PET/CT in the Diagnosis and Workup of Sarcoidosis: Focus on Atypical Manifestations

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Abbreviation: FDG = fluorine 18 fluorodeoxyglucose

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

■ Provide a brief overview of the clinical findings and management of sarcoidosis.
■ Discuss the value of PET for diagnosis, management, and treatment response assessment in cases of sarcoidosis.
■ Describe how radiologists and nuclear medicine physicians can use PET to assess sarcoidosis in specific organ systems, especially cardiac sarcoidosis, such as in patient preparation and image interpretation.

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Introduction

Sarcoidosis is a multisystem disease characterized by the formation of noncaseating granulomas. Lung and intrathoracic lymph nodes are classic sites of involvement; however, sarcoidosis can affect any site in the body. The clinical course is extremely variable, and the imaging features are diverse and dependent on the affected site, degree of inflammation, and treatment the patient receives. Atypical manifestations and imaging findings can make diagnosis and/or management challenging. In addition, assessment of treatment response can be difficult in the setting of chronic disease. Fluorine 18 fluorodeoxyglucose (FDG) PET/CT is sensitive for assessment of the inflammatory activity of sarcoidosis in any organ. Although FDG PET/CT is not included in the standard workup for sarcoidosis, there has been growing evidence that supports the value of this examination in guiding diagnosis and management. FDG PET/CT may be especially useful for assessing reversible granuloma, treatment response, disease extent, occult disease, and cardiac or osseous sarcoidosis, and determining the most suitable biopsy site. Capability to image the entire body during a single examination is advantageous in cases of systemic disease such as sarcoidosis. The authors review the use of FDG PET/CT, providing up-to-date evidence and describing various cases of sarcoidosis in which FDG PET/CT has an important role in diagnosis and/or management. They also discuss the usefulness of FDG PET/CT in cases of selective manifestations of sarcoidosis.

Clinical Overview and Treatment Approach

The clinical manifestations of sarcoidosis vary according to the organ involved. In more than 90% of patients, the manifestations of sarcoidosis are intrathoracic. In descending order, the cutaneous, nodal, and ocular systems are the next most common sites of manifestation (1,2). However, any organ system can be affected. The symptoms of pulmonary sarcoidosis include cough, dyspnea, and chest pain.
TEACHING POINTS

The goals of sarcoidosis management are to prevent or limit organ damage, relieve symptoms, and improve the patient's quality of life. However, a significant percentage of patients with sarcoidosis do not require treatment because they have asymptomatic nonprogressive disease and experience spontaneous remission.

The differentiation of reversible granulomatous disease from irreversible fibrosis is important, as treatment of sarcoidosis is predicated on the assumption that reversible granulomas are present. In this setting, FDG PET is useful for evaluating the presence or absence of active inflammation that indicates reversible granuloma.

FDG PET/CT can have an important role by enabling the detection of unexpected, clinically silent lesions.

The decreased FDG avidity of a lesion after the initiation or modification of treatment has been shown to correlate with clinical signs of improvement, showing FDG PET to be a good tool for monitoring disease activity.

Dual perfusion-inflammation PET can be helpful for diagnosis and staging of disease and assessment of treatment response. This examination enables assessment of active inflammation, myocardial fibrosis, left and right ventricular involvement, and left and right ventricular function.

Symptoms of extrapulmonary sarcoidosis are based on the organ involved. For example, skin involvement can manifest as rashes and plaques; joint involvement, as arthritis; eye involvement, as vision changes and iridocyclitis; and central nervous system involvement, as facial nerve palsy, seizures, headache, and endocrinopathy (3). In addition, patients may present with noticeable lumps due to lymphadenopathy (4).

Currently, there is no definitive examination for diagnosing sarcoidosis. According to the joint statement of the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders (5), three criteria usually are required for a diagnosis of sarcoidosis: clinical and radiologic manifestations, noncaseating granulomas, and no evidence of alternative disease.

