

# **Clinical usefulness of nuclear imaging techniques in sarcoidosis**

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Nuclear imaging techniques play a role in the assessment and management of patients with sarcoidosis. A variety of radiopharmaceuticals have been introduced for this purpose since the late 1970s. The present chapter focuses on these radiopharmaceuticals, scintigraphic imaging techniques, and their role and clinical value in sarcoidosis. Correlation with other imaging modalities, biochemical parameters and pulmonary function tests are discussed. Integration of the currently available data and the present authors' own experience have permitted the development of an algorithm, in which the current authors suggest a clinical guideline focused on optimal use of nuclear imaging techniques in the initial study of patients with sarcoidosis.

## **Gallium-67 scintigraphy**

Gallium-67 is a radioisotope that accumulates in malignant tumours, including lymphomas, and inflammatory processes [1]. <sup>67</sup>Ga is taken up in granulomatous tissue, probably by activated macrophages. Although <sup>67</sup>Ga uptake is usually suppressed by the administration of corticosteroids, uptake persistence in patients with active sarcoidosis undergoing treatment has been reported [2].

The reported sensitivity of <sup>67</sup>Ga scanning in detecting pulmonary sarcoidosis ranges 60–90%. In addition, its specificity is relatively poor because most interstitial lung disorders show positive <sup>67</sup>Ga scan results [1]. The most common <sup>67</sup>Ga uptake in sarcoidosis is intrathoracic, which typically shows bilateral hilar and right paratracheal lymphadenopathy and/or lung parenchyma uptake. Whole-body <sup>67</sup>Ga scanning is useful for studying the extent and distribution of the disease, in that it detects the presence of inflammatory activity in clinically silent but involved organs and provides extrathoracic sites for biopsy [3, 4]. Extrapulmonary accumulation of <sup>67</sup>Ga has been reported in many organs (fig. 1), indicating the systemic character of the disease [1, 4–6].

Interestingly, SULAVIK *et al.* [7] reported some combinations of different patterns of <sup>67</sup>Ga distribution as characteristic of sarcoidosis. The image produced by the <sup>67</sup>Ga uptake of the right paratracheal and bilateral hilar lymph nodes, resembling the Greek letter lambda, was classified as the lambda pattern. The image produced by the <sup>67</sup>Ga uptake of the lacrimal and parotid glands, resembling the face of a panda, was classified as the panda pattern. The lambda pattern was seen in 72% of patients with sarcoidosis, the panda pattern in 79%, and both patterns simultaneously in 62%. However, a panda pattern of itself is not specific to sarcoidosis, since it has also been observed in human

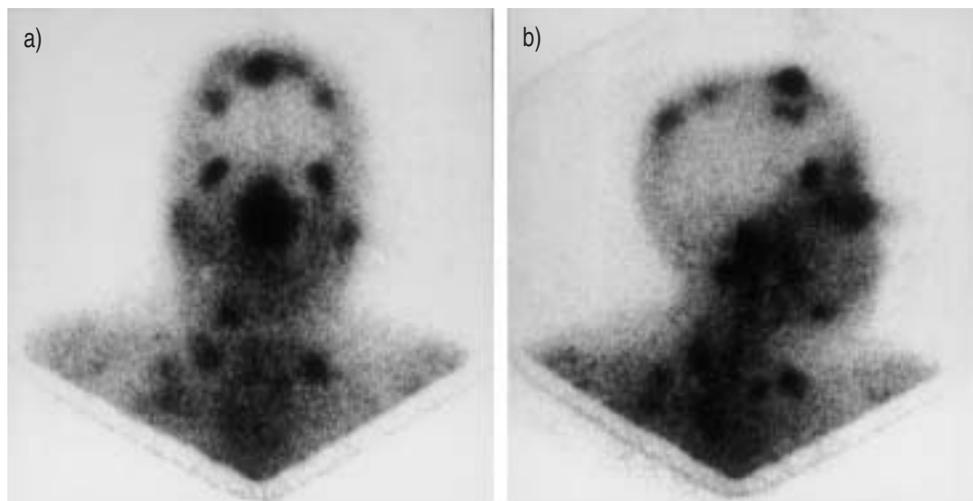


Fig. 1. – Gallium-67 scan showing multiple uptake in the skull, right mandibular bone, both parotid glands, and cervical and supraclavicular lymph nodes in a patient with positive skull and cervical lymph node biopsy results: a) front view, and b) lateral view. Images reproduced from [5] with permission.

HIV-positive patients, Sjögren's syndrome, following irradiation of the head or neck, particularly as lymphoma treatment, graft-*versus*-host disease, rheumatoid arthritis and systemic lupus erythematosus [7, 8]. ISRAEL *et al.* [3] found a lower sensitivity of the lambda pattern (29%) and panda pattern (13%) in sarcoidosis patients. Figure 2 shows the lambda and panda patterns in a patient with Löfgren's syndrome [9].

Several studies have focused on the role of the  $^{67}\text{Ga}$  scan in the prognosis of sarcoidosis. NIDEN *et al.* [10] reported that the lesser the degree of pulmonary  $^{67}\text{Ga}$  uptake the better the prognosis of the patient. Likewise, restoration and maintenance of normal  $^{67}\text{Ga}$  scan results during therapy was a good prognostic sign, since such patients did not show loss of pulmonary function. BAUGHMAN *et al.* [11] reported that 68% of patients with positive lung  $^{67}\text{Ga}$  scan results exhibited worsening of the disease at 2 yrs, whereas, negative scan results suggested a small likelihood of disease activity at 2 yrs. Other studies could not confirm these findings [12, 13].

