FDG PET-CT findings of extra-thoracic sarcoid are associated with cardiac sarcoid: A rationale for using FGD PET-CT for cardiac sarcoid evaluation

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Received Mar 10, 2017; accepted Jun 7, 2017
doi:10.1007/s12350-017-0962-4

Purpose. **This retrospective study investigates the relationship between cardiac and extra-thoracic sarcoid findings on FDG PET-CT using a 72-hour pretest high-fat, high-protein, and very low-carbohydrate (HFHPVLC) diet.**

Patients and methods. **A total of 196 consecutive FDG PET-CT scans with 72-hour HFHPVLC diet preparation were performed between December 2014 and December 2015 in known sarcoid patients. Of these scans, 5 were excluded for non-adherence to diet preparation or underlying cancer. Cardiac and extra-thoracic sarcoid lesions were categorized and measured for radiotracer uptake.**

Results. **A total of 188 patients had 191 eligible FDG PET/CT scans (3 follow-up scans), of which there were 20 (10%) positive, 6 indeterminate (3%), and 165 (86%) negative for CS. Among the 20 scans positive for CS, 8 (40%) had findings of both cardiac and extra-thoracic sarcoid.**

Conclusion. **Our study shows that 40% of CS patients also have FDG PET-CT findings of extra-thoracic sarcoid. This makes an intriguing case for FDG PET-CT use with pretest diet prep over cardiac MRI (CMR) for cardiac sarcoid evaluation, given that CMR is likely to overlook these extra-thoracic sites of disease. (J Nucl Cardiol 2019;26:486–92.)**

Key Words: Cardiac • Extra-thoracic • Sarcoid • Sarcoidosis • FDG PET-CT

Abbreviations			
HFHPVLC	High-fat, high-protein, and very low-carbohydrate	CMR	Cardiac MRI
CS	Cardiac sarcoid	IRB	Institutional review board

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Electronic supplementary material The online version of this article (doi:10.1007/s12350-017-0962-4) contains supplementary material, which is available to authorized users.

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1071-3581/$34.00

INTRODUCTION

Sarcoidosis is a systemic granulomatous disease that can affect multiple organs, which is definitively diagnosed with biopsy, usually from skin lesions, pulmonary nodules, or lymph nodes, looking for non-caseating epithelioid-cell granulomas in the absence of organisms or particles.[1] Cardiac sarcoidosis (CS) is reported to be symptomatic in only 5% of patients with sarcoidosis,[2] but it has been found in 27% of patients at autopsy.[3] CS is potentially fatal, and has a

wide spectrum of clinical manifestations, including conduction abnormality and sudden death. Diagnosing CS through endomyocardial biopsy is an invasive procedure and has a sensitivity of only 20-30% because it often misses areas of CS involvement, and usually the left ventricle is not accessible for biopsy.[4] The diagnosis of CS is therefore challenging and lacking an imaging gold standard. The imaging modality of choice for CS diagnosis is still debated.[5-7]

The background physiological FDG activity in normal myocardium can interfere with the detection of active CS and is the major hurdle in utilizing FDG PET/CT to diagnose CS.[8] Different strategies, including 12-18 hr pretest fasting, pretest administration of unfractionated heparin, and overnight high-fat, low-carbohydrate diet modification, have been proposed to minimize physiological cardiac FDG activity but only with suboptimal results.[9-15] With the use of a 72-hour pretest high-fat, high-protein, and very low-carbohydrate (HFHPVLC) diet preparation FDG PET-CT protocol,[16] we have been able to successfully suppress background FDG uptake in the myocardium and minimize the rate of indeterminate findings to diagnose CS.

As sarcoidosis is a systemic disease, we set to investigate the relationship between cardiac and extra-thoracic sarcoid findings on FDG PET-CT using this protocol. Our aim is to determine if sarcoid patients being evaluated for cardiac involvement would benefit from a more thorough imaging evaluation of the body with FDG PET-CT vs limited thoracic imaging evaluation with cardiac MRI (CMR).

