Pulmonary involvement of inflammatory bowel disease

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Summary

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases of the gastrointestinal tract with unknown etiology. Commonality between the gastrointestinal (GI) and respiratory systems provides developmental and pathophysiologic basis for respiratory involvement in IBD. Almost all the pulmonary and airways tissues may be involved, but hystology often is not specific of IBD. Pulmonary involvement may be present up to about half of the patients with IBD and it is independent from the duration and activity of disease. Nevertheless, pulmonary involvement in inflammatory bowel disease is generally responsive to steroid treatment. Early diagnosis and treatment is essential in order to prevent the development of persistent pulmonary disease. In this article, we briefly describe the pulmonary involvement during IBD.

KEY WORDS: inflammatory bowel disease, ulcerative colitis, Chron's disease, lung granuloma, airway disease, interstitial lung disease.

Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases of unknown etiology primarily involving the gastrointestinal tract, mainly the colon. Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of chronic IBD (1).
The occurence of extraintestinal manifestations (EIM) of IBD has been reported to range from 21 to 41% (2). It has been reported that patients with CD may show extraintestinal manifestations during their life in at least 25% of cases (3). These extraintestinal manifestations may involve skin (erythema nodosum, pyoderma gangrenosum), eyes (uveitis, episcleritis), liver (pericholangitis, hepatosteatosis), joints (peripheral and axial arhtropathies) and lungs (4).
Lung involvement in IBD was firstly reported in 1976 (5). Commonality between the gastrointestinal (GI) and respiratory systems provides some pathophysiologic basis for respiratory involvement in IBD. Either colon and lung epithelia share embryonic origin from the primitive foregut. Both tissues have goblet cells and submucosal glands as part of their luminal structure. In addition, both lung and GI tract have submucosal lymphoid tissue and play critical roles in host mucosal defense. The aberrations of either innate and acquired immunity may play a pathogenetic role in IBD, but the mechanisms are complex and not yet completely understood (6).

Commonality between the gastrointestinal (GI) and respiratory systems provides pathophysiologic basis for respiratory involvement of IBD.

Lung diseases associated to IBD can be classified into six subtypes according to clinicopathological features: airway disease, parenchymal disease, drug induced lung disease, pulmonary vascular disease, serositis or pleural disease (Table 1).

Airway disease

Upper Airway Obstruction

Common forms of airway involvement of IBD are glottic or subglottic stenosis and especially tracheal obstruction due to granuloma formation, expecially in patients with CD. These patients usually present with stridor and dyspnea. Hystologic features are not specific, so other causes of subglottic stenosis such as intubation, tuberculosis, sarcoidosis and amiloidosis should be excluded (7). Steroid treatment is often effective. Camus et al. (8), found 3 out of 33 patients with IBD having upper airway obstruction, 2 of them had a previous diagnosis of IBD, whilst the other one was recognized having IBD 1 month later the occurence of airways involvement. These 3 patients nearly fully recovered with both inhaled and systemic steroid treatment (8). A recently reported case of ulcerative colitis and tracheal stenosis requiring tracheostomy, showed a similar inflammatory pattern of either tracheal and colon involvement (9).

The commonest respiratory involvement during IBD is bronchiectasis of the large airways.

Table 1 - Pulmonary involvement of IBD.

Airway Disease
Upper airway obstruction
Large airway involvement
Small airway disease
Parenchymal Disease
Diffuse interstitial lung disease
Necrobiotic pulmonary nodules
Drug Induced Disease
Pulmonary vascular disease
Serositis
Other
Overlap syndrome
Anatomical disease

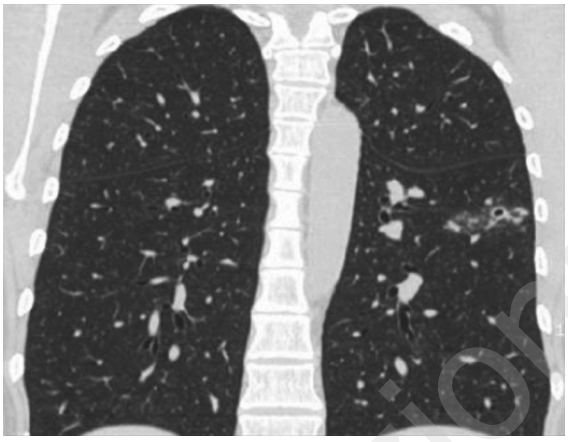

Figure 1 - Limited bronchial involvement during IBD (localized bronchiectasis).

