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Advances in PET Imaging of Sarcoidosis

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Abstract

Purpose of Review The purpose of this paper is to provide an updated review of recent advances in protocols for positron emission tomography (PET) or PET/computed tomography (PET/CT) imaging in patients with sarcoidosis.

Recent Findings There has been more research focused on developing newer and improved PET imaging modalities to diagnose and follow-up cardiac sarcoidosis (CS). Fluorine-18-fluorodeoxyglucose (^{18}F- FDG)-PET are widely used to diagnose CS, with or without concurrent rest nuclear myocardial perfusion study. There have been various patient preparation strategies for FDG PET/CT in CS. Interpretation criteria for cardiac FDG PET/CT in diagnosing CS also varies. There are emerging data utilizing new PET radiotracers (i.e., ^{68}Ga-DOTATATE, ^{18}F-Flurpiridaz) and PET/MRI imaging for CS diagnosis.

Summary Based on published imaging data, patient preparation with a 72-h high-fat, high-protein, and very-low-carbohydrate diet protocol generates the most promising results in suppression of physiological myocardial FDG uptake in cardiac PET/CT. The "focal-on-diffuse uptake" pattern on myocardial uptake is not convincing and should not be interpreted as active CS. Nuclear myocardial perfusion test might not be needed to diagnose CS if optimal suppression of myocardial background uptake of FDG is achieved. FDG PET/MRI with optimal patient preparation may increase diagnostic confidence. More data will be needed for new tracers to be used for CS diagnosis.

Keywords Cardiac sarcoidosis · Sarcoidosis · PET; PET/CT

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown cause that can affect multiple organs including the heart [1, 2]. Cardiac sarcoidosis (CS) is reported to be symptomatic in only 5% of patients with sarcoidosis [3], but it has been found in 27% of patients at autopsy [4]. CS is potentially fatal and has a wide spectrum of clinical manifestations, including conduction abnormality and sudden death.

Although the diagnosis of CS can be achieved through endomyocardial biopsy, this procedure is invasive. Because of sampling bias, it has limited sensitivity of only 20–30%, often missing areas of CS involvement especially in the left ventricle which is not accessible for biopsy [5]. Thus, the diagnosis of CS remains challenging.

Although there is currently no gold standard imaging test for the diagnosis of CS, non-invasive imaging tests can be used to support the diagnosis of CS and for guiding invasive biopsies. The imaging modality of choice for CS diagnosis, however, has been debated [6–8]. Although guidelines from the Japanese Ministry of Health and Welfare (JMHW), as revised by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders in 2006, are used as a worldwide standard for clinical diagnosis of CS [9], these guidelines have not been clinically validated and have an imperfect diagnostic accuracy [10, 11].

Given the underlying inflammatory process in sarcoidosis, Fluorine-18-fluorodeoxyglucose (18F- FDG)-PET or PET/computed tomography (PET/CT) has been explored in sarcoidosis imaging, especially in Europe and Asia [12–14]. FDG PET/CT is currently recommended by the Japanese Society of Nuclear Cardiology in 2014 [15] and the Society of Nuclear Medicine and Molecular Imaging and American Society of Nuclear Cardiology in 2017 [16•]. In the USA, FDG PET/CT, however, is less commonly used clinically

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because of its higher cost and its approval is not routinely supported by the Medicare and Medicaid. On the other hand, private insurers have approved FDG PET/CT in CS, especially in those patients with contraindications to cardiac MRI.

In this article, we review the state-of-the-art techniques of PET/CT imaging in CS, emphasize patient preparation strategies, imaging protocols, and interpretation criteria for CS.

Patient Preparation for FDG PET/CT for CS

Normal myocardium is very metabolically active and utilizes glucose as one of its main energy sources. When using FDG PET/CT to detect CS, it requires patient pre-imaging preparation to suppress physiological myocardial FDG uptake and minimize false-positive results. Many techniques have been developed for this purpose to improve pathologic CS detection. Different strategies, including 12–18 h 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 with suboptimal results [15, 17–22]. Different combinations of these approaches have also been explored [16•, 20, 23–26].