METHODS

Patients

The institutional review board (IRB) approved a retrospective study, which initially investigated a total of 196 consecutive FDG PET-CT scans with 72-hour HFHPVLC diet preparation performed between December 2014 and December 2015 with 10-22 months follow-up. Of note, patients in this study include a subset of known sarcoid patients from our prior published series.[16] Demographic information for these patients is summarized in Table 1. Of these scans, 5 were excluded for non-adherence to diet preparation ($n = 3$) and underlying cancer ($n = 2$) for a total of 191 final included scans. Suspected dietary non-compliance was initially detected by a staff nuclear medicine physician after image acquisition. Patients suspected to be non-compliant were contacted regarding their diet preparation. All 3 suspected non-compliant patients reported non-adherent dietary intake.

Imaging protocol

All patients underwent a 72-hour HFHPVLC diet preparation including breakfast approximately 4 hours before scanning.[16] Patients were then asked to fast post breakfast on scan day. The HFHPVLC diet was written as a menu of permitted and prohibited foods. A menu of the diet preparation protocol is shown in Table 2. Patients on steroids for treatment of sarcoidosis and on antidiabetic medication were instructed to hold off these medications for 24 hours before FDG PET/CT and were monitored with serum glucose levels.

All FDG PET/CT examinations were performed on a GE Discovery 690 FDG PET/CT scanner (GE Medical Systems, Milwaukee, WI) using ASNC/SNMMI guidelines.[17] All patients had a blood glucose level of less than 200 mg/dL at the time of FDG injection. Dedicated PET/CT scans from the skull base to the upper thighs were obtained 60 to 90 minutes after intravenous injection of 0.370-0.481 GBq of FDG. CT parameters were as follows: 120 kV, 120 mAs, pitch 0.813, 16 × 1.5-mm collimation, slice thickness of 3 mm with an increment of 1.5 mm. CT scan was used for attenuation correction. PET parameters were as follows: 2 min/bed for the non-cardiac fields and 10 min/bed for fields covering the heart. Image acquisition was performed using non-cardiac-gated technique.

Imaging analysis

Quantitative cardiac FDG uptake was measured as SUVmax in the myocardium and compared with SUVmean in the ascending aorta as mediastinal blood pool background. Extra-thoracic sarcoid lesions were categorized and measured for SUVmax and compared to the liver background SUVmean. All the FDG PET-CT studies were retrospectively read, or reread, by 3 imaging physicians. Imaging diagnosis was made based on data from literature[9-11,13-15,18,19] and our previous study.[16] We visually classified the pattern of cardiac FDG uptake into the following: ''none'' and ''ring-like diffuse at base'' (negative for CS),[18] ''focal''(positive for CS),[20] and ''diffuse'' (indeterminate for CS). A sample case demonstrating the myocardial suppression achieved using the 72-hour HFHPVLC diet protocol is shown in Figure 1. Final diagnoses were made with consensus among imaging physicians and a referring clinician in view of all available comprehensive clinical information and diagnostic test results, including 12-lead ECG, cardiac MRI, echocardiogram, and nuclear stress test, with

Table 1. Patient demographics

Mean age (years)	52 ± 11
Gender	
Male	55 (28%)
Female	141 (72%)
Ethnicity	
African American	76 (39%)
Caucasian	98 (50%)
Other	22 (11%)
Mean weight (kg)	92 ± 25
Mean BMI (kg/m^2)	32 ± 9

Table 2. HFHPVLC Diet[16]

