The Evaluation of FDG PET/CT Scan Findings in Patients with Organizing Pneumonia Mimicking Lung Cancer

Abstract

Objective: Organizing pneumonia (OP) is a rare lung condition that is characterized by the presence of polypoid tissues due to fibroblastic plugs within respiratory bronchioles, alveolar ducts and sacs. The three main radiologic patterns of OP include typical, solitary-focal and infiltrative forms. The maximum standardized uptake value (SUV_{\text{max}}) on positron emission tomography-computed tomography (PET/CT) may be high in benign conditions such as OP as well as malignant diseases. The aim of our study was to investigate PET-CT characteristics of OP in patients mimicking lung cancer.

Methods: The clinical and radiologic characteristics of 50 patients who were referred to our hospital for PET/CT evaluation due to suspicion of lung malignancy, and who were pathologically diagnosed as OP between 2009 and 2013 were retrospectively reviewed.

Results: The mean age of the patients was 58.2 years. Ninety-six percent of patients (48) were male. Radiologic evaluation revealed 27 (54%) focal involvement, 10 (20%) consolidation with air-bronchogram (typical), 1 (2%) infiltrative and 12 (24%) other types of involvement (multiple nodules and cavitary lesions). The mean SUV_{\text{max}} value of the lesions on PET/CT was calculated as 6.5. Mediastinal lymph node involvement (at least one station) was detected in 76% of our study group with a mean SUV_{\text{max}} value of 3.27.

Conclusion: OP may cause false positive results on PET/CT. However, PET/CT results may be used as a guide for invasive procedures that should be performed when there is suspicion of malignancy.

Key Words: Organizing pneumonia, lung cancer, positron emission tomography/computed tomography

Özet

Amaç: Organize pnömoni (OP), respiratuvar bronşiyoller, alveoler kanallar ve alveollerde fibroblastik tıkaçların oluşturduğu polipoid yapılarla karakterize histopatolojik bir durumdur. Radyolojik olarak OP’ın tipik, soliter-fokal ve infiltratif olmak üzere 3 karakteristik görünümü vardır. Pozitron Emisyon Tomografi-Bilgisayarlı Tomografi’de (PET-BT) yüksek FDG tutumu malin...
Introduction

Organizing Pneumonia (OP) is pathologically defined by the presence of buds of granulation tissue composed of fibroblasts, myofibroblasts, fibrin and collagen exudates (Masson bodies) within the respiratory bronchioles, alveolar ducts and sacs. The etiologies of OP include infectious pneumonia, connective tissue diseases, inflammatory bowel diseases, solid organ transplantation, drugs, radiotherapy or aspiration (1). It is called Cryptogenic Organizing Pneumonia (COP) if an underlying cause cannot be foundorganizing.

Three main radiologic patterns distinguished in OP are typical, solitary-focal and infiltrative forms. Multiple masses, nodules, cavitary lesions, bronchocentric distribution, inverse halo pattern, band-like opacities, pneumatocele and pleurisy may also be detected in patients with OP (2).

PET/CT, which is especially used for diagnosis, staging, evaluation of response to treatment and distant metastasis in malignant diseases, is a hybrid imaging method that combines anatomic and functional features. It is also used for central nervous system, vascular, inflammatory, and infectious diseases. Additionally, it can guide the site to be sampled, and identify the primary focus if there are multiple lesions.

The aim of this study was to investigate PET-CT findings in each radiologic subtype of organizing pneumonia.

Materials and Methods

The clinical and radiologic characteristics of 50 patients who were referred to our hospital for evaluation with PET/CT due to suspected lung malignancy, and who were pathologically diagnosed as OP between 2009 and 2013 were retrospectively reviewed. These patients were referred to our center because of radiologic abnormalities that were unresponsive to antibiotherapy, and mediastinal lymph node enlargement suspicious for malignancy. Thirty-nine patients underwent lobectomies and 1 trans-bronchial biopsy were performed for pathological diagnosis.