The goals of sarcoidosis management are to prevent or limit organ damage, relieve symptoms, and improve the patient’s quality of life (6). However, a significant percentage of patients with sarcoidosis do not require treatment because they have asymptomatic nonprogressive disease and experience spontaneous remission. Many of these patients have minimal or no organ impairment caused by sarcoidosis (1,7,8), and therefore the decision to initiate treatment of sarcoidosis is complex. Exceptions in this setting include cases of ocular sarcoidosis, which might be asymptomatic, but delayed treatment may lead to vision loss; asymptomatic renal sarcoidosis, which can lead to nephrolithiasis and renal insufficiency due to hypercalcemia; and potentially asymptomatic cardiac sarcoidosis and neurosarcoidosis.

For pulmonary sarcoidosis, assessment of pulmonary involvement is performed by evaluating the symptoms and the results of pulmonary function tests, chest imaging, and other examinations, such as diffusing capacity of the lung for carbon monoxide and 6-minute walk tests (6). Although it is a half century old, the classic chest radiography–based staging system remains an important tool for disease assessment. With this system, stage 0 indicates normal findings; stage I, hilar or mediastinal lymphadenopathy only; stage II, hilar or mediastinal lymphadenopathy plus lung parenchymal disease; stage III, lung parenchymal disease only; and stage IV, pulmonary fibrosis (9). Asymptomatic patients with stage 0–I disease often do not require therapy. Asymptomatic patients with stage II–III disease, mild functional abnormalities, and stable clinical parameters may not require treatment initially and could be followed up for up to 3 years.

Treatment is considered for those patients who have symptoms in combination with relevant findings at various other examinations, such as radiologic, serologic, funduscopic, echocardiographic, and pulmonary function tests. Treatment usually starts with inhaled corticosteroids. If this is not effective, the patient should begin taking oral corticosteroids, with the dose tapered after 3–6 months. If the disease is not controlled after steroid use is tapered or if the corticosteroid use causes toxic effects, the addition of a cytotoxic agent such as methotrexate or azathioprine should be considered. If there is no response to the combination of prednisolone and a cytotoxic agent, the clinician needs to determine whether the patient has treatable disease (ie, reversible granuloma or inflammation) or an irreversible process (ie, fibrosis or scarring) (6). FDG PET/CT can be a powerful tool for identifying residual active disease versus scarring (discussed later).

With extrapulmonary sarcoidosis, isolated involvement of a single organ is rare and the clinician needs to examine the patient thoroughly for additional manifestations (10). For patients with extrapulmonary involvement, a multidisciplinary approach is needed and a specialist referral is usually warranted (6).

Added Value of FDG PET/CT in Sarcoidosis Management

FDG is a PET radiotracer that accumulates in tissue that has increased glucose metabolism. It is produced by a cyclotron and has a physical half-life of 110 minutes. Caution is needed,
as FDG uptake is not specific for inflammation (11). FDG is most commonly used for metabolic assessment of the heart and brain and malignant tumors, and it is increasingly being used to detect infection and inflammation, including the inflammation associated with active sarcoidosis. It is a glucose analog that is taken up in the cell and phosphorylated by way of the same mechanism with which glucose is taken up and phosphorylated. The increased FDG activity seen with inflammation and infection is due to the activation of granulocytes and macrophages that have increased glucose transporter activity (12).

PET/CT is neither a first-choice modality for diagnosis of sarcoidosis nor a technique of choice for screening purposes (13). There currently is no evidence to support the use of FDG PET/CT for screening, and this is unlikely to change given the relatively high cost of PET/CT and the associated radiation exposure. In most cases, imaging evaluation should start with chest radiography followed by CT. However, in the setting of known sarcoidosis, FDG PET/CT is useful for assessment of reversible granuloma, occult disease, disease extent, and treatment response and finding the most suitable site for biopsy. It is also helpful in the evaluation of cardiac, central nervous system, and musculoskeletal involvement (14). Because sarcoidosis can affect almost any organ throughout the body, the imaging features are diverse. The clinical manifestations of sarcoidosis are listed in Table 1, and the findings of sarcoidosis seen at PET/CT and other imaging modalities are summarized in Table 2.

