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Review

The use of ^{67}Ga scintigraphy in patients with sarcoidosis

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Abstract

Sarcoidosis is a systemic disease of unknown aetiology characterised by the formation of noncaseating granulomas in various organs and tissues. The various imaging modalities that are useful in the investigation of lesions, staging and establishing indications for treatment include: conventional radiography, CT, MRI, and scintigraphy with ^{67}Ga, ^{201}Tl, ^{99m}Tc sestamibi, and somatostatin receptor scintigraphy (SRS) as well as ^{18}F-FDG-PET/CT. This paper discusses the most commonly used technique of the scintigraphic, gallium (^{67}Ga) citrate) and its role in the evaluation and monitoring of patients with sarcoidosis.

KEY words: sarcoidosis, ^{67}Ga scintigraphy, SPECT/CT

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Background

Sarcoidosis is a systemic disease of unknown aetiology characterised by the formation of noncaseating granulomas in various organs and tissues. In about 90% of the patients, mediastinal and hilar lymph nodes and the pulmonary parenchyma are involved [1].

Systemic disease and multiple organs are frequently involved with a prevalence that varies from population to population though this may be related to the ability to identify sites of disease with the technology available to a particular patient group. For example cardiac sarcoidosis is discovered on autopsy in 13–25% of the patients in the USA, while clinical manifestations are present in about 5% of these patients. In Japan, cardiac sarcoidosis is found in as many as 58–85% of patients. Cutaneous involvement is seen in 20–35% of patients, ocular involvement in 10–60%, nervous system involvement in about 5%, and musculoskeletal involvement in about 30%. In autopsy studies, hepatic involvement is seen in about 50–80% of the patients, although its clinical manifestations are much less frequent. In 5% of patients, the pancreas is affected. Renal involvement is reported in 7–23% of subjects [1].

The systemic nature of the disease means that those techniques which allow for whole body imaging are therefore more advantageous than those techniques such as in conventional radiography, ultrasound (US) and MRI, and to some extent CT. Radionuclide studies have the advantage that vertex to toe imaging is easily performed. This allows involvement in organs such as the brain and joints such as the knees and ankles to be assessed with a single investigation. Single photon agents which have been used to identify active sites of sarcoid with radionuclide studies, including conventional scintigraphy with ^{67}Ga citrate, ^{201}Tl chloride, ^{99m}Tc sestamibi and somatostatin receptor scintigraphy (SRS) using agents such as ^{99m}Tc-HYNICTOC [2–5].

The evaluation of disease activity in patients with suspected or confirmed sarcoidosis is of utmost clinical significance. It allows the establishing of indications for further management and pharmacotherapy and also when such treatment can be stopped as spontaneous remissions are observed in most patients. Though in a small percentage of patients, the clinical course of sarcoidosis may be severe and in some cases lead to death shortly following the diagnosis [6]. An accepted method of monitoring the activity of sarcoid is to look at the plasma angiotensin converting enzyme (ACE) level. When this is elevated at diagnosis this can be a very good method for monitoring disease activity with an expected reduction to a normal level in quiescent disease [7]. The major problem with use of the serum ACE is that in as many as 50% of patients levels are not elevated in active disease [8, 9]. In these patients the best alternate method is scintigraphy and at present the greatest evidence is for the use of ^{67}Ga citrate scintigraphy.

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Gallium (^{67}Ga) citrate scintigraphy

In gallium (^{67}Ga) scintigraphy a standard gamma camera is used, however, there are multiple energies emitted including those at 70 keV, 170 keV, 300 kev and 394 keV. Though the 394 keV has only a 4% abundancy it can cause significant septal penetration and scatter effect on the image unless a high energy collimator is used. This can reduce count rate, higher activity cannot normally be administered due to the poor dosimetry of ^{67}Ga imaging so that an administered activity of 300 MBq gives an effective dose of 18 mSv which is the greatest radiation dose for any common radionuclide test. However, once injected imaging can be versatile

with planar, wholebody, SPECT (Single Photon Emission Computed Tomography) views being performed and more recently hybrid imaging combining SPECT and CT (SPECT/CT).

