Metabolic Imaging Characteristics of the Granulomatous Infections as a False Positive Cause in the Investigation of Malignant Diseases of the Chest

Aim: Investigation of the malignant diseases of the chest includes CT and as well as metabolic imaging by means of F-18 fluorodeoxyglucose positron emission tomography/computed tomography. The possible false positive results during this workup are frequently due to the granulomatous diseases. The aim of this study was to investigate the metabolic imaging characteristics of the granulomatous diseases as a false positive cause. Patients: 49 patients (24 F and 25 M; mean: 58.12 ±4.84 years) with known pathologic results of granulomatous infections-inflammation were involved in this study. The patients had suspicion of malignant disease in the chest (malignant primary/metastatic lesions). Among the patients included in the study twelve patients was diagnosed previously to have a malignant tumor and nine patients had diagnosis of cancer of unknown primary. Results: The patients necessarily had lesions with high FDG uptake (>4) and the mean SUVmax level of the lesions was 13.49±8.2. The thoracic imaging features represented suspicious malignant involvement and required pathologic analysis. Additionally 30 (61%) of the patients had extrathoracic involvement. Among the patients included in the analysis two showed typical imaging features of lymphoma. Conclusion: The granulomatous infections has very similar metabolic imaging features with malignant thoracic diseases and additional involvement of extrathoracic region in more than half of the patients and not rarely mimicking lymphoma involvement.

Keywords: Granulomatous, Fdg, Malignancy, Infection, Positron Emission Tomography.

INTRODUCTION

The incidence of granulomatous diseases especially tuberculosis is unexpectedly high according to previous epidemiologic studies (Pelletier-Galarneau, M. et al., 2017 May). In the patient populations that is immunocompromised because of HIV virus infection or a malignancy the incidence of tuberculosis is higher compared to normal population. This high incidence is also a problem in the interpretation of pathologic findings in the F-18 FDG PET/CT especially in the thoracic region. The determination of possible false positive causes might be challenging in the metabolic imaging because of high frequency of tuberculosis in the patient population with malign tumors. The thoracic imaging by means of F-18 FDG PET/CT is hampered due to the conflicting granulomatous infections because the localization and uptake value of the lesions is very similar with malignant involvement (Wentsky, G. et al., 2019). However the presence of malignant nodule or lymph node changes patients’ management extremely in case of a known malignancy or suspicion of primary thoracic malignancy (Stamatis, G. 2015). This is not problematic in some countries but has incremental impact on patient management in the countries endemic for these infectious diseases (Harkinat, S. et al., 2008). On the other hand F-18 FDG PET/CT is gaining an increasing role in the management of thoracic pathologies including solitary pulmonary nodule management and routine imaging algorithm in the most of the malignancies. Previous studies confirm that PET/CT might decrease the number of unnecessary thoracic surgery (Lejeune, C. et al., 2005). A recent study has shown direct association of decrease in specificity of the F-18 FDG PET/CT in solitary pulmonary nodule evaluation due to the endemic infectious diseases (Purandare, N. C. et al., 2017). Furthermore Huber et al., found higher SUVmax levels for the granulomatous lesions compared to malignant lesions in their analysis (Huber, H. et al., 2015).

The aim of this study is to evaluate the metabolic imaging features of the thoracic lesions with the diagnosis of granulomatous diseases.
MATERIALS AND METHODS

Patients
The patients included in the study were selected from the database of the Pathology who had diagnosis of granulomatous infections determined in the thoracic region (mediastinum, pleura or parenchyma lesions). The pathology results of the patients were analyzed and compared to the preoperative F-18 FDG PET/CT results. The study was approved by the Local Ethics Committee. The patients were informed and informed consents of the patients were obtained about the diagnostic procedures.

