Chapter

Early Diagnosis of Sarcoidosis

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Abstract

Sarcoidosis is a rare unknown etiology multisystem inflammatory disease in which noncaseating granulomas (a collection of inflammatory cells) forms and growth in various organs, involving predominantly lungs, intrathoracic lymph node, skin, and eyes. Most commonly, affecting patients between 20 and 40 years old of age, although could be observed at any age (female predominance; rare in Asians). The areas of the body usually affected by sarcoidosis are lungs, skin, or lymph nodes; pulmonary and mediastinal involvement is seen in over 90% of patients. Less commonly eyes, liver, heart, and brain are involved. Any organ, however, can be affected. Early diagnosis of sarcoidosis can be difficult due to few signs and symptoms in its early stages, and when disease does occur, it may mimic other pathologies, and it is achieved through chest X-ray, computed tomography (CT)-high resolution CT (HRCT), gallium scans. Fluoro-deoxy glucose-positron emission tomography (FDG-PET) is another useful tool to assess the extent of disease and has a potential to evaluate the clinical management of patients responding or not to the treatment. Imaging gives, moreover, an important contribution to the evaluation of prognosis and follow-up.

Keywords: sarcoidosis, diagnosis, early diagnosis, chest X-ray, computed tomography (CT)-high resolution CT (HRCT), gallium scans, fluoro-deoxy glucose-positron emission tomography (FDG-PET)

1. Introduction

Sarcoidosis is a rare unknown etiology multiorgan granulomatous disease. The most affected organs by the pathology are the lungs, skin, or lymph nodes (especially intrathoracic lymph nodes). Less commonly are involved eyes, liver, heart, and brain, in a percentage ranging between 25 and 50%. Any organ, however, can be involved by sarcoidosis [1].

Signs and symptoms depend on which organs are affected and the presentation varies with the extent and severity of organ involvement [2].

The first state is *asymptomatic phase* (incidentally detected on chest imaging), approximately in 5% of patients. Then, *systemic complaints* are possible, which manifest itself with fever and anorexia (about 45% of cases). The most common condition (about 50% of cases) is *pulmonary complaints* with clinical presentation of dyspnea on exertion, cough, chest pain, and rarely hemoptysis. Pulmonary findings usually are normal but crackles may be audible; furthermore in a little part of patients exertional oxygen desaturation may be present [2].

Another possible clinical presentation is *Löfgren syndrome*, which consists in fever, bilateral hilar lymphadenopathy, erythema nodosum (an acute, nodular, cutaneous rash), and arthritis with polyarthralgias and is common in Scandinavian

patients, but quite uncommon in African-American and Japanese patients. *Cutaneous involvement* may be present not only with erythema nodosum associated with Löfgren syndrome, but also with lupus pernio, violaceous rash on the cheeks or nose (quite common) and maculopapular plaques (quite uncommon) [2].

Ocular involvement is also possible, which may lead to blindness for untreated anterior or (most frequent) posterior granulomatous uveitis, conjunctival lesions and scleral plaques.

Other uncommon possible manifestations are [2] *nervous system involvement* with lymphocytic meningitis (rare), cranial nerve palsies, hypothalamic/pituitary dysfunction (rare) with diabetes insipidus and myelopathy; *heart failure* from cardiomyopathy (rare) or heart block and sudden death; *osseous involvement* with arthritic syndromes; *blood abnormalities*: anemia, leukopenia, thrombocytopenia and hemolytic anemia with or without splenomegaly (without splenomegaly may reflect bone marrow involvement); *gastrointestinal and genitourinary involvement* (rare): hepatomegaly, cholestasis, portal hypertension, Crohn's disease, pancreatic involvement, nephrocalcinosis, vulva itchiness and male infertility (rare); *exocrine and endocrine manifestations* with hyperprolactinemia, amenorrhea, galactorrhea, or nonpuerperal mastitis in women; hypercalciuria and hypercalcemia likely result from the increased 1,25-dihydroxy vitamin D production (rare) [2].

2. Diagnosis

The diagnosis is based on clinical and imaging features, histological confirmation, and exclusion of other diseases that can create similar histopathological and clinical findings.

Imaging is mandatory for diagnosis of sarcoidosis and includes as follows:

- chest radiography (is fundamental for a first evaluation);
- routine chest computed tomography (CT), usually high-resolution CT (HRCT) scanning of the chest [2] (has a significantly superior detection rate to chest X-ray for mediastinal and pulmonary parenchymal changes and is also useful to identify active alveolitis or fibrosis), and the agreement between findings and biopsy yield [2]; and
- fluoro-deoxy glucose-positron emission tomography (FDG-PET) combined with CT-scan (is fundamental to determinte the extent of organ involvement and the disease activity and to evaluate the response to pharmacological therapy) [3].