In a European multicentric study [14] that included 632 patients, there was no strict correlation between  $^{67}\text{Ga}$  uptake and the presence of abnormalities on chest radiography (CXR) (table 1). According to these results,  $^{67}\text{Ga}$  scintigraphy was more accurate in detecting the presence of intrathoracic involvement in a significant number of cases with normal CXR results. However, 23% of cases with evidence of intrathoracic involvement on CXR failed to show  $^{67}\text{Ga}$  uptake. In addition, the  $^{67}\text{Ga}$  scan was more sensitive than CXR in detecting changes, either improvement or prediction of relapses, in the follow-up of untreated patients.

Some studies have compared thoracic high-resolution computed tomography (HRCT) with pulmonary  $^{67}\text{Ga}$  scan results, and have shown only limited correlation between the two techniques. LYNCH *et al.* [15] found that five patients with positive  $^{67}\text{Ga}$  scan results showed some degree of pulmonary involvement on HRCT, but two out of five patients with normal  $^{67}\text{Ga}$  scan results also showed parenchymal lung disease on HRCT. In addition, the extent of nodularity seen on HRCT did not correlate with activity on the  $^{67}\text{Ga}$  scan. BERGIN *et al.* [16] also reported a lack of correlation between the two techniques, although patches of parenchymal involvement on computed tomography (CT) corresponded in location to focal areas of  $^{67}\text{Ga}$  uptake. LEUNG *et al.* [17], however,



Fig. 2. – Gallium-67 scan showing bilateral hilar and right paratracheal lymphadenopathy uptake (lambda pattern) and lacrimal and parotid gland uptake (panda pattern) in a patient with Löfgren's syndrome. Image reproduced from [9] with permission.

studied a series of 29 patients with pulmonary sarcoidosis and reported good correlation between findings on HRCT and indices of disease activity measured by  $^{67}\text{Ga}$  scan. Nevertheless, more recent studies have shown that HRCT appears to be a more appropriate tool for assessing the pathological changes and functional impairment associated with the inflammatory activity of sarcoidosis [18–20]. DRENT *et al.* [21]

**Table 1. – Gallium-67 (<sup>67</sup>Ga) uptake in untreated patients at different chest radiographic (CXR) stages of sarcoidosis**

CXR stage	Patients n	Elevated <sup>67</sup> Ga uptake n (%)		Non-elevated <sup>67</sup> Ga uptake n (%)
		Mediastinal and/or pulmonary	Pulmonary	
0	82	36 (43.9)	10 (12.2)	46 (56.1)
I	190	164 (86.3)	40 (21.1)	26 (13.7)
II	248	213 (85.9)	160 (64.5)	35 (14.1)
III	112	71 (63.4)	65 (58.0)	41 (36.6)
All	632	484 (76.6)	265 (41.9) <sup>#</sup>	148 (23.4)

<sup>#</sup>: the number of patients with elevated pulmonary uptake expressed as a percentage of those with elevated mediastinal and/or pulmonary uptake is 54.8%. Image reproduced from [14] with permission.

reported good correlation between pulmonary abnormalities on HRCT, but not CXR, with respiratory functional impairment, particularly abnormal gas exchange. In consequence, HRCT is considered superior to <sup>67</sup>Ga scan for assessing the inflammatory activity and severity of intrathoracic involvement in sarcoidosis.

In the aforementioned European study [14], serum angiotensin-converting enzyme (SACE) level was increased in 29% of patients with negative scans results; this measure was more sensitive than the <sup>67</sup>Ga lung scan in only 7% of all untreated patients. Conversely, <sup>67</sup>Ga scan results were positive in 58% of patients with normal SACE level, and more sensitive than SACE level in 30% of untreated patients. Consequently, the <sup>67</sup>Ga scan was more sensitive than SACE level in detecting active sarcoidosis, although SACE was a superior indicator in a small number of cases. Other authors have also confirmed the higher sensitivity of the <sup>67</sup>Ga scan result over SACE level as an indicator of disease activity [2, 22–24], although some have suggested that SACE level is more specific [23]. In contrast, other studies found a strong correlation between both techniques [25, 26]. These different results could be explained by the fact that the two techniques, SACE level and <sup>67</sup>Ga scan, represent different aspects of granuloma formation, and the presence of an ACE inhibitor in the serum of 30% of patients with sarcoidosis, which would explain the normal SACE level in some cases with active sarcoidosis [26].

In the European study [14], SACE level and <sup>67</sup>Ga uptake during corticosteroid therapy for active pulmonary sarcoidosis were increased in 17 and 38% of patients, respectively. One month after stopping therapy, the percentages rose to 70 and 59%, which suggests that SACE level detects relapses sooner than the <sup>67</sup>Ga scan does. Another study found the <sup>67</sup>Ga scan to be more sensitive than bronchoalveolar lavage (BAL) in detecting changes during corticosteroid therapy [27]. Close correlation between the degree of <sup>67</sup>Ga uptake and the increase in vital capacity after treatment has been described [28]. However, <sup>67</sup>Ga uptake was not of value in predicting treatment response [12]. TURNER-WARWICK *et al.* [29] reported that serial <sup>67</sup>Ga scans, lavage lymphocyte counts and SACE level measurements were no more sensitive than serial CXR and pulmonary function tests in monitoring patients during therapy. An abnormal <sup>67</sup>Ga scan, of itself, is not an indication for therapy. Similarly, the presence of new <sup>67</sup>Ga uptake during or after discontinuation of corticosteroid therapy may be useful in confirming a relapse in doubtful cases, but is not an indication of the need to reintroduce corticosteroids. Nevertheless, NOSAL *et al.* [22] reported that the combination of SACE level and <sup>67</sup>Ga scan result had a diagnostic specificity of 99%, and suggested that, if the results of both examinations were negative, the diagnosis of sarcoidosis was highly improbable.

