CASE REPORT

TJG
The Turkish Journal of Gastroenterology

A case of ulcerative colitis complicated with bronchiolitis obliterans organizing pneumonia (BOOP) and air leak syndrome

Müge AYDOĞDU[1], Gül GÜRSEL[1], Ezgi ÖZYILMAZ[1], Nalan AKYÜREK[2], Leyla MEMİŞ[2]

Departments of [1]Pulmonary Diseases and [2]Pathology and the Intensive Care Unit Gazi University School of Medicine, Ankara

Extraintestinal manifestations of inflammatory bowel diseases are well recognized and mainly affect the joints, skin, liver, and eyes; however, clinically significant pulmonary involvement is very rare. Early identification of pulmonary involvement is important and will be life-saving. We report herein a case of an ulcerative colitis patient, presenting with acute respiratory distress syndrome and bilateral recurring pneumothorax, pneumomediastinum and subcutaneous emphysema, i.e., air leak syndrome. He was diagnosed with open lung biopsy as bronchiolitis obliterans organizing pneumonia most probably due to viral etiology and responded well to steroid therapy, with almost complete resolution of radiographic and clinical findings. In inflammatory bowel disease patients, bronchiolitis obliterans organizing pneumonia developing due to viral or fungal infectious etiology or due to the inflammatory bowel disease itself may progress to acute respiratory distress syndrome and may present with air leak syndrome. Early detection is important and life-saving, since bronchiolitis obliterans organizing pneumonia often responds well to steroid treatment provided an infectious etiology has been excluded or adequate antimicrobial therapy has already been initiated.

Key words: Ulcerative colitis, air leak syndrome, bronchiolitis obliterans organizing pneumonia, spontaneous pneumothorax

Bronşiolitis obliterans organize pnömoni (BOOP) ve hava kaçış sendromu ile komplike olan bir ülseratif kolit olgusu

İnflamatuar barsak hastalıklarının eklemleri, cildi ve gözleri tutan ekstraintestinal bulguları sıklıkla tanımlanmıştır ancak akciğer tutulumu oldukça nadirdir. Akciğer tutulumunun erken tespit ve tedavi edilmesi oldukça önemli ve hayat kurtarıcıdır. Burada akut solunumsal distres sendromu ve bilateral tekrarlayan pnömotoraks, pnömomediastinum ve subkütan amfizem (hava kaçış sendromu olarak tanımlanır) tablosu ile yoğun bakım ünitemizde izlenen bir ülseratif kolit hastası sunuldu. Kendisine açık akciğer biyopsisi ile büyük olasılıkla viral enfeksiyon sonrası gelişen bronşiolitis obliterans organize pnömoni tanısı konuldu ve hasta steroid tedavisi ile başarılı bir şekilde tedavi edildi. Viral veya fungal enfeksiyonlara veya inflamatuvar barsak hastalığının kendisine bağlı olarak gelişen bronşiolitis obliterans organize pnömoni akut respiratuvar distres sendromuna ilerleyebilir ve hava kaçış sendromu ile kendini gösterebilir. Bu hastalarda erken tanı ile birlikte, enfeksiyonun dikkatli bir şekilde ekarte edilmesinden veya uygun antimikrobial tedavi başlanmasından sonra uygulanacak steroid tedavisi hayat kurtarıcı olabilir.

Anahtar kelimeler: Ülseratif kolit, hava kaçış sendromu, bronşiolitis obliterans organize pnömoni, spontan pnömotoraks

INTRODUCTION

Ulcerative colitis (UC) and Crohn disease (CD) are inflammatory bowel diseases (IBDs) with unknown etiology that present with chronic inflammation of the gastrointestinal system. Although extraintestinal manifestations of IBDs are well recognized (13-45%), mainly affecting the joints, skin, liver, and eyes, clinically significant pulmonary involvement is very rare (1-4).