Large Airways disease

Large airways involvement in IBD mainly presents as bronchiectasis and chronic bronchitis. Expectoration of abundant purulent sputum may occur in these patients. Sometimes, the bronchial involvement is localized and involved only few bronchial branches (Figure 1). Pulmonary function tests may show an obstructive defect with decreased FEV1/FVC ratio. Bronchoscopy reveals erythematous mucosal edema and inflammation. As shown in gut biopsy specimen, bronchial biopsy specimen shows submucosal lymphocyte, plasmocyte infiltration and mucosal squamous metaplasia and neutrophil infiltration (11).

Pathologically, bronchiolitis is the most commonly reported disease involving the small airways in patients with IBD, and it is frequently associated with peribronchiolar granuloma formation.

Black et al. (11), reported 171 respiratory pathologies in 155 patients, being the "large airways" 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, detected in a surprisingly high proportion (81%) of nonsmoker patients (11). These results confirm the previous findings of Camus et al. where 15 of 33 patients (45,4%) with IBD had large airways involvement, where 6 of them (40%) had bronchiectasis (8). It has been shown that exacerbation of bronchiectasis and intestinal disease occur at the same time (8, 10, 12, 13). In 2010, Yilmaz et al. found 2 bronchiectasis cases among 39 patients with IBD whereas, Ozyilmaz et al. found that among 25 patients with IBD prevalance of bronchiectasis was 66% (14, 15). Interestingly, a case of bronchiectasis associated with mesalazine use was also reported (16). The mechanism of pulmonary toxicity of mesalazine is unknown but an immune-mediated alveolitis is one possibility (17).

Small Airways Disease

Clinically, small airways are rarely affected in IBD. However, high resolution computed tomography (HRCT) has increased the detection rate of small airway involvement in these patients (18).

Pathologically, bronchiolitis is the most commonly reported disease involving the small airways in patients with IBD, and it is frequently associated with peribronchiolar granuloma formation (8, 19, 20). Both Vandenplas et al. and Trow et al. reported granulomatous bronchiolitis in women with CD who had undergone bowel resection (22). Less frequently reported findings include peribronchiolar inflammation with either neutrophils or lymphocytes and plasma cells, concentric small airway fibrosis, and diffuse panbronchiolitis (11). It has been reported that young people affected by CD may have bronchial hyperreactivity and asthma respectively up to 71% and 17% of cases (23). Kullman et al. showed that metacholine test was positive in 18% of patients with Crohn's disease and in 8% of patients with ulcerative colitis patients, respectively (24).

Parenchymal diseases

Diffuse Interstitial Lung Disease

Different diffuse parenchymal lung diseases may be variously associated with IBD. According to the review of Black et al., 40 out of 155 patients with IBD had pulmonary parenchymal involvement. Among these patients, 21 had OP, 6 pulmonary nodule, 6 fibrosing interstitial lung disease, 3 pulmonary interstitial emphysema, 1 desquamative interstitial pneumonia (DIP), 1 nonspecific intertitial pneumonia (NSIP), 1 fibrosing alveolitis/UIP pattern and 1 had eosinophilic pneumonitis (11).

Lung parenchymal involvement is relatively common in IBD patients, and organizing pneumonia (COP) is the most common reported manifestation.

Yilmaz et al. showed that among 33 patients with IBD, HRCT revealed reticulonodular pattern in 1 and ground-glass opacity in 8 patients

(14). Omori at al. found 10 patients with non specific ILD among 22 with IBD (25).
Lung parenchymal involvement are relatively common in IBD patients, and organizing pneumonia (OP) is the most commonly reported pattern (11). In most patients OP generally follows the onset of IBD, and presents with fever, dyspnea, dry cough, pleuritic chest pain and weight loss (11, 26). In the study of Camus et al., OP was detected in 6 of 33 patients (of these 6 patients 5 had UC and 1 had crohn disease). Interval between diagnosis of IBD and OP was found to be 2 months to 36 years. Association between colectomy and OP was not found. No association was also found between drugs used for IBD (such as sulfasalasine and 5-ASA) and development of OP (11). Organizing pneumonia associated with IBD is observed in a younger patient population when compared with cryptogenic OP and other forms of OP (27). However, treatment with oral corticosteroid can either improve IBD-related interstitial disease (8) and OP (28, 29).