There is a variable physiological uptake of ^{67}Ga. Initially there is high blood pool and urinary excretion is seen when the ^{67}Ga is unbound [10, 11]. By 24 hours, however, most of the ^{67}Ga is bound to transferrin and lactoferrin as it is an iron analogue. These proteins act as acute phase proteins and concentrate around the sites of focal infection and inflammation. There is also physiological activity in the liver and large intestine. The colonic activity can be very variable even within the same patients with no evidence that these changes in colonic activity has any pathological consequences. Slightly lower physiological uptake of the radiotracer is evident in the spleen, in the bone marrow (though in patients with activated bone marrow due to anaemia this bone marrow uptake can be intense), oral cavity and perineum. Other variants of physiological radiotracer uptake are associated with the activity of the glandular parenchyma of both breasts during the menstrual cycle, with a particularly high uptake being seen during lactation (such that following the administration of ^{67}Ga breastfeeding should be discontinued). There can be low grade uptake in lacrimal and salivary glands. Due to these physiological constraints image acquisition is usually performed 48 hours after i.v. administration of the radiotracer. In exceptional cases, if unequivocal images are obtained after 48 hours, an additional acquisition should be carried out after 72 hours, although this is not often done. Given the timing of radiotracer administration and the image acquisition that follows 48 hours later, the patient needs to come to the imaging facility twice.

Changes in thoracic lymph nodes and pulmonary parenchyma

In patients with sarcoidosis, the disease process most commonly affects hilar and mediastinal lymph nodes. Involvement is most commonly symmetrical, as is also evident on ^{67}Ga citrate scintigraphy in the form of symmetrical radiotracer uptake over the lymph nodes of both hilar and the upper mediastinum producing the so called lambda sign (Fig. 1, 2) [12, 13]. The disease less frequently affects other local lymph node groups. This pattern of uptake is the most commonly seen in sarcoid and can be considered diagnostic

Involvement of lymph nodes other than hilar and mediastinal and unilateral involvement usually suggests a different diagnosis such as a well-differentiated Hodgkin or non-Hodgkin lymphoma, although in some cases it is caused by other rare diseases (e.g. IgG4-related disease) [14]. However as stated previously sarcoid uptake tends to be symmetrical, if there is doubt, however, biopsy of a ^{67}Ga citrate avid node is diagnostic. The use of SPECT may allow the mediastinal and hilar nodal activity to be seen more clearly (Fig. 4).

Of greater concern because it can carry a much worse prognosis ins parenchymal diffuse uptake of ^{67}Ga citrate uptake by the pulmonary parenchyma showing a diffuse (usually) pattern, but in some cases a geographic or even a focal pattern, which may suggest an alternate active inflammation or infectious process [15].

As the intensity of parenchymal lung disease can have an impact on patient survival it has been found useful to quantify the uptake of ^{67}Ga citrate using the 5 point, Kramer scale originally used in patients with HIV but often re-applied to patients with sarcoid [16] (Table 1).