Address for correspondence: Müge AYDOĞDU
University of Gazi, School of Medicine, Pulmonary Diseases Department and Intensive Care Unit, Ankara, Turkey
E-mail: mugeaydogdu@yahoo.com

Manuscript received: 26.07.2011 **Accepted:** 14.11.2011

Turk J Gastroenterol 2012; 23 (5): 590-595
doi: 10.4318/tjg.2012.0428

We report herein a male UC patient with a severe life-threatening pulmonary complication as bronchiolitis obliterans organizing pneumonia (BOOP) probably due to viral etiology. He presented with recurrent bilateral pneumothorax, pneumomediastinum and subcutaneous emphysema, i.e., air leak syndrome.

CASE REPORT

A 57-year-old male patient with a 32-year history of UC had been treated with 1.5 g 5-aminosalicylic acid (ASA) (mesalazine) for four years. He had never smoked and had no history of allergic or respiratory diseases. In March 2007, under mesalazine treatment with the complaints of anorexia, weight loss (10 kg), frequent bowel movements (20 times a day with bloody diarrhea), and abdominal pain, a colonoscopy was performed, and severe active extensive UC was observed. He was started on 15 mg p.o. daily prednisolone therapy in addition to mesalazine in April 2007. One month later, although the manifestations of UC had improved, he developed cough, shortness of breath, fever, myalgia, and malaise. He was first examined by his gastroenterologist, and with the identification of diffuse bilateral reticular infiltration in his chest X-ray, he was referred to a pulmonary clinic. He was hospitalized, and a nonspecific antibiotic therapy as moxifloxacin 400 mg i.v. 1x1 was initiated. A thorax computerized tomography (CT) was performed, and multifocal areas of ground-glass opacifications and mediastinal emphysema were identified (Figure 1). Fiberoptic bronchoscopy was planned but could not be performed due to his deteriorating clinical status, and he was transferred to the intensive care unit (ICU). Physical examination on admission revealed a respiratory rate of 48/min, temperature of 38.2°C, heart rate of 122/min, bilateral fine crackles on whole lung fields, cyanosis, and clubbing in fingers. Blood chemistry values were found as erythrocyte sedimentation rate (ESR) 62 mm/hr, C-reactive protein (CRP) 136 mg/L, hemoglobin (Hb): 13.5 g/L, hematocrit (Hct) 40.3%, white blood cells (WBC): 9160/mm^3, platelet count 140,000, and procalcitonin 0.1 ng/ml (normal range: 0-0.5 ng/ml). On admission, nasal oxygen supplementation was initiated as 10 L/min with a PaO_2/FiO_2= 180. Because of the possibility of a severe opportunistic infection, prednisolone treatment was tapered gradually and then stopped. He was started on piperacillin tazobactam 3x4.5 g i.v., clarithromycin 2x500 mg i.v. and trimethoprim-sulfamethoxazole (TMP-SMX) treatment. Since 5-ASA-associated pneumonitis was another suspected diagnosis, it was also stopped. His repeat chest radiographs revealed a significant progression of the interstitial shadowing in both lungs. The radiological appearance as bilateral infiltration, PaO_2/FiO_2 ratio of <200, and absence of left heart failure findings in the echocardiography were suggestive of acute respiratory distress syndrome (ARDS). On the day of admission, in addition to routine biochemical and hematological tests, all cultures (pharynx, sputum, urine, and blood) were obtained for bacterial, fungal and viral [cytomegalovirus (CMV), influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, metapneumovirus] analysis. Urine antigen tests for Legionella, blood and sputum polymerase chain reaction (PCR) analyses for *Pneumocystis carinii* pneumonia and mycobacterial, viral (CMV), and fungal infections were carried out. Serum connective tissue markers such as perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic (c)-ANCA, anti-nuclear antibody (ANA), and anti-dsDNA were studied, and all were identified as negative except for p-ANCA. Fiberoptic bronchoscopy was performed under noninvasive mechanical ventilation, and bronchial lavage samples were obtained from both lower lobes. Due to his low PaO_2/FiO_2 ratio, transbronchial biopsy could not be performed. Bronchial lavage samples were also sent for the same cultures as described above. Among the microbiologic analyses, all cultures were identified as negative except