2.1 Chest X-rays and HRCT scan

A correct staging of pulmonary sarcoidosis based on radiological stage of the disease is necessary to evaluate the sarcoidosis prognosis [1]. Particularly, there are five radiologic stages (forms) of intrathoracic sarcoidosis on chest radiography [2–4] as follows:

- Stage 0: normal chest radiographic findings;
- Stage I: bilateral mediastinal lymphadenopathy (hilar lymphadenopathy);

- Stage II: bilateral mediastinal lymphadenopathy (hilar lymphadenopathy) and infiltrates with parenchymal lesion;

- Stage III: infiltrates alone, parenchymal disease only; and

- Stage IV: pulmonary fibrosis.

HRCT, however, is more accurate in identifying the different manifestations of pulmonary sarcoidosis as well its complications, but we are still searching for an accepted HRCT scoring system.

Main findings of HRCT sarcoidosis are as follows:

- hilar and/or mediastinal lymph node enlargement (sometimes with calcifications), classically bilateral hilar and right paratracheal nodal enlargement (Garland triad); left paratracheal and aortopulmonary nodes can be also enlarged. Atypical pattern of nodal enlargement can be observed in patients older than 50 years old of age;

- pulmonary interstitial nodules (micro or macronodules) in a perilymphatic distribution;

- thickening of the peribronchovascular interstitium;

- pulmonary ground glass opacity;

- consolidation or large nodular opacities;

- coarse linear opacities, interlobular septal thickening, honeycombing, and cysts;

- architectural distortion, superior hilar retraction, or traction bronchiectasis; and

- pulmonary fibrosis (Stage IV) with linear bands of fibrosis from hila to all directions with distortion of normal lung architecture; honeycombing is rare, only in patients with severe fibrosis, mainly in the middle and upper lung zones and with subpleural involvement.

Pleural disease is rare and may be observed when disease is extensive.

The diagnosis of pulmonary sarcoidosis requires a compatible clinical picture supported by radiologic (X-rays chest and/or HRCT of lungs) and pathologic data (pulmonary functional tests and laboratory tests). But for a certain diagnosis, biopsy is required in most cases, and endobronchial biopsy via bronchoscopy is often performed; its results may be positive even in patients with normal chest radiographs. The central histologic finding is the presence of noncaseating granulomas with special stains negative for fungi and mycobacteria [2].

2.2 Cardiopulmonary and laboratory tests

Pulmonary function tests are also routinely used in sarcoidosis for early diagnosis and follow-up. They include the evaluation of forced vital capacity (FVC), forced expiratory volume in one second (FEV1), the total lung capacity determination (TLC), vital capacity (VC), residual volume (RV) associated with body

plethysmography, and a carbon monoxide diffusion capacity test of the lungs for carbon monoxide (DLCO).

Sarcoidosis is commonly considered a restrictive disorder, but more recent studies are demonstrating some opposite results.

Restrictive disorders (infiltrative) are characterized by a reduction in lung volume, with difficult in taking air inside the lungs and decreased total lung capacity. Other restrictive disorders are chest wall disorders (neuromuscular, e.g., polio, kyphoscoliosis, pleural disease, and severe obesity); chronic interstitial and infiltrative disease (pulmonary fibrosis, pneumoconioses, granulomatous diseases, pulmonary eosinophilia, and pulmonary alveolar proteinosis); Acute diseases (ARDS and infections).

Typical symptoms are dyspnea, tachypnea, end inspiratory crackles without airway obstruction, honey-comb lung, secondary pulmonary hypertension, and cor pulmonale.

In restrictive pulmonary disease, lung volume is decrease, but flow rate is normal as follows:

- TLC decrease;
- RV decrease;
- FEV1 decrease;
- FVC decrease;
- FEV1/VC is equal to or more than 70%;
- DLCO decrease; and
- compliance decrease.

Usually, a significant correlation between radiological stage and pulmonary function tests is found.

Cardiopulmonary exercise testing (CPET) is another useful tool to identify and quantify the extent of pulmonary involvement and also may suggest cardiac involvement that otherwise is not evident [2]. It provides an integrative assessment of involving the pulmonary, cardiovascular, muscular, and cellular oxidative systems and involves measurements of gas exchange as follows:

- primarily oxygen uptake (VO_2): VO_2 at maximal exercise (peak VO_2) is considered the best index of aerobic capacity and cardiorespiratory function;
- carbon dioxide output (VCO_2);
- minute ventilation; and
- anaerobic threshold (lactic acid).

In patients who have normal gas exchange at rest, CPET unmasks the gas exchange abnormalities.

Laboratory tests can identify some serum abnormalities as high blood calcium with a normal parathyroid hormone level and hypercalciuria, or elevated levels of angiotensin converting enzyme (ACE) in the blood [1].

2.3 FDG-PET

FDG-PET is a metabolic imaging technique and provides an insight into metabolism of this disease. It relies on the principle of increased accumulation and metabolism of glucose by the malignant or inflammatory areas. FDG is a radioactive analog of glucose that enters cells through the same receptors that are involved in glucose uptake and gets converted into FDG 6 phosphate by the enzyme hexokinase, similar to glucose metabolism by the glycolytic pathway. FDG 6 phosphate is not metabolized further and gets entrapped in the cell. Tissues with high glucose metabolism such as brain tissue gray matter, cancer cells, and inflammatory changes show increased fluorine – 18 fluorodeoxyglucose ((18) F-FDG) accumulation on PET imaging.