The optimal patient preparation methods for CS, however, remain controversial [27]. Most of these proposed patient preparation methods are either based on findings in small cohorts [22], "expert consensus" [16•] or study spanning over more than 5 years [28] or results from various patient groups other than sarcoidosis [23, 29]. Patient preparation approaches have also varied among centers over the years.

Recent studies have compared these different approaches in effort to identify the most optimal patient preparation. Morooka et al. [20] reported that a long fasting (LF) approach of 16 h or more is better than heparin loading plus a 12-h fasting (HEP) preparation for inhibition of myocardial FDG uptake. Among healthy volunteers, complete inhibition of myocardial uptake (grade 1), physiological "basal ring-like" uptake (grade 2–3), and failed suppression of diffuse myocardial uptake (grade 4) were 63.2% (12/19), 26.3% (5/19), and 10.5% (2/19) in the LF group compared with 10.5% (2/18), 61.1% (11/18), and 27.8% (5/18), respectively in HEP group. Further validation in large cohorts from additional centers is needed.

Many physicians, however, have found that prolonged fasting (18 h or even longer) is not a feasible/practical approach in patients with sarcoidosis. Scholtens et al. [23] reported data from mixed groups of patients receiving FDG PET/CT with indications of cancer, inflammation, and infection detection. The study found that a carbohydrate-restricted, fat- and protein-allowed diet administered for at least 12 h before a fast of at least 12 h combined with 50 IU/kg intravenous dose of heparin 15 min before administration of FDG significantly increased cardiac suppression compared with both the standard oncologic FDG PET/CT protocol and other low-carbohydrate-diet-alone protocols. Heparin use, however, carries a risk of heparin-induced thrombocytopenia. Based on the published data, we are not convinced of the necessity of adding heparin to other patient preparation protocols and are uncertain whether, if there is any additional benefit of adding heparin to inhibit physiological FDG uptake. The theoretical benefit of using heparin does not outweigh the risk of heparin-induced thrombocytopenia or bleeding.

In addition to the strategies above, an overnight high-fat, low-carbohydrate diet modification has been proposed to remove background FDG uptake. This strategy produces low insulin levels and high fatty acid levels, resulting in the least amount of glucose metabolism. Importantly, most carbohydrate restricted diet preparation protocols are for only 24 h or less [17, 23, 25, 26, 30, 31]. Harisankar et al. [19] showed that dietary modification with high-fat diet the night before and 4 h prior to FDG injection had 53% (31/60) complete suppression of background FDG uptake in the myocardium and was superior to the 32% (16/50) of prolonged fasting (> 12 h) group.

Collectively, these 24 h or shorter diet preparation protocols with and without prolonged fasting or heparin administration only showed suboptimal suppression of physiological myocardial uptake of FDG. To address the limitations of current protocols based on our review of the literature in addition to our preliminary unsatisfying results using a 24-h high-fat, high-protein, and very low-carbohydrate (HFHPVLC) diet preparation protocol for sarcoid patients with suspected CS, we developed a 72-h HFHPVLC diet preparation plus a boost breakfast at 4 h prior to the scheduled FDG PET/CT [32••]. Our study [32••] consisted of 215 patients with biopsy-proven sarcoidosis and clinical suspicion of CS in a 1.5-year period (between July 2014 and December 2015). All the PET/CT exams were performed on the same scanner with same imaging protocol. This is so far the largest reported CS FDG PET/CT patient data with minimal variance. We found that [32••] in 72-h HFHPVLC diet group, the optimal suppression of physiological myocardial FDG uptake reached 86.6% (167/193), with only 3.6% (7/193) failed suppression rate, while the numbers were 50% (6/12) and 41.7% (5/12) respectively in 24-h HFHPVLC diet group.

In summary, we strongly recommend a 72-h HFHPVLC diet preparation including a boost breakfast at 4 h prior to the scheduled FDG PET/CT for patients with suspected CS. We also found that, it is not really necessary to provide a quantitative diet goal for patients. Actually, a qualitative diet guideline is sufficient and with less confusion, because it is much easier for patients to follow. We provided every patient with written instructions, including the diet guide and physician contact number, and encourage the patients to call us for any questions. This approach has given us very satisfying results.