Necrobiotic Pulmonary Nodules

When examined, these cavitary nodules of lung parenchyma reveal fibrinous exudates and neutrophilic infiltration in necrotic areas. Pyoderma gangrenosum may also accompany these radiological findings in those patients (30).
In a review of 155 patients, Black et al. found high prevalance of pulmonary nodule in IBD patients. Histologically, these lesions have been reported to be necrobiotic (25%), granulomatous (12,5%), or otherwise (11).
Necrotic granuloma should come be considered for differential diagnosis. In cavitary lesions associated with IBD, central necrosis is present without formation of giant cells. Absence of vasculitis (there may be accumulation of secondary inflammatory cells in some vessels) and granuloma formation is important for differentiation from Wegener granulomatosis. Steroids are effective for the treatment of necrobiotic pulmonary nodules but infectious pathologies should be rulled out (7).

Drug induced diseases

Sulfasalazine (a combination of 5-ASA and sulfapyridine linked through a diazo bond) and mesalamine (5-ASA) have long been used as maintenance therapy in IBD. The most common disease entity associated with these drugs is eosinophilic pneumonia (9-16), which is defined as an infiltration of the lungs with eosinophils with or without excessive eosinophils in the peripheral blood. The differential diagnosis of pulmonary eosinophilia includes asthma, infection, sarcoidosis, malignancy, and collagen vascular diseases (31).

Treatment of IBD with sulfasalazine may cause a drug-induced eosinophilic pneumonia, which is defined as an infiltration of the lungs with eosinophils with or without excessive eosinophils in the peripheral blood.

Sulfasalazine is responsible for 71% of drug induced pulmonary pathologies, whereas mesalazine is responsible for the rest 29%.
Up to 40% of these patients has peripheral eosinophilia and 27% has pulmonary fibrosis. Upon drug withdrawal, pulmonary disease resolves within days to weeks. Steroid therapy accelerates recovery time (32, 33).
Methotrexate which has recently been shown to be effective when used for long-term maintenance therapy in CD, is associated with a drug induced pneumonitis that can become life threatening (31).
Anti-TNF agents are among treatment options for IBD. Recently, increasing number of tuberculosis and pulmonary sarcoidosis cases associated with these agents have been reported. Attention should be paid for secondary infections because of immunosuppression associated with these agents (7).

Pulmonary vascular diseases

Both arterial and venous thrombosis have been described in association with UC and CD, with an incidence between 1 and 8% (34). The pathogenesis of thromboembolic disease in patients with IBD is unclear. Individuals with UC and CD have not been found to have a higher incidence of thrombophilic factors such as activated protein C resistance or factor V Leiden mutation than the general population (35). Hyperhomocysteinemia, a risk factor for arterial and venous thrombosis, has been described in patients with IBD (36). However this state can becaused by genetic factors, medications (sulfasalazine, methotrexate, corticosteroids) and nutritional deficiencies (folate, B6, B12 deficiency), all of which can be linked to IBD (31).

Pleural diseases

According to the review of Black et al. pleural and pericardial manifestations of IBD are uncommon. Most patients described with serositis are young, male, and have UC. Pleural involvement is nearly always unilateral; when examined, pleuralfluid tends to be exudative in nature (11). These patients present with dyspnea, chest pain, or both, which is often pleuritic in nature. No correlation has been found between gastrointestinal symptoms and disease. Most symptoms resolve with steroid treatment (8, 31). In a review including 41 patients, Camus et al. found a positive correlation between serositis and active IBD (8).

Other pulmonary diseases

Overlap Syndrome

Sarcoidosis and CD are both granulomatous diseases, of the lung and bowel respectively, with unknown etiology. Interestingly some cases of IBD and concomitant sarcoidosis have been reported. Genetically, both

α1 antitrypsine deficiency and IBD may accompany each other.