As a key component of the inflammatory process, inflammatory cells consume glucose at a much higher level than peripheral noninflammatory cells, leading to higher glucose metabolism and increased uptake of (18) F-FDG within inflammatory foci. Therefore, the level of FDG uptake is proportional to the level of glycolysis in the tissue. This explains the mechanism of increased uptake of FDG in malignancy, inflammatory, and infectious processes [3].

The role of fluoro-deoxy glucose-positron emission tomography (FDG-PET) scanning in assessing the extent of disease spread or metastasis and its utility in assessing response to treatment in the form of chemotherapy or radiotherapy is well defined in many neoplastic conditions, and its utility has also been recognized in certain inflammatory conditions, like sarcoidosis.

During the last years, FDG-PET imaging has been shown to have a central role to detect inflammation activity and has become a novel fundamental tool, playing also an increasingly important role in the management of patients with any inflammatory conditions. FDG-PET can afford precious information in patients with pulmonary and extrapulmonary sarcoidosis and has become a centerpiece for testing the efficacy of different therapies [5]. In difficult clinical cases, it can also be useful to plan the site of biopsy in order to determinate a histopathological diagnosis.

A combined modality using FDG-PET and CT scanning (FDG-PET/CT) has been found to be more sensitive than PET in diagnosing. FDG-PET and a combination of this procedure with computed tomography scanning (FDG-PET/CT) has gained prominent attention in patients with sarcoidosis over the last two decades as a means to assess disease activity and response to therapy. Radionuclide imaging techniques have increasingly been used in the evaluation of organ involvement in sarcoidosis. F-FDG-PET/CT scanning has received increasing attention in last several years [3].

The usefulness of F-FDG-PET/CT is to identify the disease activity and the extent of organ involvement in patients affected by sarcoidosis; F-FDG-PET/CT is still useful to determinate its utility in the evaluation of response to drug treatment, comparing the agreement between clinical, radiological (with chest radiography and/or HRCT of lungs), and metabolic indices (FDG-PET/CT) of disease activity.

Monitoring disease activity in sarcoidosis still remains a clinical goal as there is no gold standard. The term "activity" in sarcoidosis means ongoing inflammation that necessitates appropriate drug therapy [3]. PET imaging is a new tool to assess the metabolic activity, but there is still limited data on the role of serial PET scans in monitoring the sarcoidosis activity [6].

Conventional imaging techniques used in sarcoidosis are chest radiography and CT. Even though chest radiography and HR-CT are still the fundamental for diagnosing pulmonary involvement, F- FDG PET appears to be superior to both techniques to identify active sites of disease. F- FDG- PET also correlates well with serum biomarkers, such as soluble interleukin-2 receptor in symptomatic patients,

and in lung parenchyma correlates with decrease of lung function values over time. Moreover F-FDG-PET even visualizes active lesions (in pulmonary and extrapulmonary sites) in the context of normal serum biomarkers. Also in cardiac involvement in sarcoidosis, FDG-PET is a promising tool associated or complementary to magnetic resonance imaging, especially in planning treatment [7].

Magnetic resonance imaging (MRI) is the main imaging method for diagnosis and follow-up of neurosarcoidosis and for evaluation of cardiac involvement. However, these mentioned methods are unable to identify active inflammation; instead, FDG-PET/CT has an important advantage in the detection of reversible, inflammatory, active granulomatous disease in patients with sarcoidosis [8].

PET provides high-resolution three-dimensional images of the whole body that facilitates precise localization of abnormalities. Localization is enhanced with PET/CT. Fluorodeoxyglucose is extremely sensitive with a high negative predictive value; however, the limiting factor of the test is specificity [9, 10]. (18) F-FDG PET/CT allows to obtain a complete morphofunctional cartography of inflammatory active localizations and to follow treatment efficacy in patients with sarcoidosis, particularly in atypical, complex, and multisystemic forms.

Disseminated lesions should alert clinician to consider sarcoidosis-lymphoma syndrome (SLS) or tuberculosis in the differential diagnosis. However, histological confirmation with biopsy will be required in such complex cases.

2.3.1 Pulmonary sarcoidosis

Pulmonary sarcoidosis is the main localization site in the majority of patients (>90% cases) typically with bilateral mediastinal (hilar) lymphadenopathy diagnosed on chest radiography; and its severity ranges from asymptomatic involvement of mediastinal lymph nodes (mostly hilar) to progressive pulmonary fibrosis and chronic respiratory failure that is unresponsive to therapy. The most common clinical presentations of pulmonary involvement are cough and dyspnea.