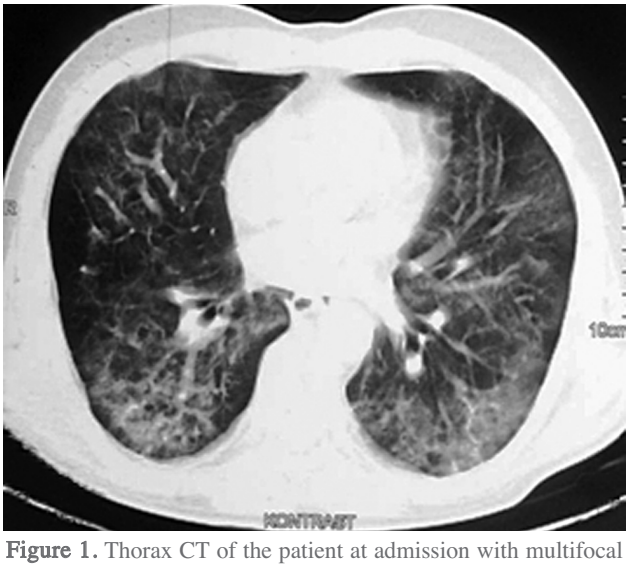

Figure 1. Thorax CT of the patient at admission with multifocal areas of ground-glass opacifications and mediastinal emphysema.

the positive panfungal PCR test results and *Candida tropicalis* growth in cultures of both sputum and bronchial lavage samples. CMV PCR was found as positive at a concentration of >1000 copies in bronchial lavage samples. According to these results and with the worsening clinical status of the patient, a high resolution computerized tomography (HRCT) was repeated and revealed progression in the multifocal ground-glass opacities and mediastinal emphysema, multiple pneumocysts and multiple patchy consolidation areas (Figure 2). Ganciclovir 2x300 mg i.v. and fluconazole 2x400 mg i.v. (found as susceptible in the antibiotic susceptibility tests for *C. tropicalis*) were initiated. During his follow-up in the ICU, progression of mediastinal emphysema led to severe subcutaneous emphysema with severe coughing. Then, multiple recurring pneumothorax episodes developed spontaneously first in the right lung and then in the left. Chest drainage tubes were inserted several times and pleurodesis was performed to the right lung. In order to prevent the progression of this air leak syndrome presenting as mediastinal and subcutaneous emphysema and pneumothorax, codeine p.o. was initiated for cough suppression. Since his respiratory status deteriorated further, he was intubated and mechanically ventilated. On the same day, mini thoracotomy was performed and lung biopsy was obtained. Pathologic examination of the biopsy material revealed that the normal structure of the lung parenchyma was disturbed; alveolar distortion and immature collagen tissue proliferations inside the alveoli macrophages were observed. Diffuse metabolic transformation of the alveolar epithelium and changes in the alveolar epithelium nuclei compatible with the viral cytopathic effect were identified (Figures 3, 4). All these findings were interpreted as BOOP, most likely due to viral etiology. After this diagnosis, possible viral etiologies were investigated from the tissue biopsy material. CMV, adenovirus, Epstein-Barr virus (EBV), herpesvirus, and BK virus were all found negative. With the diagnosis of BOOP, methylprednisolone 1 mg/kg (60 mg) daily was added to the previously administered treatment including also antiviral therapy. After methylprednisolone therapy, the clinical status of the patient dramatically and rapidly improved. With successful weaning, he was extubated five days later. In his follow-up chest radiographs and HRCT, significant improvement was identified, and ground-glass opacifications and mediastinal emphysema regressed significantly (Figure 5). Twenty