CD and sarcoidosis seem to have a genetic component as they are more common in monozygotic than in dizygotic twins. Recently, it has been suggested that CD may be linked to genetic regions on chromosome 12 and 16 (31).
Crohn disease and sarcoidosis may also involve eyes, joints and skin apart from intestinal and pulmonary manifestations (37).
Storch et al. (31) documented 46 cases of IBD and concomitant sarcoidosis in a review of the literature in 2003. Black et al. also documented 7 cases of IBD and concomitant sarcoidosis in a review of the literature in 2007 (11). According to our literature search (2007 and onwards), 5 new pulmonary and extra-pulmonary sarcoidosis cases had been reported. 3 of these cases were skin sarcoidosis that developed during anti-TNF treatment. Two of these 3 patients had CD and the other had UC. Other two patients were diagnosed with systemic sarcoidosis during routine follow-up (38-43). We have identified 7 more reports about this association, bringing the total reported cases of coexisting disease to 58.
α1 antitrypsine deficiency and IBD may be associated, and at least thirteen patients with α1 antitrypsin deficiency and IBD have been reported in the literature (44-47).

Bronchial fistula (anatomical disease)
Fistula formation is frequent in Crohn's disease and occurs in approximately 33% of patients (48). On the other hand, fistulous communication between the pleural cavity and adjacent organs below the diaphragm is an extremely rare complication of Crohn's disease. The pathophysiology of fistulous tract development in Crohn's disease is yet unknown (49). Colobronchial fistulas have been quite frequently described in Crohn's disease, in most cases between splenic flexure of colon and left bronchial tree and in one case between splenic flexure of colon, stomach and left bronchial tree (50-53). Recurrent pneumonia with feculent sputum in patients with Crohn's disease should raise suspicion of colobronchial fistula (49).

Why it is important to detect pulmonary involvement?

A number of reports indicated that the respiratory system is involved more frequently than expected in IBD. Pulmonary involvement is present in about half of the patients with IBD and it is independent from the duration and activity of disease (15). Interstitial pulmonary disease, necrobiotic nodules and serositis respond well to steroid treatment. It is possible to prevent development of persistent airway and parenchymal injuries by early detection of pulmonary involvement. Evidence exists regarding usefulness of exhaled nitric oxide (FE_{NO}) to show activity of pulmonary involvement in IBD patients. In a study including 25 IBD patients, Ozyilmaz et al. showed that in patients with active pulmonary involvement higher FE_{NO} levels were found when compared to controls (15). However, further studies are warranted regarding FE_{NO}.

Pulmonary involvement is present in about half of the patients with IBD and it is independent from the duration and activity of disease, but it is responsive to steroids treatment.

Conclusion

In light of above-mentioned data, pulmonary involvement secondary to IBD is substantially relevant. Bronchiectasis is the most common form of respiratory tract abnormality seen among patients with IBD, but the spectrum of involvement spans the entire respiratory system, from larynx to pleura. Early diagnosis and treatment is essential in order to prevent development of persistent pulmonary disease.

References

1. D'Andrea N, Vigliarolo R, Sanguinetti CM. Respiratory involvement in inflammatory bowel diseases. Multidisciplinary Respiratory Medicine 2010;5 (3): 173-182.
2. Rankin GB, Watts HD, Melnyk CS, Kelley ML Jr. National Cooperative Crohn's Disease Study: extra intestinal manifestations and perianal complications. Gastroenterology 1979;77:914-20.
3. Ephgrave K. Extra-intestinal manifestations of Crohn's disease. Surg Clin North Am 2007;87:673-680.
4. Su CG, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Clin North Am 2002;31:307-27.
5. Kraft SC, Earle RH, Rossler M, Estarly JR. Unexplained bronchopulmonary disease with inflammatory bowel disease. Arch Intern Med 1976;136:454-9.
6. Bamias G, Nyce MR, De La Rue SA, Cominelli F. New concepts in the pathophysiology of inflammatory bowel disease. Ann Intern Med 2005;143:895-904.
7. Ceyhan B. Inflammatory bowel disease and lung. TuberkToraks 2006;54(3):292-298.
8. Camus P, Piard F, Ashcroft T, Gal AA, Colby TVL. The lung in inflammatory bowel disease. Medicine (Baltimore) 1993;72:151-83.
9. Nakamura M, Inoue T, Ishida A, Miyazu YM, Kurimoto N, Miyazawa T. Endobronchial ultrasonography and magnetic resonance imaging in tracheobronchial stenosis from ulcerative colitis. J Bronchology Interv Pulmonol 2011 Jan;18(1):84-7.
10. Kinnear W, Higenbottam T. Pulmonary manifestations of inflammatory bowel disease. Intern Med Specialist 1983;4:104-11.
11. Black H, Mendoza M, Murin S. Thoracic manifestations of inflammatory bowel disease. Chest 2007; 131:524-532.
12. Spira A, Grossman R, Balter M. Large airway disease associated with inflammatory bowel disease. Chest 1998;113:1723-6.