Start the meals at 3 days before scheduled FDG PET/CT study	
Encouraged/permitted foods	Non-processed poultry, fish, and meat; eggs; non-sweet butter; non-processed real cheese; animal and vegetable oil; non-starchy vegetables; coffee without milk or sugar; water and other non-sugar-containing beverages
Prohibited foods	Sugar in any form, sugar substitutes, pastas, bread, rice, cake, cereal, starchy vegetables, fruits, processed meat and cheese, any carbohydrate-containing milk or other beverages, candy or gum, salad dressing, barbeque sauce, wine, and other alcohol
Breakfast the day of FDG PET/CT study, approximately 4 h before FDG injection	Fried chicken or bacon; omelet with 4 eggs; at least 2 spoons of olive oil; water, or black coffee

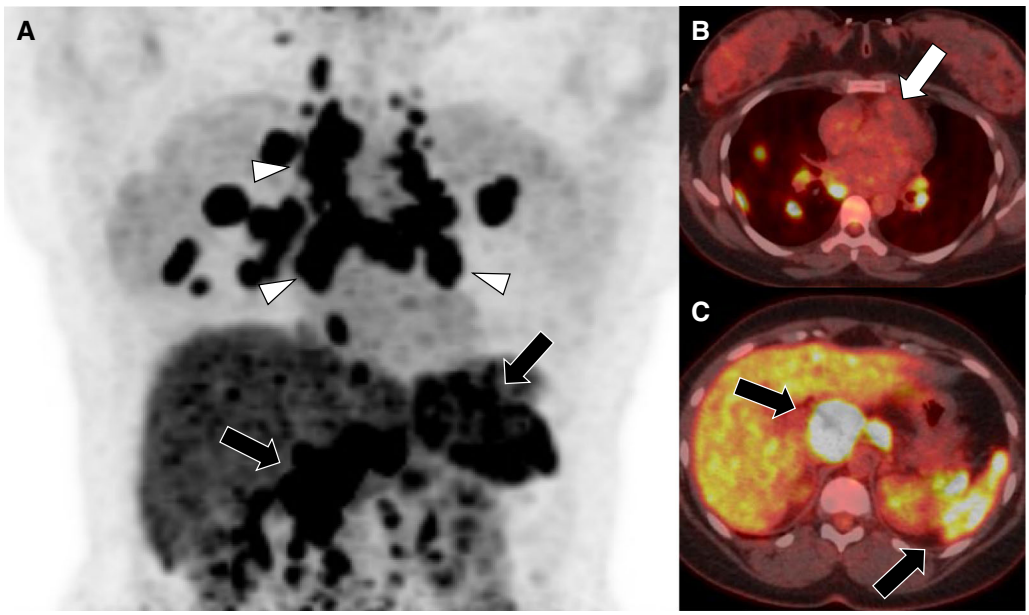

Figure 1. Coronal MIP (**A**) and fused axial chest (**B**) and upper abdominal (**C**) images in a patient with typical thoracic sarcoid disease consisting of mediastinal and bilateral hilar lymphadenopathy (*white arrowheads*). Note the myocardial suppression achieved with 72-hour HFHPVLC diet preparation (*white arrow*). This patient also has upper abdominal lymphadenopathy and splenic involvement (*black arrows*).

reference to the modified Japanese Ministry of Health and Welfare criteria.[21]

RESULTS

A total of 188 patients had 191 eligible FDG PET/CT scans (3 follow-up scans), of which there were 20 (10%) positive, 6 indeterminate (3%), and 165 (86%) negative for CS. Myocardial uptake patterns are summarized in Table 3. The SUVmax of PET positive myocardial lesions ranges from 3.4 to 12.5, while mediastinal blood pool SUVmean ranges from 1.1 to 3.6. All positive myocardial activity was higher than liver background which had an average SUV mean of 2.7 ± 0.6 (SD). Among the 20 scans positive for CS, 8 (40%) had findings of both cardiac and extra-thoracic sarcoid and 12 (60%) had findings of cardiac but no extra-thoracic sarcoidosis. Of the 165 scans negative for CS, 56 (34%) had findings of extra-thoracic sarcoid but no CS, and 109 (66%) were negative for extra-thoracic sarcoidosis. Of the 6 indeterminate scans, 2 (33%) were positive for extra-thoracic sarcoid and 4 (66%) were negative for extra-thoracic sarcoid. These results are summarized in Fig. 2.

