TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2016) 46: 1712-1718

doi:10.3906/sag-1508-114

Cryptogenic organizing pneumonia: clinical and radiological features, treatment outcomes of 17 patients, and review of the literature

Elif Yelda NİKSARLIOĞLU*, Gülcihan Zehra ÖZKAN, Nur Dilek BAKAN, Sibel YURT, Lütfiye KILIÇ, Güngör ÇAMSARI
Department of Chest Diseases, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Received: 25.08.2015 • **Accepted/Published Online:** 04.03.2016 • **Final Version:** 20.12.2016

Background/aim: We evaluated patients with cryptogenic organizing pneumonia (COP) who attended our clinic.

Materials and methods: We retrospectively investigated the clinical and radiological findings, diagnostic methods, treatment, and follow-up outcomes of 17 patients who had been histopathologically diagnosed with COP.

Results: The mean age of the patients was 49.8 ± 10.4 years. The most common symptom was cough (n = 15; 88.2%) and the most common radiological finding (n = 10) was consolidation in the inferior lobes on thoracic computed tomography. The diagnosis of COP was made by open lung biopsy in 11 (64.7%) patients, transbronchial biopsy in 5 (29.4%), and video-assisted thoracoscopic surgery biopsy in 1 (5.9%). The mean follow-up period was 28.7 ± 25.0 (range: 3–85) months. Twelve patients received oral corticosteroid therapy and seven of them improved without any fibrotic changes. One patient refused treatment; a chest radiography of that patient was found to be normal at the end of the 20-month follow-up period. Three patients received no other therapy, as the lesion had been completely excised.

Conclusion: Common symptoms included cough and dyspnea, while the main radiological presentation of COP was consolidation. Corticosteroids are a good treatment option in general, but relapse may occur.

Key words: Cryptogenic organizing pneumonia, follow-up, radiology, symptom, treatment

1. Introduction

Cryptogenic organizing pneumonia (COP) is a disease of unknown etiology, which is characterized by granulation tissue obstructing the alveolar ducts and chronic inflammation occurring in contiguous alveoli (1). Collagen vascular diseases, drugs, malignancies, and aspiration can all lead to the clinical diagnosis of secondary organizing pneumonia; the term COP, however, is used for cases of unknown etiology. COP is included in the class of idiopathic interstitial pneumonia in the joint statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS), which was revised in 2013 (2). Although there are various publications on the clinical findings, radiological findings, and treatment of this disease, most of the papers are case reports (3–5). In the present study, we present the clinical and radiological findings, as well as the treatment and follow-up outcomes, of 17 patients diagnosed with COP.

2. Materials and methods

A total of 17 patients who attended the Yedikule Training and Research Hospital for Chest Diseases and Thoracic Surgery and were subsequently diagnosed with COP were retrospectively evaluated. Diagnosis of COP was made by bronchoscopic transbronchial biopsy (TBB), video-assisted thoracoscopy (VATS), and open lung biopsy (OLB). All patients were followed between October 2006 and April 2014 at the hospital. Those with confirmed diseases that might cause organizing pneumonia were excluded from the study. The demographic data, symptoms, radiological findings, diagnostic methods, and treatment regimen for each patient were collected from the patients' hospital records.

2.1. Statistical analysis

Descriptive statistics only are given. Statistical comparisons were not performed because of the limited number of cases. Continuous variables are presented as mean and standard deviation, whereas categorical variables are presented as a number and a percentage.

3. Results

Seventeen COP patients (49.8 ± 10.4 years; range: 29–69) were retrospectively evaluated. Seven (41.2%) of the patients were men. The demographic data are shown in

* Correspondence: eyelda2003@yahoo.com

Table 1. The mean duration of cough, which was the most common symptom, was 54 ± 30 days. Of those patients with pleuritic chest pain, one had a pleural effusion and four had peripheral lesions. Pulmonary function tests (PFTs) were performed in 14 patients: one patient had an obstructive pattern and five patients had restrictive patterns, whereas PFTs were considered to be normal in the others (Table 2).