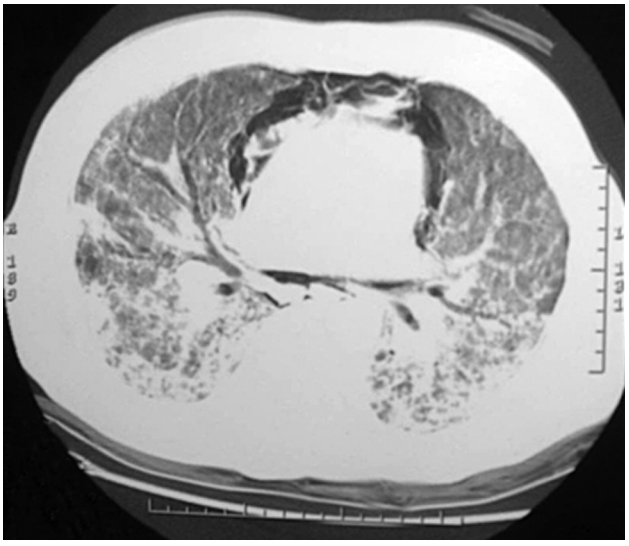

Figure 2. HRCT of the patient revealing a progression in the multifocal ground-glass opacities and mediastinal emphysema, multiple pneumocysts and multiple patchy consolidation areas.

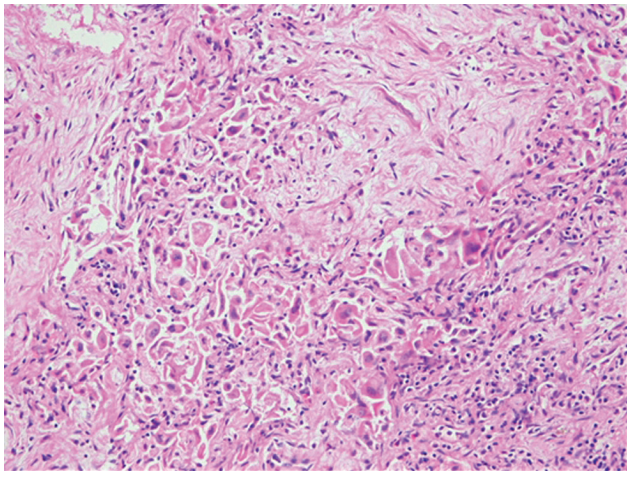

Figure 3. Branching plugs of granulation tissue in alveoli with a few larger cells suggestive of viral cytopathic effect (HE, x200).

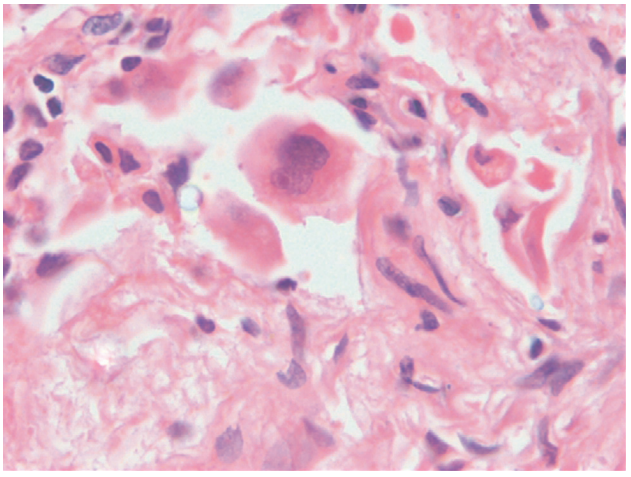

Figure 4. High power showing large alveolar cells with cytomegaly (HE, x400).