Table 3. Observed myocardial uptake patterns

Negative	None	161/191
	Ring-like diffuse at base	4/191
Positive	Focal	20/191
Indeterminate	Diffuse including focal on diffuse	6/191

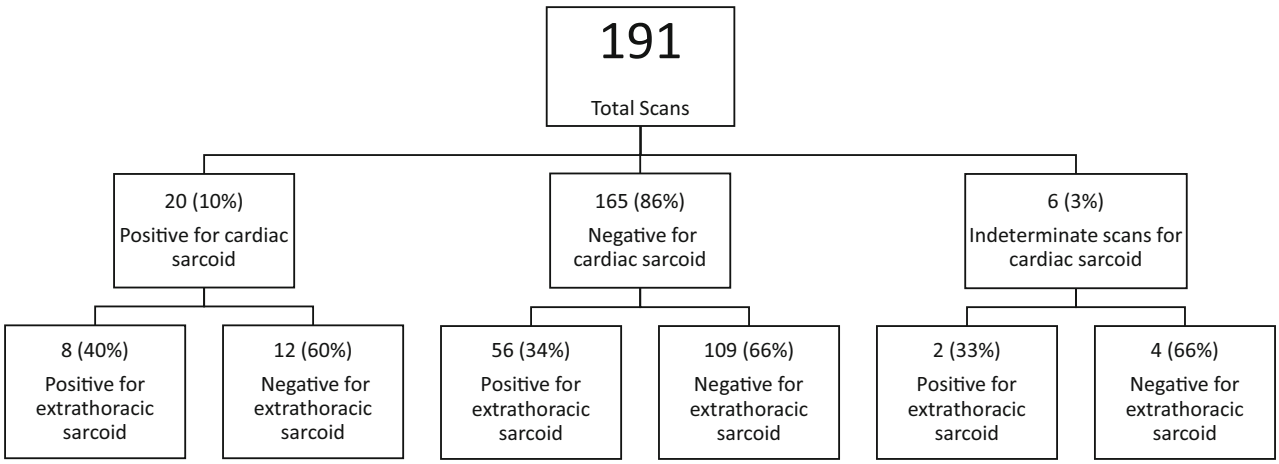

Figure 2. Organizational diagram summarizing occurrence of FDG PET-CT findings of cardiac and extra-thoracic sarcoid.

Table 4. FDG PET-CT imaging characteristics of extra-thoracic sarcoid lesions

Site of extra-thoracic disease	Number of patients (%)	SUVmax range	SUVmax mean±SD
Bone	17 (9%)	3.8-34.4	8.3±7.8
Liver	23 (12%)	3.3-18.7	6.6±3.6
Spleen	21 (11%)	3.1-14.8	7.7±3.2
Extra-thoracic nodal	40 (21%)	3.7-22.1	10.3±4.9
Cutaneous	5 (3%)	5.1-14.4	10.1±3.4

Average liver background SUVmean was 2.7 ± 0.6. SUVmax ranges for extra-thoracic organ involvement were as follows: 3.8-4.4 for bone, 3.3-18.7 for liver, 3.1-14.8 for spleen, 3.7-22.8 for extra-thoracic lymph node, and 5.1-14.1 for cutaneous nodules. Extra-thoracic FDG PET-CT findings are summarized in Table 4.

DISCUSSION

Previous studies have established that extra-thoracic sarcoid and CS occur with significant frequency.[2,3,22-31] Our results show an association between FDG PET-CT findings of extra-thoracic and CS, with 40% of CS patients (8 out of 20 patients) also having extra-thoracic sarcoid, while 60% of CS patients (12 out of 20) had CS without findings of extra-thoracic sarcoid. This makes an intriguing case for using FDG PET-CT over cardiac MRI (CMR) for CS evaluation given that the narrower field of view with CMR is likely to overlook these extra-thoracic sites of disease. An example of extra-thoracic sarcoid lesions in a CS patient which would customarily be outside the field of view and thus non-detectable by CMR is illustrated in Fig. 3.