The most common radiological finding was consolidation in the left (n = 10) and right (n = 6) lower lobes (Figure; Table 3). While lesions were present in more than one segment on computed tomography/high-resolution computed tomography (CT/HRCT) in nine (53%) patients, only one segment was involved in the remaining eight patients. One of the patients had a mass lesion on thorax CT with minimal pleural effusion on the

Table 1. General characteristics and symptoms of the patients.

Variables	Results
Number of patients	17
Age, years	49.8 ± 10.4 (range: 29–69)
Sex (female)	10 (58.8)
Smoking	6 (35.3)
Current smoker	2 (12.5)
Ex-smoker	4 (25)
Cough	15 (88.2)
Dyspnea on exertion	8 (47.1)
Weakness	6 (35.3)
Pleuritic chest pain	6 (35.3)
Fever	4 (23.5)
Hemoptysis,	2 (12.5)
Comorbidity*	3 (18.5)

Data are presented as n (%), *: Vertigo, asthma, obstructive sleep apnea syndrome.

Table 2. Laboratory findings and pulmonary function tests of patients.

Findings	Value
Hemoglobin, g/dL	12.8 ± 2.3
Leukocyte count, /mm^3	8488 ± 2077
Platelet count, /mm^3	313,700 ± 9150
Eosinophil, %	3.3 ± 1.8
Sedimentation, mm/h	45.8 ± 40.0
CRP, mg/L	5.9 ± 5.3
FEV1 (L)*	2.7 ± 0.8
FEV1 (%, predicted)*	88.1 ± 16.3
FVC (L)*	3.0 ± 0.9
FVC (% predicted)*	86.4 ± 18.6
FEV1/FVC*	84.2 ± 10.1
DLCO (mL/min/mmHg)**	36 ± 35
DLCO (% predicted)**	69.6 ± 5.5

Data are presented as mean ± standard deviation, * n = 13 cases; ** n = 3 cases, FEV1: forced expiratory volume in 1 s, FVC: forced vital capacity, DLCO: diffusion capacity of carbon monoxide.