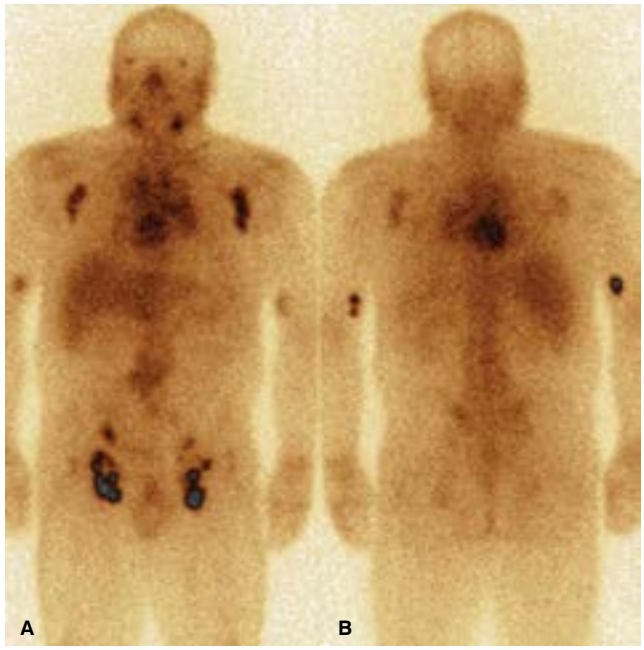

Figure 1. Whole-body (WB) ^{67}Ga scintigraphy in the AP (**A**) and PA (**B**) views. Active sarcoidosis in a 50-year-old male. Involvement of the mediastinal lymph nodes and bilateral involvement of the hilar lymph nodes. High radiotracer uptake in the submandibular glands, less pronounced over the parotid and lacrimal glands. High radiotracer uptake over the matted axillary and inguinal lymph nodes and involvement of iliac lymph nodes, aortic bifurcation and inferior vena cava. Additionally evident skin lesions on both arms. The nodular and cutaneous form of sarcoidosis predominates

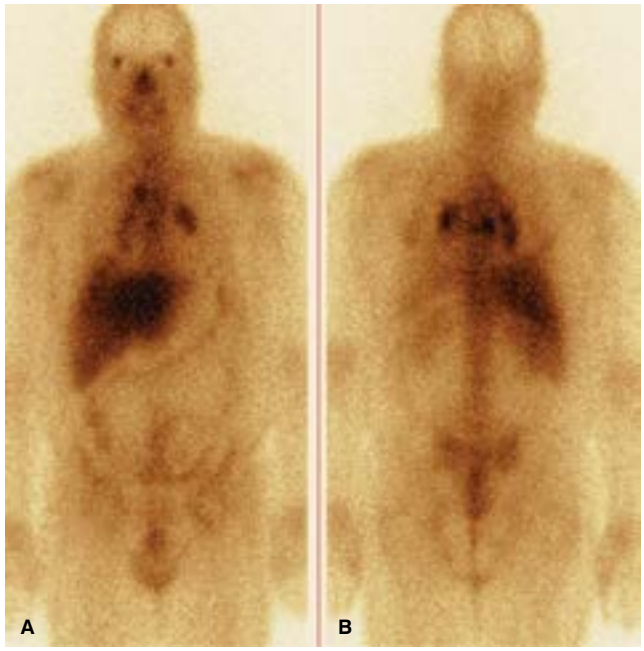

Figure 2. Whole-body (WB) ^{67}Ga scintigraphy in a 38-year-old male with confirmed sarcoidosis in the AP (**A**) and PA (**B**) views. Pathologically high radiotracer uptake over the hilar lymph nodes bilaterally and over the mediastinal lymph nodes: the lambda sign. Pronounced radiotracer uptake over the lacrimal glands and nasopharynx