A prior study by Blankstein et al. shows that the presence of extra-cardiac sarcoid did not alter patients' prognosis, whereas CS was a prognostic indicator.[32] While the presence of extra-cardiac sarcoid may not alter immediate management, it does serve as a way to

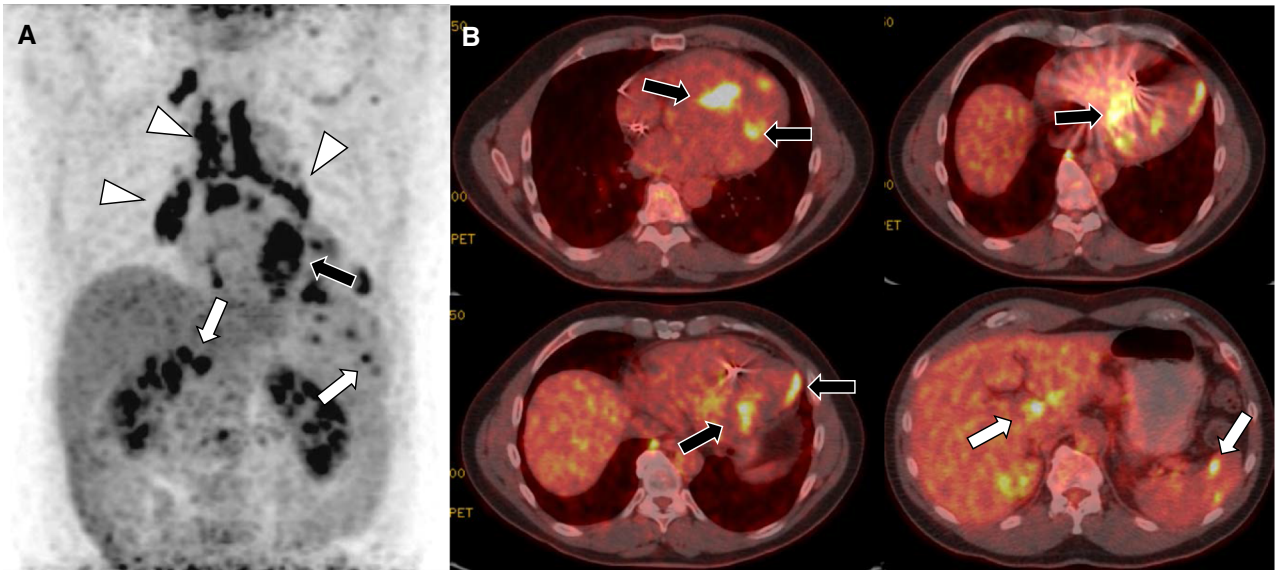

Figure 3. Coronal MIP (**A**) and a set of fused axial chest and upper abdominal images (**B**) from FDG PET-CT after 72-hour HFHPVLC diet preparation. This patient demonstrates typical mediastinal and bilateral hilar lymphadenopathy of sarcoid (*white arrow heads*). There are also multiple foci of myocardial radiotracer uptake consistent with CS (*black arrows*). Inspection of the upper abdomen reveals sarcoidosis in the spleen and porta hepatic lymph nodes (*white arrows*).