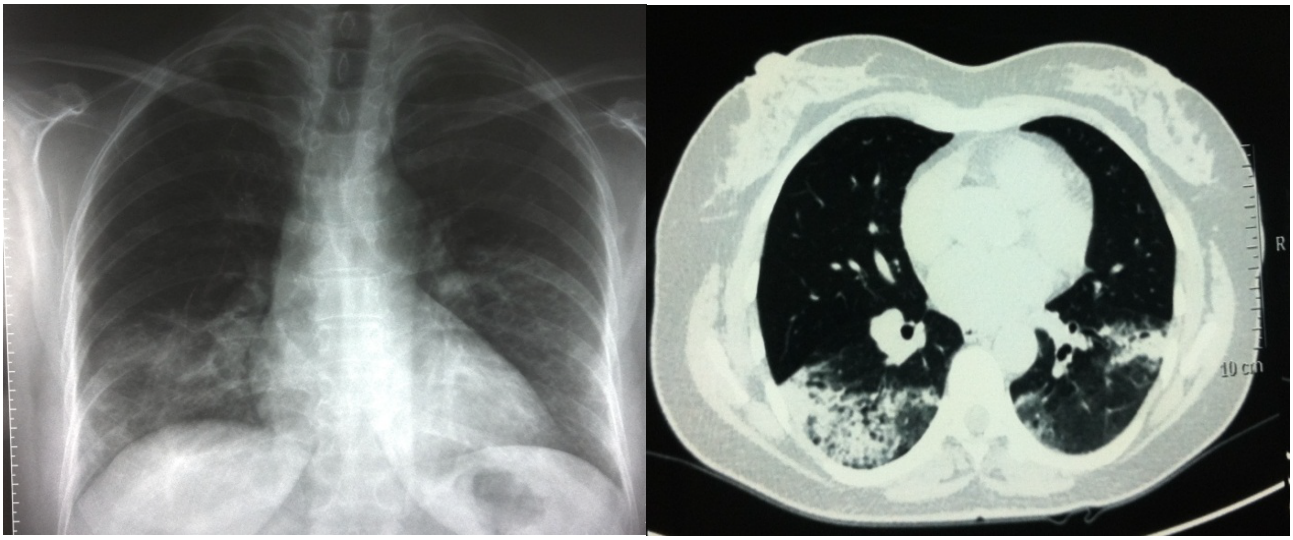

Figure. Chest radiography of a patient with COP. Bilateral consolidation and ground glass opacities are seen on thoracic computed tomography.

Table 3. Thoracic computed tomography findings of the cases.

Findings	N (%)
Consolidation	8 (47.1)
Consolidation and ground glass opacities	3 (17.7)
Consolidation and nodules	2 (11.8)
Mass	3 (17.6)
Pleural effusion and nodule	1 (5.9)

same side. This patient had undergone positron emission tomography (PET-CT) scanning at another center due to a suspicion of malignancy before admission to our hospital, and the maximum standardized uptake value (SUV_{max}) was reported to be 10. In a second patient with a mass lesion, PET-CT scans revealed no FDG uptake. The third patient with a mass on thoracic CT was not evaluated with PET-CT scan.

Fifteen patients had undergone fiberoptic bronchoscopy. Bronchoalveolar lavage (BAL) was performed in five patients. Three of the patients had a normal cellular pattern on BAL, whereas two patients had an elevated lymphocyte count (30% and 25%). No growth was observed in bronchoalveolar lavage cultures. The diagnosis of COP was made by OLB in 11 (64.7%) patients, by TBB in 5 (29.4%), and by VATS biopsy in 1 (5.9%) Hepatitis markers were found to be negative. Collagen markers were also negative in 15 patients. Among the collagen vascular markers, antinuclear antibody (ANA) positivity was determined in one patient, and anticardiolipin antibody positivity was determined in another. However, no pathology was detected upon rheumatologic evaluation. None of the patients were further diagnosed with collagen vascular disease over the course of the follow-up period.

The mean follow-up period of the patients was 28.7 ± 25.0 months (median: 23 months; range: 3–85 months). Eleven patients (64.7%) received oral corticosteroid (OCS) therapy; the mean starting dose of methylprednisolone was 23.2 ± 3 mg (median: 20 mg, range: 16–32 mg) and the mean treatment period was 8.5 ± 4.7 months (median: 8 months, range: 2–18 months). There was a complete improvement without any fibrotic changes in eight patients who received OCS. Five patients did not receive treatment; one of them, having refused treatment, subsequently showed a spontaneous improvement in symptoms and chest radiography was also normal at the end of the 21st month. Four patients who did not receive treatment had mass lesions at the start of treatment and a total excision of the lesion was performed in all. Fibrotic

changes secondary to the procedure were observed in the four patients who had undergone excision. No recurrence was observed in these patients over the course of the approximately 20-month follow-up period. One patient couldn't use OCS because her serum glucose level was at the upper limit of normal values, so clarithromycin and an inhaled corticosteroid/long-acting beta-mimetic combination therapy were started. Partial regression was seen on chest X-rays within 2 months but pulmonary symptoms like cough and dyspnea persisted and a new infiltration was observed in a different location in the 3rd month of follow-up. After excluding infectious etiologies, 32 mg of methylprednisolone was added to the existing clarithromycin therapy. The patient is currently still being followed. None of the patients in this study died over the course of the follow-up period.