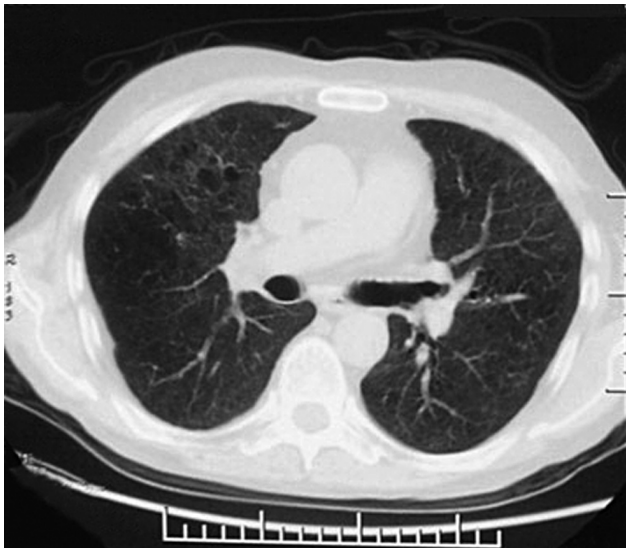

Figure 5. Thorax CT before discharge of the patient from the intensive care unit. Ground- glass opacities and mediastinal emphysema had all regressed. Only small air cysts can be seen in the lung parenchyma.

days later, he was discharged from the hospital without a need for oxygen, with PaO_2/FiO_2 of 360, and methylprednisolone level was tapered to 32 mg p.o. He was asked to present for outpatient follow-up monthly, and his steroid treatment was lowered to 10 mg methylprednisolone daily. He was started once again on the mesalazine therapy for his UC. One month later, although he was receiving both mesalazine and 10 mg methylprednisolone daily, he was once again hospitalized in the Gastroenterology Department due to frequent bowel movements (30-40/day) and abdominal pain. With the suspicion of activation of UC, colonoscopy was performed and CMV colitis was diagnosed. Once again, ganciclovir treatment was initiated. During his follow-up in the Pulmonary Diseases Department outpatient clinic, no further deterioration in his respiratory status was detected.

DISCUSSION

This patient demonstrates a serious, nearly fatal pulmonary involvement of UC as BOOP presenting with ARDS and air leak syndrome. To the best of our knowledge, air leak syndrome has been reported in a few patients with BOOP (5,6), but this is the first case of an UC patient presenting with BOOP, most probably associated with CMV infection, and progressing to air leak syndrome that responded well to the steroid therapy.

Ulcerative colitis (UC) and CD mainly affect the gastrointestinal tract but may also involve other organs since they are systemic disorders (2-4). Recently, Storch et al. (3) reported in their study that pulmonary involvement is more frequent in female UC patients. Camus and coworkers (7) described a number of pulmonary manifestations in adult patients with UC, such as upper airway stenosis, tracheobronchitis, bronchiectasis, constrictive bronchiolitis, panbronchiolitis, necrobiotic nodules, interstitial lung disease, BOOP, sarcoidosis, pulmonary vasculitis, eosinophilic pneumonia, serositis, and thromboembolic events.

Bronchiolitis obliterans organizing pneumonia (BOOP) is characterized by polypoid endobronchial connective tissue masses composed of myxoid fibroblastic tissue resembling granulation tissue filling the lumens of the terminal and respiratory bronchioles and extending in a continuous fashion into alveolar ducts and alveoli, representing an organizing pneumonia (8). Other histological features include central clusters of mononuclear inflammatory cells possibly found in the intraluminal polyps, chronic inflammation in the walls of the surrounding alveoli with reactive type II cells, increased foamy macrophages in the alveoli, and preserved lung architecture. BOOP may be classified into three categories according to its etiology: organizing pneumonia of determined cause, organizing pneumonia of undetermined cause but occurring in a specific and relevant context, and cryptogenic (idiopathic) organizing pneumonia (9). BOOP can be seen in UC due for several reasons, such as reaction to viral, bacterial and fungal infections, the IBD itself, or drug reactions (10-13). Persistent airway inflammation can result in airway narrowing, dependent on the localization, resulting in tracheal stenosis, bronchiectasis or bronchiolitis obliterans. We considered the possible causes of BOOP in our patient as viral or fungal infections due to immune suppression, drug reactions, i.e., the use of mesalazine, or presence of an IBD.