FDG PET/CT Imaging Interpretation

Both qualitative and quantitative approaches have been used to interpret CS FDG PET/CT studies [20, 23, 31, 32••, 33–37]. If the myocardium uptake is equal or less than left ventricle blood pool, the FDG PET/CT is usually interpreted as negative for CS. When myocardium uptake is higher than left ventricle blood pool, some authors even further categorize it into higher or lower than liver background [23], which we disagree. We think once the myocardium uptake is higher than left ventricle background, it is due to failed suppression of physiological myocardium FDG uptake or is actually positive for CS. To decide whether the higher than background uptake is truly positive for CS, uptake patterns can be quantitative. Quantitative analysis is more useful in clinical follow-up and assessment of treatment response in CS patients [32••, 38]. There is no cutoff SUV, however, which can differentiate CS versus physiological myocardium uptake.

In regard to the myocardium uptake pattern on CS FDG PET/CT, there is controversy in interpretation when the myocardium uptake is higher than left ventricle background uptake in the myocardium. Most authors categorized these cardiac FDG uptake patterns as "focal", "diffuse", and "focal on diffuse", with "focal" and "focal on diffuse" interpreted as positive for CS [16•, 28, 31]. We think this interpretation of "focal on diffuse" pattern was inherently subjective and could easily be confused with the "diffuse" pattern. In addition, there is no convincing data verifying the utility of this uptake pattern for active CS. In fact, based on most published "focal on diffuse" images, it is very debatable that the uptake pattern is due to physiological myocardium and papillary muscle uptake. Thus, we think the "focal on diffuse" is indeed "diffuse" uptake (Fig. 1), and most likely due to suboptimal suppression of background cardiac FDG uptake. Eliminating the "focal on diffuse" visual classification rendered the interpretation of cardiac FDG PET/CT makes interpretation easier to follow. We agree the "ring-like diffuse at base" pattern is negative for CS, as it is a common variant seen in normal healthy volunteers [20, 33]. In our published data [32••], which consists of 215 FDG PET/CT tests from a total of 207 patients with an established diagnosis of sarcoidosis and clinical suspicion for CS between July 2014 and December 2015, the largest patient cohort with suspected CS, we visually classified the pattern of cardiac FDG uptake into (Fig. 1): "none" and "ring-like diffuse at base" (negative for CS) [33]; "focal" (positive for CS) [39]; and "diffuse" (indeterminate for CS). When using only "focal" as positive for CS and "none" and "ring-like at base" as negative for CS, we reached 100% inter-observer agreement upon visual analyses of the sarcoid PET/CT scans with readers including senior radiology residents, radiology, and nuclear medicine attending physicians. Furthermore, we achieved satisfactory suppression of physiological myocardial uptake with only 3.6% (7/193) indeterminate rate when implementing the 72-h HFHPVLC diet preparation protocol. With this diet preparation protocol, we were able to successfully detect sarcoid pericarditis and large vessel vasculitis [40] in patients with CS at follow-up (Fig. 2) [32••, 38, 41].

The SNMMI, ASNC, and Society of Cardiovascular Computed Tomography recommended that two sets of images should be obtained at rest to differentiate the spectrum of CS: myocardial perfusion images acquired with either 13N-ammonia or 82Rb and cardiac 18F-FDG PET images [16•, 42]. The decreased myocardial perfusion at rest on cardiac PET/CT has been observed in CS and recommended in CS diagnoses criteria [16•, 28]. We have to point out that, however, the joint SNMMI/ASNC expert consensus did not include our data using the 72-h HFHPVLC diet preparation protocol for CS diagnosis consisting of 215 FDG PET/CT tests from a total of 207 sarcoid patients within a 1.5-year period between July 2014 and December 2015, the largest sarcoid patient cohort with clinical suspicion for CS to date [32••], that was published 6 months ahead of their publication. The SNMMI/ASNC recommendation was mainly based on the 2014 publication from Brigham and Women's Hospital (BWH) that included 118 patients over a 5-year period who underwent "a high-fat, high-protein, low-carbohydrate diet followed by a fast of at least 3 h" prior to FDG PET for inflammation evaluation and rubidium-82 PET to assess perfusion defects [28]. The BWH group authors categorized the PET images as follows: normal perfusion and metabolism, abnormal perfusion or metabolism, or abnormal perfusion and metabolism. Although they reported a poor correlation between JMHW criteria and cardiac PET results (positive and negative for abnormalities in perfusion and/or metabolism), they did not mention definitive cardiac PET criteria in diagnosing CS. Their proposed interpretation of the representative cardiac FDG uptake patterns as "focal", "focal increased", and "focal on diffuse" are somewhat difficult for physicians outside their group to follow, which may cause inter-observer disagreement when the same criteria are to be applied by other physicians. The authors' interpretations on cardiac PET results also appear difficult to understand. For example, these authors interpreted 15 FDG PET with diffuse cardiac uptake as "due to failure to suppress FDG from normal myocardium", which we would categorized as "non-diagnostic for CS" but they read as "normal metabolism" and included these cases in the PET negative group. Moreover, they interpreted the six scans with "focal on diffuse" uptake as "areas of inability to suppress FDG from normal myocardium vs diffuse inflammation" but categorized them into "abnormal metabolism" and "PET positive". We think these data are not convincing, somewhat subjective, and difficult to validate [43]. Rather, our categorization of "none" and "ring-like diffuse at base" (negative for CS); "focal" (positive for CS); and "diffuse" (indeterminate for CS) is very straightforward and