The diagnosis of pulmonary sarcoidosis requires a compatible clinical picture supported by radiologic (X-rays chest and/or HRCT of lungs) and pathologic data (pulmonary functional tests and laboratory tests). A recent innovation in diagnosing of pulmonary sarcoidosis is endobronchial ultrasound that increases the yield of transbronchial needle aspiration of hilar and/or mediastinal lymph nodes. F-FDG-PET is highly sensitive in detecting occult sites of disease and is very useful in guiding biopsies of these sites. A combined imaging modality using both FDG-PET and CT scan is more sensitive than PET alone and is now the main proceeding of care in patients needing biopsies of active lesions [11].

For staging of pulmonary disease on chest radiograph, Scadding stages (**Figure 1**) are still widely used depending on the presence of hilar lymph node enlargement and pulmonary opacities on chest radiography as follows:

- Stage 0: normal chest radiographic findings;
- Stage I: bilateral mediastinal lymphadenopathy (hilar lymphadenopathy);
- Stage II: bilateral mediastinal lymphadenopathy (hilar lymphadenopathy) and infiltrates with parenchymal lesion;
- Stage III: infiltrates alone, parenchymal disease only; and
- Stage IV: pulmonary fibrosis.

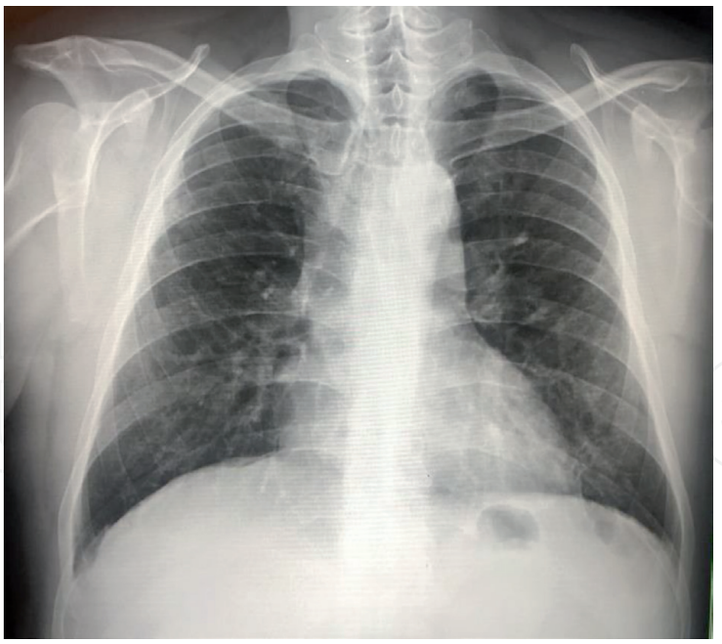

Figure 1.
Chest X-rays: reticulonodular pattern with perihilar distribution.

HRCT, however, is still the gold standard imaging modality for primary diagnosis of sarcoidosis and is more accurate than chest X-rays, which is the first imaging level, in identifying the different manifestations of pulmonary sarcoidosis as well its complications. F-FDG-PET, instead, is a new highly sensitive tool in detecting occult sites of disease at the chest CT scan.

HRCT most common signs are: micronodules (*miliary sarcoidosis*) and macronodules with perilymphatic distribution, for the most part, symmetrically in the middle zones of the lungs; rarely solitary opacity (*alveolar sarcoidosis*) and with a mass-like presentation (1–4 cm in diameter) may mimic consolidation containing air bronchograms, from confluence of many smaller nodules with irregular margins and presenting as *sarcoid galaxy sign* (mass-like region from confluence of numerous smaller granulomas with a central core and multiple peripheral nodules; central cavitation may occur, and the lesion can be surrounded by ground-glass opacity), more frequent in patients older than 50 years of age of presentation; linear opacities, mostly, in the upper and middle parts of the lungs, most common of stage II or III of disease; and ground glass opacities represent interstitial sarcoid granulomas under resolution rather than alveolitis, above all, located in the lower zones of the lungs [12] (**Figures 2–6**).

Functional imaging of sarcoidosis nowadays is performed with (18) F-FDG PET-CT, which improves anatomical localization of sites of abnormality and has a relatively short delay time between radiotracer injection and image acquisition. (18) F-FDG PET-CT can identify disease activity better than conventional makers in a large proportion of patients (very high sensitivity about 80–100%). In patients with positive HRCT but no parenchymal fluorodeoxyglucose F18 uptake, pay attention to initiation or intensification of immunosuppressive treatment [1, 13].