In the series of Camus (7), BOOP was identified in 6 of the 33 IBD patients (5 with the diagnosis of UC and 1 with CD). The development of BOOP was found to be independent of previously used medications such as sulfasalazine and 5-ASA. The most commonly seen side effect with these medications (5-ASA-mesalamine and sulfasalazine) is eosinophilic pneumonia, which is characterized by fever, infiltration in the lungs and/or skin eruptions and/or peripheric eosinophilia. This clinical

picture subsides rapidly with the cessation of drugs, within days or weeks (14). Although our patient was using mesalazine, he had no signs of eosinophilic pneumonia (no skin eruptions and/or peripheric eosinophilia). Although Camus et al. (7) reported BOOP as independent of sulfasalazine and 5-ASA, in several other reports, sulfasalazine therapy was found to be associated with BOOP (15,16). Drug-induced lymphocyte stimulation test (DLST) must be performed for the exact diagnosis of mesalazine-induced lung disease. We could not perform this test in our patient so we could not exclude the possibility of BOOP developing due to mesalazine therapy. However, since his clinical picture worsened even with drug cessation, CMV colitis was diagnosed one month later in colonoscopic biopsy material, and the pathologic examination of the lung tissue material indicated the organizing pneumonia as most probably due to viral etiology, CMV was considered the most probable pathogen.

In BOOP, the typical patient presents with dyspnea, cough, fever, weight loss, and single or multiple alveolar opacities on the chest radiograph (17,18). Although the clinical presentation of our patient was also compatible with BOOP, since he had been receiving deltacortril therapy from the beginning, we first eliminated it from our possible diagnoses and focused mostly on immunosuppressive pneumonia and drug-related interstitial lung disease. Open lung biopsy revealed the exact diagnosis, and it was important for our case because BOOP usually responds well to steroid therapy, as also seen in our patient (5).

Cough and dyspnea in BOOP may lead to development of air leak syndrome, as first presented in the case report of Iwanaga et al. (5). In that case report, it was mentioned that BOOP should be included in the differential diagnosis of patients presenting with air leak syndrome. Although lung function studies show no airflow obstruction in BOOP except in smokers, localized or regional peripheral obstruction can result in a ball-valve effect and distal overdistension, leading to a burst alveoli and entry of air into the bronchovascular sheath followed by manifestation of any form of aberrant air trapping or air leak syndrome (18). Both BOOP itself and severe cough in our patient might have caused the overpressurization of the alveoli.

Pulmonary complications of UC resembling the appearance of Wegener's granulomatosis have also been reported in several case reports (19-22). Most of them were responsive to steroids, and only one of them was treated with the discontinuation of sulfasalazine treatment. Most of the cases were thought to have an association with ANCA. Focal areas of BOOP have been found on the periphery of 44% of the Wegener's granulomatosis cases. These pulmonary manifestations might thus represent a BOOP-like variant of Wegener's granulomatosis. UC has been emphasized to have an immunological basis. The majority of patients with UC (50-80%) exhibit a positive test for pANCA (23,24). Kasuga et al. (25) commented in their case report that patients with immune system dysregulation, having pANCA (+), could display extrapulmonary complications of UC such as BOOP-like variant of Wegener's granulomatosis. Although our patient also had the diagnosis of BOOP and pANCA positivity, we did not think the diagnosis of BOOP-like variant of Wegener's granulomatosis was suitable in this case since he had bilateral parenchymal disease progressing into ARDS instead of the previously reported focal areas of BOOP.

In summary, in IBD patients, BOOP developing due to viral or fungal infectious etiology or due to the IBD itself may progress to ARDS and may present with air leak syndrome. Early detection is important and life-saving, since BOOP often responds well to steroid treatment provided an infectious etiology has been excluded or adequate antimicrobial therapy has already been initiated.

REFERENCES

1. Jose FA, Heyman FB. Extraintestinal manifestations of inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2008; 46: 124-33.
2. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. World J Gastroenterol 2006; 12: 4819-31.
3. Storch I, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. Inf Bowel Dis 2003; 9: 104-15.
4. Ceyhan B. Inflammatory bowel disease and lung. Tuberk Toraks 2006; 54: 292-8.
5. Iwanaga T, Hirota T, Ikeda T. Air leak syndrome as one of the manifestations of bronchiolitis obliterans organizing pneumonia. Intern Med 2000; 39: 163-5.
6. Vogel M, Brodoefel H, Bethge W, et al. Spontaneous thoracic air-leakage syndrome in patients following allogeneic hematopoietic stem cell transplantation: Causes, CT-follow up and patient outcome. Eur J Radiol 2006; 60: 392-7.