### Table 1: Clinical Manifestations of Sarcoidosis

<table>
<thead>
<tr>
<th>Affected Body System</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>No symptoms, cough, dyspnea, chest pain</td>
</tr>
<tr>
<td>Skin</td>
<td>Papules, subcutaneous nodules, erythema nodosum</td>
</tr>
<tr>
<td>Ocular</td>
<td>No symptoms, eye pain, redness, vision loss, floaters</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Cranial neuropathies (most commonly facial nerve palsy), headache, neuroendocrine dysfunction (polyuria, problems with sleep, appetite, body temperature, libido, etc), seizures, myopathy, radiculopathy (spinal sarcoidosis), mononeuropathy</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Cervical lymphadenopathy, painless swelling of salivary glands, dry mouth, pain</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Palpitations, syncope, dizziness, chest pain, sudden death</td>
</tr>
<tr>
<td>Gastrointestinal, hepatic</td>
<td>No symptoms, elevated liver function enzyme levels, abdominal pain, hepatosplenomegaly</td>
</tr>
<tr>
<td>Renal</td>
<td>Hypercalcemia, nephrolithiasis, vitamin D dysregulations</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthropathy, bone pain, myopathy (muscle pain, numbness, muscle weakness)</td>
</tr>
</tbody>
</table>

### Evaluating Reversible Granuloma

Pulmonary sarcoidosis can be challenging to assess because the pulmonary symptoms may be discordant with the conventional imaging (chest radiography, CT) findings and physiologic impairment (determined at pulmonary function testing) (7). Chest radiographic findings usually correlate poorly with the physiologic changes and symptoms related to pulmonary sarcoidosis (15). With stage IV pulmonary sarcoidosis, fibrosis is the most common imaging finding, and it is often associated with confluent masslike opacities (16). However, the fibrosis often goes unchanged for a long period, making it difficult to assess disease activity.

The differentiation of reversible granulomatous disease from irreversible fibrosis is important, as treatment of sarcoidosis is predicated on the assumption that reversible granulomas are present (17,18). In this setting, FDG PET is useful for evaluating the presence or absence of active inflammation that indicates reversible granuloma (13,17) (Figs 1, 2). In a retrospective study involving 89 patients with sarcoidosis, Mostard et al (19) found that 14 (93%) of 15 patients with chest radiography–defined stage IV sarcoidosis (fibrosis) had active disease at FDG PET/CT, and the majority of them (85%) had serologic signs of inflammation. They stressed that chest radiographic stage IV disease does not exclude inflammatory activity in the pulmonary parenchyma (19).

### Detection of Occult Disease

Depicting occult disease is another important role of FDG PET/CT, given that sarcoidosis is a multisystem disorder. FDG PET/CT typically can depict a large longitudinal area, and patients can be scanned from head to toe. The thorax is the most common site of involvement of sarcoidosis; however, patients can develop hidden disease elsewhere. Although asymptomatic patients typically do not require treatment, occult granulomatous inflammation at unexpected sites can lead to
fibrosis and scar formation, potentially followed by irreversible organ damage. In a study involving 345 sarcoidosis cases, Ungprasert et al (20) reported that hepatic, cardiac, splenic, or neurologic involvement with or without intrathoracic disease was associated with increased mortality. Older age and male sex also correlated with increased mortality. Although asymptomatic granulomatous inflammation related to sarcoidosis is often reversible, it is important to carefully monitor and evaluate the findings in each patient (7). Cases in which an unexpected site of disease was detected at FDG PET/CT are shown in Figures 3–6.

FDG PET/CT can have an important role by enabling detection of unexpected, clinically silent lesions. Data from two large cohorts (17,21) indicated that FDG PET and FDG PET/CT can depict previously unknown sites of active disease. In a retrospective study (19) involving 89 patients with sarcoidosis in whom FDG PET/CT scans were obtained, extrapulmonary inflammatory activity was found in 80% of patients with active pulmonary sarcoidosis. Ocular sarcoidosis is an important condition with which untreated disease can cause permanent vision loss. Uveitis is the most common manifestation, and there have been reports of FDG PET/CT depicting unexpected ocular involvement and thus leading to timely intervention (22). In addition, cardiac sarcoidosis and neurosarcoidosis can be life threatening if left untreated.