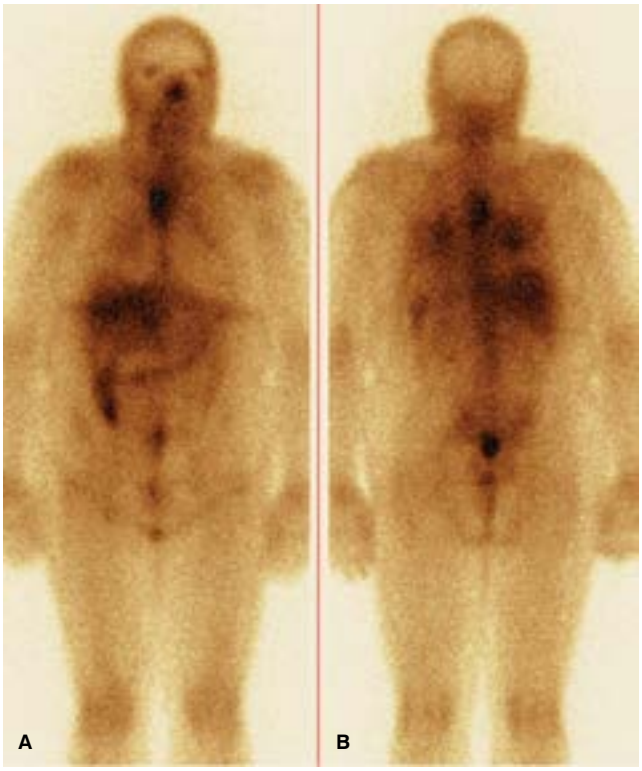

Figure 3. Whole-body (WB) ^{67}Ga scintigraphy in the AP (**A**) and PA (**B**) views. Active sarcoidosis in a 54-year-old female patient with evident radiotracer uptake over the mediastinum and both lung zones

Table 1. Kramer grading for intensity of lung uptake of ^{67}Ga citrate

Grade	Uptake intensity
0	No radiotracer uptake
1	Minimal uptake over structures other than those that show physiological radiotracer uptake
2	Uptake clearly visible but below the physiological high hepatic uptake
3	Uptake equal to the physiological hepatic uptake
4	Uptake above the physiological hepatic uptake

Lacrimal and salivary glands

As mentioned above, ocular changes are reported in 10–60% of sarcoidosis patients, depending on the author. They most commonly affect patients aged 20–40 years but can also be seen in children and the elderly. Their most common manifestation is uveitis [1]. Thirty percent of uveitis cases are associated with sarcoidosis and most commonly precede the onset of other manifestations of this disease [17].

The diagnostic criteria for ocular sarcoidosis (IWOS) include ocular changes in correlation with radiological studies (chest radiography and CT) and laboratory test results (plasma ACE if positive) [17]. Increased ^{67}Ga uptake by the lacrimal glands in patients with sarcoidosis is correlated with lacrimal gland biopsy results, which reveal non-caseating granulomas [18]. Involvement of parotid glands is reported in 6% of sarcoidosis patients [17, 19, 20].

In ^{67}Ga scintigraphy, increased radiotracer uptake by the lacrimal and parotid glands coupled with uptake by nasopharyngeal structures results in the characteristic "panda" sign (Fig. 2). Although this sign can also be seen in Sjögren syndrome, lymphomas (especially after head and neck radiotherapy), AIDS and IgG4-related disease, the sensitivity of this sign is 80% and 74% in patients with sarcoidosis in stage I and stage II, respectively. According to some authors, the sensitivity of the panda sign is even higher (96%), and in diseases other than sarcoidosis, e.g. IgG4-related disease, is only 62% [14]. At the same time, the presence of the panda sign and of the already discussed lambda sign is very characteristic of sarcoidosis [17–21]. There can be some confusion as there may be normal physiological uptake in the lacrimal and salivary glands and it may need experience to differentiate normal uptake from the elevated uptake seen in sarcoid.

Skeletal muscle

Muscles involvement in sarcoidosis is often asymptomatic and laboratory tests do not provide any indication of the possibility of this pathology either. Gallium scintigraphy is characterised by a high sensitivity in imaging superficial changes (located in skeletal muscles and skin) [12]. The increased radiotracer uptake by skeletal muscles observed on ^{67}Ga scintigraphy is confirmed on MRI, which reveals changes consistent with sarcoid granulomas in locations with increased radiotracer uptake [22]. Skeletal muscle involvement combined with the involvement of hilar and mediastinal lymph nodes, lacrimal glands and skin is manifested on ^{67}Ga scintigraphy by a pattern that is sometimes called the dappled-body sign or leopard-man sign [23]. Remission of skeletal muscle changes as a result of glucocorticosteroid treatment is also visible on ^{67}Ga scintigraphy [24].

Central nervous system

Central nervous system (CNS) involvement in sarcoidosis patients may manifest clinically by cranial nerve palsies, aseptic meningitis, peripheral neuropathy (e.g. Guillain-Barre syndrome [25]) or myopathy. The diagnostic criteria for neurosarcoidosis published in 1999 are still in use [26].