Some authors have reported a strong correlation between lung parenchymal <sup>67</sup>Ga uptake and the intensity of alveolitis defined by the number of T-lymphocytes in BAL

fluid [30–32], although others found no such correlation [2]. One reason for this lack of correlation is that BAL fluid reflects the intensity of the T-lymphocytic alveolitis, which may predominate in the early phases of the disease, whereas  $^{67}\text{Ga}$  lung scan results reflect the presence of activated macrophages and granulomas, which usually prevail in later phases.

In pulmonary sarcoidosis, pulmonary function test results can be normal in the presence of alveolitis. LINE *et al.* [31] found little correlation between the degree of alveolitis measured by BAL or  $^{67}\text{Ga}$  scan and the extent of lung function impairment. In contrast, some studies found that even low-grade  $^{67}\text{Ga}$  uptake by the pulmonary parenchyma was associated with some degree of lung restriction, whereas others showed close correlation between the degree of  $^{67}\text{Ga}$  uptake and the increase in vital capacity after corticosteroid therapy [28].

Owing to reduced sensitivity and specificity, the  $^{67}\text{Ga}$  scan is of limited value in the assessment of activity, diagnosis and management of sarcoidosis. In consequence, its routine use is not currently recommended in the initial evaluation of sarcoidosis except in certain select clinical settings. The most appropriate use of the  $^{67}\text{Ga}$  scan in sarcoidosis is assisting in the diagnosis and determination of the extent and distribution of the disease in cases with diagnostic difficulties. Patients with normal CXR results and a clinical picture suggestive of isolated extrathoracic sarcoidosis, such as uveitis, inflammatory central nervous system disease or monovisceral granulomatosis of unknown origin, particularly liver and lymph node granulomatosis, may benefit from the  $^{67}\text{Ga}$  scan. The finding of the typical lambda and/or panda patterns supports the diagnosis and reinforces the indication of histological confirmation [8]. Whole-body scanning may also detect other clinically silent extrathoracic uptake of  $^{67}\text{Ga}$ , providing sites for biopsy [3, 4]. Likewise, in the cases of Löfgren's syndrome and asymptomatic stage I with doubtful hilar lymphadenopathy on CXR, without histological confirmation, the finding of a lambda pattern on  $^{67}\text{Ga}$  scan may contribute to more confidence in the diagnosis [33]. However, normal  $^{67}\text{Ga}$  scan results do not preclude the presence of granulomas in any organ. The  $^{67}\text{Ga}$  scan has not been proved useful in predicting prognosis and should not be used as an indicator of therapy [12, 13]. Nevertheless, it may be useful in distinguishing fibrotic from active lung disease, contributing to the decision as to whether to suppress or continue corticosteroid therapy, confirming a relapse after discontinuation of therapy in doubtful cases and assessing activity before lung transplantation [1].

## Thallium-201 scintigraphy

The radioisotope thallium-201 accumulates in normal myocardial cells. The  $^{201}\text{Tl}$  scan permits noninvasive estimation of the regional distribution of myocardial blood perfusion. In cardiac sarcoidosis,  $^{201}\text{Tl}$  scintigraphy performed under resting conditions typically shows segmental areas of decreased perfusion in the ventricular myocardium that correspond to areas of fibrogranulomatous replacement [34, 35]. In the absence of coronary artery disease, these defects suggest cardiac involvement by sarcoidosis, particularly if they disappear or decrease in size during  $^{201}\text{Tl}$  stress imaging [34, 36–38]. This phenomenon, called reverse distribution, suggests the presence of granulomas in the myocardium and is useful in differentiating cardiac sarcoidosis from myocardial ischaemia [35, 36]. However, this finding is not always present and is not specific to cardiac sarcoidosis since it may also occur in other cardiomyopathies [35]. TELLIER *et al.* [39] reported that perfusion defects were also partially or totally reversible after the intravenous administration of dipyridamole, a potent vasodilator of the coronary microcirculation, and suggested that the mechanism for the perfusion defects could be

the presence of reversible disorders at the coronary microvascular level rather than myocardial granulomas or fibrosis. However, because of the possibility of small focal lesions, normal  $^{201}\text{Tl}$  scan results do not exclude the presence of cardiac sarcoidosis [34].

KINNEY *et al.* [40] noted the presence of abnormalities on  $^{201}\text{Tl}$  scan in >30% of patients with sarcoidosis without clinically suspected cardiac involvement. SHARMA *et al.* [35] found positive resting  $^{201}\text{Tl}$  scan results in 34% of patients with systemic sarcoidosis and observed that all left ventricular defects decreased in size on stress imaging. HAYWOOD *et al.* [36] detected either left or right ventricular defects in 37% of patients in whom two-dimensional echocardiography had failed to show segmental ventricular contraction abnormalities. In another study, performed on 41 patients with sarcoidosis, myocardial  $^{201}\text{Tl}$  single-photon emission computed tomography (SPECT) was performed and mean washout ratios measured. Abnormal findings, including all types of abnormality, were found in 26 patients [38].

The combined use of  $^{201}\text{Tl}$  and  $^{67}\text{Ga}$  imaging of the heart, particularly with SPECT, may increase recognition of cardiac sarcoidosis [41, 42]. However, OKAYAMA *et al.* [43] reported that, when  $^{201}\text{Tl}$  revealed myocardial defects, cardiac  $^{67}\text{Ga}$  uptake did not add more diagnostic information; it was, however, predictive of the efficacy of corticosteroid treatment. KINNEY and CALDWELL [44] found that positive  $^{201}\text{Tl}$  scan results had no prognostic significance, although the periodic evaluation of perfusion defects was useful in monitoring the progress of myocardial sarcoidosis and its response to therapy [36, 37]. In consequence, the  $^{201}\text{Tl}$  scan should not be used indiscriminately in screening for the presence of cardiac involvement in sarcoid patients without cardiac symptoms [1, 9]. In addition to cardiac sarcoidosis, marked uptake of  $^{201}\text{Tl}$  has also been reported in bone lesions resulting from sarcoidosis [45]. Other heart perfusion imaging agents, such as technetium-99m-sestamibi ( $^{99\text{m}}\text{Tc}$ ) [46, 47], or metabolic imaging using iodine-123-labelled free fatty acid scintigraphy [48] have also been reported to be useful in the assessment of myocardial sarcoidosis.