### Assessment of Treatment Response

Monitoring disease activity in sarcoidosis is challenging because there is no reference-standard method for this task (1,18). Owing to the lack of well-defined tools, treatment response is usually assessed comprehensively on the basis of symptoms and the results of blood tests (eg, angiotensin-converting enzyme test) and organ-specific examinations such as pulmonary function testing for pulmonary sarcoidosis, echocardiography for

<table>
<thead>
<tr>
<th>Affected Body System</th>
<th>CT, MRI, and Scintigraphic Findings*</th>
<th>PET/CT Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Perilymphatic nodules and/or masses</td>
<td>Hypermetabolic bilateral mediastinal and hilar lymph adenopathy</td>
</tr>
<tr>
<td></td>
<td>Bilateral mediastinal and hilar lymphadenopathy</td>
<td>Hypermetabolic upper lung–predominant parenchymal disease (perilymphatic nodules and/or masses)</td>
</tr>
<tr>
<td></td>
<td>Sign at 67Ga scintigraphy</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Skin thickening</td>
<td>Hypermetabolic skin thickening</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous nodules</td>
<td>Hypermetabolic subcutaneous nodules</td>
</tr>
<tr>
<td>Ocular</td>
<td>Enlarged enhancing lacrimal gland</td>
<td>Increased FDG uptake in lacrimal gland or optic nerve, or orbital or periorbital mass</td>
</tr>
<tr>
<td></td>
<td>Orbital or periorbital soft-tissue mass</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Enlargement of cranial nerves</td>
<td>Increased FDG uptake in brain parenchyma (including pituitary and hypothalamic lesions)</td>
</tr>
<tr>
<td></td>
<td>Abnormal enhancement in brain parenchyma (including pituitary and hypothalamic lesions), leptomeninges, and/or spine</td>
<td>Enlarged cranial nerves, leptomeninges, and/or spinal cord</td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>Cervical lymphadenopathy</td>
<td>Hypermetabolic cervical lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Enlargement of salivary glands</td>
<td>Increased FDG uptake in salivary glands</td>
</tr>
<tr>
<td></td>
<td>Panda sign at 67Ga scintigraphy</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Delayed enhancement at cardiac MRI</td>
<td>Decreased perfusion with increased FDG uptake in myocardium</td>
</tr>
<tr>
<td>Gastrointestinal, hepatic</td>
<td>Hypoattenuating lesions in liver or spleen</td>
<td>Hypermetabolic foci in liver or spleen</td>
</tr>
<tr>
<td></td>
<td>Hepatosplenomegaly</td>
<td>Hypermetabolic lymphadenopathy</td>
</tr>
<tr>
<td>Renal</td>
<td>Hypoattenuating or enhancing nodules</td>
<td>Diffuse or patchy FDG uptake in kidney</td>
</tr>
<tr>
<td></td>
<td>Interstitial nephritis, nephrocalcinosis, nephrolithiasis, and interstitial calcium deposition</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Lacy bone destruction in bones (most commonly in distal extremities)</td>
<td>Increased FDG uptake around joints</td>
</tr>
<tr>
<td></td>
<td>(with or without CT correlation)</td>
<td>Increased FDG uptake in bones (with or without CT correlation)</td>
</tr>
<tr>
<td></td>
<td>Tiger man sign</td>
<td>Increased FDG uptake in muscles</td>
</tr>
</tbody>
</table>

*Unless otherwise stated, the given findings are those seen at CT and/or MRI. 67Ga = gallium 67.
Cardiopulmonary sarcoidosis diagnosed at lung biopsy in a 48-year-old man. (a, b) Initially obtained axial chest CT image (a) and follow-up axial chest CT image obtained 6 years later (b) show similar symmetric bilateral peribronchovascular and perihilar masslike consolidations. It is difficult to determine whether the disease is active. (c) Axial FDG PET image obtained directly after follow-up CT shows increased FDG uptake, which is suggestive of active inflammation and thus indicates reversible granuloma. This finding prompted additional treatment.