Whole body scan by Siemens Biography 6 HI-REZ PET/CT scanner (Siemens Medical Solutions, Knoxville, TN, USA) was performed in patients who had fasted at least 6 hours, and had a blood glucose level below 180 mg/dl. The images of 6-8 bed positions from the base of the skull to high-thigh were obtained an hour after the intravenous bolus injection of fluorodeoxyglucose (FDG) with a dosage ranging from 370 MBq to 555 MBq (10-15 mCi). The patients were positioned with the arms above the head. Some patients were given oral contrast for a better visualization of bowels. A whole-body PET study was followed by enhanced whole-body CT study, and it was used for attenuation correction.

Mediastinal lymph node enlargements detected by thorax CT were classified according to the American Thoracic Society guidelines.

Data analysis was performed by IBM SPSS Statistics 21.0 software package. The normality for continuous variables was checked by using Kolmogorov-Smirnov test. Mann Whitney U test was performed to compare the distribution of two groups for numerical data. Kruskal Wallis test was used for comparison of three groups. When comparing mean SUVmax values of radiologic subtypes, the infiltrative group that consisted of only one patient was omitted. Chi-square test was used to examine the difference between groups for categorical variables. Descriptive statistics were presented as median (min-max) for quantitative data, and as frequency (percentages) for qualitative data. A value of p<0.05 was considered as statistically significant.

Results

The mean age of the patients was 58.2 (±9.39) years. Ninety-six percent of patients (48) were male. The average tobacco consumption of patients was 31.6 packages/year.
The medical history of 20 patients revealed environmental exposure to asbestos, and 16 patients stated biomass exposure.

Twenty-two patients were on regular medication for at least one co-morbid disease (diabetes mellitus, hypertension, chronic obstructive lung disease, rheumatoid arthritis, asthma). Breast cancer (1 patient), colon cancer (1 patient), lung tuberculosis (1 patient) and coronary bypass grafting (3 patients) were other diseases detected in patients’ past medical history.

All patients had at least one symptom (cough 68%, dyspnea 28%, chest pain 44%, fatigue 38%, weight loss 30%, fever 22%, sweating 16%, hemoptysis 12%, arthralgia and myalgia 4%).

The physical examinations of 32 patients (76%) were completely normal. Abnormal physical examination signs included crackles (3 patients), rhoncus (4 patients) on chest auscultation, and hypoxemia (3 patients).

Laboratory tests revealed elevated sedimentation rate in 30 patients (60%), high levels of C-reactive protein in 20 patients (40%), gamma glutamyl transferase in 7 patients (14%), and alkaline phosphatase in one patient. The results of sputum and bronchial aspirate smear and culture for acid-fast bacilli, which were performed in all patients at least once, were all negative. Among 15 patients who were evaluated for connective tissue markers, positive cytoplasmic antineutrophilic antibody (c-ANCA) was detected only in one patient.

All patients underwent fiberoptic bronchoscopy. Anthracotic pigmentation was present in five cases. No endobronchial lesion was observed.

OP was related to infection in 8 patients, to radiotherapy for breast cancer in 1 patient, to granulomatosis with polyangitis in 1 patient, to medications in 8 patients (beta-blockers in 4, statins in 2, sulfasalazine in 1 patient, and paroxetine in 1 patient. The remaining 32 patients were accepted as cryptogenic. We could not detect a statistically significant difference between PET-CT findings of cryptogenic and secondary organizing pneumonia patients in terms of mean SUVmax values (p>0.05).

The most common sites of involvement were the left upper, right lower and right upper lobes (30%, 26%, 24%, respectively).

Radiologic findings included focal involvement, consolidation with air-bronchogram (typical), infiltrative, and other types of involvement (multiple nodules and cavitary lesions). Focal lesions consisted of 12 cavitary lesions, 3 ground glass opacities, and 12 solid masses (Figure 1-3). The other radiologic manifestations in our study were multiple cavitary nodules seen in 1 patient, and multiple solid nodules in 11 patients (Figure 2) (Table 1). The mean SUVmax values of radiologic subtypes (typical, focal and the others) were statistically similar (p=0.142) (Table 2). The mean diameter of the primary lesion was 37.7 mm. The mean SUVmax value of the lesions on PET/CT was calculated as 6.5. Mediastinal lymph node involvement (at least one station) was detected in 38 patients (76%). High SUVmax values (SUVmax>2) were observed in N1, N2 and N3 lymph nodes in 37, 30 and 2 patients, respectively. The ratio of N1 and N2 lymph node involvement in different radiologic subtypes did not show a statistically significant difference (Table 3). The mean SUVmax value of these lymph nodes was 3.27.