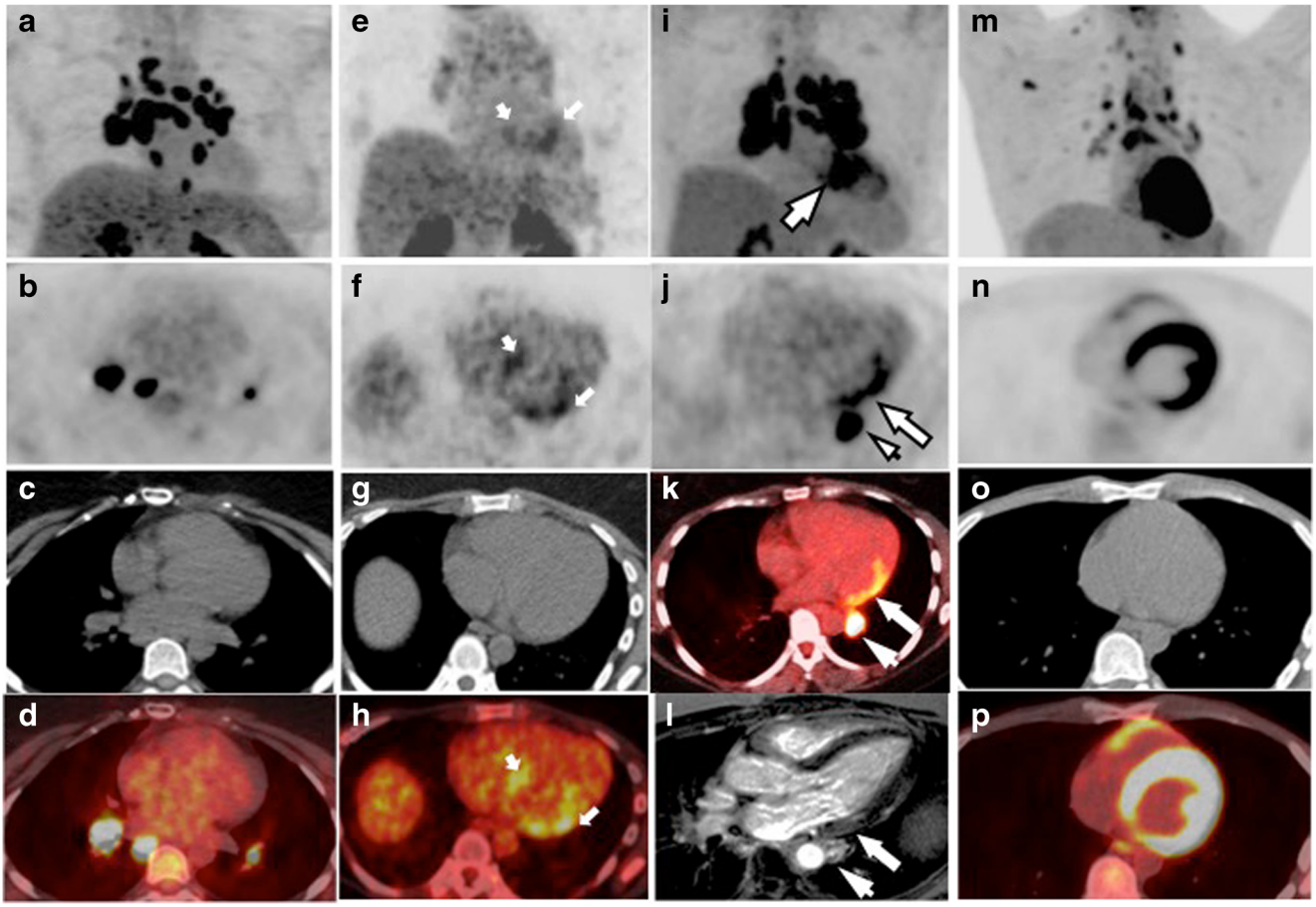

Fig. 1 Four patterns of cardiac FDG uptake on PET/CT for patients with suspected CS. (1) None. a, MIP PET; b, axial PET; c, axial CT; d, axial PET/CT. Although the patient has multiple hypermetabolic mediastinal and bilateral hilar lymph nodes in a typical symmetric distribution pattern, there is no higher-than-background FDG uptake in the myocardium. (2) Ring-like diffuse FDG uptake at the base of the LV. e, MIP PET; f, axial PET; g, axial CT; h, axial PET/CT. The ring-like FDG uptake at the base of left ventricle (*short arrows* in e, f, h), representing physiologic activity at the atrial-ventricle junction. (3) Focal. i, MIP PET; j, axial PET; k, axial PET/CT; l, axial cardiac MRI (CMR). The focal uptake in the proximal lateral wall (*long arrows* in i, j, k) corresponds to the focal delayed enhancement of myocardium in cardiac MRI (*long arrow*, l), representing active CS. Bilateral pulmonary nodules and hilar lymph nodes are in a butterfly-shaped distribution pattern, representing active sarcoidosis. One hypermetabolic left lower lob nodule seen on the axial PET images (*arrowheads* in j, k) correlates with delayed enhancement on CMR (*arrowhead* in l). (4) Diffuse. m, MIP PET; n, axial PET; o, axial CT; p, axial PET/CT. The typical symmetrically distributed hypermetabolic mediastinal and bilateral hilar lymph nodes represent sarcodosis. However, the diffuse increased FDG uptake in biventricular myocardium, more on the left, is indeterminate for active CS. (modified by permission from Wolters Kluwer Health, Inc. from: Lu Y, Grant C, Xie K, Sweiss NJ. Clin Nucl Med. 2017;42(2):88–94) [32••]