2.3.2 Cardiac sarcoidosis

Cardiac involvement in sarcoidosis is uncommon (5%) and is associated with very poor prognosis [1], because of many complications of cardiac as follows: ventricular tachycardia, conductional abnormalities, congestive heart failure, and sudden cardiac death. Moreover, cardiac sarcoidosis (CS) is an important prognostic factor in patients with this disease. However, early diagnosis of CS in still

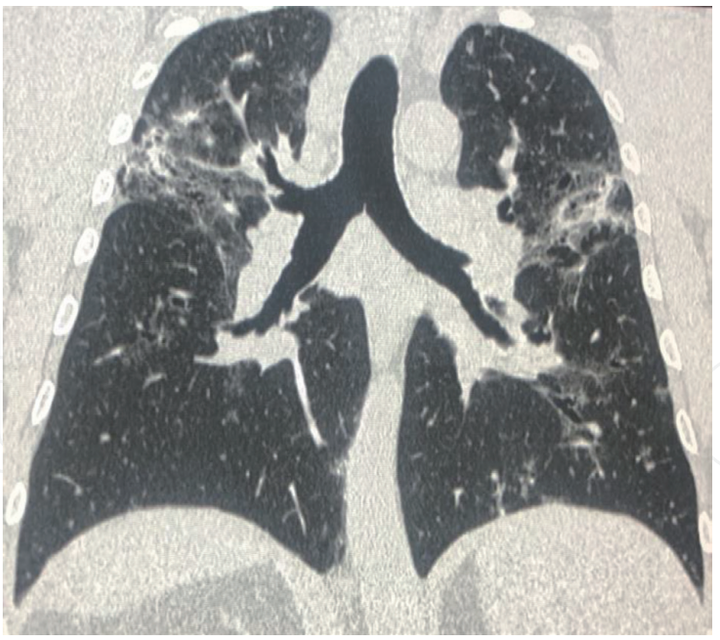

Figure 2.
HRCT: coarse linear opacities, architectural distortion, superior hilar retraction, and traction bronchiectasis.

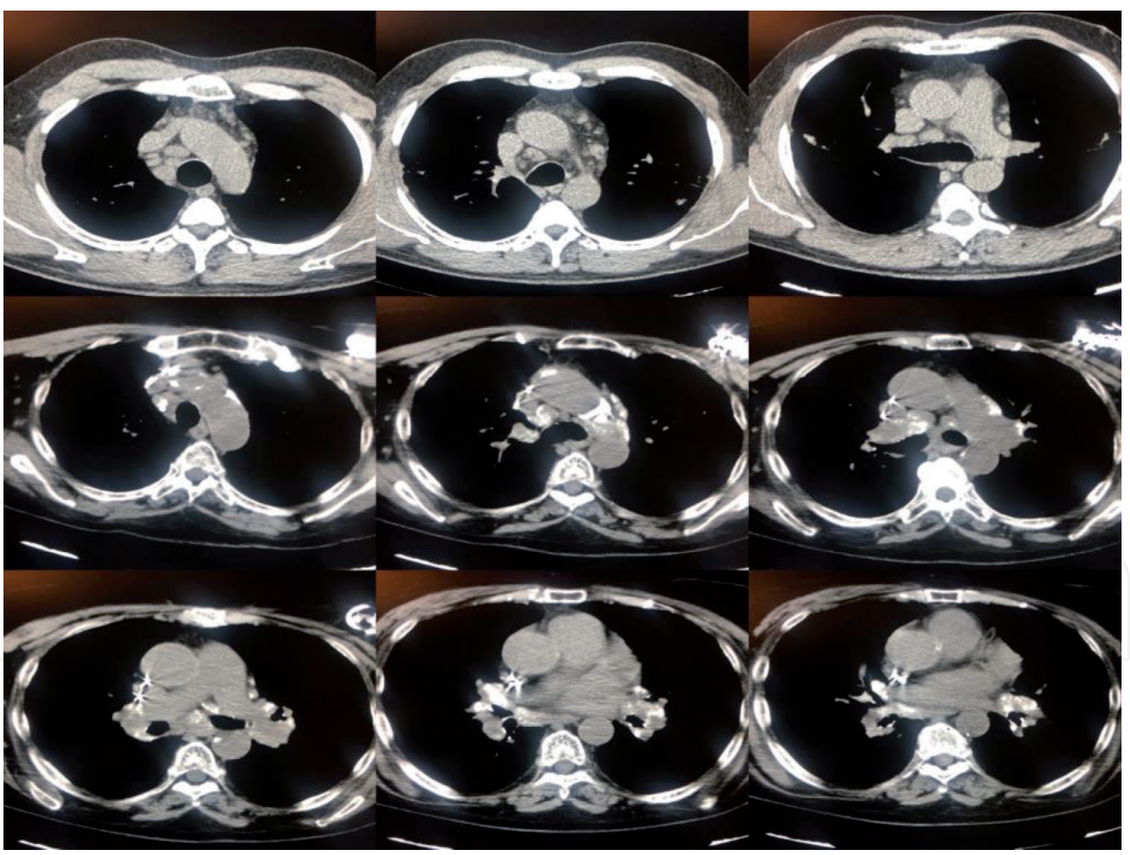

Figure 3.
HRCT: hilar and mediastinal lymph node enlargement, sometimes with calcification.

really difficult due to the nonspecific clinical manifestations of the disease, inhomogeneous myocardial involvement, and the limited diagnostic yield of diagnostic tests. Therefore, there are no standardized tests for the early diagnosis of cardiac sarcoidosis, although early detection of CS is very important for effective treatment. Besides a history and physical examination, electrocardiography (ECG) and transthoracic echocardiography are useful for cardiac evaluation.

