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PET/CT Imaging in Cardiac Sarcoidosis

Adil Gümüş[1*] Pınar Pelin Özcan Zehra Pınar Koç[3] Mahmut Süleymanoğlu[4] Zeynep Selcan Sağlam[5]

**Corresponding Author*
[1,2,3,4,5]Mersin University, Faculty of Medicine, Department of Nuclear Medicine, Mersin, Turkey

Abstract
Sarcoidosis is a systemic granulomatous disease of unknown cause. The most commonly affected structures are the thoracic lymph nodes and the lungs, but any organ can be involved . In sarcoidosis, the heart can be affected both due to lung involvement and direct disease involvement. Clinically detected cardiac involvement is around 5%; However higher rates are reported in autopsy series. Endomyocardial biopsy, which is the definitive diagnostic method, is difficult and has low diagnostic value. Effective and reliable advanced cardiac imaging methods are needed in cardiac sarcoidosis . As well as the diagnosis of cardiac sarcoidosis, it is also important to determine disease activation, determine the treatment strategy, evaluate the severity, estimate the prognosis, and adjust steroid therapy . The most commonly used molecular imaging method in clinical practice for these purposes is Fluorodeoxyglucose (FDG) PET/CT imaging labeled with Fluorine-18 (F-18). Increased uptake in the myocardium on F-18 FDG PET/CT imaging is considered an important finding reflecting the activity of inflammation in cardiac sarcoidosis. In this report, two patients whose sarcoidosis diagnosis was confirmed histopathologically and who underwent PET CT examination due to cardiac sarcoidosis in our department are presented.

Keywords**:** *cardiac sarcoidosis, PET, CT, Imaging.*

Introduction

Sarcoidosis is a multisystem disease of unknown cause, characterized by the infiltration of various organ systems by non-caseating granulomas. Although lymph nodes in the thorax and lung involvement are most commonly observed; the first clinical finding may be due to involvement in any organ system (1). Its prevalence in the population is estimated to be 4-20/100,000 (2,3). It is frequently associated with vascular involvement and microangiopathic lesions. Narrowing of the lumen and endothelial swelling of the capillaries and venules of the skin, lungs, heart and skeletal muscle, retina, bronchi and renal glomeruli, associated with sarcoidosis; therefore, inadequate circulation has been shown (4). Cardiac involvement in sarcoidosis is a cause of high mortality and morbidity. Five-year mortality rates are around 25-66% (5). Although it is seen in all age groups, it is mostly a disease of young adults. It is most common in both genders around the age of 30.

Address for Correspondence: Adil Gümüş, Mersin University Training and Research Hospital, Clinic of Nuclear Medicine, Mersin, Turkey
Phone: + 90-324-2410000/22522 **E-mail:** adilgumus1993@gmail.com **ORCID ID:** orcid.org/0000-0003-3428-7778
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Another period when it is more common in women over the age of 50. Although in some series the male/female ratio is reported to be equal in the young age group, according to our country's data, the female/male ratio is 2.08; The average age of women is 10 years higher than the average age of men. Seventy five percent of the cases are non-smokers (2). Regarding the genetics of sarcoidosis, studies have been conducted on HLAs and variants of many non-HLA genes. Some genetic characteristics have been found to be associated with the frequency of sarcoidosis, the way sarcoidosis occurs or its prognosis. For example, HLA-DQB1*0201 and HLADRB1*0301 are associated with acute sarcoidosis such as Löfgren syndrome and good prognosis (6). The main event in the development of sarcoidosis is the development of granulomas. In the first stage, the antigen that triggers sarcoidosis, which we do not know today, is presented to CD4+ T lymphocytes by antigen-presenting cells. Activated CD4+ T lymphocytes (Th0) transform into T helper type 1 (Th1) effector cells under the influence of interleukin (IL) 12 and 18. Continuation of antigen presentation by alveolar macrophages to effector Th1 cells and production of many cytokines and chemokines; provides granuloma formation through migration, collection and local proliferation of cells (especially T lymphocytes, monocytes/macrophages). In later periods, in some cases, granulomas disappear with spontaneous resolution, while in others they continue and progress to chronic disease. In a very small group of patients, granulomas are replaced by fibrotic changes, and if this condition is progressive, end-stage fibrosis may develop (6). Some patients with sarcoidosis present with nonspecific constitutional symptoms such as fever, fatigue, and weight loss. The fever usually does not get very high, but sometimes it can reach 39-40° C. Although fever is not as common as in infectious diseases, sarcoidosis is one of the important causes of fever of unknown origin. Weight loss is usually around 2-6 kg in the last 2-3 months. Weakness and fatigue are common.