easy to follow. This explains how we can reach 100% inter-observer agreement when analyzing the data. Needless to say, the 72-h HFHPVLC diet preparation protocol is very important to obtain satisfactory suppression of physiological myocardial FDG uptake. Our experience showed that rest Tc-99m nuclear myocardial perfusion SPECT/CT could also add CS diagnoses confidence. However, as decreased myocardial perfusion is not a universal finding in CS and prone to subjective interpretation, we do not recommend it as a routine test for CS diagnoses. Furthermore, with the 72-h HFHPVLC diet preparation protocol, it is not necessary to have additional myocardial perfusion test [38]. Actually, the Heart Rhythm Society (HRS) expert consensus statements did not even include myocardial perfusion test in CS diagnosis criteria [44].

Others and we have found that extra-thoracic sarcoid and CS occur with significant frequency [45, 46, 47•]. An example of extra-thoracic sarcoid lesions in a suspected CS patient which would customarily be outside the field of view (FOV) and thus non-detectable by cardiac MRI (CMR) is illustrated in Fig. 3. This makes an intriguing case for using FDG PET-CT over CMR for CS evaluation, given that the narrower FOV with CMR is likely to overlook these extra-thoracic sites of disease. While the presence of extra-cardiac sarcoid may not alter immediate management, it does serve as a way to stage disease and get a sense of granuloma burden. Identifying extra-cardiac involvement alerts the treating physicians to which symptoms need attention and close follow-up. For more