FDG PET/CT imaging
The F-18 FDG PET/CT imaging was performed to the patients because of an underlying malignancy (staging, restaging, and treatment response evaluation) or suspicion of a malignant disease. F-18 FDG (mean: 10 mCi-370 mBq; adjusted according to the body weight) was administered with saline flush after fasting for at least 4 hours. PET/CT imaging was performed by an integrated PET/CT scanner (Siemens MCT PET/CT scanner; Germany) as early and late phase imaging. Firstly a whole body CT scan without intravenous contrast administration with 130 kV, 50 mAs, a pitch of 1.5, a section thickness of 5 mm, and a field of view of 70 cm and just and later whole body PET imaging was performed with an acquisition time of 1 min per bed position in cranio-caudal direction from skull base to proximal thigh. In case of solitary pulmonary nodule evaluation of late phase (approximately in 2nd hour) images including thorax were provided additionally.

Image analysis
The PET/CT images were evaluated by two experienced Nuclear Medicine physicians with additional CT and fusion images. Additionally SUVmax levels of the lesions were determined by the workstation. The results of PET/CT were compared according to the gold standard pathology.

Statistics
The numeric variables were compared by Student T test by SPSS version 16.0.

RESULTS
Totally 49 patients were included (24 F, 25 M) and the mean age of the patients was 58.12±14.84 years. The patients pathology results were diagnosed as tuberculosis (n=32), sarcoidosis (n=12), antrocosis (n=1), fungus infection (n=1) and Wegener granulomatosis (n=1). The pathologic samples of the patients were obtained from lung parenchyma (n=12), mediastinum (lymph node; 26), pleural lesions (n=6) and axillary, parasternal and serival lymph nodes in the rest of the patients.

Imaging findings might be categorized in three groups; group 1: lymphoid dominant, group 2: parenchyma dominant group and group 3: pleural dominant group. In the first group (n=20) the predominant finding was the lymph nodes whether mediastinal or servical-abdominal-axillary. Second group consist of parenchyma presentation group (n=25) with the diagnosis of solitary pulmonary nodule and/or mass like lesions (consolidation-infiltration). The third group of patients (n=4) presented with severe pleural lesions in the thorax. The SUVmax level of the predominant lesions in the whole groups was 13.49±8.2. The mean SUVmax levels of the first, second and third groups were 15.31±6.97, 10.98±5.83 and 16.8±14.6 respectively. The distribution of primary diagnosis of the patients is listed in the following table (Table 1). The comparison of the lesions SUVmax values revealed significant difference between Group 1 and Group 2 (p=0.36). Parenchyma lesion group showed lower uptake values compared to lymph node group. Pleura lesion group consist of higher and lower uptake values but a small group. The pathology diagnoses of the patients were tuberculosis (n=34), sarcoidosis (n=12), antrocosis (n=1), Wegener granulomatosis (n=1) and fungal infection (n=1). The only patient with diagnosis of Wegener granulomatosis was in Group 2 (Figure 1). However the distribution of the patients with Tuberculosis or sarcoidosis was not accordingly among Groups; both pathologies might be presented with lymph nodes, lung nodules and both (Figure 2). One patient with sarcoidosis presented with PET/CT findings very similar with lymphoma (Figure 3).

DISCUSSION
According to the results of this present study the patients with diagnosis of tuberculosis and sarcoidosis present with very similar findings in FDG PET/CT. In case of parenchyma involvement of the both diseases the uptake values of the lesions might be lower compared to the lymph node involvement. The granulomatous diseases present with similar imaging findings with malign involvement of the thorax. Additionally sarcoidosis might present with very similar findings with lymphoma this entity might require further attention.

Recently a study including 209 PET/CT exams showed the term ‘flip flop finding’ in the thorax which
indicates benignity with specificity of 100% that can be summarized as the rule that a lymph node with benign involvement should have equal or higher uptake value compared to the lung lesion (Nagelschneider, A. A. et al., 2017). Significant overlap exists between lung carcinoma and tuberculosis infection according to previous studies the false positive results might be as high as 57-92% in endemic regions (Li, Y. et al., 2011; & Niyonkuru, A. et al., 2018). Furthermore in a recent article it is suggested to confirm suspicious results by histopathologic evaluation (Chaudhary, P. et al., 2017). In a comparative analysis Ga-68 DOTATE PET/CT imaging was found to be more specific compared to FDG PET/CT in the evaluation of solitary pulmonary nodules with equal accuracy of 87% (Walker, R. et al., 2017). Dual time point imaging of the chest is an accepted methodology in determination of malignant lesions (Sathkege, M. M. et al., 2010). Matthies et al., determined that a %10 increase between two time points of imaging might achieve accurate results for malignancy in their study (Matthies, A. et al., 2002).

