%) in eosinophilis. At surgical biopsy a pattern of interstitial fibrosis with few non-caseating epithelioid granulomas was demonstrated, together with sparse lesions of bronchiolitis obliterans and desquamative interstitial pneumonia. This was the first description of a necrobiotic pulmonary nodule associated with interstitial pneumonia and eosinophilia. However, the hypothesis – albeit unlikely - that mesalazine treatment was responsible was difficult to confirm or exclude because, while the first pneumonia resolved without the withdrawl of the drug, the relapse improved after corticosteroid therapy and discontinuation of treatment with 5-ASA.

As to the pulmonary complications derived from the use of drugs for IBD, sulfasalazine was first prescribed in the management of these chronic bowel diseases in the 1940s [80]. It is a compound of sulfapyridine linked to 5-ASA (mesalazine) [19]. It is known that the drug may have clinically important side-effects, including pulmonary toxicity [80]. In this respect, a retrospective study on published reports between 1972 and 1999 [80] revealed that lung toxicity caused by sulfasalazine is more common in ulcerative colitis, where it mainly manifests with dyspnea (80% of cases), fever (70%) and cough (64%). Peripheral eosinophilia was reported in 52% of cases. Interestingly, the respiratory function assessment showed abnormalities in 28 out of 29 tests performed, consisting in a restrictive defect in 66% of cases. Chest radiography was abnormal in all cases, showing mainly pulmonary infiltrates, that were confirmed at CT scan, where it revealed typical infiltrates, ground glass opacities, and pulmonary nodules with central cavitation. BAL was performed in 11 patients, with 5 (45.4%) demonstrating an increase in eosinophils ranging from 23 to 69%. Based on the histological findings, the final diagnosis was eosinophilic pneumonia in 11 cases, and in 4 fibrosing alveolitis. Other less common histological diagnoses included COP, desquamative interstitial pneumonia (DIP) and less specified pneumopathies, like sulfasalazine lung disease or pulmonary hypersensitivity reaction.

Averbuch et al. [81] reported a case of rash urticaria and generalized angioedema in a 58-year-old man suffering from UC and treated with sulfasalazine therapy, where the adverse symptoms resolved with the discontinuation of the drug. The patient underwent a protocol of desensitization (gradually increasing doses of sulfasalazine with progressive tapering of prednisone), and after two months he developed a dry cough, fever and progressive dyspnea. A chest X-ray showed diffuse bilateral interstitial infiltrates which dramatically improved with sulfasalazine discontinuation and administration of high dose prednisone. In this case the first manifestations may be interpreted as a typical allergic reaction, whereas the parenchymal lung alterations likely reflect a direct toxicity of the drug. Alternatively, both features could be due to the same steroid-responsive mechanism, but with higher doses of prednisone necessary for the prevention of the interstitial pneumonia. In a case of eosinophilic pneumonia in a 35-year-old woman treated with oral mesalazine, who improved after discontinuation of therapy, the lymphocyte stimulation test with the drug was positive for mesalazine and negative for sulfasalazine and sulphapyridine [65].

Only few cases [82,83] of pneumonitis have been reported in patients treated with methotrexate for IBD, whereas one series reported 70 cases of tuberculosis in IBD patients given therapy with infliximab (anti-tumor necrosis factor monoclonal antibody) [84].

Inhaled steroids are very effective, also for the long term control of the respiratory disease, in patients with chronic bronchitis, in symptomatic asthmatic patients, and in upper airways disease too [70]. Oral corticosteroids can improve interstitial disease [35], COP [76,78], granulomatous bronchiolitis [43], and drug-induced pneumonia [81], while intravenous administration is the initial management of life-threatening subglottis stenosis or extensive interstitial lung disease [35]. A surgical approach is sometimes necessary to repair the sequels of destructive inflammatory processes, like tracheal and bronchial stenosis.

Causes of mortality in IBD

Despite the marked improvement in medical and surgical therapy, it remains a debated issue whether the death risk is greater in IBD patients compared to the general population, also because dissimilar results have been reported in many studies, where the most severe patients, bearing the worse prognosis, are prevalently included [85]. Other factors like