Cardiac involvement in sarcoidosis is an independent indicator for mortality and is associated with poor prognosis (7,8). Many patients with subclinical histological myocardial sarcoid lesions remain asymptomatic, but sudden death occurs in 30-65% of cases due to arrhythmia (9). Likewise, the beneficial effects of corticosteroids have been shown in the treatment of cardiac sarcoidosis (10). Therefore, it is important to detect cardiac involvement in sarcoidosis at an early stage. In patients with sarcoidosis, cardiac involvement may occur with clinical conditions such as conduction system disorders, mitral valve insufficiency, congestive heart failure, left ventricular aneurysm, pericardial efusion and associated cardiac tamponade, pericarditis, ventricle-derived arrhythmias and sudden death (11). In cardiac sarcoidosis (CS), granulomas can appear in any focal area of the heart. Involvement is most frequently observed in the left ventricular free wall, followed by the interventricular septum (12). The clinical course of cardiac sarcoidosis varies from asymptomatic to severe heart failure and sudden cardiac death, depending on the extent and severity of involvement. Early diagnosis of the disease is vital, so that effective treatment is provided and the risk of arterioventricular block, ventricular arrhythmias, heart failure and sudden death is reduced . According to both criteria, the diagnosis of CS is made with direct findings of cardiac or extracardiac involvement and cardiac inflammation proven by endomyocardial biopsy (EMB) (13). The sensitivity of EMB is limited in sarcoidosis due to heterogeneous patchy cardiac involvement (14). Due to the high rate of false negativity in EMB, a diagnosis of clinically suspected or probable (more than 50%) CS can be made according to both criteria. In both criterion classifications, in addition to histological evidence of extracardiac involvement, major and minor electrocardiography (ECG), imaging and non-specific EMB findings according to the Japanese criteria and at least one of the 7 clinical ECG and imaging diagnostic criteria according to the Heart Rhythm Association must be present. According to current diagnostic criteria, indirect findings of cardiac inflammation can be listed as cardiac Ga-67 or F-18 FDG uptake, perfusion defect representing scar, cardiac wall motion disorder, ECG

conduction disorders, and pathological cardiac magnetic resonance (MR) findings (13). Therefore, it is important to use non-invasive imaging methods such as echocardiography (ECHO), cardiac MRI and molecular imaging methods in diagnosis. Evaluation of active CS with F-18 FDG PET/CT imaging has become generally accepted in recent years (15).

CASE REPORT

Case 1: Bilateral supraclavicular, multiple mediastinal, abdominal and inguinal hypermetabolic lymphadenopathies, the largest of which were in the subcarinal area, were observed in a 51-year-old female patient who underwent PET-CT examination in our department due to suspicion of malignancy. The biopsy result taken from the subcarinal lymph node was found to be compatible with non-necrotizing granulomatous inflammation and the patient was evaluated for cardiac sarcoidosis. The patient was evaluated with rest GATED myocardial perfusion SPECT (single photon emission computed tomography) findings. Perfusion of all myocardial walls was evaluated as normal in Tc-99m MIBI SPECT sections, and wall movements and thickening in all walls of the left ventricle were evaluated as normal in Rest GATED SPECT images. Following an appropriate diet and 12 hours of fasting, the patient was given 50 IU/kg IV heparin injection, followed by 7.57 mCI FDG injection 15 minutes later. The patient was taken for imaging after 50 minutes. Metabolism was observed within normal limits in the patient's left ventricular myocardium. The patient was evaluated as negative for cardiac sarcoidosis because her perfusion and metabolism were within normal limits (Figure1).