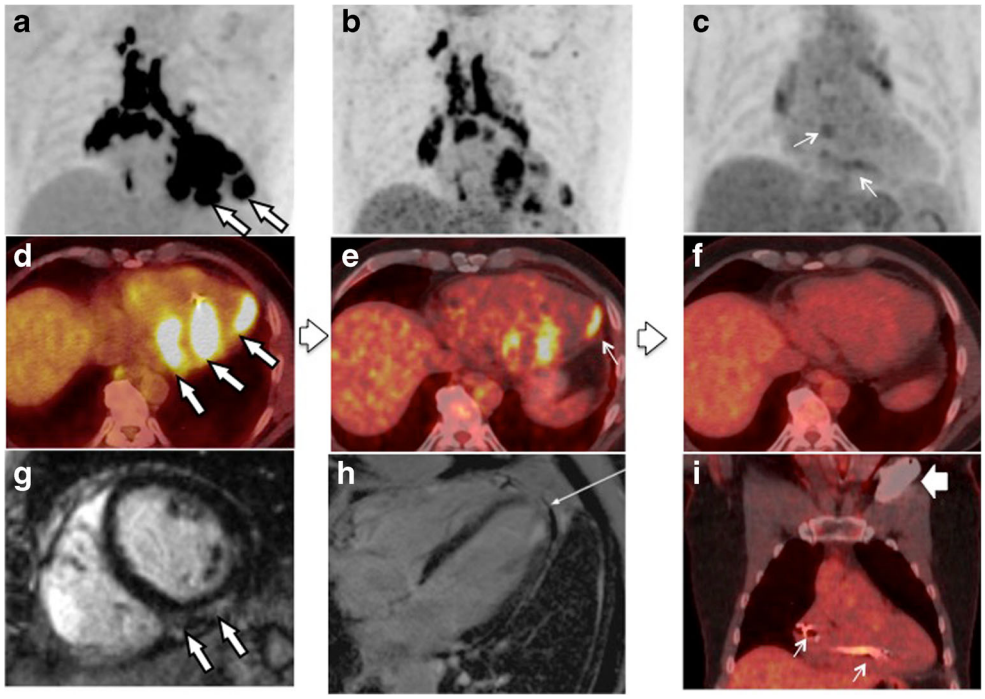

Fig. 2 FDG PET/CT showing complete response of CS to adalimumab treatment. Initial PET/CT demonstrated multiple hypermetabolic lymph nodes in the mediastinum and bilateral hila, in a characteristic "Christmas Tree" distribution pattern indicating active sarcoidosis; additional multifocal FDG uptake in the myocardium (*arrows*, a, MIP PET; b, axial PET/CT) correlated with the focal delayed enhancement on cardiac MRI (*arrows*, c), representing active CS. Follow-up PET/CT (d, MIP PET; e, axial PET/CT) showed decreased extent and intensity of persistent hypermetabolic lymph nodes in the mediastinum and bilateral hila, and multifocal myocardial uptake after 12-month treatment with methotrexate and glucocorticosteroids. The apical lesion (*arrow* in e) corresponding to a focal delayed enhancement on cardiac MRI (f, *long white arrow*). Further treatment switched to adalimumab. Follow up PET/CT (g, MIP; h, axial PET/CT; i, coronal PET/CT) showed nearly resolved hypermetabolic thoracic lymph nodes, and complete resolution of abnormal uptake in the myocardium upon 3-month treatment with weekly adlimumab injection (*block arrow* indicated patient's pacer, *small arrows* in g and i showed residual FDG uptake attributed to attenuation correction artifact from pacemaker leads in the right ventricle). (modified by permission from Wolters Kluwer Health, Inc. from: Miller CT, Sweiss NJ, Lu Y. Clin Nucl Med. 2016;41(5):417–8) [41]