## Technetium-99m bone scintigraphy

Bone scintigraphy shows high sensitivity and somewhat lower specificity in assessing bone processes. Localised increased uptake can be seen in a variety of processes, such as bone metastasis, traumatism, infections and inflammatory lesions, including sarcoidosis and degenerative lesions [49]. The frequency of bone involvement in sarcoidosis ranges 3–13%, although, as bone involvement is often asymptomatic, the true prevalence is not known. The small bones of the hands and feet are more commonly involved, but any bone can be affected (fig. 3). The most frequent means of detecting bone sarcoidosis is looking for the presence of a bone radiological abnormality in a patient with known sarcoidosis. However, the differential diagnosis of these types of bones lesion is often broad [50]. Bone scintigraphy is more sensitive than either radiography or  $^{67}\text{Ga}$  scintigraphy in the detection of skeletal bone lesions caused by sarcoidosis [51]. YAGHMAI [52], in a series of 136 cases of sarcoidosis involving bone, demonstrated that the bone scan depicted 30% more lesions than plain radiography. For this reason, the true frequency of bone involvement by sarcoidosis is probably underestimated due to the asymptomatic nature of most of these lesions and the absence of justification for bone scanning in all patients with sarcoidosis. A bone scan, unlike the  $^{67}\text{Ga}$  scan, is not able to detect intrathoracic and other extrathoracic sites of involvement by sarcoidosis [10, 53]. Recently, MILMAN *et al.* [49] assessed the value of routine bone scintigraphy in the detection of osseous and joint lesions in a series of 63 Caucasian patients with pulmonary sarcoidosis, none of whom exhibited symptoms suggesting bone involvement. Minor

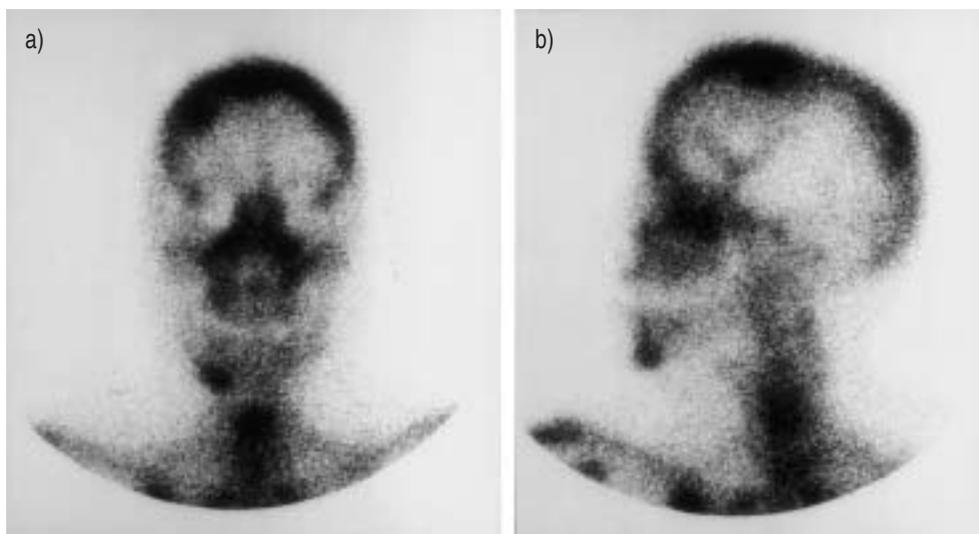


Fig. 3. – Radionuclide bone scan revealing hot spots in the skull, right mandibular bone and right clavicle in the same patient as shown in figure 1: a) front view, and b) lateral view. Images reproduced from [5] with permission.

scan abnormalities were present in 24 (38%) patients, in bones, joints or both. Radiographically, only one of these patients showed a typical bone lesion of sarcoidosis. As the diagnostic yield of bone scanning in sarcoidosis appears to be very small, it should be reserved for cases with symptomatic osseous involvement and patients with abnormal radiography results suggesting bone or joint involvement.

## <sup>111</sup>Indium-octreotide scintigraphy

Scintigraphy using indium-111-diethylenetriamine penta-acetic acid-D-Phe<sup>1</sup>-octreotide (octreotide) is useful in the assessment and management of neuroendocrine and other malignant tumours [54]. It has been reported that normal and activated lymphocytes and macrophages express somatostatin receptors [55, 56]. As a consequence, several reports have focused on the usefulness of this radiolabelled somatostatin analogue in detecting somatostatin receptors expressed on cells in granulomatous diseases, including sarcoidosis.