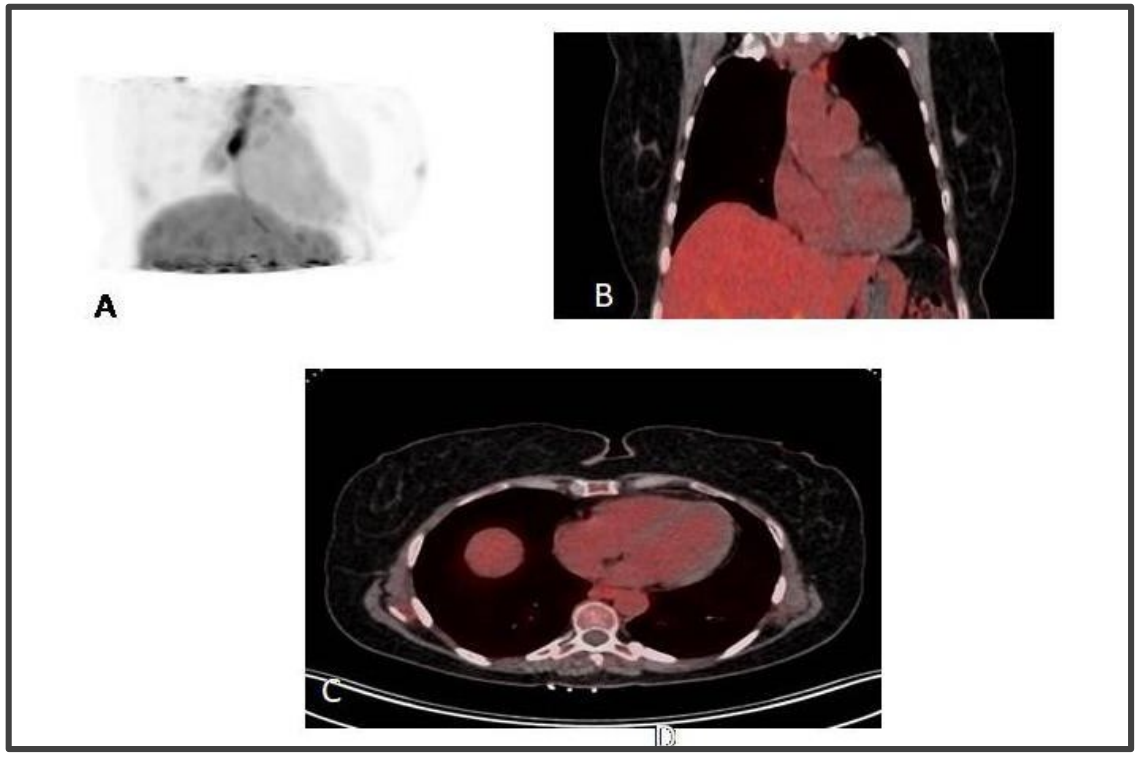

Figure 1: MIP image showing increased FDG uptake in the subcarinal lymph node (A), FDG PET-CT fusion image showing myocardial metabolism within normal limits (Coronal section-B), FDG PET-CT image showing myocardial metabolism within normal limits (Transverse section-C).

