

Pleuropulmonary Manifestations of Inflammatory Bowel Disease

Abdullah Rashed Alharbi* and Abduellah Alanazi

Department of Pulmonology, King Saud University, Saudi Arabia

***Corresponding Author:** Abdullah Rashed Alharbi, Department of Pulmonology, King Saud University, Saudi Arabia.

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Abstract

Pleuropulmonary clinical presentations are extraintestinal manifestations of the inflammatory bowel diseases (IBD). These manifestations are concerns for both pulmonary physicians and gastroenterologists. The objective of the present review was to gather and summarize information on this particular matter, on the basis of available up-to-date literature. Pleuropulmonary manifestations are frequent seen and diagnosed either pre or after diagnosed of inflammatory bowel airway diseases the most common presentation, whereas IBD-related interstitial lung disease is less presentation. Pulmonary infection should always consider either from disease itself from immunosuppression treatment. The common link between intestinal disease and lung pathology is unknown, but many hypotheses have been proposed. It is speculated that environmental pollution, common immunological mechanisms and predisposing genetic factors may play a role.

Keywords: *Inflammatory Bowel Disease (IBD); Pleuropulmonary Manifestation*

Introduction

Extra-intestinal manifestations of IBDs are recognized with an overall prevalence ranged from 6 - 47% [3,7,8,11,14].

Every organ may be affected, but musculoskeletal, ocular and mucocutaneous are the most commonly involved pulmonary complication is quiet uncommon, ranged from 0.6 to less than 1% [1], some mentioned 0,4% [10,12]. The true prevalence expected to be much higher, because those patient with IBD have no respiratory symptoms - had Subclinical lung involvement and this estimated to be ranged from 40 - 60% [11].

But recently found that there is an association between IBD and respiratory symptoms.

The pulmonary manifestations do not correlate with the duration of IBD OR the severity of the disease [2,18] and some mentioned that the pulmonary diseases in most patient with IBD are correlate with the disease activity [10,18].

The association between the pulmonary manifestations in IBD patients been linked to that they have the same embryonic origin from the primitive for gut [10,17].

Circulating immune-complex and autoantibodies thought to play a role in a patient with IBD [10].

In addition to some environmental factors for example: smoking.

Some factors like smoking or persistent chronic lung disease prior to the onset of IBD make the correlation between this disease 'IBD' and the pulmonary manifestations or symptoms very difficult [9].

The pulmonary manifestations become more clinically obvious after surgery, colectomy may aggravate the respiratory symptoms [12] and considered as a risk factor to develop pulmonary disease in IBD patient [6], airway involvement after colectomy tend to be more severe [13].

This explained by that the inflammatory process been shifted from the bowel to the bronchial tree because they originate from the same embryonic origin, primitive foregut [19].

The pulmonary involvement in IBD divided into airway disease, pleural diseases, interstitial lung disease and drug induced lung injury.

Pulmonary manifestations in IBD patients

Airway disease in association to IBD

Tracheobronchial involvement

Non-specific respiratory symptoms such as cough, SOB wheezing was ranged from 25 - 50% in IBD patients [1] and some reported that it reached upto 85% [1].

The airway involvement was the most common pulmonary manifestations with a prevalence ranged from 40 - 63% [1,17], bronchiectasis, bronchitis, tracheobronchitis, bronchiolitis, granulomatous bronchiolitis all been reported [5,10] from the airway involvement, large airway disease is the most common form of pulmonary manifestations in IBD patients.

Large airway involvement and chronic bronchiolitis are strongly associated with UC rather than CD [13].

Small airway disease tends to occurs early in the course of the disease and in the younger ages [3].

The bronchiolitis equally relevant with the same incidence in the CD and UC, while the rest of airway diseases more prevalent in UC.

Upper airway particularly the trachea in form of stenosis sub-glottic or nodule are rarely involved but was documented.

The airway disease occurs many years after or may proceed the IBD [17], co-incidence with active IBD and post colectomy.

Parallel exacerbation of the airway disease during the disease activity also been described as well [13].

Fistula formation between the colon and the pleural cavity is extremely rare complication, colo-bronchial, colo-pleural is life threatening complications of CD [19].

The respiratory symptoms followed the onset of IBD by 12 years as an average. The duration ranged from 4 months to 35 years) [13].

Respiratory symptoms may be related to the disease activity but most of the time it is not parallel to the exacerbation of the disease [19].

Symptoms may precede the IBD symptoms by years, but most of the time it happened after long standing history of IBD [19].

Signs of airway involvement may happened after surgery (colon surgery) from days to months [19].