ÖZTÜRK *et al.* [57] communicated two cases of sarcoidosis that showed increased uptake of <sup>111</sup>In-octreotide. VANHAGEN *et al.* [55] investigated the usefulness of whole-body somatostatin receptor scintigraphy (SRS) in 13 patients with sarcoidosis. Granuloma localisations were visualised in all patients, and additional sites were found in 69%. In addition, scintigraphy results became negative in two patients successfully treated with corticosteroids, whereas, in three patients in whom corticosteroids were unsuccessful, scintigraphy results remained positive. EKLUND *et al.* [58] evaluated the usefulness of this technique in detecting extrathoracic manifestations of sarcoidosis. They found that four out of five patients with sarcoidosis displayed extrathoracic findings. KWEKKEBOOM *et al.* [59] analysed the value of SRS in the assessment of disease activity, prediction of prognosis and correlation with clinical course in 46 patients with sarcoidosis. Previously known mediastinal, hilar and interstitial involvement was recognised in 36 out of 37 patients. In addition, these findings were also made in a further seven patients with normal CXR

results, and, in five of these, it pointed to interstitial disease. In 13 patients, SRS revealed previously undetected extrathoracic uptake, particularly in parotid glands, supraclavicular lymph nodes, nose, eyes and granulomatous skin lesions. No uptake of radioactivity was seen in three patients at the site of skin eruption caused by erythema nodosum. In the whole series, SRS detected new granuloma sites in 23 out of 46 (50%) patients, but missed known granuloma sites, including cutaneous, ocular, liver and brain sites, in 28% of patients. Significant relationships were not found between SRS results and the need for corticosteroid treatment. Neither the degree of radioactive accumulation nor any specific pattern of pathological uptake was predictive of disease prognosis. SRS results usually correlated with the progression of the disease. In five out of six patients who showed CXR improvement under corticosteroid therapy, a decrease in pathological uptake was also demonstrated on the scintigram. LEBTAHI *et al.* [60] compared SRS with  $^{67}\text{Ga}$  scan results in the evaluation of pulmonary and extrapulmonary involvement in 18 patients with sarcoidosis. The  $^{67}\text{Ga}$  scan revealed abnormalities in 16 out of 18 (89%) patients, and detected 64 out of 99 (65%) clinically involved sites. SRS found abnormalities in 18 out of 18 (100%) patients, and detected 82 out of 99 (83%) clinically involved sites. Of the nine treated patients, the  $^{67}\text{Ga}$  scan showed abnormalities in seven (78%), detecting 23 out of 39 (59%) clinically involved sites, whereas SRS found abnormalities in nine (100%), detecting 32 out of 39 (82%) clinically involved sites. However, 40% of extrathoracic sites were missed by SRS. Recently, SHORR *et al.* [61] studied 22 subjects with sarcoidosis, predominantly with intrathoracic involvement, and reported a strong correlation between positive scan results and sarcoidosis activity, particularly with CXR stage and pulmonary function. SRS revealed intense uptake in two cases of cardiac involvement and also in one case of neurosarcoidosis. Apart from one patient with cutaneous involvement, the remaining subjects did not show clinical evidence of extrathoracic sarcoidosis. They emphasised, however, that SRS does not preclude the need for biopsy to confirm the diagnosis of sarcoidosis or to exclude malignancy. The possible usefulness of  $^{111}\text{In}$ -octreotide in the study of cardiac sarcoidosis is currently undergoing evaluation [62].

## Iodine-123-meta-iodobenzylguanidine scintigraphy

$^{123}\text{I}$ -meta-iodobenzylguanidine (MIBG), an analogue of noradrenaline, is a tracer for the functioning of sympathetic neurons. Cardiac sympathetic nerves take up  $^{123}\text{I}$ -MIBG. This permits visualisation of the presynaptic sympathetic innervation of the heart. Defects on MIBG scans in sarcoidosis have been reported [63–65], but, to date, the underlying mechanism has remained unclear. One possible explanation postulated is that local ischaemia or myocardial inflammation may play an important role. Recently, it was found that small fibre neuropathy (SFN) occurs frequently in sarcoidosis [66].

Moreover, an imbalance of sympathetic tone is considered to increase the propensity for developing ventricular arrhythmias in various cardiac diseases and conditions [67]. Autonomic dysregulation might contribute to fatal arrhythmias and unexplained sudden death in sarcoidosis. It is known from patients with neuropathy that the involvement of small autonomic nerve fibres is a predictor of cardiovascular mortality [68, 69]. Sudden death is a rare but dramatic complication [70]. In the case of sarcoidosis, it is thought to be due mainly to cardiac involvement. Active granulomatous infiltration and resulting myocardial fibrosis are considered to be the substrate.

Cardiac sympathetic dysfunction, assessed by use of myocardial  $^{123}\text{I}$ -MIBG scanning, appears to be heterogeneous in sarcoidosis patients and dependent on the presence or absence of SFN [71]. In 18 out of 47 (38%) of these cases, mild-to-moderate heterogeneity of  $^{123}\text{I}$ -MIBG uptake in the myocardium was demonstrated.

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## Positron emission tomography

The role of whole-body positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (FDG) is well established in the management of patients with cancer. In recent years,  $^{18}\text{F}$ -FDG-PET imaging has also been proposed to have a role in the diagnosis and management of patients with several types of infection, inflammatory processes and a variety of benign thoracic disorders [72, 73]. The technique is based on the demonstration, in experimental studies, of increased glucose metabolism in tumours and inflamed tissues [74]. LEWIS and SALAMA [75] first described  $^{18}\text{F}$ -FDG uptake by intrathoracic and extrathoracic sarcoid lymph nodes, as well as by lesions of erythema nodosum. The uptake disappeared after corticosteroid treatment. BRUDIN *et al.* [76] reported an increase in pulmonary  $^{18}\text{F}$ -FDG uptake in patients with active sarcoidosis, reflecting inflammatory activity that was confirmed by lung biopsy. SAZON *et al.* [77] demonstrated a strong correlation between the presence of  $^{18}\text{F}$ -FDG uptake and the presence of sarcoidosis activity measured by conventional procedures.  $^{18}\text{F}$ -FDG-PET also detected recurrence of sarcoidosis in transplanted lung, confirmed by transbronchial biopsy [78].