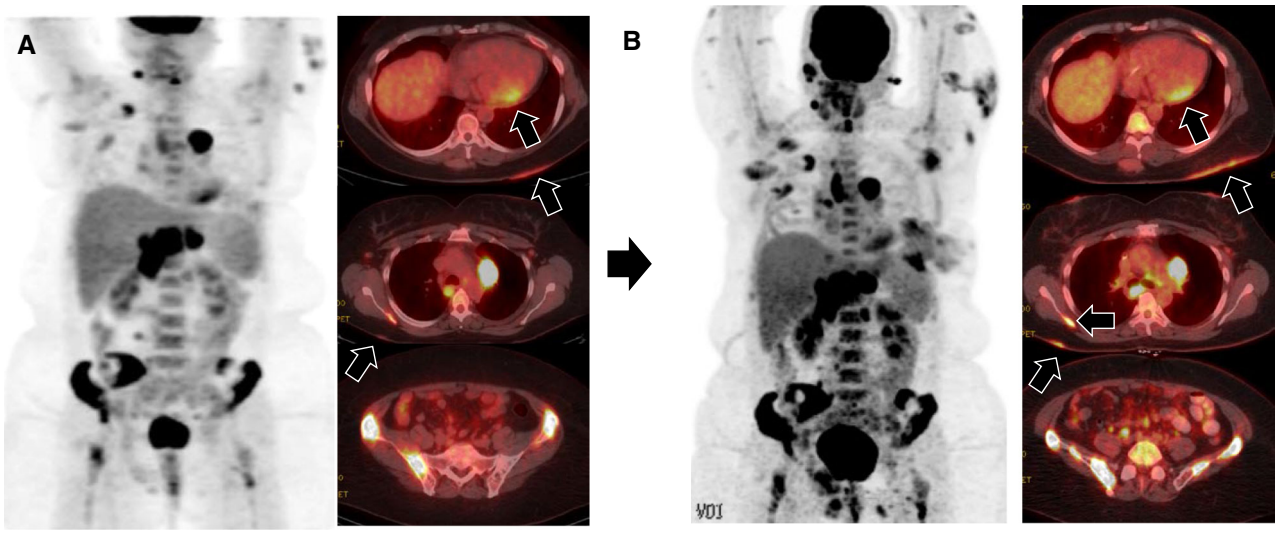

Figure 4. Coronal MIP and sample fused axial FDG PET-CT images using 72-hour HFHPVLC diet preparation before (**A**) and after (**B**) 17-month steroid therapy demonstrating progression of disease. Predominant disease is present in the mediastinum, upper abdomen, and bony pelvis. More subtle disease progression is present in the myocardium, skin, and right scapula (*arrows*).

stage disease and provides a sense of granuloma burden. Identifying extra-cardiac involvement alerts the treating physicians to which symptoms need attention and possible follow-up. Although not the focus of our study, FDG PET-CT also has an added benefit of easily being able to monitor therapeutic response, thus allowing for adjustments in treatment if necessary. A sample case of disease progression after 17-month steroid therapy prompting therapy change is shown in Fig. 4.

Prior meta-analysis has reported sensitivity and specificity of FDG PET-CT for detection of CS at 89% and 78%, respectively.[33] This is similar, if not better than prior studies showing CMR sensitivity and specificity of 75%-100% and 76.9%-78%, respectively.[34,35]

Reservations regarding the use of FDG PET-CT have focused on incomplete myocardial suppression[36] which can be interpreted as indeterminate or intermediate evidence for CS. FDG PET-CT using a 72-hour HFHPVLC diet preparation has been shown to be very effective in evaluation of CS.[16] The indeterminate rate in our study was only 3%.

Although ours was a retrospective single-center study, it is the largest to date case series comparing the occurrence of CS and extra-thoracic sarcoid and it is the only one using a 72-hour HFHPVLC diet protocol. It reaffirms the association between cardiac and extra-thoracic sarcoid on FDG PET-CT that highlights the benefits of its wide field of view over CMR for CS evaluation.

NEW KNOWLEDGE GAINED

When performing FDG PET-CT using a 72-hour HFHPVLC diet preparation for detection of cardiac sarcoid, 40% of patients with cardiac sarcoid patients also have extra-thoracic sarcoid disease. These sites of extra-thoracic disease would be non-detectable on CMR.