Chronic pulmonary sarcoidosis in a 70-year-old woman. (a) Axial chest CT image shows a perihilar masslike consolidation. (b) Axial FDG PET image shows the FDG uptake to be less than the blood pool in the perihilar masslike consolidation. These findings suggest nonviable fibrosis.

Cardiac sarcoidosis, funduscopic examination for opthalmologic sarcoidosis, and radiography (18). FDG PET and PET/CT are useful for assessing treatment response (Figs 7–10). The decreased FDG avidity of a lesion after the initiation or modification of treatment has been shown to correlate with clinical signs of improvement (17,23), showing FDG PET to be a good tool for monitoring disease activity.

FDG uptake can also be used to identify patients who do not respond to treatment. In a study (21) involving 90 patients, positive FDG PET/CT findings prompted a change in therapy during the course of follow-up. In 73 (81%) patients with positive FDG PET/CT results, the clinical management changed: Either the previous treatment was modified or a new treatment was introduced (21). Maturu et al (24) conducted a prospective study involving 27 patients with sarcoidosis who were treated with systemic corticosteroids and found that the patients with a metabolic response at FDG PET/CT had significantly fewer relapses.
compared with the patients who did not have a metabolic response. Keijser et al (23) reported a considerable correlation between FDG PET findings and clinical improvement in patients who underwent treatment with infliximab. No such correlation between chest radiographic findings and clinical improvement was noted. Patel et al (25) cited the benefit of evaluating treatment response with PET when they presented a case study of disease progression after 17-month steroid therapy, with PET findings prompting treatment change.

**Evaluation to Determine Optimal Biopsy Site**

Histopathologic confirmation of noncaseating granuloma is necessary to establish a diagnosis of sarcoidosis. Ideally, biopsy of the most accessible lesions, such as cutaneous or subcutaneous nodules identified at clinical examination, superficial lymph nodes, conjunctival lesions, and lacrimal or parotid gland lesions, should be performed. FDG PET/CT can be used to image a broad area of the body and is an excellent modality for locating the most metabolically active lesion, which is likely to have the highest biopsy yield. In the majority of sarcoidosis cases, the diagnosis is made by using mediastinal nodal biopsy or bronchoalveolar lavage, as the chest is the most common site of involvement. FDG PET/CT can facilitate a high biopsy yield by depicting the most FDG-avid mediastinal or hilar lymph node or lung parenchymal disease. If the lesion is located in an area that is difficult to access, FDG PET/CT can help identify an alternative biopsy site in another location. For patients without apparent lung involvement, FDG PET is useful for identifying extrapulmonary disease and thus the optimal biopsy site (1) (Fig 5).

**Assessment of Selective Organ Involvement**

**Cardiac Sarcoidosis**

Cardiac involvement is estimated to manifest clinically in 5% of patients with sarcoidosis; however, the prevalence at autopsy has ranged from 25% to 58% (26, 27). Clinical manifestations of cardiac sarcoidosis include conduction abnormalities, arrhythmias, congestive heart failure, and sudden death (28). The left ventricle is the most commonly involved chamber (26). The typical patchy involvement lowers the sensitivity of endomyocardial biopsy to less than 20%. In addition, although endomyocardial biopsy is highly specific, it is an invasive procedure with associated complications and potential mortality. The current complication rate is less than 6%, with a serious acute complication rate of less than 1% (29). Owing to these factors, imaging has an important role in the diagnosis and follow-up of cardiac sarcoidosis. Steroids remain the mainstay of treatment; however, patients may require a pacemaker or defibrillator to prevent ventricular tachycardia and sudden death (27).