YAMADA *et al.* [79] described how both  $^{18}\text{F}$ -FDG and carbon-11-labelled methionine uptake on PET were useful for imaging patients with sarcoidosis. In addition, they reported that the  $^{18}\text{F}$ -FDG/ $^{11}\text{C}$ -methionine uptake ratio was of prognostic value and useful in pre-treatment evaluation. Increased  $^{18}\text{F}$ -FDG accumulation in sarcoidosis was subsequently reported by other groups [72, 73]. However, one of the main limitations of  $^{18}\text{F}$ -FDG-PET uptake is in differentiating benign lesions, particularly sarcoidosis, from malignant ones. PITMAN *et al.* [80] suggested that all masses or nodules with increased  $^{18}\text{F}$ -FDG uptake should be considered malignant once sarcoidosis and tuberculosis have been excluded. ALAVI *et al.* [73] retrospectively compared  $^{18}\text{F}$ -FDG-PET images with thoracic CT results and described several patterns of  $^{18}\text{F}$ -FDG uptake in sarcoidosis, suggesting that their recognition could be helpful in differentiation from malignancy. The most common pattern, present in 71% of cases, was the so-called typical pattern, in which PET images consisted of bilateral hilar, mediastinal and pulmonary uptake, similar to those seen on  $^{67}\text{Ga}$  scan. These lesions correlated with thoracic CT results, and most patients had had their diagnosis of sarcoidosis confirmed prior to PET imaging. Therefore, the new diagnostic value provided by PET was minimal. The second pattern was seen in 19% of cases and was called discrepant because PET showed multiple foci of intense uptake, both intrathoracic and extrathoracic, and particularly splenic, whereas CT showed only a solitary nodule. This pattern was indistinguishable from those of malignant processes such as lymphoma. In the presence of this  $^{18}\text{F}$ -FDG-PET pattern, findings on CT may help to define the nature of the lesions. Malignant lesions usually grow slowly and are often only visible initially on PET and not on CT. In contrast, inflammatory lesions are metabolically more active, and they can change quickly, grow in a short interval of time and cause discrepancies, such as the presence of a single or a few lesions on CT and numerous lesions on  $^{18}\text{F}$ -FDG-PET. In consequence, a significant discrepancy between  $^{18}\text{F}$ -FDG-PET and CT results is more suggestive of sarcoidosis. The third pattern of  $^{18}\text{F}$ -FDG uptake in sarcoidosis, seen in 10% of cases, was called the "tumour of unknown primary". In this pattern, both CT and  $^{18}\text{F}$ -FDG-PET revealed multiple small pulmonary lesions, suggestive of metastases from an unknown primary tumour. Owing to the high sensitivity of  $^{18}\text{F}$ -FDG-PET in detecting malignancy, the detection of multiple metastases without detecting a primary tumour would support the diagnosis of sarcoidosis rather than malignancy.

ORIUCHI *et al.* [81] compared the use of another PET tracer,  $^{18}\text{F}$ -fluoro- $\alpha$ -methyltyrosine (FMT), with that of  $^{18}\text{F}$ -FDG and showed that, although both sarcoid

and malignant lesions contained increased  $^{18}\text{F}$ -FDG, only malignant lesions showed increased  $^{18}\text{F}$ -FMT accumulation. Consequently,  $^{18}\text{F}$ -FMT seems to be a useful PET tracer when sarcoid lesions need to be differentiated from lung cancer.  $^{18}\text{F}$ -FDG-PET uptake has also been reported to occur at extrathoracic sites of sarcoidosis involvement, such as skeletal sarcoidosis [82–84], cardiac sarcoidosis [85] and neurosarcoidosis [86].

The extent of involvement and quantification of sarcoidosis activity are probably more accurately assessed by  $^{18}\text{F}$ -FDG-PET than by  $^{67}\text{Ga}$  scan and other imaging studies. In addition, hybrid  $^{18}\text{F}$ -FDG-PET and CT study, with high-resolution images, may help to better differentiate active from fibrotic residual lesions. Therefore, it may be useful in the follow-up of selected patients with sarcoidosis. Figure 4 shows a hybrid  $^{18}\text{F}$ -FDG-PET and CT study in a patient with sarcoidosis.

The dual-isotope technique of nitrogen-13-ammonia/ $^{18}\text{F}$ -FDG-PET could also identify cardiac involvement in patients with sarcoidosis [87]. Seventeen patients with cardiac sarcoidosis underwent cardiac  $^{13}\text{N}$ - $\text{NH}_3$ / $^{18}\text{F}$ -FDG PET. Systemic sarcoidosis was diagnosed by histologically proven noncaseating epithelioid granuloma. Only six patients showed myocardial  $^{201}\text{Tl}$  defects and only three exhibited abnormal  $^{67}\text{Ga}$  accumulation in the heart. Thirteen patients showed  $^{13}\text{N}$ - $\text{NH}_3$  defects and 14 increased  $^{18}\text{F}$ -FDG uptake in the heart; 12 patients exhibited both  $^{13}\text{N}$ - $\text{NH}_3$  defects and increased  $^{18}\text{F}$ -FDG uptake, two increased  $^{18}\text{F}$ -FDG uptake but no  $^{13}\text{N}$ - $\text{NH}_3$  defect, and one  $^{13}\text{N}$ - $\text{NH}_3$  defects but no increased  $^{18}\text{F}$ -FDG uptake.  $^{13}\text{N}$ - $\text{NH}_3$  defects were observed frequently in the basal anteroseptal wall of the left ventricle, and increased  $^{18}\text{F}$ -FDG uptake was observed frequently in the basal and mid-anteroseptal lateral wall of the left ventricle. Involvement of the apex was rare. Seven patients were treated with steroid hormone and underwent follow-up cardiac PET 1 month after steroid therapy.  $^{13}\text{N}$ - $\text{NH}_3$  defects exhibited no significant change after steroid therapy, whereas increased  $^{18}\text{F}$ -FDG uptake was markedly diminished in magnitude and intensity in five patients and disappeared completely in two.