The diagnosis of definite neurosarcoidosis (presence of non-caseating granulomas on histopathological examination of nerve tissue) is only possible in few patients [27]. Most cases carry the diagnosis of probable neurosarcoidosis, which depends on the clinical symptoms and signs and the diagnosis of sarcoid made from a non CNS site by biopsy or characteristic extra CNS lesions seen ^{67}Ga citrate scintigraphy coupled with changes on MRI or in the cerebrospinal fluid suggestive of sarcoidosis. At the same time, histopathological examination of lesions outside the CNS reveals non-caseating granulomas that confirm the presence of sarcoidosis.

^{67}Ga scintigraphy is therefore an auxiliary investigation in the diagnosis of sarcoidosis. In some cases, especially where no clinical manifestations are found outside the CNS, increased radiotracer uptake may indicate the optimal biopsy site and provide the highest likelihood of establishing the final pathological diagnosis [28, 29].

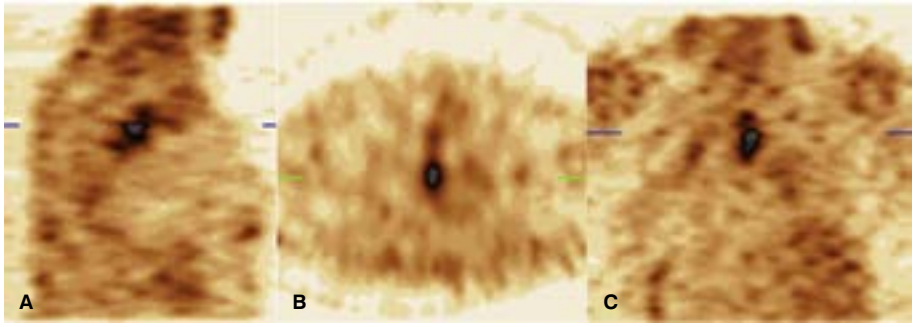

Figure 4. A SPECT scan in the transverse view (**A**), sagittal view (**B**) and coronal view (**C**) in the patient presented in Figure 2. The mediastinal changes are much more evident