13. Moles KW, Varghese G, Hayes JR. Pulmonary involvement in ulcerative colitis. Br J Dis Chest 1988;82:79-83.
14. Yilmaz A, Demirci N, Hosgun D. Pulmonary Involvement in Inflammatory Bowel Disease. World Gastroenterol 2010 October 21;16(39):4952-4957.
15. Ozyilmaz E, Yildirim B, Erbas G, Akten S, Oguzulgen IK, Tunc B, et al. Value of Fractional Exhaled Nitric Oxide (FENO) for the Diagnosis of Pulmonary Involvement Due to Inflammatory Bowel Disease. Inflamm Bowel Dis 2010;16:670-676.
16. Price LC, Poullis, S Grubnic, Kang JY, Rayner CFJ. Mesalazine-induced bronchiectasis and eosinophilia in a patient with ulcerative colitis: a case report. J R Soc Med 2007;100:151-152.
17. Foster R, Zander D, Mergo PJ, Valentine JF. Mesalamine-Related lung disease: clinical, radiographic and pathological manifestations. Inflamm Bowel Disease 2003;9:308-15.
18. Mahadeva R, Walsh G, Flower CD, Shneerson J.M. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. Eur Respir J 2000;15:41-48
19. Kraft SC, Earle RH, Roesler M, Esterly JR. Unexplained bronchopulmonary disease with inflammatory bowel disease. Arch Intern Med 1976;136:454-459.
20. Vandenplas O, Casel S, Delos M, Trigaux JP, Melange M, Marchand E. Granulomatous bronchiolitis associated with Crohn's disease. Am J Respir Crit Care Med 1998;158:1676-1679.
21. Desai SJ, Gephardt GN, Stoller JK. Diffuse panbronchiolitis preceding ulcerative colitis. Chest. 1989 Jun;95(6):1342-4.
22. Trow TK, Morris DG, Miller CR, Homer RJ. Granulomatous bronchiolitis of Crohn's disease successfully treated with inhaled budesonide. Thorax 2009; 64:546-547.
23. Mansi A, Cucchiara S, Greco L, Sarnelli P, Pisanti C, Franco MT, et al. Bronchial hyperresponsiveness in children and adolescents with Crohn's disease. Am J Respir Crit Care Med 2000;161:1051-4.
24. Kullman M, Kullman F, Andus T. Pulmonary involvement in inflammatory bowel disease. Am J Respir Crit Care Med 1998;157:807.
25. Omori H, Asahi H, Inoue Y, Irinoda T, Saito K. Pulmonary involvement in Crohn's disease. Report of a case and review of the literature. Inflamm Bowel Dis 2004;10:129-34.
26. Veloso FT, Carvalho J, Magro F. Immune-related manifestations of inflammatory bowel disease. A prospective study of 792 patients. J Clin Gastroenterol 1996;23:29-34.
27. Swinburn C, Jakson G, Cobden I. Bronchiolitis obliterans organizing pneumonia in a patient with ulcerative colitis. Thorax 1981;43:735-6.
28. Swinburn CR, Jackson GJ, Cobden I, Ashcroft T, Morritt GN, Corris PA. Bronchiolitis obliterans organising pneumonia in a patients with ulcerative colitis. Thorax 1988;43:735-736.
29. Carratù P, Dragonieri S, Nocerino MC, Trabucco SM, Lacedonia D, Parisi G, et al. A case of cryptogenic organizing pneumonia occurring in Crohn's disease. Can Respir J 2005;12:437-439.
30. Kemeny JL, Andre M, Charlotte F, Piette JC, Amouroux J, Aumaitre O. Aseptic abscesses in eight patients with inflammatory bowel disease. Ann Pathol 1999;19:294-8.
31. Storch I, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. Inf Bowel Dis 2003;9:104-15.
32 . Lazaro M, Garcia-Tejero M, Diaz-Lobato S. Mesalamin induced lung disease. Arch Intern Med 1997; 154:462.
33. Baillie J. Sulfasalazine and pulmonary infiltrates. Am J Gastroenterol 1984;79:77.
34 . Bernstein CN, Blanchard JF, Houston DS, Wajdu A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease; a population based cohort study. Thromb Haemost 2001;85:430-4.
35. Novacek G, Miehsler W, Kapiotis S, Katzenschlager R, Speiser W. Thromboembolism and resistance to activated protein C in patients with inflammatory bowel disease. Am J Clin Gastroenterol 1999;94:685-90.
36. Aichbichler BW, Petritsch W, Reight GA, Wenzl HH, Eherer AJ, Hinterleitner TA. Anti-cardiolipin antibodies in patients with inflammatory bowel disease. Dig Dis Sci 1999;44:852-6.
37. Fries W, Grassi SA, Leone L, Giacomin D, Galeazzi F, Naccarato R, et al. Association between inflammatory bowel disease and sarcoidosis. Report of two cases and review of the literature. Scan J Gastroenterol 1995;30:1221-3.
38. Hayashi T, Nakamura T, Kurachi K, Asai Y, Nakajima A, Suzuki S, et al. Ulcerative colitis accompanied with sarcoidosis and dermatomyositis: report of a case. Dis Colon Rectum 2008 Apr;51(4):474-6.
39. Kallel L, Fekih M, Ben Ghorbel I, Chelly I, Houman H, Filali A. A rare case of systemic sarcoidosis followed by Crohn's disease: a fortuitous association or etiopathogenic link?. Presse Med 2010 Jan;39(1): 148-50.
40 . Takahashi H, Kaneta K, Honma M, Ishida-Yamamoto A, Ashida T, Kohgo Y, et al. Sarcoidosis during infliximab therapy for Crohn's disease. J Dermatol 2010 May;37(5):471-4.
41. Parisinos CA, Lees CW, Wallace WA, Satsangi J. Sarcoidosis complicating treatment with natalizumab for Crohn's disease. Thorax 2011 Dec;66(12):1109-10.
42. Izumikawa K, Motoi N, Takaya H, Miyamoto A, Eishi Y, Yoshimura K, et al.A case of concurrent sarcoidosis, aortitis syndrome and Crohn's disease. Intern Med 2011;50(23):2915-7.
43. Fok KC, Ng WW, Henderson CJ, Connor SJ.Cutaneous sarcoidosis in a patient with ulcerative colitis on infliximab. J Crohns Colitis 2012 Jul;6(6):708-12.
44. Yang P, Tremaine WJ, Meyer RL Prakash UB. Alpha-1 antitrypsin deficiency and inflammatory bowel diseases. Mayo Clin Proc 2000;75:450-455.
45. Lewis M, Kallenbach J, Zaltzman M, Levy H, Lurie D,