OKUMURA *et al.* [88] compared  $^{18}\text{F}$ -FDG PET images with scintigraphic findings using  $^{99\text{m}}\text{Tc}$ -methoxyisobutylisonitrile (MIBI) and  $^{67}\text{Ga}$ . Ten out of 16 patients were considered to exhibit cardiac complications on clinical grounds with tissue confirmation,

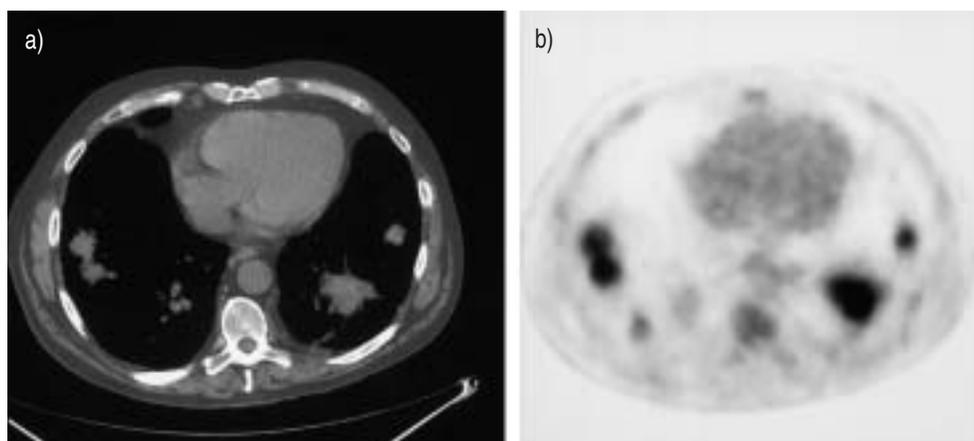


Fig. 4. – a) Hybrid computed tomography and b)  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (PET) study showing multiple pulmonary lesions with a high glucose metabolism rate in a 63-yr-old male diagnosed as having pulmonary sarcoidosis 30 yrs earlier, with apparent remission. One year previously he had been diagnosed as having rectal cancer and was treated with surgery and radiotherapy. Biopsy of pulmonary lesions showed noncaseating granulomas. Images obtained from C. Gámez and A. Fernández, PET Unit, Imaging Diagnosis Institute, Bellvitge University Hospital, Barcelona, Spain.

such as positive endomyocardial biopsy, severe ventricular arrhythmia, greater than second degree atrioventricular block and echocardiographically proven ventricular dysfunction. Among these patients with cardiac complications, abnormal myocardial uptake of  $^{18}\text{F}$ -FDG was observed in all (100%), which confirms the significantly higher frequency compared to  $^{99\text{m}}\text{Tc}$ -MIBI-SPECT (80%) and  $^{67}\text{Ga}$  scintigraphy (50%). Although abnormal  $^{18}\text{F}$ -FDG accumulation was observed in regions with decreased uptake of  $^{99\text{m}}\text{Tc}$ -MIBI in many cases, localisation of regional abnormality of each tracer was frequently independent. This discrepancy may reflect the inflammatory and degenerative process of the myocardium in cardiac sarcoidosis. Recently, OKUMURA *et al.* [89] also demonstrated that  $^{18}\text{F}$ -FDG PET was more sensitive than either  $^{99\text{m}}\text{Tc}$ -MIBI-SPECT and  $^{67}\text{Ga}$  scintigraphy in detecting the early stage of cardiac sarcoidosis that is associated with fewer perfusion defects and greater inflammatory activity, before advanced myocardial impairment.

PET may have great potential in the diagnosis and management of cardiac sarcoidosis, particularly for patients with an implanted pacemaker or cardioverter. However, larger prospective studies using cardiac magnetic resonance imaging (MRI), PET and  $^{111}\text{In}$ -octreotide are needed to better evaluate its role in the assessment of cardiac sarcoidosis [90].

Of great promise in the future could be the use of the positron emitter  $^{68}\text{Ga}$  (instead of  $^{67}\text{Ga}$ ), either as radioisotope or labelled with the somatostatin receptor ligand 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid-D-Phe<sup>1</sup>-Tyr<sup>3</sup>-octreotide (DOTA-TOC) [91]. Since  $^{68}\text{Ga}$  can be obtained from a generator system, it could be easily implemented in clinical practice.

## Clinical approach and flow chart

The best means of assessment of pulmonary sarcoidosis is good quality CXR and pulmonary function test results (fig. 5). When CXR results are doubtful or atypical for sarcoidosis, HRCT is better than  $^{67}\text{Ga}$  scan for studying the mediastinum and pulmonary parenchyma. Bronchoscopy with BAL and transbronchial biopsy completes the study of pulmonary sarcoidosis. In this context, neither  $^{67}\text{Ga}$  nor other nuclear imaging techniques provides more significant information. Nevertheless, in the cases of Löfgren's syndrome and asymptomatic stage I with doubtful hilar lymphadenopathy on CXR, without histological confirmation, the finding of a lambda pattern on  $^{67}\text{Ga}$  scan may contribute to more confidence in the diagnosis. In the follow-up of patients with pulmonary sarcoidosis,  $^{67}\text{Ga}$  scan may be useful in distinguishing fibrosis from active inflammation, confirming relapses after suppression of treatment and assessing activity before lung transplantation. A hybrid  $^{18}\text{F}$ -FDG-PET and CT study may be very useful in better differentiating active from fibrotic residual lesions in the lung.