Historically, thallium and gallium radiotracer studies have been used to evaluate cardiac sarcoidosis; however, these procedures have low sensitivity and specificity. Cardiac MRI and PET are currently the imaging modalities of choice for assessing cardiac sarcoidosis. Although cardiac MRI is sensitive for detecting cardiac sarcoidosis, active inflammation (edema) or scarring (30) can cause delayed enhancement. Use of a T2-weighted MRI sequence can be helpful for differentiating inflammation versus scarring (31). In our experience, inflammation has an
Figure 4. Moderate or progressive cardiac sarcoidosis in a 35-year-old man. (a) Short-axis delayed-enhancement cardiac MR image shows subepicardial to midwall late gadolinium enhancement, which can represent inflammation or scarring (arrow). (b) Dual cardiac PET images show decreased perfusion (arrows, top row) involving the basal one-half of the inferolateral wall, with an associated focus of increased FDG activity (arrows, bottom row), consistent with moderate or progressive myocardial inflammation. (c) Coronal FDG PET image obtained during the same examination shows multiple extracardiac FDG-avid foci involving the lung, mediastinal and hilar lymph nodes, liver, and spleen.

Figure 5. Sarcoidosis in a 49-year-old woman who presented with acute onset of severe diplopia, ataxia, and vertigo. (a) Gadolinium-based contrast material–enhanced T1-weighted MR image of the brain shows subtle leptomeningeval enhancement (arrows), which was missed initially, in the cerebellum. (b) Coronal FDG PET image shows diffuse intense FDG uptake (arrow) in the cerebellum. There are mildly hypermetabolic axillary (arrowheads) and mesenteric (circle) lymph nodes. The uptake in the right forearm represents contamination. Biopsy of the cerebellum is invasive; thus, axillary node biopsy was performed on the basis of the PET findings, and a diagnosis of sarcoidosis was established. Subsequently, treatment with systemic steroids was started.
increased T2 signal; however, the image quality at T2-weighted imaging is often suboptimal.

PET scans can be used to distinguish inflammation from scarring, enabling assessment of the treatment response (Figs 4, 11). Furthermore, cardiac MRI might not be feasible for patients with implanted cardiac devices, for whom PET is the best available modality (32).

Patient preparation consists of a low-carbohydrate diet 24 hours before undergoing scanning. This results in a metabolic shift from glucose to fatty acid in cardiac myocytes, which is commonly referred to as myocardial suppression. In this setting, FDG uptake will be seen in activated immune cells or stimulated myocytes (33).

According to guidelines from the American Society of Nuclear Cardiology and the Society of Nuclear Medicine and Molecular Imaging, PET perfusion scans and PET inflammation scans should be obtained at the same time to correlate the findings (33).

Cardiac perfusion PET can be performed with use of several tracers. Nitrogen 13 ammonia and oxygen 15–labeled water are true perfusion agents that are taken up by myocytes by means of passive diffusion. Because the half-lives of these agents are very short, an on-site or nearby cyclotron is needed, and this may not be practical. Rubidium 82 is a potassium analog that is actively taken up by way of the Na+-K+ pump, which can be produced on site from a generator (34). In addition to aiding in the assessment of cardiac disease, FDG PET can be used to detect active inflammation in the chest and the imaged upper abdomen (Figs 9, 12). Ishiyama et al (35) reported that the maximal standardized uptake value across all involved organs of the chest and upper abdomen, rather than in the heart alone, could be a predictor of the response to corticosteroid therapy in patients presumed to have active cardiac sarcoidosis.

Dual perfusion-inflammation PET can be helpful for the diagnosis and staging of disease and the assessment of treatment response. This examination enables assessment of active inflammation, myocardial fibrosis, left and right ventricular involvement, and left and right ventricular function. On the basis of analysis conducted by the American College of Cardiology, it is recommended that imaging findings be correlated with four disease stages (36), which are summarized...
Figures 7, 8. (7) Systemic sarcoidosis in a 37-year-old woman. (a) Coronal initial FDG PET scan shows hypermetabolic lymphadenopathy involving the mediastinum, hila, abdomen, and pelvis. The increased FDG uptake in the spleen and liver also suggests sarcoidosis involvement. (b) Coronal posttreatment PET scan shows interval resolution of the hypermetabolic foci, consistent with resolution of active inflammation. (8) (a) Axial pretreatment FDG PET scan in a 36-year-old woman with sarcoidosis shows intense FDG uptake in the spleen and gastrohepatic lymph nodes. (b) Axial follow-up FDG PET/CT scan obtained in the same woman after 6 months of methotrexate therapy shows resolution of the lesions.