malnutrition, infection, and side effects of medical and surgical therapy may increase the fragility of these patients.
Cucino et al. [86], with the aim to analyze the comorbidities possibly contributing to increased mortality of patients with IBD, pooled the data from 6 consecutive years (1991-1996) and analyzed them together. In patients affected with UC the comorbidities were most frequently represented by shock and protein/calorie malnutrition, volume depletion and anemia, septicemia, and peritonitis, whereas CD patients often showed nutritional, volume and electrolyte disturbances, besides surgical complication and pulmonary insufficiency.
A meta-analysis was carried out to ascertain the overall and cause-specific mortality in a cohort of UC patients published in the literature from 1965 to 2006 [85]. Five Scandinavian studies included in this meta-analysis reported higher mortality rates (SMR 1.2, p = 0.001) than did non-Scandinavian countries, similarly to an EC-IBD study (European Collaborative group of Inflammatory Bowel Disease) that reported a slightly higher mortality in North Europe than in Southern Europe [87]. The studies which presented SMRs stratified for age at diagnosis did not show significant differences, whereas those which considered the extent of UC at diagnosis showed a higher SMR when the inflammation was close to the rectum (1.2). Similarly, the SMR was higher during the first 5 years after the diagnosis (1.4) and especially during the first year (2.2) (88). Lower SMR (0.8) was encountered in UC patients who had not been given immunosuppressive drugs (6-mercaptopurine, azathioprine or infliximab) and in non-colectomized patients (0.9). The mean percentage of deaths ascribed to UC was 17% (ranging from 11% to 30%), the most common causes being colorectal cancer and surgical or postoperative complications. Six out of ten series reported SMRs for specific causes of deaths. A significantly lower risk of dying from lung cancer was observed (SMR 0.3, p = 0.04), whereas a greater, but not significant, risk of dying from COPD (SMR 1.6, p = 0.26) and a significant risk for pneumonia (SMR 3.1, p > 0.001) were found. Only one study estimated the risk of dying from pulmonary embolism, reporting a significantly higher SMR of 4.0. The lower SMR reported for lung cancer may be due to the fact that UC patients often are non smokers, so that the difference in smoking habits between the UC patients and the healthy population may act as a confounding factor. The other reported causes of death include cardiovascular, renal and liver diseases, leukemia and non-Hodgkin's lymphoma.
The EC-IBD study [87] on mortality in UC in Europe did not find a higher mortality risk in UC patients compared with the normal population. The mortality was slightly higher in females than in males (SMR 1.39 and 0.92 respectively) and slightly higher in older patients. A comparison of disease specific mortality between North European region and South European region also revealed a higher SMR only for pulmonary disease (SMR 1.19 and 0,82 respectively).
Similarly, investigating the overall and cause-specific mortality in CD, Duricova et al. [89] examined the results from nine studies, six of which also reported cause-specific mortality. A slightly but significantly increased pooled SMR (1.39) for mortality in general was observed, with no significant gender difference although it was higher in women, whereas a higher significant SMR for mortality due to pulmonary diseases was found in CD compared to the general population and UC patients. In this meta-analysis a significantly increased risk of death from lung cancer was detected (SMR 2.72), as well as from COPD (SMR 2.55), that led to a tendency of risk of overall death from respiratory disease to be increased (SMR 1.44). This can likely be explained by a higher prevalence of smokers among CD patients compared to the general population and to UC patients, and it is known that smoking has detrimental effects on the clinical course of CD [90]. Another meta-analysis by Canavan et al. [91], performed in the same type of patients, revealed higher SMR in hospital and referral centers with respect to community-based studies.

CONCLUSIONS

In conclusion, the inflammatory process of IBD is not necessarily restricted to the gastrointestinal tract, since many studies have demonstrated that latent or patent pulmonary involvement can occur in these patients even in the complete absence of symptoms [92]. The available diagnostic tools may make us able to detect early IBD-related respiratory syndromes.
A bronchial hyperresponsiveness in patients affected with UC or CD and no respiratory symptoms can easily be detected by methacholine challenge, so indicating that in the airways an inflammation not detectable by routine PFTs may exist [53]. Use of the density dependence of air-flow technique may help to clarify if small airways are affected [41], and a defect in the transfer of respiratory gases, as expressed by the decrease in the DL_{CO}, suggests the presence of a process involving the interstitial pulmonary district possibly not identifiable by standard chest radiographs [27]. In this context, HRCT scan obtained at full expiration is a valid tool to show air trapping mainly in patients with emphysema [93], asthma [94] and hypersensitivity pneumonia [95] even in the absence of recognizable morphologic abnormalities on inspiratory scans [40]. This method can be useful to detect small airways involvement also in asymptomatic IBD patients.
As previously reported, pulmonary involvement, encountered in about 60% of IBD patients [96], can range from a simple defect of pulmonary function without symptoms to fibrosing alveolitis with a greater risk of mortality. For this reason the early detection of latent abnormalities of pulmonary function is important to prevent future and more severe respiratory impairment [56]. Early detection is all the more war-

ranted in view of the fact that IBD-related respiratory syndromes generally respond well to inhaled or systemic corticosteroid treatment [25,35,70].

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