One patient was excluded for recurrence analyses because the follow-up period was shorter than 5 months (6). Three patients (18.7%) who received OCS developed a recurrence of the disease during the course of the follow-up period. Radiologic and clinic recurrence was detected in two cases after the steroid dose had been decreased; therefore, the methylprednisolone dose was increased to 8 mg (stable dose for symptoms and radiological regression) and regression was determined in the symptoms and radiological findings during follow-up. The patients were in the 9th and 5th months of treatment when this article was written and are still being followed. Partial regression was observed in one patient receiving OCS.

4. Discussion

COP is a disease of unknown etiology and is diagnosed histopathologically. (7). It was observed predominantly in women and patients were aged between 29 and 69 years in our study. Common symptoms included cough and dyspnea on exertion. Pleuritic chest pain and weakness were seen in one-third of the patients. The main radiological presentation of COP was consolidation in the lower lobe. Corticosteroids are a good treatment option in general, but relapse may occur. Clarithromycin therapy did not prevent relapse in our patient.

COP is a subacute disease seen approximately between the ages of 50 to 60 years, with an equal prevalence in males and females (7–9). In the present study, the mean age of our patients was 49.8 years and 10 of them were female. The number of female patients was slightly higher in the present study, and this was similar to the study of Lazor et al. (10). COP is, in particular, more prevalent in nonsmoking females and/or females who have stopped smoking (10). In our patient group, 11 of the 17 patients were nonsmokers, and two of the three female smokers had stopped smoking. Despite the limited number of patients in this study it can be seen that COP was more prevalent in nonsmokers or in those who had stopped smoking.

The duration of symptoms varied between 1 and 3 months, with a mean duration of 1 month. Some studies have reported a prolonged duration of symptoms, up to 2–4 months (10–12). COP cases are frequently diagnosed as pneumonia based on clinical, laboratory, and radiological findings. However, a definitive diagnosis is made from further analyses performed in patients who are unresponsive to treatment. The duration from onset of symptoms to diagnosis varies between studies, and this may lead to 6 to 10 weeks of delay in reaching a diagnosis (8).

The most common symptoms encountered in our patients were cough, dyspnea, pleuritic chest pain, and weakness. Oymak et al. conducted a study of 26 cases with bronchiolitis obliterans organizing pneumonia (BOOP) and reported cough, dyspnea, pleuritic chest pain, hemoptysis, and fever as being the most common symptoms (3). Two patients were determined to have mild hemoptysis in the present patient series. Hemoptysis has been rarely determined in many previous studies, with no information on the prevalence. A paper published in 2011 reported cough, fever, weakness, and dyspnea as the most common symptoms in a group of 40 cases (12). In that study, fever frequency was higher than in our study (25% vs. 71.8%). Pleuritic chest pain is present particularly in cases of peripheral lesions and pleural effusion. In the present group, pleuritic chest pain was determined in six cases. The prevalence of this symptom was close to the rates found in some previous studies (3,13).

Considering the results of laboratory tests, previous studies have reported slightly elevated ESR and serum CRP levels and nonspecific increases in the peripheral neutrophil count (5,14). In the present study, ESR was found to be elevated in five cases, CRP in four cases, and peripheral eosinophil count in two cases in comparison to the reference values. In another study, ANA positivity was detected in 18.2% of patients and rheumatoid factor positivity was detected in 10.3% (12). Yoo et al. compared cases with COP with cases with connective tissue disease-related organizing pneumonia and reported ANA positivity in 31.9% of COP patients (15). In our patient group there was isolated ANA positivity in one case and anticardiolipin antibody positivity in another. No rheumatologic disease was determined during follow-up in any of the cases.