Figure 9. Systemic sarcoidosis in a 70-year-old woman. (a, b) Axial pretreatment CT (a) and FDG PET (b) scans show prominent partially calcified lymph nodes in the mediastinum, hila, and left internal mammary region, with increased FDG activity. (c, d) Axial posttreatment scans show that the lesions are stable in size and appearance at CT (c) but have decreased FDG avidity at FDG PET (d), indicating a favorable treatment response.
in Table 3. With classic cardiac sarcoidosis, there is normal or decreased perfusion in the involved region of the myocardium, with increased FDG uptake (Figs 3, 13). Fibrosis usually demonstrates decreased perfusion but no or minimal FDG uptake (Fig 12).

**Nervous System Sarcoidosis**

Involvement of the nervous system is seen clinically in approximately 5%–15% of cases of sarcoidosis and is estimated to be seen at autopsy in about 25% of cases (1,37). The diagnosis of neurosarcoidosis can be delayed because of the wide spectrum of clinical findings, including hydrocephalus, headache, ataxia, cognitive dysfunction, weakness, seizures, and symptoms resulting from cranial nerve palsies (38). Sarcoidosis can involve any part of the nervous system, including the cranial nerves, meninges, brain parenchyma, pituitary gland, spinal cord, and peripheral nerves (39). Cranial neuropathy is the most common manifestation and is seen in 50%–70% of cases of neurosarcoidosis; the facial nerves are the most commonly involved organs (37).

Gadolinium-enhanced MRI is the modality of choice for diagnosis of neurosarcoidosis; however, PET can be used for staging and to determine the optimal biopsy site (37,40). The abnormalities seen at MRI include periventricular white matter lesions, meningitis or meningoencephalitis, solid parenchymal enhancing lesions, cranial neuritis, and myelopathy (40).

Although intense physiologic uptake in the brain limits accurate evaluation of brain lesions, the FDG PET findings may be first in suggesting a diagnosis of sarcoidosis involving only neurologic symptoms (Fig 5). Depending on the part of the brain involved, a sarcoidosis lesion can be hypo- or hypermetabolic. For instance, lesions in the cerebral gray matter can appear iso- to hypometabolic (40). This is because the basal metabolism of the cerebral gray matter is very high, minimizing the lesion-to-brain ratio (40,41). In contrast, spinal cord lesions appear hypermetabolic because the basal metabolism of the spinal cord is one-third that of the cerebral gray matter (40).

FDG PET/CT can be useful in cases in which other imaging modalities have been unsuccessful in the detection of nervous system involvement, since neurologic involvement can result in a change in the therapeutic regimen (41). Because of its capability to depict metabolic changes, FDG PET can also be used to monitor therapy before morphologic changes are detected at conventional imaging (42). The brain can be included in whole-body PET/CT examinations with only marginal increases in examination time and radiation dose (due to the extended field of low-dose CT scanning).

**Musculoskeletal Sarcoidosis**

Musculoskeletal involvement in sarcoidosis has been estimated to occur in up to 40% of cases (43). Manifestations of musculoskeletal sarcoidosis...
include arthropathies (joint sarcoidosis), bursa sarcoidosis, muscular sarcoidosis, and osseous sarcoidosis. In a large cohort of 345 sarcoidosis cases, arthralgia was noted in 12% of the population (20). Joint sarcoidosis usually manifests as monoarthropathy, and the ankles are the most frequently affected joint (43,44). Muscular sarcoidosis is classified into four types: nodular, chronic myopathy, acute myositis, and asymptomatic (45).