Baynes R, et al. Severe deficiency of alpha 1-antirypsin associated with cutaneous vasculitis, rapidly progressive glomerulonephritis and colitis. Am J Med 1985;79:489-94.
46. Gambichler T, Reich S, Banasch M, Altmeyer P. Complex extra-intestinal complications of ulcerative colitis in a patient with alpha1 antitrypsin deficiency.Eur J Med Res 2006 Mar 27;11(3):135-8.
47. Halsey K, Reichelderfer M, Callicott RW, Schwartz DC. Collagenous colitis presenting after orthotopic liver transplantation for alpha-1-antitrypsin deficiency. Dig Dis Sci 2007 Jan;52(1):217-9.
48. Singh D, Cole C, Cali L, Proctor D.Colobronchial fistula: an unusual complication of Crohn's disease. Am J Gastronterol 1994,89:2250-2.
49. Barišiæ G, Krivokapiæ Z, Adžiæ T, Pavloviæ A, Popoviæ M, Gojniæ M. Feco pneumothorax and colopleural fistula – uncommon – complications of Crohn's disease. BMC Gastroenterology 2006,6:17.
50. Flueckiger F, Kullnig P, Melzer G, Posch E.Colobronchial and gastrocolic fistulas: rare complication of Crohn's disease. GastrointestRadiol 1990, 15:288-90.
51. Mera A, Sugimoto M, Fukuda K.Crohn's disease associated with colo-bronchial fistula. Inter Med 1996,35:957-60.
52. Karmy-Jones R, Chagpar A, Vallieres E, Hamilton S.Colobronchial fistula due to Crohn's disease. Ann Thorac Surg 1995,60:446-8.
53. Domej W, Kulling P, Petritish W.Colobronchial fistula: a rare complication of Crohn's colitis. Am Rev Respir Dis 1990,142:1225-7.