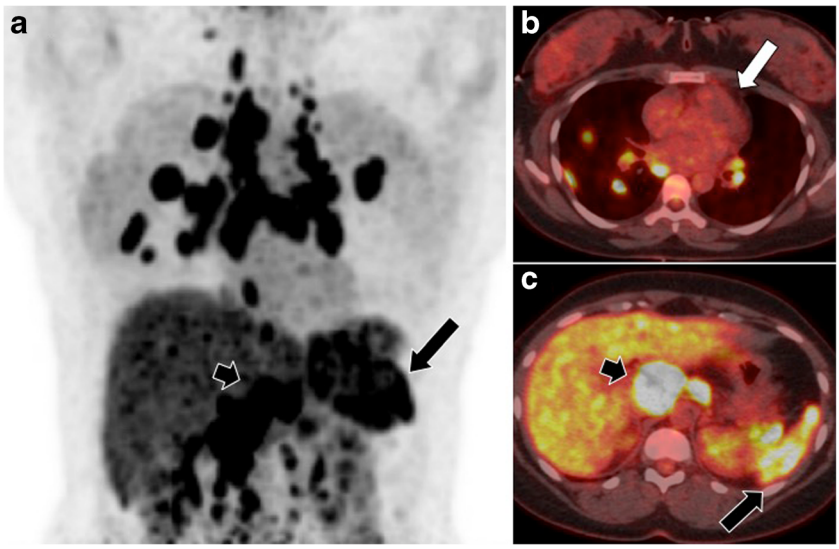

Fig. 3 Sarcoidosis usually has both thoracic and extra-thoracic disease. FDG PET/CT images (A, MIP; B, fused axial chest PET/CT; C, fused axial upper abdominal PET/CT) in a patient with typical thoracic sarcoid disease consisting of relative symmetric distributed hypermetabolic mediastinal and bilateral hilar lymphadenopathy, and scattered hypermetabolic pulmonary nodules. Note the myocardial suppression achieved with 72-h HFHPVLC diet preparation (*white arrow*, B). This patient also has upper abdominal lymphadenopathy (*short black arrows*, A and C) and splenic involvement (*long black arrows*, A and C). (modified by permission from Springer Nature: Patel DC et al. J Nucl Cardiol 2017. https://doi.org/10.1007/s12350-017-0962-4) [47•]

complete disease extent evaluation, expanding the PET/CT FOV from the skull base to thigh or to at least include both the chest and abdominal organs would provide better evaluation of the extent of sarcoidosis.

Other PET Imaging Modalities for CS Diagnosis

Other than FDG, other alternative PET imaging tracers have been explored in CS evaluation. The potential PET tracers include Ga-68 DOTATOC/NOC, which show the absence of significant background activity within the myocardium [48, 49]. However, there is data limited to studies that include small numbers of patients. Their claimed higher specificity and sensitivity than FDG in CS diagnosis will need more investigation and further validation.

It is reasonable to think combined FDG PET/MRI can be more sensitive and specific than FDG PET/CT in CS diagnose. While the active phase of sarcoidosis inflammation is detected with great sensitivity by FDG PET, cardiac tissue remodeling associated with the CS, progressively leading to the fibrosis formation is well characterized by CMR. As much as the FDG PET/MRI sounds promising in CS evaluation, the inherent expensive cost limits its utilization in CS evaluation. Thus, only few centers have investigated its use in a small number of suspected CS patients [50, 51]. Many CS patients also have pacemaker implants which may not be suitable for MRI evaluation.

Conclusion

Patient preparation with a 72-h high-fat, high-protein, and very-low-carbohydrate diet protocol generated the most promising results in suppression of physiological myocardial FDG uptake in cardiac PET/CT, thus could minimize the rate of indeterminate/non-diagnostic findings. The “focal-on-diffuse uptake” pattern on myocardial uptake is not convincing and should not be interpreted as positive CS, rather, than as indeterminate/non-diagnostic for CS. Nuclear myocardial perfusion test may not be needed to diagnose CS if optimal suppression of myocardial background uptake of FDG can be achieved. Given the high incidence of co-existing thoracic and extra-thoracic sarcoidosis, the FOV of FDG PET/CT should extend from the skull base to thigh, or, at a minimum, include both the chest and abdominal organs to better evaluate the extent of sarcoidosis disease. When the patient has not contraindications to undergo MRI, FDG PET/MRI with optimal patient preparation might increase diagnose confidence and accuracy. More data will be needed for new PET tracers to be used for CS diagnosis.

Compliance with Ethical Standards

Conflict of Interest Yang Lu and Homer A. Macapinlac declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent For the retrospective studies involve human participants performed by the authors, informed consent is not required. No animal research involved.

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