Case 2: A biopsy performed on the right supraclavicular lymph hypermetabolic lymph node in a 38-year-old female patient followed up with nonhodgkin's lymphoma was detected as non-necrotizing granulomatous lymphadenitis. According to the patient's cardiac MRI result, focal contrast enhancement was observed in the anteroseptal wall, which may be suspicious for cardiac sarcoidosis. FDG PET-CT examination for cardiac sarcoidosis was performed in our department. The patient was evaluated with rest GATED myocardial perfusion SPECT (single photon emission computed tomography) findings. Perfusion of all myocardial walls was evaluated as normal in Tc-99m MIBI SPECT sections, and wall movements and thickening in all walls of the left ventricle were evaluated as normal in Rest GATED SPECT images. Following an appropriate diet and 12 hours of fasting, the patient was given 50 IU/kg IV heparin injection, followed by 10-15 mCI FDG injection 15 minutes later. The patient was taken for imaging after 50 minutes. Non-homogeneous FDG uptakes were observed in the patient's left ventricular wall, and focal increased FDG uptakes in the anteroseptal area midventricle and lateral wall midventricular area were evaluated as compatible with cardiac sarcoidosis (Figure 2).

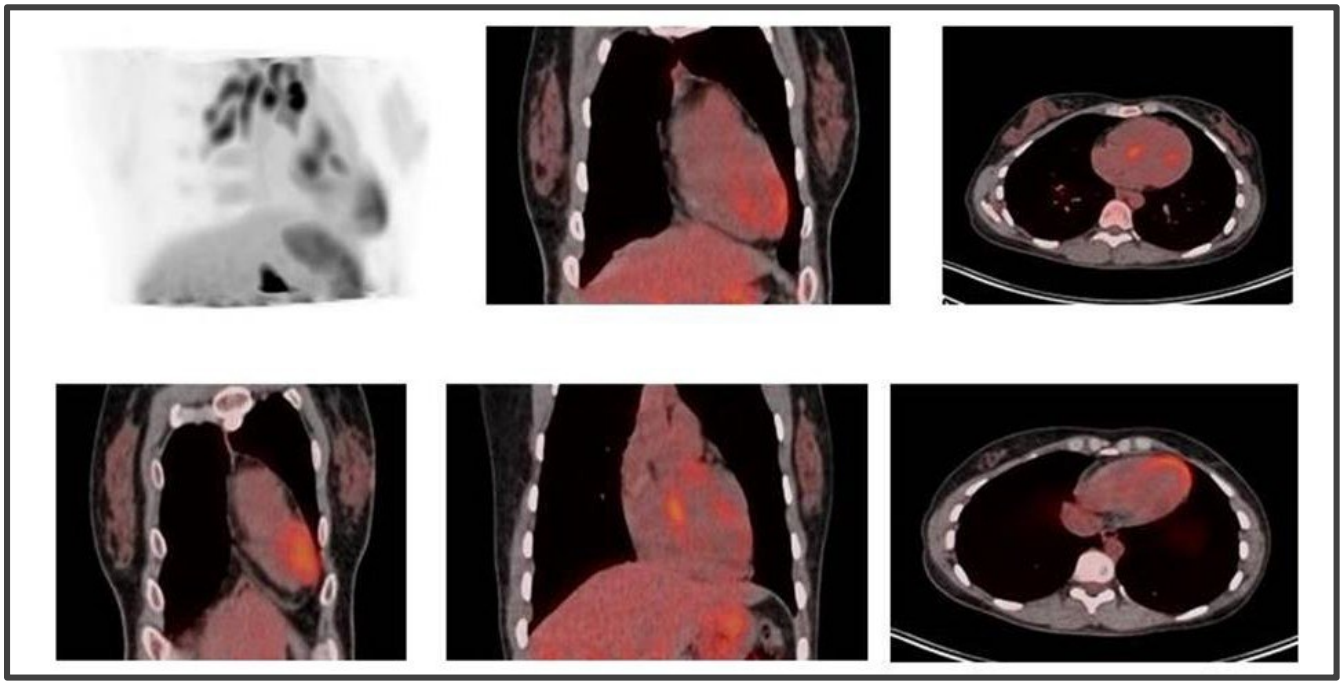

Figure 2: PET-CT images showing focal increased FDG uptake, which may be compatible with cardiac sarcoidosis