There are three main imaging patterns of COP: the most prevalent is the alveolar opacities, followed by solitary opacities and infiltrative opacities. Migratory bilateral patchy alveolar infiltrates are the most typical imaging patterns of COP (2,8,13). Alveolar opacities were reported with a prevalence of 69% to 82% (10,12,16). Drakopanagiotakis et al. determined consolidation in 82% of their cases and observed migrating infiltrates in 11.5%

of them (12). There are also publications that suggest that a reversed halo sign is especially typical of COP (18,19). Similar to the previous studies, consolidation was observed in 76.6% (n = 13) of our cases. In addition, consolidations with millimetric nodules (11.8%) or ground glass opacities (17.7%) were observed in some cases. However, migrating infiltrates were observed in only four patients. The reversed halo sign was not observed in any patient. Lee et al. evaluated radiological findings in COP patients and found that consolidation was present in 17 (77%) out of 22 cases, in agreement with the results of our patient group. Moreover, 86% of the patients had ground glass opacities and 32% had nodules (19). The second most prevalent radiological pattern in COP is solitary opacities or mass lesions. The diagnosis of such cases is made by OLB since these lesions may be radiologically confused with alveolar adenocarcinoma (7). Drakopanagiotakis et al. observed mass lesions in 8.2% of COP cases (12). Among our cases, a diagnosis of COP was made by OLB in four (23.5%) patients who had a mass image on thoracic CT. Three patients with mass lesions were evaluated by PET-CT; the FDG uptake (SUV_{max}) was 7.5 and 10, respectively, in two cases. FDG uptake was not determined in one of these cases. In the literature, a study of COP patients with PET-CT reported that the mean SUV_{max} value was 2.47 (20). Tateishi et al. reported that SUV_{max} is higher in consolidations with an air bronchogram as compared to those without, and that it is correlated with disease activity (21). Two patients with FDG uptake on PET-CT showed a complete radiological regression with no sign of malignancy over the course of a 23-month and 22-month follow-up period, respectively.

In some publications, it has been stated that 10%–20% of patients might have unilateral or bilateral pleural effusion (22–24). In our group, minimal pleural effusion was detected in only one patient with a mass lesion. In all probability, there will be radiological diversity as the number of patients increases.

The most common PFT finding in COP patients was a mild to moderate restrictive ventilatory pattern and decreased diffusion capacity (7,8). An obstructive pattern may be observed in smokers. In our study, a restrictive pattern was determined in five patients, and an obstructive pattern was determined in one patient who was a smoker. Normal PFT was determined in the remaining patients. Only three patients had DLCO test findings with decreased diffusion capacity, which was consistent with the literature.

In our patient group, 15 patients had undergone bronchoscopy, and infectious etiologies were excluded based on the examination of the lavage fluid. In our group, diagnosis was made by OLB in 11 (64.7%) cases, by TBB in 5 (29.4%), and by VATS in only one case. Contrary to the present study, Oymak et al. diagnosed by TBB in 46% of their cases (3). Lazor et al. diagnosed COP by OLB/VATS in 69% of 48 cases and by TBB in 31% (10). Although the number of patients was different than ours, the rate of diagnostic methods used was similar to that used in our study. Patients with mass lesions had been diagnosed by OLB since the provisional diagnosis also included malignancy. Moreover, patients that could not been diagnosed by TBB also underwent OLB.

Standard treatment of COP includes corticosteroids. Regression in symptoms and radiological improvement are usually observed over the course of days (7). Lee et al. stated that response to corticosteroids is better in lesions with an air bronchograms (25). In previous studies, the starting daily dose of corticosteroid therapy was 0.75–1.5 mg/kg. Treatment was continued at those doses for 2–4 weeks and then discontinued at 6–12 months by gradually decreasing the dose (7,8,10). In our study, 12 patients (70.6%) received OCS: eight patients showed a complete resolution, but three (18.7%) developed recurrence as the dose of corticosteroid was decreased. Radiological regression in patients that received OCS is consistent with the literature (7,10). In this study, one patient showed regression while undergoing clarithromycin therapy. In that case, OCS was added to the treatment regimen as the patient showed progression during follow-up. Treatment with different agents such as macrolides has become a current issue in the presence of steroid-related adverse effects or where steroids are contraindicated due to various reasons. The antiinflammatory activity of macrolides has been known for a long time. Their usage in organizing pneumonia is based on this activity (26–28). However, publications on this topic have usually been in the form of case reports.