CONCLUSION

Our study shows an association between FDG PET-CT findings of CS and extra-thoracic sarcoidosis. This makes an intriguing case for FDG PET-CT use with 72-hour pretest HFHPVLC diet preparation over MRI for cardiac sarcoid evaluation given that CMR is likely to overlook these extra-thoracic sites of disease. If cardiac involvement is the only clinical concern, then cardiac PET or CMR might be considered as the imaging modality of choice. However, for more complete disease extent evaluation, the expanded field of view from skull base to thigh achieved with full body FDG PET-CT would provide complete evaluation of disease extent. For this reason, in these cases where extra-thoracic disease is suspected or complete extent of disease is unknown, preference may be given to FDG PET-CT with 72-hour HFHPVLC diet preparation over MRI for cardiac sarcoid evaluation.

Disclosure

All the authors, Darshan C. Patel, Senthil S. Gunasekaran, Christopher Goettl, Nadera J. Sweiss, and Yang Lu, state that they have nothing to disclose.

References

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007;357:2153-65.
2. Sharma OP, Maheshwari A, Thaker K. Myocardial sarcoidosis. Chest 1993;103:253-8.
3. Albert CM, Chae CU, Grodstein F, Rose LM, Rexrode KM, Ruskin JN, et al. Prospective study of sudden cardiac death among women in the United States. Circulation 2003;107:2096-101.
4. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: A scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 2007;50:1914-31.
5. Hamzeh NY, Wamboldt FS, Weinberger HD. Management of cardiac sarcoidosis in the United States: A Delphi study. Chest 2012;141:154-62.
6. Hulten E, Aslam S, Osborne M, Abbasi S, Bittencourt MS, Blankstein R. Cardiac sarcoidosis-state of the art review. Cardiovasc Diagn Ther 2016;6:50-63.
7. Mantini N, Williams B, Stewart J, Rubinsztain L, Kacharava A. Cardiac sarcoid: A clinician's review on how to approach the patient with cardiac sarcoid. Clin Cardiol 2012;35:410-5.
8. Schatka I, Bengel FM. Advanced imaging of cardiac sarcoidosis. J Nucl Med 2014;55:99-106.
9. Williams G, Kolodny GM. Suppression of myocardial 18F-FDG uptake by preparing patients with a high-fat, low-carbohydrate diet. Am J Roentgenol 2008;190:W151-6.
10. Langah R, Spicer K, Gebregziabher M, Gordon L. Effectiveness of prolonged fasting 18f-FDG PET-CT in the detection of cardiac sarcoidosis. J Nucl Cardiol 2009;16:801-10.
11. Harisankar CN, Mittal BR, Agrawal KL, Abrar ML, Bhattacharya A. Utility of high fat and low carbohydrate diet in suppressing myocardial FDG uptake. J Nucl Cardiol 2011;18:926-36.
12. Ishida Y, Yoshinaga K, Miyagawa M, Moroi M, Kondoh C, Kiso K, et al. Recommendations for (18)F-fluorodeoxyglucose positron emission tomography imaging for cardiac sarcoidosis: Japanese Society of Nuclear Cardiology recommendations. Ann Nucl Med 2014;28:393-403.
13. Morooka M, Moroi M, Uno K, Ito K, Wu J, Nakagawa T, et al. Long fasting is effective in inhibiting physiological myocardial 18F-FDG uptake and for evaluating active lesions of cardiac sarcoidosis. EJNMMI Res 2014;4:1.
14. Okumura W, Iwasaki T, Toyama T, Iso T, Arai M, Oriuchi N, et al. Usefulness of fasting 18F-FDG PET in identification of cardiac sarcoidosis. J Nucl Med 2004;45:1989-98.
15. Soussan M, Brillet PY, Nunes H, Pop G, Ouvrier MJ, Naggara N, et al. Clinical value of a high-fat and low-carbohydrate diet before FDG-PET/CT for evaluation of patients with suspected cardiac sarcoidosis. J Nucl Cardiol 2013;20:120-7.
16. Lu Y, Grant C, Xie K, Sweiss NJ. Suppression of myocardial 18F-FDG uptake through prolonged high-fat, high-protein, and very-low-carbohydrate diet before FDG-PET/CT for evaluation of patients with suspected cardiac sarcoidosis. Clin Nucl Med 2017;42:88-94.
17. Dilsizian V, Bacharach SL, Beanlands RS, Bergmann SR, Delbeke D, Dorbala S, et al. ASNC imaging guidelines/SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. J Nucl Cardiol 2016;23:1187-226.
18. Ito K, Okazaki O, Morooka M, Kubota K, Minamimoto R, Hiroe M. Visual findings of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with cardiac sarcoidosis. Intern Med 2014;53:2041-9.
19. Ohira H, Tsujino I, Ishimaru S, Oyama N, Takei T, Tsukamoto E, et al. Myocardial imaging with 18F-fluoro-2-deoxyglucose