**Discussion**

There have been multiple reports of benign thoracic conditions demonstrating hyper-metabolism on F18-FDG.
PET including granulomatous infections, benign tumors and autoimmune diseases (A). Organizing pneumonia is an inflammatory disease that can mimic lung cancer by causing a positive F18-FDG PET (3,4,5). Our study indicates that secondary and cryptogenic organizing pneumonia should be considered as part of differential diagnosis in patients with false positive results on F18-FDG PET.

The symptoms, clinical presentation, physical examination and radiology findings may also be identical to lung cancer. However, patients with OP are usually younger (aged between 50-60) than those with lung cancer (6,7). Likewise, in our study, the mean patient age was 58.2 (±9.39). Women are influenced as much as men and smoking history is uncommon in disease etiology (6,7,8). However, in our study, only two patients were female and 36 patients had a history of smoking, with an average lifetime exposure of 31.6 packages/year. Hemoptysis, which is exceedingly rare, may raise suspicion of malignancy (9). The most common symptoms in our study group were cough, dyspnea, chest pain and malaise. Hemoptysis was present in six patients. Four of them had solitary lesions while the remaining two had consolidations with air bronchogram.

There are no specific laboratory findings for OP. There is a moderate leukocytosis in half of the patients. The erythrocyte sedimentation rate and C reactive protein levels are increased in about 70-80% of patients. Gamma-glutamyl transferase and alkaline phosphatase levels may be high in relapsing cases (10,11). In our study group, laboratory tests revealed elevated sedimentation rate in 60%, and high levels of C-reactive protein in 40%, gamma glutamyl transferase in 14%, and alkaline phosphatase in 2%. There is no specific connective tissue marker for OP, unless there is an underlying connective tissue disease (10).

In our study, positive cytoplasmic antineutrophilic antibody (c-ANCA) was detected only in one patient that showed the underlying cause of OP as granulomatosis with polyangiitis.

Chest X-ray and high-resolution computed tomography are primary imaging methods in the diagnosis of COP. However, chest X-ray may be normal in 4-10% of patients. Three main imaging patterns distinguished in COP are typical (classical), solitary-focal and infiltrative forms. The most frequent and typical imaging profile of COP is in the form of multiple patchy alveolar opacities, with a peripheral and bilateral distribution in the lower lobes. These opacities often migrate spontaneously, and are rarely unilateral. Air bronchogram is usually present in consolidated areas. Bronchioloalveolar carcinoma and primary pulmonary lymphoma should be kept in mind as part of differential diagnosis. Additionally, eosinophilic pneumonia, multifocal pneumonia, alveolar hemorrhage, multiple pulmonary infarcts, alveolar sarcoidosis or ANCA-associated vasculitis can all have a similar appearance (12).