Productive and non-productive cough, SOB, wheezing, hemoptysis, chest pain all been reported as non-specific pulmonary involvement [19].

PFT found to be abnormal in about 50% (40 - 60%) of UC patients without clinical or radiological abnormalities [1,3,5,9,15], some studies mentioned that the PFT worsen during the disease activity - parallel to the luminal disease [8] and from those abnormalities decrease DLCO was found the most common abnormality in PFT [5,13]. DLCO is reduced in severe cases [19].

In one study showed that about 41% had positive methacholine test [19].

Fractional exhaled nitric oxide 'FeNO' found to be elevated in asymptomatic patient with IBD which may reflect long standing inflammatory process latent inflammation of the bronchial tree [5,10].

Lung transfer factor for carbon monoxide abnormalities related to the disease activity and based on that may be used as non-invasive test to determine the disease activity.

Lymphocytosis in BAL of IBD patient is also typical finding for airway involvement [5].

Lung function test in patient with tracheobronchitis secondary to IBD showed obstructive non-respond to bronchodilator.

Bronchoscopy, lavage and biopsy results [19].

Mucosal edema and hyperemia was found to be the most typical finding, stricture as well as inflammatory nodules was mentioned also.

Lymphocytosis in a patient with IBD who underwent BAL is typical [19].

Radiology

HRCT is useful to confirm bronchiectasis, in bronchiolitis showed irregular and patchy infiltration with different attenuation [19]. HRCT patterns includes: bronchiectasis, air trapping, 'tree in bed' changes [6] as well as bronchial wall thickness, dilated airways, bronchial opacities due to mucoid impaction [7] all been mentioned in the literature as a radiological manifestations that seen in airway diseases.

The most common HRCT patterns that are frequently seen are enlarged bronchial internal diameter, peri-bronchial wall thickening and air-trapping [11].

Prognosis and Tx

Corticosteroids are the most common drug used in the treatment of pulmonary diseases secondary to CD and the prognosis is generally favorable with high response rate upto 90% [15].

Inhaled or systemic steroid is generally effective, with large airway inflammation respond well to inhaled steroid than bronchiolitis. Patient with bronchiectasis less likely to respond to inhaled steroid and required oral steroid, in sever form of airway obstruction IV steroid is usually required. In general, systemic steroids are the treatment of choice [19].

Association between obstructive airway diseases and IBD

High incidence of bronchial hyper-responsiveness been reported in patients with IBD [9] reached upto 48%, and this has no relation to age, gender, time of the diagnosis of IBD or disease activity [9].

The prevalence of IBD was 4 times greater in patients with an airway disease [11], some studies mentioned if the airway disease was persisted for more than 10 years [9].

Airway diseases such as asthma, COPD and bronchiectasis increased the risk of IBD occurrence [11].

Genetics

- DENND1B, SMAD3 and SLC22A4/5 found to be associated with both asthma and CD
- ORMDL3 present in both CD and UC were found to be associated with childhood onset asthma
- NOD2 associated with both CD and COPD

All these supports the gene susceptibility hypothesis.

Smoking is an important risk factor for both airway diseases and CD.

Air pollution also is another environmental risk factor for both airway diseases and CD [11].

Asthma was found the most comorbidity in IBD patients after arthritis [4,11].

In asthmatic patient the incidence of CD is increased in all age groups [11].

In patient with COPD the incidence of both UC and CD increased in all age groups compared to the general population [11].

Younger age at the time of COPD diagnosis found to be associated with high prevalence of UC [11].

Compared to normal population the risk of COPD in CD patient was 2.7 times and in UC the risk is 1.8 times [19].

Interstitial lung disease

Organizing pneumonia from the ILD forms is highly frequent and considered the most common ILD associated with IBD [7], along with non-specific lymphocytic infiltrations and non-caseating granuloma, with no specification if it is related to CD or UC.

Eosinophilic pneumonia and pulmonary nodule have moderate frequency.

Induced by drugs that commonly been used in IBD treatment like sulfasalazine and 5ASA like bronchiolitis obliterans with organizing pneumonia BOOP or pulmonary infiltrates and eosinophilia 'PIE' [13].

Still controversial if BOOP and IBD are randomly associated or as extra-intestinal manifestations.

Clinical presentation [19]

Is very similar to tracheo-bronchial signs and symptoms. The ILD signs and symptoms do not correlated with the disease activity, general symptoms includes fever, weight loss, malaise, arthralgia was described. Is frequent in patient with OP and COP. Again it may precede the IBD signs and symptoms but usually it appears with long standing hx of IBD.

Lung function tests

May be normal or showed mild to severe restrictive pattern.