positron emission tomography and magnetic resonance imaging in sarcoidosis. Eur J Nucl Med Mol Imaging 2008;35:933-41.
20. Lu Y, Sweiss NJ. MRI and FDG PET/CT imaging manifestations of cardiac sarcoidosis. Clin Nucl Med 2015;40:973-4.
21. Soejima K, Yada H. The work-up and management of patients with apparent or subclinical cardiac sarcoidosis: With emphasis on the associated heart rhythm abnormalities. J Cardiovasc Electrophysiol 2009;20:578-83.
22. Rose AS, Tielker MA, Knox KS. Hepatic, ocular, and cutaneous sarcoidosis. Clin Chest Med 2008;29:509-24, ix.
23. Singh G, Sangolli P, Dash K, Grove S. Cutaneous sarcoidosis without systemic involvement. Indian J Dermatol Venereol Leprol 2000;66:43-4.
24. Okamoto H, Mizuno K, Ohtoshi E. Cutaneous sarcoidosis with cardiac involvement. Eur J Dermatol 1999;9:466-9.
25. Mana J, Marcoval J, Graells J, Salazar A, Peyri J, Pujol R. Cutaneous involvement in sarcoidosis. Relationship to systemic disease. Arch Dermatol 1997;133:882-8.
26. Marchell RM, Judson MA. Chronic cutaneous lesions of sarcoidosis. Clin Dermatol 2007;25:295-302.
27. Warshauer DM, Lee JK. Imaging manifestations of abdominal sarcoidosis. Am J Roentgenol 2004;182:15-28.
28. Judson MA. Extrapulmonary sarcoidosis. Semin Respir Crit Care Med 2007;28:83-101.
29. CerfPayrastre I, Liote F. Bone, joint, and muscle involvement in sarcoidosis. Sem Hop Paris 1997;73:945-52.
30. Holmes J, Lazarus A. Sarcoidosis: Extrathoracic manifestations. Dis Mon 2009;55:675-92.
31. James DG, Sharma OP. Extrathoracic sarcoidosis. Proc R Soc Med 1967;60:992-4.
32. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol 2014;63:329-36.
33. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G, et al. The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: A systematic review and metaanalysis including the Ontario experience. J Nucl Med 2012;53:241-8.
34. Ohira H, Tsujino I, Sato T, Yoshinaga K, Manabe O, Oyama N, et al. Early detection of cardiac sarcoid lesions with (18)F-fluoro-2-deoxyglucose positron emission tomography. Intern Med 2011;50:1207-9.
35. Smedema JP, Snoep G, van Kroonenburgh MP, van Geuns RJ, Dassen WR, Gorgels AP, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol 2005;45:1683-90.
36. Gropler RJ, Siegel BA, Lee KJ, Moerlein SM, Perry DJ, Bergmann SR, et al. Nonuniformity in myocardial accumulation of fluorine-18-fluorodeoxyglucose in normal fasted humans. J Nucl Med 1990;31:1749-56.