Although COP is generally a disease with good prognosis, recurrence might develop while decreasing the dose or stopping treatment in patients receiving corticosteroids. In the literature, recurrence rates vary between 9% and 58% (10,29). In our study, the recurrence rate was 18.7%. The difference between the recurrence rates found in studies might have resulted from the difference in the frequency and the duration of follow-up. In addition, the recurrence rates of both COP and secondary organizing pneumonia have been reported together in some publications. Nevertheless, a delay in diagnosis and treatment increases the rate of recurrence, as was reported by Lazor et al. (10). Moreover, elevated gamma-glutamyl transferase, alanine aminotransferase, and alkaline phosphatase enzyme concentrations were detected in cases with multiple recurrences (10). In the present study, the concentrations of these enzymes were normal in the three patients with recurrence. In a recent study, recurrence rates were found to have increased in the three event zones (upper, intermediate, lower) of the lungs involved (30). In our study, such an involvement

was not observed in the patients that showed recurrence. In Nishino et al.'s study, patients with high fibrin in pathologic specimens were associated with COP relapse (6). We retrospectively evaluated pathologic specimens and only one patient had fibrin in biopsy. No relapse was determined in this patient.

The most important limitations of the present study are its retrospective nature and the limited number of cases.

In conclusion, COP was more prevalent in middle-aged female patients in our study group, while cough and dyspnea on exertion were the most common symptoms in these cases. Analogous with the previous studies, consolidation is the predominating radiological pattern. Diagnosis can be reached by performing OLB or TBB. The recurrence rate of COP is relatively low.