Staging	Description
0	Absence of chest X-ray abnormalities
1	Bilateral hilar lymphadenopathy that may be accompanied by right paratracheal and aortopulmonary window adenopathy
2	Bilateral hilar lymphadenopathy and parenchymal infiltration with a bilateral symmetric micronodular or reticulonodular pattern with predominant perihilar distribution, in middle and upper lung fields
3	Parenchymal infiltration without hilar adenopathy
4	Fibrosis with evidence of reticular pattern with traction bronchiectasis, masses causing architectural distortions, or honeycomb cysts, predominantly in the upper fields

Figure 4.
Scadding stages for staging of pulmonary disease on chest X-rays.

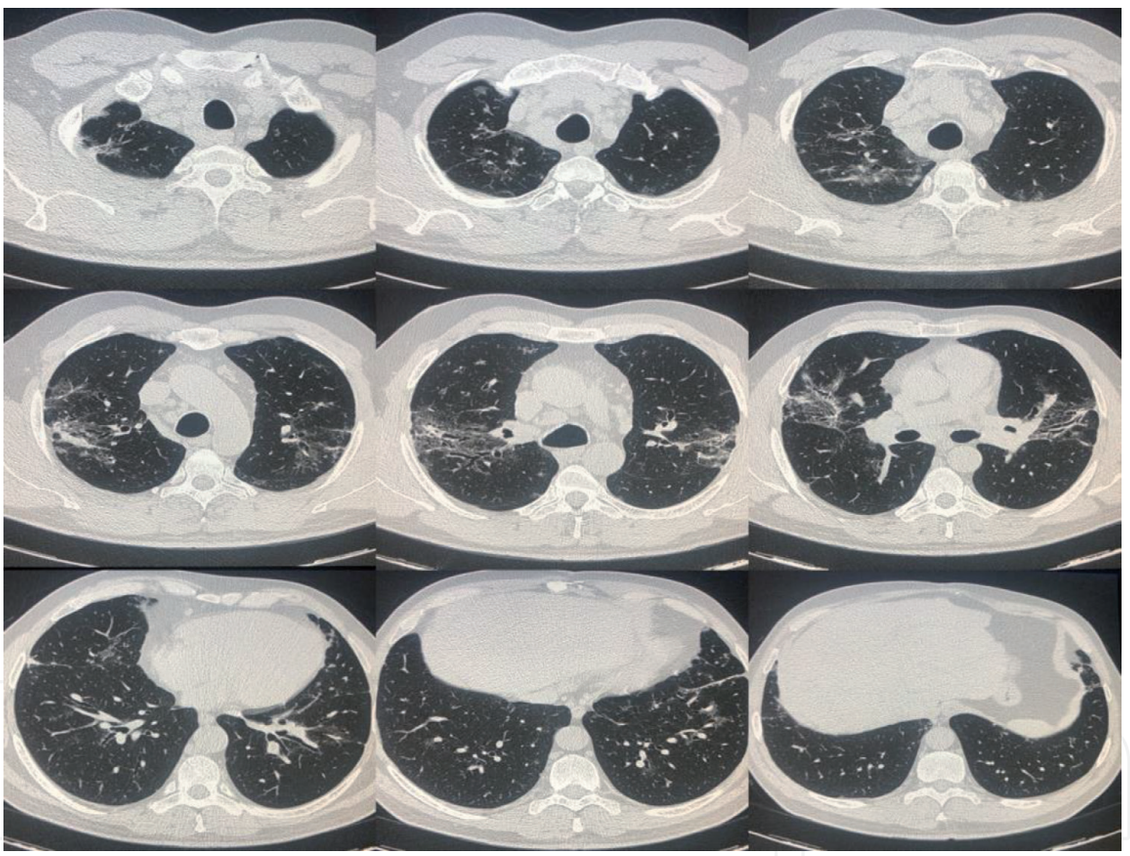

Figure 5.
HRCT: micronodules and macronodules with perilymphatic distribution, for the most part, symmetrically in the middle zones of the lungs; pulmonary ground glass areas; thickening of the peribronchovascular interstitium; coarse linear opacities and interlobular septal thickening; and architectural distortion, superior hilar retraction, and traction bronchiectasis.

CS can be diagnosed using (18) F-FDG-PET/CT (PET) and cardiovascular magnetic resonance (CMRI) that nowadays have been emerged as well for this purpose in recent clinical practice [1]. Imaging modalities that can both identify disease and predict response to therapy are supreme to improve management of cardiac sarcoidosis.

(18) F-FDG-PET has many practical advantages in identifying disease activity and monitoring treatment response in patients with CS [1]. In (18) F-FDG, increased uptake, indicating active inflammation, can be seen in CS in the myocardial wall [14, 15].