Lesions in eight out of ten patients with typical pattern were located in the lower lobes, one in the right middle lobe, and one in the left upper lobe. These lesions mimicked lung cancer due to resistance to antibiotherapy, and high SUV_{max} value (mean SUV_{max}: 5.47). COP with focal involvement is usually seen as nodules or masses in upper lobes that may be cavitary. In our study, the mean SUV_{max} value of focal lesions was found as 6.72. The differential diagnosis should include tuberculosis, granulomatosis with polyangiitis, aspergillosis and septic embolism (12). In 27 (54%) patients with focal involvement, the most common location was upper lobes (61.5%). Cavitation and ground glass opacity was observed in 12 (44.4%) and 3 (11.1%) patients with focal lesions, respectively. A few patients presented with diffuse bilateral infiltration associated with interstitial opacities, and small superimposed alveolar opacities. Alveolar and interstitial opacities may be detected in a variety of interstitial disorders, infectious diseases and lymphangitic carcinomatosis. Only one patient presented with infiltrative pattern, which showed multiple nodules with irregular borders. This patient underwent PET/CT scan due to suspicion of metastatic disease, which showed high FDG uptake of the nodules with a SUV_{max} value of 3.44.
Multiple masses, nodules, cavitary lesions, bronchocentric distribution, inverse halo pattern, band-like opacities, pneumatocele and pleurisy are other radiologic findings in patients with OP (2,13). In our study, 11 patients (28.2%) presented with unilateral and/or bilateral multiple solid masses, and 1 (2.7%) patient had multiple cavitary nodules. Mean $SUV_{\text{max}}$ value of these lesions was calculated as 7.96. The differential diagnosis of multiple cavitary nodules should include lung cancer (squamous cell carcinoma, bronchioloalveolar carcinoma), Hodgkin lymphoma, metastatic disease, granulomatosis with polyangiitis, septic embolism, rheumatoid nodules, hydatid cyst, and traumatic pneumatoceles (14). Mean $SUV_{\text{max}}$ values in patients with different radiologic subtypes (typical, focal and others) were statistically similar ($p=0.142$) (Table 2).

Mediastinal lymphadenopathy is uncommon in COP. Souza et al. reported mediastinal lymphadenopathy in 6 out of 16 patients with COP (15). The presence of lymphadenopathy strengthens the probability of malignancy. Mediastinal lymph node involvement (at least one station) was detected in 38 patients (76%) in our study group. The mean $SUV_{\text{max}}$ value of these lymph nodes was 3.27. We could not detect a statistically significant difference between different radiologic patterns in terms of N1-N2 involvement rate or $SUV_{\text{max}}$ values of lymph nodes ($p>0.05$). Nevertheless, almost all cases with N2 lymph node involvement (29 out of 30 cases) also had N1 lymph node involvement, suggesting a lymphatic pathway for disease progression.

$^{18}$F-Fluorodeoxyglucose uptake is not specific for malignancy (16). Various degrees of $^{18}$F-FDG uptake have been reported in infiltrative lung diseases, including idiopathic pulmonary fibrosis, collagen vascular disease-associated interstitial pneumonia, drug-induced pneumonia and radiation pneumonia. However, data on increased $^{18}$F-FDG uptake in organizing pneumonia is limited (17). The mean $SUV_{\text{max}}$ value of the lesions on PET/CT was calculated as 6.5 (min: 1.71-max: 16.74) for our study group. High $^{18}$F-FDG uptake may raise suspicion for malignancy, but histopathologic examination is required for diagnosis due to false positive results. High $^{18}$F-FDG uptake in organizing pneumonia was previously reported by Tateishi et al. They also proved that the patients with air-space consolidation had a significantly higher maximal SUV than those without consolidation (17). In the study by Tateishi et al., the most common CT finding was airspace consolidation with ground glass attenuation. The lowest median $SUV_{\text{max}}$ value was observed in the group of patients with typical radiologic involvement in our study. However, we could not show a significant difference in median $SUV_{\text{max}}$ values between radiologic subtypes. Our study group included cases mimicking malignancy, therefore, the number of cases with typical radiologic appearance were proportionally lower while the number of focal, multiple cavitary and nodular lesions were higher.

There are studies indicating that enhanced $^{18}$F-FDG accumulation and retention index, obtained by dual time point $^{18}$F-FDG PET scan, reflect disease activity in COP (16,18). While PET-CT may be helpful in predicting prognosis in OP, histopathological evaluation remains to be absolutely necessary in differential diagnosis, due to dramatic differences in both prognosis and therapy (5,16,18).

Conclusion

All radiologic subtypes of organizing pneumonia may demonstrate hyper-metabolism on $^{18}$F-FDG PET scan. Mediastinal lymph nodes may also show high $SUV_{\text{max}}$ values in all subtypes. In this study, $SUV_{\text{max}}$ values were statistically similar in both cryptogenic and secondary organizing pneumonia. Thus, $^{18}$F-FDG PET-CT cannot be used as a tool in distinguishing cryptogenic OP from secondary OP, or organizing pneumonia from lung cancer. Benign disorders like organizing pneumonia must be kept in mind in differential diagnosis of PET positive lung diseases. Therefore histopathologic examination is a must for definitive diagnosis for these lesions.