DLCO may reduced but normal value are frequently reported, but during exacerbation in respiratory free-symptoms DLCO was reduced [19].

Radiology [19]

In patient with OP, pneumonia-like-opacities is frequently seen.

Multiple nodules with different sizes may be present, also small cavitation may be present.

Interstitial pneumonitis is another radiological presentation. HRCT reveal ground-glass opacities, reticular pattern.

Upper lobe fibrosis also is another radiological picture that seen in ILD patient.

Pleural opacities and air-bronchogram are another CT finding in IBD patients who developed ILD [10].

Bronchoscopy and lavage

The cellular pattern is abnormal, increased total cell count and mild lymphocytosis are the typical findings. The diagnosis is usually confirmed by biopsy.

Treatment

ILD usually required systemic steroid e.g. Prednisolone 0.5 - 1 mg/kg/day depend on the clinical course [7] relapses may occur if the doses of steroids tapered down or withdrawn, in severe cases in addition to high dose of systemic steroids, cyclophosphamide may added to achieve good outcome. Anti-TNF is an alternation to systemic steroid and been used in the literature with good response.

Pleural diseases that are related to IBD

The pleural and pericardium are rarely involved as an EIM of IBD but been described in the literature as a case reports [16].

Thoracic serositis - pleuritis, pleural effusion, pericarditis, pleuropericarditis all been mentioned in the literature [16].

In the literature mentioned that about 3% of patient with IBD had pleuritis and pleural effusion 10% had pleuropericarditis. This was a total of 131 patient with IBD [16].

Pleural effusion related to IBD disease is a diagnosis of exclusion, had negative work-up for either infections or other auto-immune diseases and is related to the systemic inflammatory nature of IBD.

Is exudative in nature, unilateral, neutrophilic predominant, sterile on gram stain.

Medications induced serositis been described in the literatures as well such as sulfasalazine and 5-ASA.

The duration for pleuritis and pleural effusion to develop in a patient with IBD was ranged from few months to 10 years, some-times tend to precede the diagnosis of IBD [16].

Pleuropericardial diseases that are related to IBD disease is generally respond to anti-inflammatory systemic treatment, systemic steroid is usually needed in symptomatic patients to achieve adequate response.

Drug induced lung disease in IBD

Sulfasalazine and mesalazine

Interstitial disease, eosinophilic pleuritis and eosinophilic pneumonia all been described as lung pathology related to the use of these medications [10,13].

PIE induced by sulfasalazine was reported in about half of the cases that been reported in the literature [13], followed by ILD and BOOP.

Eosinophilic pneumonia was found the most common side effect associated with sulfasalazine and mesalazine [9], also it cause BOOP, interstitial pneumonitis.

5-ASA is superior to the sulfasalazine regarding the safety issue [13].

5-ASA had less side effect compared to sulfasalazine [13].

Recurrence of lung disease that caused by these medications after withdraw the drugs was described as well [13].

Sulfasalazine - reported to cause pulmonary diseases after at least two months on this medication (8) and some mentioned from 2 - 6 months [10].

With the use of systemic steroid along with withdraw of these medications these pulmonary diseases tend to be reversible [10]. But most of the patients could be managed by withdraw of the medication without needs for systemic steroid [13]

Azathioprine and 6-mercaptopurine are used in moderate to severe form of CD. Pulmonary toxicity, interstitial pneumonitis, BOOP, fibrosis and pulmonary edema described in the literature as lung related pathology associated with the use of these medications.

In addition to withdraw of the medications cyclophosphamide was needed and been used in some cases that been reported in the literature.

Methotrexate

The mechanism of How methotrexate can cause lung pathology remain unclear.

Interstitial pneumonia, granuloma formation and bronchiolitis found to be caused by the methotrexate.

Clinical picture includes fever, dyspnea, non-productive cough for that it is difficult to differentiate MTX -related lung pathology from other pulmonary diseases.

Lung function showed restrictive pattern with low carbon monoxide diffusion capacity, the BAL findings include: increase eosinophil and reversed CD4/CD8 ratio.

Thrombo-embolic events

IBD itself is a risk factor for thrombo-embolic events with an incidence ranged from 1 - 8% [3] with significant morbidity and mortality, venous is more common than arterial embolism. The risk is increasing during the disease activity.

The risk of thromboembolic events increased up-to 4 times in IBD patients compared to normal population [7,17].

Conclusion

Pleuropulmonary manifestations of inflammatory bowel diseases, lately frequently recognized extraintestinal manifestations of IBD the pathogenesis of the disease itself as well the complications of medications should be considered in all patients with IBD and pulmonary manifestations.

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