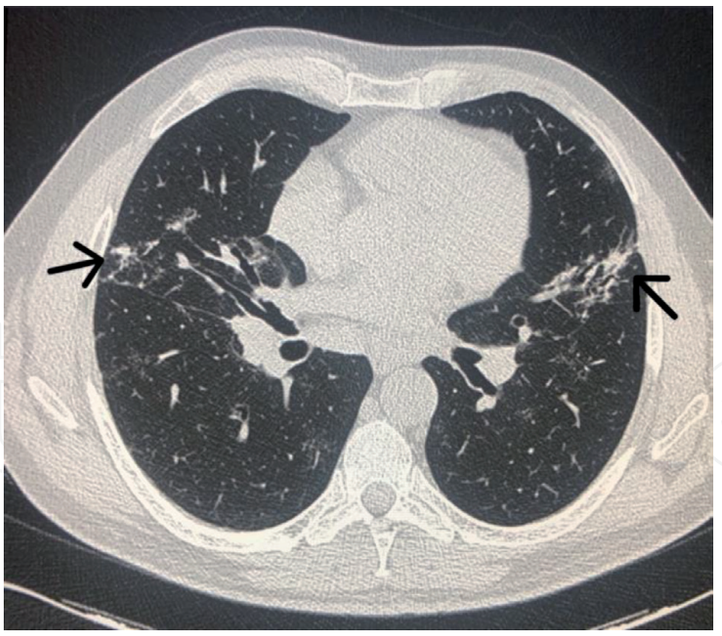

Figure 6.
Sarcoid galaxy sign*: mass-like region from confluence of numerous smaller granulomas with a central core and multiple peripheral nodules (arrows).*

Focal hypermetabolic activity or a focal increase of activity with a diffusely increased background on (18) F-FDG- PET is characteristic for cardiac sarcoidosis but this technique has some limitations. Normal myocardial cells use glucose as one of main energy substrates [14], and so physiologic (18) F-FDG uptake may be found in myocardium of healthy subjects; also papillary muscles and lateral wall of left ventricle may also show normal uptake of (18) F-FDG. Then, special patient preparation is, therefore, needed prior to F-FDG-PET scan in patients with sarcoidosis, with three different approaches: prolonged fasting, dietary modification with high-fat diet and i.v. administration of unfractionated heparin, trying to suppress (18) F-FDG uptake promoting fatty acid metabolism.

In cardiac sarcoidosis, the combined use of FDG-PET/CT and CMRI may provide optimal detection of the disease by enabling the differentiation between patients with active granulomatous inflammation and those with fibrous lesions. CMRI is a sensitive technique to assess the locations and extent of disease. Myocardial sarcoidosis may present on CMRI as segmental wall motion abnormality, focal wall thickening or thinning, or nodules with a patchy distribution [3].

On CMRI scan, in CS, we can find late gadolinium enhancement (LGE) related to the presence of fibrous granulomatous tissue, areas with an increased signal on T2-weighted sequences consistent with myocardial edema and with hypointensity suggesting fibrosis [10]. Recently, the value of LGE on CMRI, which allows visualization of even minute amounts of myocardial damage, has been emphasized in diagnosing CS, and it might be a promising tool for determining the prognosis of patients with biopsy-proven extracardiac sarcoidosis [1, 16].

However, it is not easy to differentiate between active and inactive sarcoidosis lesions, which is important for patient management. In addition, cardiac MRI is generally contraindicated in patients with pacemakers or implantable cardioverter defibrillators (ICDs).

2.3.3 Neurosarcoidosis

Nervous system involvement is not an uncommon manifestation of sarcoidosis and can be clinically symptomatic neurosarcoidosis, which occurs in 5–16% of

patients with sarcoidosis, and subclinical neurosarcoidosis, with an incidence of subclinical disease that may be higher [17–19]. The neurological manifestations depend on the areas of the nervous system involved.

The most commonly involved part are cranial nerves, though any part of neuroaxis can be affected. The facial nerve is the most common cranial nerve involved presenting with facial palsy, and the second most common nerve affected is the optic nerve presenting with diplopia or impaired visual acuity [3, 19].

Neurosarcoidosis in the brain can present with leptomeningeal and intraparenchymal infiltration of granulomas resulting, for example, in cranial nerve palsies, basal meningitis, and endocrine dysfunction. It can cause also peripheral neuropathies (such as sensorimotor polyneuropathy, radiculopathy, and myopathy) [3]. For all of these reasons, neurosarcoidosis is an important cause of morbidity and mortality in patients with sarcoidosis.

Diagnosis and management of patients with neurosarcoidosis are still challenging because the gold standard is tissue-proven biopsy but, in most cases of nervous system involvement, it is really difficult to obtain [3, 18].

Contrast-enhanced MRI for the detection of intracranial and spinal cord lesions is the imaging modality of choice for evaluating neurosarcoidosis. However, the findings on MRI are often nonspecific.

In central nervous system (CNS) involvement, the hypointensity of signal of the dural and of parenchymal lesions in T2-weighted sequences is useful to identify sarcoidosis. Contrast-enhanced MRI is a sensitive tool in the detection of CNS inflammation but has a low specificity, making the correct diagnosis of neurosarcoidosis still a clinical challenge.