Dual time point imaging is a standard methodology in patients with solitary pulmonary nodule thus we performed dual time point imaging in the patients included in this study. However in patients with determined previous malignancy standard imaging procedure was performed. Additionally in patients with unknown primary tumor an imaging field including whole body was preferred. A recent analysis investigated 3 hour late phase imaging in patients with solitary pulmonary nodule in endemic region for the granulomatous disease and suggested the methodology according to their results (Huang, Y.E. et al., 2016).

FDG PET/CT has advantages of being a hybrid imaging modality and previous reports showed that determining the pathological findings in correlation with CT features of the lesions might improve diagnostic accuracy and decrease the false positive results (Yasar, Z. et al., 2015). Another publication supported this observation; among the patients who were evaluated for granulomatous diseases those patients who were diagnosed as malign tumors were found to have higher age and different CT patterns (Huber, H. et al., 2015). The authors additionally suggested diagnostic chest CT imaging in the workup of patients with solitary pulmonary nodule (Huber, H. et al., 2015; & Grgic, A. et al., 2010). However in the patients with lesions with significant FDG uptake malignancy exclusion by means of CT findings might be problematic and in these cases suggestion of biopsy is required in order to exclude malignancy.

Sarcoidosis as a granulomatous disease has similar imaging characteristics with malign diseases of chest and lymphoma which was also observed in one of the patients in this series. In a previous series including 14 patients and literature analysis the study reported the importance of careful interpretation in this context and necessity of biopsy confirmation (Huang, Y.E. et al., 2016). Although it is expected from PET/CT to rule out the malignancy in solitary pulmonary nodule evaluation it is not easy in the presence of granulomatous diseases. In these circumstances it is necessary to confirm or exclude malignancy by pathology results especially in case of presence of a primary malignancy.

Granulomatous diseases is one of the potential false positive cause in interpretation of FDG PET/CT results and requires attention in the patients living in endemic regions.

REFERENCES
8. Matthies, A., Hickson, M., Cuchiara, A., & Alavi, A. (2002). Dual time point 18F-FDG PET for the


**Figures**

**Figure 1.** 49 years male patient presented with lung mass like lesion in the upper lobe of the left lung which was hypermetabolic in the PET/CT (SUVmax=3.9) (Figure 1a) but pathology results showed Wegener Granulomatosis. Wegener's granuloma with epitheloid cells and several giant cells, with inflammatory destruction of lung parenchyma (H-E, x10). The patient who has Wegener's granulomatosis, microscopic findings showed, an infiltrate of lymphocytes, histiocytes and giant cells (Figure 1b)
Figure 2. 72 years female patient who was in the follow up with diagnosis of Nonhodgkin Lymphoma suspicious mediastinum lymph nodes with significant FDG accumulation (SUVmax=6) (Figure 2a) revealed Tuberculosis. Tuberculosis granuloma showed caseous necrosis and granulomas composed of epithelioid cells and Langhans giant cells with surrounding lymphocytes (H&E, x20). The patient showed caseating granulomas, often confluent and numerous of lymphocytes with giant cells (Figure 2b).

Figure 3. 51 years female patient with primary unknown disseminated lymph node involvement in the multiple intensity projection images (SUVmax=21.2) was diagnosed as Sarcoidosis. Sarcoidal type granulomas showed nonnecrotizing epithelioid granulomas surround within a broncoscopic biopsy (H-E, x20). The patient showed nonnecrotizing epithelioid granulomas surrounded with giant cells near a bronchiole with sarcoidal type granuloma (Figure 3b).