7. Camus P, Piard F, Ashcroft T, et al. The lung in inflammatory bowel disease. Medicine (Baltimore) 1993; 72: 151-83.
8. Epler GR. Bronchiolitis obliterans organizing pneumonia. Arch Intern Med 2001; 161: 158-64.
9. Cordier JF. Organizing pneumonia. Thorax 2000; 55: 318-28.
10. Swinburn CR, Jackson GJ, Cobden I, et al. Bronchiolitis obliterans organising pneumonia in a patient with ulcerative colitis. Thorax 1988; 43: 735-6.
11. Haralambou G, Teirstein AS, Gill J, Present DH. Bronchiolitis obliterans in a patient with ulcerative colitis receiving mesalamine. Mt Sinai J Med 2001; 68: 364-8.
12. Kevans D, Greene J, Galvin L, et al. Mesalazine-induced bronchiolitis obliterans organizing pneumonia (BOOP) in a patient with ulcerative colitis and primary sclerosing cholangitis. Inflamm Bowel Disease 2011; 17: E137-8.
13. Baron FA, Hermanne JP, Dowlati A, et al. Bronchiolitis obliterans organizing pneumonia and ulcerative colitis after allogeneic bone marrow transplantation. Bone Marrow Transplant 1998; 21: 951-4.
14. Lazaro M, Garcia-Tejero M, Diaz-Lobato S. Mesalamine induced lung disease. Arch Intern Med 1997; 154: 462.
15. Williams T, Eidus L, Thomas P. Fibrosing alveolitis, bronchiolitis obliterans and sulfasalazine therapy. Chest 1982; 81: 766-8.
16. Salerno SM, Ormseth EJ, Roth BJ, et al. Sulfasalazine pulmonary toxicity in ulcerative colitis mimicking clinical features of Wegener's granulomatosis. Chest 1996; 110: 556-9.
17. Epler GR. Bronchiolitis obliterans organizing pneumonia: definition and clinical features. Chest 1992; 102 (Suppl): 2S-6S.
18. Mahadeva R, Walsh G, Flower CDR, Shneerson JM. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. Eur Respir J 2000; 15: 41-8.
19. Yano S, Kobayashi K, Kato K, Nishimura K. A limited form of Wegener's granulomatosis with bronchiolitis obliterans organizing pneumonitis-like variant in an ulcerative colitis patient. Intern Med 2002; 41: 1013-5.
20. Kedziora JA, Wolff M, Chang J. Limited form of Wegener's granulomatosis in ulcerative colitis. Am J Roentgenol Radium Ther Nucl Med 1975; 125: 127-33.
21. Stebbing J, Askin F, Fishman E, Stone J. Pulmonary manifestations of ulcerative colitis mimicking Wegener's granulomatosis. J Rheumatol 1999; 26: 1617-21.
22. Uner AH, Rozum-Slota B, Katzenstein AL. Bronchiolitis obliterans-organizing pneumonia (BOOP)-like variant of Wegener's granulomatosis. A clinicopathologic study of 16 cases. Am J Surg Pathol 1996; 20: 794-801.
23. Dubinsky MC, Ofman JJ, Urman M, et al. Clinical utility of serodiagnostic testing in suspected pediatric inflammatory bowel disease. Am J Gastroenterol 2001; 96: 758-65.
24. Targan SR. The utility of ANCA and ASCA in inflammatory bowel disease. Inflamm Bowel Dis 1999; 5: 61-3.
25. Kasuga A, Mandai Y, Katsuno T, et al. Pulmonary complications resembling Wegener's granulomatosis in ulcerative colitis with elevated proteinase-3 anti- neutrophil cytoplasmic antibody. Inter Med 2008; 47: 1211-4.