The most common imaging finding in T2-weighted sequences are hyperintense parenchymal lesions (gray matter) and in T1-weighted sequences, after intravascular administration of contrast agents, are meningeal enhancement (basilar meningitis involving of cranial nerves is thought to be a common phenomenon), and swelling and/or enhancement of optic nerves or chiasm maybe with associated visual loss. Other imaging presentations include intracranial masses simulating neoplasms and vasculitic infarcts. Moreover, in a small part of cases, brain MRI can be normal. Cervical or thoracolumbar spine abnormalities, such as spinal cord swelling, meningeal enhancement, and parenchymal contrast enhancing lesions, can also be detected [20].

Electromyography (EMG) can be an additional useful tool for peripheral neuropathy evaluation, although the findings are not specific.

The usefulness of (18) F-FDG in neurosarcoidosis is poor because of the physiologic uptake of (18) F-FDG activity in normal gray matter. However, granulomatous inflammation shows hypermetabolism, whereas neuronal damage presents as hypometabolism. (18) F-FDG-PET may reveal additional occult lesions amenable to biopsy in some patients with inaccessible intracranial lesions, but the literature on (18) F-FDG and neurosarcoidosis is very limited.

2.3.4 Bone sarcoidosis

Bone involvement is a rare manifestation of sarcoidosis usually associated with pulmonary findings. The exact prevalence of bone sarcoidosis is still not known, depending on the studied population and the used diagnostic tools [21]. The prevalence of bone sarcoidosis is between 3% and 5%, above all affecting the phalanges [22].

Both (18)F-FDG-PET/CT and conventional MRI are sensitive in detecting sarcoidosis bone lesions but are not always reliable in differentiating sarcoidosis bone lesions from metastatic disease, thus often requiring bone biopsy [17].

(18) F-FDG-PET/CT is highly sensitive in detecting granulomatous bone marrow infiltration, but an increased (18) F-FDG uptake can mimic metastatic

disease, reducing the specificity of (18) F-FDG-PET/CT when both sarcoidosis and a tumor, which may develop bone metastases, occur in the same patient. Bone assessment in sarcoidosis patients is also performed using MRI, commonly relying on T1-weighted and T2-weighted images. However, routine MRI is not reliable in differentiating sarcoidosis bone lesions from metastatic disease [17].

Multifocal skeletal sarcoidosis may present as a false positive for bone metastases on (18) F-FDG PET/CT since granulomatous bone marrow infiltration may have an uptake of (18) F-FDG, which mimics that of metastatic disease. When false positive findings on (18) F-FDG PET/CT cannot be totally excluded, biopsy or MRI may represent the second choice to achieve diagnosis. Since conventional MRI may not be accurate in distinguishing between sarcoidosis and metastatic bone lesions, it is possible to perform diffusion whole-body MRI: T1-weighted, T2-weighted STIR, and diffusion-weighted imaging (with different *b* values) [17]. The latter is able to evaluate microscopic tissue water motions average at the millimeter scale of MR images. The ADC value reflects the degree of freedom of water movement at the cellular level, which is determined by architectural tissue properties such as cellular density, cellular arrangements, vascularity, extracellular space tissue viscosity, and nuclear/cytoplasmic ratio. Water movement is impeded in many tumors because of their high cellular density and T2 relaxation times, resulting in high signal intensity on diffusion-weighted images and low ADC values [1].

On conventional imaging the pelvic bone lesions appeared with a signal pattern not specific for sarcoidosis bone lesions or metastatic disease (low signal on T1-weighted images and high signal on STIR images). On diffusion-weighted imaging the pelvic bone lesions showed high signal, which is often seen in bone metastases, but the ADC (<700 $\mu m^2/s$) was too low to be suspicious for metastases from breast cancer [1], which enables to differentiate normal bone marrow from malignant marrow [17, 23, 24].

3. Conclusions

Imaging gives an important contribution to the assessment of prognosis and follow-up in sarcoidosis. FDG-PET/CT is routinely used for the diagnosis, staging, and therapeutic assessment of several malignancies and becomes nowadays a relevant tool for the management of several infectious and inflammatory diseases, such as sarcoidosis. PET can also be a useful tool for the diagnosis of sarcoidosis by identifying potential biopsy sites in organs that might be accessible. FDG-PET/CT plays a crucial role in sarcoidosis disease, especially for the diagnosis of potentially rare extrapulmonary involvement, and is also an interesting tool for assessing therapeutic efficacy of inflammatory diseases and for management of patients.

Conflict of interest

The author declares no conflict of interest.

Thanks

Dedicated to all people who made my dreams come true.

To my beloved parents for the unwavering faith that I would have achieved all the goals I had set for myself.

To those who love me, and loved me, and believed in me, giving me the strength to always go ahead and never give up, standing by my side even when things became difficult.

Often against the wind, but never against my heart.

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