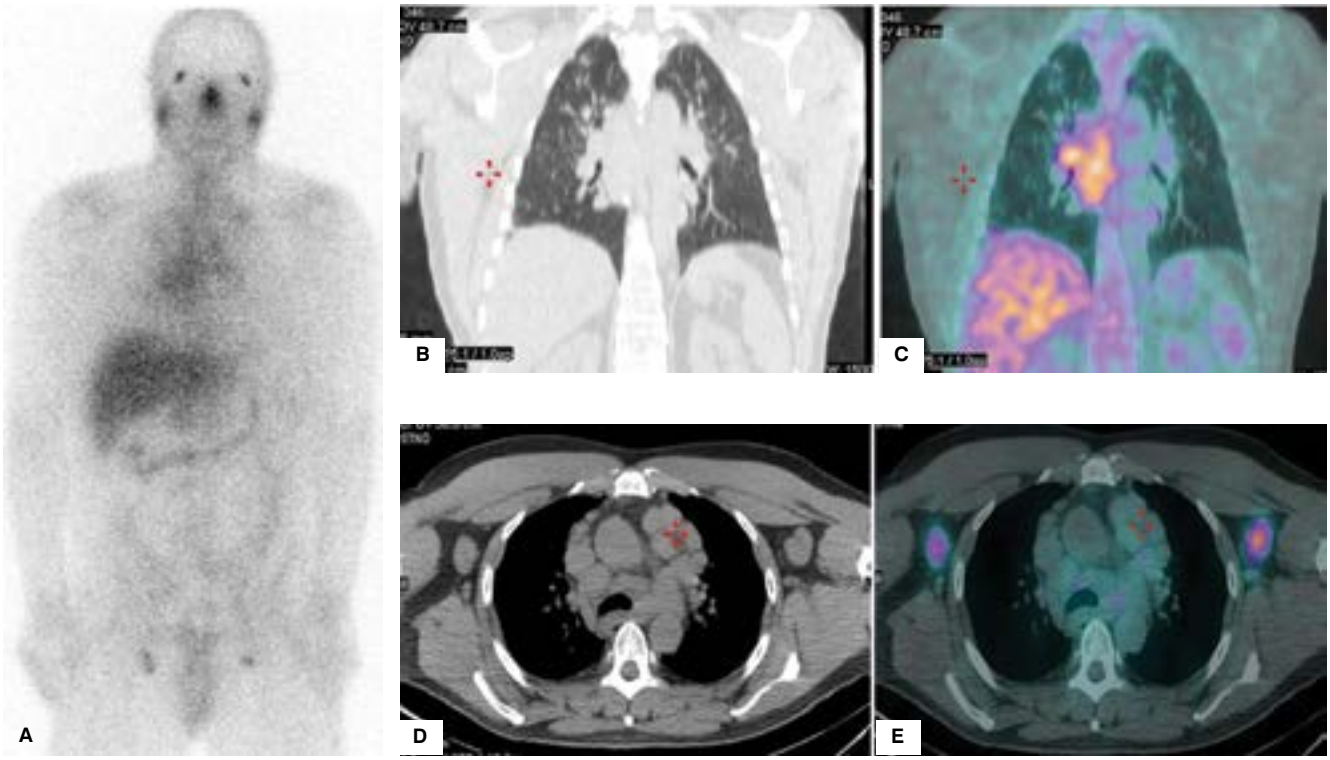

Figure 5. Whole-body (WB) ^{67}Ga scintigraphy in the AP view conducted in a 46-year-old male with active sarcoidosis (**A**) and a chest SPECT/CT scan in the coronal (**B** and **C**) and transverse (**D** and **E**) views in the same patient. Active pathology evident over the chest lesions: in the mediastinal lymph nodes and in both pulmonary hili. An evident panda sign in the lacrimal and salivary glands and the nasopharynx. Additionally, bilateral involvement of inguinal lymph nodes

Bones and joints

Involvement of joints, which may be acute or chronic, is reported in 15–25% of sarcoidosis patients. Acute articular involvement most commonly occurs in the early stages of the disease and may be its first manifestation. Clinically, it takes the form of arthralgia, arthritis or polyarthritis. Both wrists and ulnar joints are most commonly affected. The changes may migrate and are often accompanied by erythema nodosum [30].

Chronic joint disease associated with sarcoidosis is much less common or less frequently diagnosed due to its chronic nature and relatively mild clinical manifestations compared to other symptoms of active sarcoidosis. It may be accompanied by skeletal muscle and bone involvement. It shows predilection for sacroiliac joints and spondyloarthritis [31, 32].

On ^{67}Ga citrate scintigraphy, joint changes appear as areas of usually increased diffuse radiotracer uptake over the affected joint, usually including the articular capsule and synovium, usually with its hypertrophy and mild inflammation (Fig. 5).

Bone changes in sarcoidosis are often asymptomatic, although in some patients, they can cause severe pain. Bones of the hands and feet are most commonly affected [31]. Radiographic and CT images reveal osteosclerotic or osteolytic lesions (the so-called lacy pattern) and are not specific for sarcoidosis. It should