Discussion

Conventional scintigraphic methods such as Ga-67 citrate and In-111 octreotit somatostatin receptor scintigraphy are largely out of date. PET studies with Ga-68 DOTA analogues and Rb-82 and PET/MRI as hybrid imaging are promising for the future. F-18 FDG PET/CT reflects the inflammatory activity of the disease, and the underlying physiopathological mechanism is the increase in macrophage-mediated glucose metabolism in the inflammation areas caused by sarcoidosis. According to the results of the meta-analysis of seven studies, the diagnostic accuracy of F-18 FDG PET is quite high, with sensitivity reported as 89% and specificity as 78% (16). F-18 FDG PET/CT may provide earlier findings than MRI in the diagnosis of CS (17). Cardiac sarcoidosis is

increasingly common today compared to the previous decade, and current literature studies also show that there is a more than tenfold increase compared to the 2010s. The biggest reason for this is the improvement in diagnostic methods and its widespread use and the increase in awareness of the disease (18,19). F-18 FDG PET and contrast-enhanced MR imaging have facilitated the detection of cardiac sarcoidosis. Sarcoid-associated myocardial inflammation is associated with regional impairment of coronary circulatory function (20). The combined use of FDG PET/CT and myocardial perfusion imaging is currently recommended. The risk of death or ventricular arrhythmia is high in cardiac sarcoidosis patients with both perfusion defects and abnormal FDG uptake (21). Patient preparation for cardiac FDG PET/CT imaging for sarcoidosis is based on reducing the physiological uptake of glucose in the myocardium and increasing the delivery of fatty acids to the heart. Current practice guidelines recommend a carbohydrate-free, high-fat diet 12-24 hours before imaging and/or the use of intravenous unfractionated heparin (15-50 units/kg) 15 minutes before F-18 FDG injection (22,23). It has been stated that if a diet containing high fat, high protein and very low carbohydrates is followed for 72 hours before the extraction, physiological myocardial uptake is more significantly suppressed, and the rate of indeterminate (diffuse involvement) in terms of cardiac sarcoidosis is significantly lower in the evaluation (24,25). Detailed diet preparation improves interobserver agreement in assessing FDG uptake (26). A 10-minute cardiac image is taken 60 minutes after the administration of 10 mCi (2.5-5 MBq/kg) F-18 FDG. Since sarcoidosis is a systemic disease, limited whole-body imaging from the cerebellum to the mid-thigh is also recommended to identify areas of non-cardiac disease and to determine a potential suitable area for biopsy (23).

Imaging protocol steps are presented below:

1. Diet preparation and fasting the day before the shooting

2. Resting myocardial PET/SPECT

3. Heparin (15 minutes before FDG injection)

4. F-18 FDG PET injection and 60-90 minutes waiting time

5. Cardiac F-18 FDG PET (10 minutes/bed for 3D, 20-30 minutes/bed for 2D) 6. Partial whole body F-18 FDG PET including lung-mediastinum (3 minutes/bed for 3D, and 4 minute/bed for 2D)

Conclusion

F-18 FDG PET makes a significant contribution to patient management by being used in the diagnosis of CS, detection of myocardial inflammation and its severity, detection of non-cardiac involvement of the disease, differential diagnosis of active/inactive disease, monitoring of treatment response and predicting prognosis.

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Authorship Contributions

Concept: A.G., P.P.O., Z.P.K., M.S., Z.S.S., **Design:** A.G., P.P.O., Z.P.K., M.S., Z.S.S., **Supervision:** A.G., P.P.O., Z.P.K., M.S., Z.S.S., **Data Collection and/or Processing**: A.G., P.P.O., Z.P.K., M.S., Z.S.S., **Analysis and/or Interpretation:** A.G., **Literature Review:** A.G., **Writer:** A.G.

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