References

1. Colby TV. Pathologic aspects of bronchiolitis obliterans organizing pneumonia. Chest 1992; 102: 38S-43S.
2. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013; 188: 733-748.
3. Oymak FS, Demirbas HM, Mavili E, Akgun H, Gulmez I, Demir R, Ozesmi M. Bronchiolitis obliterans organizing pneumonia. Respiration 2005; 72: 254-262.
4. Kıter G, Yuncu G, Bir F, Karabulut N, Özkurt S, Evyapan F. Cryptogenic organizing pneumonia: two cases and an update. Toraks Dergisi 2008; 9: 43-48 (in Turkish with English abstract).
5. Kivanc T, Ekici ZU, Dogan CR, Kiyici H, Eyuboglu FO. Cryptogenic organising pneumonia: four cases with different radiological manifestations. Eurasian J Pulmonol 2011; 13: 114-120.
6. Nishino M, Mathai SK, Schoenfeld D, Digumarthy SR, Kradin RL. Clinicopathologic features associated with relapse in cryptogenic organizing pneumonia. Hum Pathol 2014; 45: 342-351.
7. Cottin V, Cordier JF. Cryptogenic organizing pneumonia. Semin Respir Crit Care Med 2012; 33: 462-475.
8. Cordier JF, Costabel U, du Bois R. Cryptogenic organizing pneumonia. Orphanet Encyclopedia, October 2004. Available online at http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=1302.
9. Wells AU. Cryptogenic organizing pneumonia. Semin in Respir Crit Care Med 2001; 22: 449-459.
10. Cordier JF. Cryptogenic organizing pneumonia. Eur Respir J 2006; 28: 422-446.
11. Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Codier JF. Cryptogenic organizing pneumonia: characteristics of relapses in a series of 48 patients. Am J Respir Crit Care Med 2000; 162: 571-577.
12. King TE Jr, Mortenson RL. Cryptogenic and organizing pneumonitis. The North American experience. Chest 1992; 102: 8S-13S.
13. Drakopanagiotakis F, Paschalaki K, Abu-Hijleh M, Aswad B, Karagianidis N, Kastanakis E, Braman SS, Polychronopoulos V. Cryptogenic and organizing pneumonia. Chest 2011; 139: 893-900.
14. Codier JF, Loire R, Brune J. Idiopathic BOOP: definition of characteristic clinical profiles in a series of 16 patients. Chest 1989; 96: 999-1004.
15. Cordier JF. Cryptogenic organizing pneumonitis. Bronchiolitis obliterans organizing pneumonia. Clin Chest Med 1993; 14: 677-692.
16. Yoo JW, Song JW, Jang SJ, Lee CK, Kim MY, Lee HK, Jegal Y, Kim DS. Comparison between cryptogenic organizing pneumonia and connective tissue disease-related organizing pneumonia. Rheumatology 2011; 50: 932-938.
17. Sara AG, Hamdan AJ, Hanaa B, Nawaz KA. Bronchiolitis obliterans organizing pneumonia: pathogenesis, clinical features, imaging and therapy review. Ann Thorac Med 2008; 3: 67-75.
18. Kim SJ, Lee KS, Ryu YH, Yoon YC, Choe KO, Kim TS, Sung KJ. Reversed halo sign on high-resolution CT of cryptogenic organizing pneumonia: diagnostic implication. AJR Am J Roentgenol 2003; 180: 1251-1254.
19. Maimon N. A 47-year-old female with shortness of breath and reversed halo sign. Eur Respir Rev 2010; 19: 1251-1254.
20. Lee JW, Lee KS, Lee HY, Chung MP, Yi CA, Kim TS, Chung MJ. Cryptogenic organizing pneumonia: serial high resolution CT findings in 22 patients. AJR Am J Roentgenol 2010; 195: 916-922.
21. Umeda Y, Demura Y, Ishizaki T, Ameshima S, Miyamori I, Saito Y, Tsuchida T, Fujibayashi Y, Okazawa H. Dual-time point 18F-FDG PET imaging diagnosis of disease type and disease activity in patients with idiopathic interstitial pneumonia. Eur J Nucl Med Mol Imaging 2009; 36: 1121-1130.
22. Tateishi U, Hasegawa T, Seki K, Terauchi T, Moriyama N, Arai Y. Disease activity and 18F-FDG uptake in organising pneumonia: semi-quantitative evaluation using computed tomography and position emission tomography. Eur J Nucl Med Mol Imaging 2006; 33: 906-912.
23. Kim SJ, Lee KS, Ryu YH, Yoon YC, Choe KO, Kim TS, Sung KJ. Reversed halo sign on high-resolution CT of cryptogenic organizing pneumonia: diagnostic implications. AJR Am J Roentgenol 2003; 180: 1251-1254.

24. Lee KS, Kullnig P, Hartman TE, Muller NL. Cryptogenic organizing pneumonia: CT findings in 43 patients. AJR Am J Roentgenol 1994; 162: 543-546.

25. Muller NL, Staples CA, Miller RR. Bronchiolitis obliterans organizing pneumonia: CT features in 14 patients. AJR Am J Roentgenol 1990; 154: 983-987.

26. Lee JS, Lynch DA, Sharma S, Brown KK, Muller NL. Organizing pneumonia: prognostic implication of high-resolution computed tomography features. J Comput Assist Tomogr 2003; 27: 260-265.

27. Stover DE, Mangino D. Macrolides: A treatment alternative for bronchiolitis obliterans organizing pneumonia. Chest 2005; 128: 3611-3617.

28. Patnak V, Kuhn JM, Durham C, Funkhouser WK, Henke DC. Macrolide use leads to clinical and radiological improvement in patients with cryptogenic organizing pneumonia. Ann Am Thorac Soc 2014; 11: 87-91.

29. Radzikowska E, Wiatr E, Gawryluk D, Langfort R, Bestry I, Chabowski M, Roszkowski K. Organizing pneumonia – clarithromycin treatment. Pol Pneumonol Allergol 2008; 76: 334-339.

30. Izumi T, Kitaichi M, Nishimura K, Nagai S. Bronchiolitis obliterans organizing pneumonia: clinical features and differential diagnosis. Chest 1992; 102: 715-719.