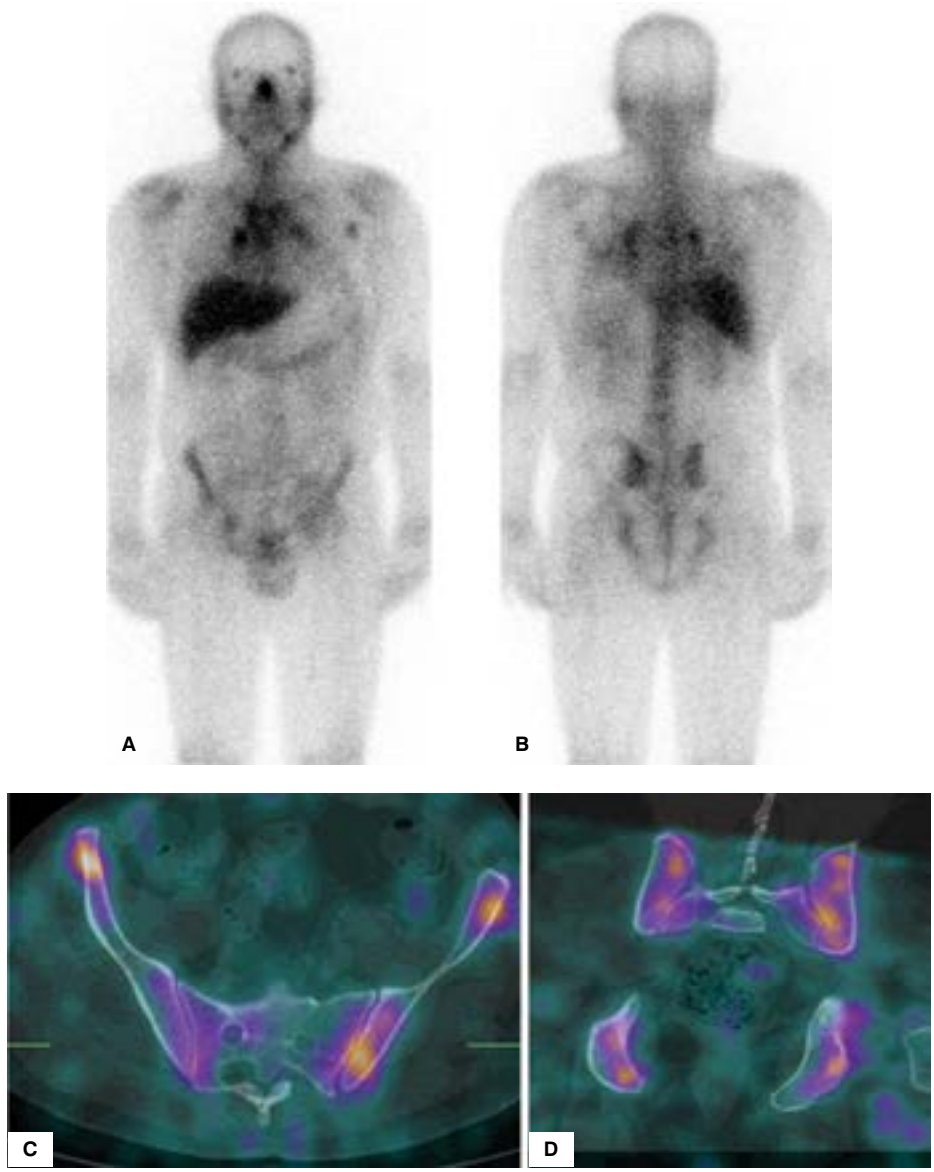

Figure 6. Whole-body (WB) ^{67}Ga scintigraphy in the AP (**A**) and the PA (**B**) views and a SPECT/CT scan in the transverse (**C**) and the coronal (**D**) views with SPECT and CT image fusion. Active sarcoidosis in a 38-year-old male. Evident involvement of the salivary glands, nasopharynx and lacrimal glands (the panda sign). Additionally, evident pathology in the mediastinum and both pulmonary hili: nodal lesions (the lambda sign). Diffuse, slightly increased radiotracer uptake over both lung zones. Bilateral involvement of inguinal lymph nodes. Additionally, involvement of sacroiliac joints in the course of sarcoidosis, more on the left than on the right

be emphasised that ^{67}Ga scanning reveals any infectious and inflammatory changes, including tuberculosis in the lungs and other organs [32].