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References

1. Maldonado F, Daniels CE, Hoffman EA, Yi ES, Ryu JH. Focal organizing pneumonia on surgical lung biopsy: causes, clinicoradiologic features, and outcomes. Chest 2007;132:1579-1583.
2. Okonomou A, Hansell DM. Organizing pneumonia: the many morphological faces. Eur Radiol 2002;12:1486-1496.
3. Shin L, Katz DS, Yung E. Hypermetabolism on F-18 FDG PET of multiple pulmonary nodules resulting from bronchiolitis obliterans organizing pneumonia. Clin Nucl Med 2004;29:654-656.
4. Orino K, Kawamura M, Hatazawa J, Suzuki I, Sazawa Y. Efficacy of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scans in diagnosis of pulmonary nodules. Jpn J Thorac Cardiovasc Surg 1998;46:1267-1274.
5. Marques G, Annweiler T, Raoux D, Tiffet O, Vergnon JM, Bertolletti L. Nodular presentation of a cryptogenic organizing pneumonia. Rev Pneumol Clin 2011;67:314-317.
6. Wells AL. Cryptogenic organizing pneumonia. Semin Respir Crit Care Med 2001;22:449-460.
7. Cordier JF. Update on cryptogenic organising pneumonia: Idiopathic bronchiolitis obliterans organising pneumonia. Swiss Med Wkly 2002;132:588-591.

8. Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Cordier JF. Cryptogenic organizing pneumonia. Characteristics of relapses in a series of 48 patients. The Groupe d’Etudes et de Recherche sur les Maladies “orphelines” Pulmonaires (GERM’O’P). Am J Respir Crit Care Med 2000;162:571-577.

9. Mroz BJ, Sexauer WP, Meade A, Balsara G. Hemoptysis as the presenting symptom in bronchiolitis organizing pneumonia. Chest 1997;111:1775-1778.

10. King TE Jr, Flaherty KR. Cryptogenic organizing pneumonia. Available from: URL: www.uptodate.com 2013; 03/09/2013.

11. Cordier J. Cryptogenic organizing pneumonitis, bronchiolitis obliterans organizing pneumonia. Clin Chest Med 1993;14:677-692.

12. Baque-Juston M, Pellegrin A, Leroy S, Marquette CH, Padovani B. Organizing pneumonia: What is it? A conceptual approach and pictorial review. Diagn Interv Imaging 2014;95:771-777.

13. Cordier JF. Cryptogenic organizing pneumonia. Eur Respir J 2006;28:422-446.

14. Ödev K, Özbiner H. Imaging Findings of Focal and Multiple Cystic and Cavitory Lung Lesions. Eur J Gen Med 2012;9:3-14.

15. Althoff Souza C, Muller NL, Lee KS, Jokoh T, Mitsuhiro H, Chong S. Idiopathic interstitial pneumonias prevalence of mediastinal lymph node enlargement in 206 patients. AJR Am J Roentgenol 2006;186:995-999.

16. Ponnuswamy A, Mediratta N, Lyburn JD, Finnerty JP. False positive diagnosis of malignancy in a case of cryptogenic organizing pneumonia presenting as a pulmonary mass with mediastinal nodes detected on fluorodeoxyglucose-positron emission tomography: a case report. J Med Case Rep 2009;3:124.

17. Tateishi U, Hasegawa T, Seki K, Terauchi T, Moriyma N, Arai Y. Disease activity and F-FDG uptake in organizing pneumonia: semi-quantitative evaluation using computed tomography and positron emission tomography. Eur J Nucl Med Mol Imaging 2006;33:906-912.

18. 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 for diagnosis of disease type and disease activity in patients with idiopathic interstitial pneumonia. Eur J Nucl Med Mol Imaging 2009;36:1121-1130.