Whole-body  $^{67}\text{Ga}$  scan is also very useful in cases which present with normal CXR results and a clinical picture suggestive of isolated extrathoracic sarcoidosis, such as uveitis, inflammatory central nervous system disease or monovisceral granulomatosis, particularly liver and lymph node granulomatosis, of unknown origin. The finding of a lambda and/or panda pattern supports the diagnosis of sarcoidosis. Whole-body  $^{67}\text{Ga}$  scan is also useful in assessing the extent of the disease and may provide sites for biopsy.

$^{18}\text{F}$ -FDG-PET and SRS are not specific for the diagnosis of sarcoidosis. However, they probably better assess the extent of involvement and quantification of sarcoidosis activity than do the  $^{67}\text{Ga}$  scan and other radionuclide imaging examinations, and may be of value in subgroups of patients in whom there are diagnostic difficulties.

In the case of suspicion of cardiac sarcoidosis,  $^{201}\text{Tl}$  scintigraphy is a complementary

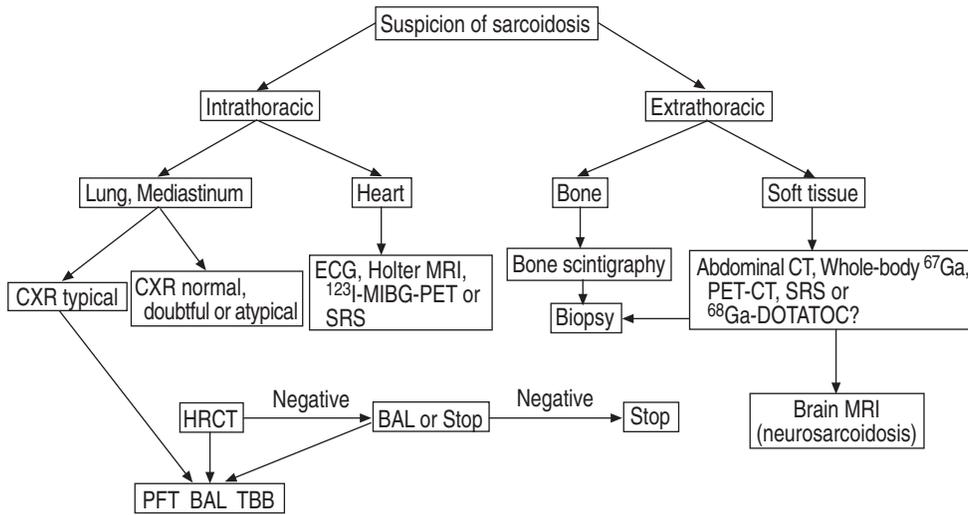


Fig. 5. – Flow chart suggesting which tests are best to use in the assessment of sarcoidosis. CXR: chest radiography; MRI: magnetic resonance imaging; MIBG: meta-iodobenzylguanidine; PET: positron emission tomography; SRS: somatostatin receptor scintigraphy; CT: computed tomography; DOTATOC: 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid-*D*-Phe<sup>1</sup>-Tyr<sup>3</sup>-octreotide; HRCT: high-resolution CT; BAL: bronchoalveolar lavage; PFT: pulmonary function test; TBB: transbronchial biopsy.

tool to two-dimensional echocardiography, 24-h monitoring and cardiac catheterisation with endomyocardial biopsy. A normal <sup>201</sup>Tl scan, however, does not rule out the presence of cardiac involvement. <sup>99m</sup>Tc-sestamibi is currently replacing <sup>201</sup>Tl in some centres. <sup>18</sup>F-FDG-PET has been reported to be better than <sup>201</sup>Tl scan for studying cardiac sarcoidosis, and the value of SRS is currently under evaluation. <sup>123</sup>I-MIBG scintigraphy can be useful in assessing cardiac autonomic dysfunction, which is often associated with the presence of SFN. Cardiac MRI has recently been introduced as a very accurate tool in the diagnosis and management of cardiac sarcoidosis.

Brain involvement of sarcoidosis is better assessed by MRI, although nuclear imaging techniques have been reported as capable of detecting the presence of neurological involvement. Bone scintigraphy is very sensitive for detecting the presence of sarcoid bone lesions.

## Conclusions

Nuclear imaging in sarcoidosis is a rapidly changing field, with new possibilities appearing on the horizon as others are discontinued. At present, the role of scintigraphy in confirming diagnosis and guiding therapy in sarcoidosis is limited. The most appropriate use of <sup>67</sup>Ga scintigraphy in sarcoidosis is assisting in the determination of the extent and distribution of the disease in cases in whom there are diagnostic difficulties, particularly in those with isolated extrathoracic sarcoidosis. It is conceivable that the extent of involvement and quantification of sarcoidosis activity can be more accurately assessed in the future by <sup>18</sup>F-FDG-PET, particularly when combined with CT or in combination with new tracers such as <sup>68</sup>Ga DOTATOC or <sup>68</sup>Ga alone. Nuclear imaging techniques are particularly helpful in the follow-up of patients for differentiating active inflammation from fibrosis.

## Summary

Nuclear imaging techniques play a role in the assessment of sarcoidosis. Several possibilities are available, and promising new techniques are in development. Scintigraphic techniques are useful in distinguishing fibrotic from active lung disease, confirming relapse in doubtful cases, assessing activity before lung transplantation and the detection of cardiac involvement and extrathoracic localisation.

The improvement in image resolution in modern positron emission tomography and single-photon emission computed tomography scanners, with or without computed tomography, allows more accurate imaging and quantification, whereas the use of new radiopharmaceuticals could provide more insight into the physiology and extent of the disease. In this chapter, a flow chart has been created in order to facilitate clinicians' decisions about which tests are best to use in the assessment of sarcoidosis.

**Keywords:** Gallium-67 scintigraphy, indium-111-octreotide scintigraphy, iodine-123-meta-iodobenzylguanidine scintigraphy, positron emission tomography, technetium-99m bone scintigraphy, thallium-201 scintigraphy.

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