Heart

Cardiac involvement is the most common cause of death in patients with sarcoidosis in Japan (58–85% of the cases). The death rate in other countries is lower (eg. 13–25% in the United States) [1]. Cardiac sarcoidosis may manifest clinically as rhythm and conduction disorders (ventricular tachycardia [VT] or atrioventricular [AV] block) and congestive heart failure [33]. Cardiac involvement most commonly occurs before the age of 50 years and is more common in women. While clinical manifestations of cardiac involvement occur in 2–7% of the patients, autopsy studies reveal sarcoid granulomas in 50% of the patients. It is therefore recommended that patients with both histologically detected extracardiac changes suggestive of sarcoidosis and clinical manifestations suggestive of cardiac involvement should be evaluated for this possibility [34].

The lesions in the heart are most commonly located in the interventricular septum and the inferior wall of the left ventricle. The scintigraphic diagnosis no longer depends on the use of ^{67}Ga citrate scintigraphy in detecting cardiac lesions as the sensitivity is low (0–36%) [35], although in symptomatic patients with episodes of VT or AV block, it can be up to 80% [36]. The specificity

is, however, very high (94–100%) [34]. Increased ^{67}Ga uptake by sarcoid granulomas may predispose to a good response to corticosteroids [37].

^{67}Ga scans performed in patients during treatment of sarcoidosis with systemic steroids reveal a decrease in radiotracer uptake by the lesions as a result of the treatment. This can be seen as early as 30 days into treatment [31, 32]. Such differences are not observed in heart scintigraphy with ^{201}Tl or ^{99m}Tc MIBI [37–39].

The recommended method for diagnosis of cardiac sarcoid is to perform ^{18}F-FDG, though this needs preparation with a low carbohydrate high glucose diet for 48 hours post scan. Focal uptake of ^{18}F FDG is seen in the presence of cardiac sarcoid but can only be used in the presence of normal myocardial perfusion.

Kidneys

Renal involvement in sarcoidosis may manifest by nephrolithiasis, nephrocalcinosis, nephrogenic diabetes insipidus, acute interstitial nephritis, granulomatous pseudotumour, and renal failure [1, 40]. There is little published data on the role of ^{67}Ga scintigraphy in the evaluation of renal changes. Isolated case reports indicate that patients with renal involvement do not reveal increased renal uptake of ^{67}Ga, which is contradicted by our yet unpublished findings of increased radiotracer uptake over the affected kidneys [40, 41].

Pathologically increased ^{67}Ga uptake by the kidneys in a female patient with sarcoidosis is illustrated in Figures 6A and 6B.

Has ^{67}Ga citrate imaging a future in the time of PET

There is increasing evidence that ^{18}F-FDG may be more accurate than ^{67}Ga citrate and pick up unsuspected sites of disease [42–44]. In a prospective comparative study 18 patients with sarcoid was imaged with both ^{18}F-FDG and ^{67}Ga citrate. The sensitivity of ^{67}Ga citrate in the lungs was 84% compared to 100 with ^{18}F-FDG. In extra-pulmonary disease the sensitivity of ^{67}Ga citrate was 48% compared to 90% with ^{18}F-FDG [45]. ^{18}F-FDG was also noted to predict clinical response to treatment faster than changes in ^{67}Ga citrate. European and North American guidelines confirm that the overall accuracy of ^{18}F-FDG PET in studies including 173 patients [46]. Whilst ^{18}F-FDG seems the more accurate test in many countries there is no reimbursement for PET in sarcoidosis so until that time it is unlikely to replace ^{67}Ga citrate imaging

Conclusion

^{67}Ga citrate scintigraphy has been used is sarcoidosis for over 30 years. Imaging is improved by the use of SPECT and SPECT-CT and can find and determine the activity of the patient's sarcoid in all but some cases of neurosarcoid and may be essential when the serum ACE is unhelpful. Many recent publications have compared the sensitivity and specificity of ^{18}FDG-PET/CT with those of ^{67}Ga, revealing superiority of the former. Until PET imaging in sarcoid is reimbursed. ^{67}Ga citrate scintigraphy remains the scintigraphic method of choice in sarcoid.

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