The nodular type usually manifests as multiple intramuscular masses. With the chronic myopathy type, muscle weakness and atrophy are the major manifestations. The acute myositis type is characterized by muscle swelling and pain. With the asymptomatic type, muscle involvement can be detected with biopsy only (46). In cases of muscular sarcoidosis, MRI is useful for localizing disease and assessing disease extension when the patient has localized disease. However, FDG PET/CT is useful for examining patients with diffuse disease. Active muscular sarcoidosis usually demonstrates avid FDG activity (Fig 14), which can be used to detect other sites of disease and localize the most suitable biopsy site (47–49).
Figure 13. Early inflammation from cardiac sarcoidosis in a 59-year-old man. Dual cardiac PET perfusion images (top row) and FDG inflammation images (bottom row) show intense FDG uptake in the basal lateral wall, with almost normal perfusion, consistent with the early stages of inflammation. There are no corresponding perfusion defects (arrows, top row) associated with the areas of increased FDG uptake (arrows, bottom row).

Table 3: Classification of Cardiac Sarcoidosis Disease Stage Based on PET Perfusion and Metabolism Patterns

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Perfusion and Metabolism Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Normal perfusion and no FDG uptake</td>
</tr>
<tr>
<td>Stage 2: mild or early disease</td>
<td>Patchy FDG uptake in an area with normal or only mildly decreased perfusion</td>
</tr>
<tr>
<td>Stage 3: moderate or progressive disease</td>
<td>FDG uptake in an area with a corresponding moderate perfusion defect</td>
</tr>
<tr>
<td>Stage 4: severe or fibrous disease</td>
<td>Severe perfusion defect but no or minimal corresponding FDG uptake</td>
</tr>
</tbody>
</table>

Note.—Reprinted, with permission, from reference 36.

Figure 14. Myositis-type sarcoidosis in a 22-year-old man with a skin rash, granulomatous nephritis, elevated serum calcium levels, and bilateral leg swelling. He underwent FDG PET and MRI for evaluation of the sites of increased inflammation. (a, b) FDG PET scans show multiple areas of increased FDG uptake in the bilateral supraspinatus and infraspinatus muscles (a) and thigh and calf muscles (b). (c) Axial T2-weighted MR image of the right thigh shows increased signal intensity mainly within the right vastus lateralis muscle and an adjacent fluid collection, consistent with myositis. The diagnosis of sarcoidosis was established by using clinical findings and biopsy of the right vastus lateralis muscle.
Osseous sarcoidosis is rare and usually associated with systemic sarcoidosis. The exact prevalence is unknown, and the reported prevalence varies according to the population involved and diagnostic techniques used. Osseous sarcoidosis is classically known to demonstrate lacelike lytic bone lesions (most frequently in the phalanges of the hands or feet) during the advanced stages.

Osseous involvement of sarcoidosis often cannot be visualized at radiography or CT (Fig 10). When Grozdic Milojevic et al (50) examined 98 patients with FDG PET/CT, chronic sarcoidosis and the presence of prolonged symptoms or other findings were suggestive of active disease. Active disease was found in 82 patients at FDG PET/CT, and 18 (22%) of these patients had FDG-avid osseous involvement. A corresponding CT abnormality was found in only five (5%) of the 98 patients (50).

In another study (51) involving 122 patients with sarcoidosis who underwent FDG PET/CT, bone or bone marrow involvement was detected in more than one-third (32 of 94) of the patients with positive FDG PET/CT findings (ie, presence of FDG-avid lesion at any site), and most of the lesions (94%) could not be detected at low-dose CT. Therefore, in the setting of musculoskeletal sarcoidosis, FDG PET/CT has an important role in disease detection, including the identification of occult disease and assessment of treatment response (50,52).

### Conclusion

Although FDG PET/CT is not included in the standard workup for sarcoidosis, it is valuable in the initial diagnosis and for disease management. FDG PET/CT may be especially useful for assessing cardiac involvement and response to treatment. It can also be used to evaluate reversible granulomas and determine the most suitable target site for biopsy.

### References


