

## THE VALUE OF CHEST RADIOGRAPH AND COMPUTED TOMOGRAPHY IN PULMONARY SARCOIDOSIS

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**ABSTRACT.** Imaging makes a significant contribution to the diagnosis, prognosis and follow-up in sarcoidosis. Despite its increasing use, the role of computed tomography (CT) scanning in patients with known or suspected pulmonary sarcoidosis is still undefined. This review aims to compare the utility and limitations of chest radiograph and CT in patients with pulmonary sarcoidosis, with regards to the most critical clinical issues such as the diagnostic sensitivity, the differential diagnosis, and the prediction of the disease reversibility. (*Sarcoidosis Vasc Diffuse Lung Dis* 2014; 31: 108-116)

**KEY WORDS:** Sarcoidosis, computed tomography, diagnosis

### INTRODUCTION

Sarcoidosis is a chronic systemic inflammatory disorder of unknown etiology, characterized histologically by the presence of non-caseating epithelioid cell granulomas at disease sites (1). Sarcoidosis affects almost universally the lungs and the lymphatic system, with highly variable clinical manifestations, disease behavior and prognosis. The diagnosis is established in the presence of compatible clinical and radiological findings, histological demonstration of non-caseating granulomas, and exclusion of other known causes of granulomatous inflammation.

Imaging makes a significant contribution to the appraisal of diagnosis, prognosis and follow-up in sarcoidosis, but many aspects remain undefined. In typical cases, chest radiograph may be sufficient to establish the diagnosis with little margin of error and computed tomography (CT) is not necessary. On the other hand, CT, which is better able to detect subtle parenchymal

abnormalities and otherwise hidden mediastinal lymph node enlargement, plays a critical role in a number of scenarios: atypical clinical and/or radiographic findings; normal or near normal chest radiograph but clinical suspicion of sarcoidosis; unexpected or unexplained changes in symptoms; and detection of complications (i.e., mycetoma formation, vascular involvement, bronchial stenosis). In addition, CT findings are often atypical and unfamiliar to most radiologists (sarcoidosis mimicking other lung diseases and vice versa).

The aim of our review is to discuss the utility and limitations of chest radiograph and CT in patients with pulmonary sarcoidosis, with emphasis on the more difficult imaging aspects of sarcoidosis.

### CLINICAL UTILITY OF CHEST RADIOGRAPH AND CT

A number of radiographic staging systems for sarcoidosis have been reported but the most widely adopted is that developed by Scadding more than five decades ago (2) and modified by DeRemee in 1983. This staging system provides important prognostic information (it may predict the likelihood of remission or irreversible abnormalities) although drawbacks in

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the reproducibility of reading have recently been underlined (3). Untreated stage I patients reach out complete resolution of both symptoms and radiographic findings in up to 50-90% of the cases but this percentage decreases to 30-70% for stage II, 10-20% for stage III and 0% for stage IV disease (4).

Imaging may also play an important role in the diagnosis of sarcoidosis. For instance, in patients presenting acutely with fever, bilateral hilar lymphadenopathy and erythema nodosum with or without periarticular inflammation of the ankles (Löfgren's syndrome), the presence of typical imaging features allows a correct diagnosis to be made without the need of histological confirmation (5,6).

Furthermore, routine radiological follow-up of pulmonary sarcoidosis is almost invariably by chest radiography, which allows monitoring of parenchymal and nodal disease as well as the detection of supervening fibrosis with minimal exposure of the patient to radiation.

The role of chest CT in sarcoidosis remains not fully defined. Once the diagnosis is established, CT offers no particular advantage to radiographs. Conversely, a number of circumstances should prompt referral for CT:

- Atypical clinical or radiographic findings (e.g., monolateral hilar enlargement or subtle parenchymal changes)
- Negative chest radiograph but clinical features of the disease

- detection of complications (e.g. mycetoma, bronchial stenosis or pulmonary hypertension)
- pre-transplant evaluation of a patient with end-stage pulmonary sarcoidosis

The use of CT in clinical management of sarcoidosis is broad. CT may guide transbronchial biopsy, thus enhancing its diagnostic yield. In this regard, disease extent on CT correlates with the positive predictive value of trans-bronchial biopsy (7,8). CT may also corroborate the interpretation of functional data by quantifying the involvement of each thoracic compartment in terms of both parenchymal and airways changes. This information is less likely to be captured by chest radiograph. Conversely, CT is not recommended in routine follow-up mainly due to the radiation exposure that represents a significant concern in younger patients. Nevertheless, CT may identify progression to fibrosis and add crucial information to those obtained by pulmonary function test, with potential therapeutic and prognostic implications. Therefore, the use of follow-up CT should always be tailored based on patient age and clinical features (9)

#### SENSITIVITY OF CHEST RADIOGRAPHY VS. CT

Conventional chest radiography should be performed in all patients with sarcoidosis. It is abnormal in the vast majority of cases and is often the first in-



**Fig. 1.** 35-year-old man from Senegal with negative chest X-ray. (a). CT scan shows some micronodules adjacent to the fissure and in the right upper lobe (arrows b).

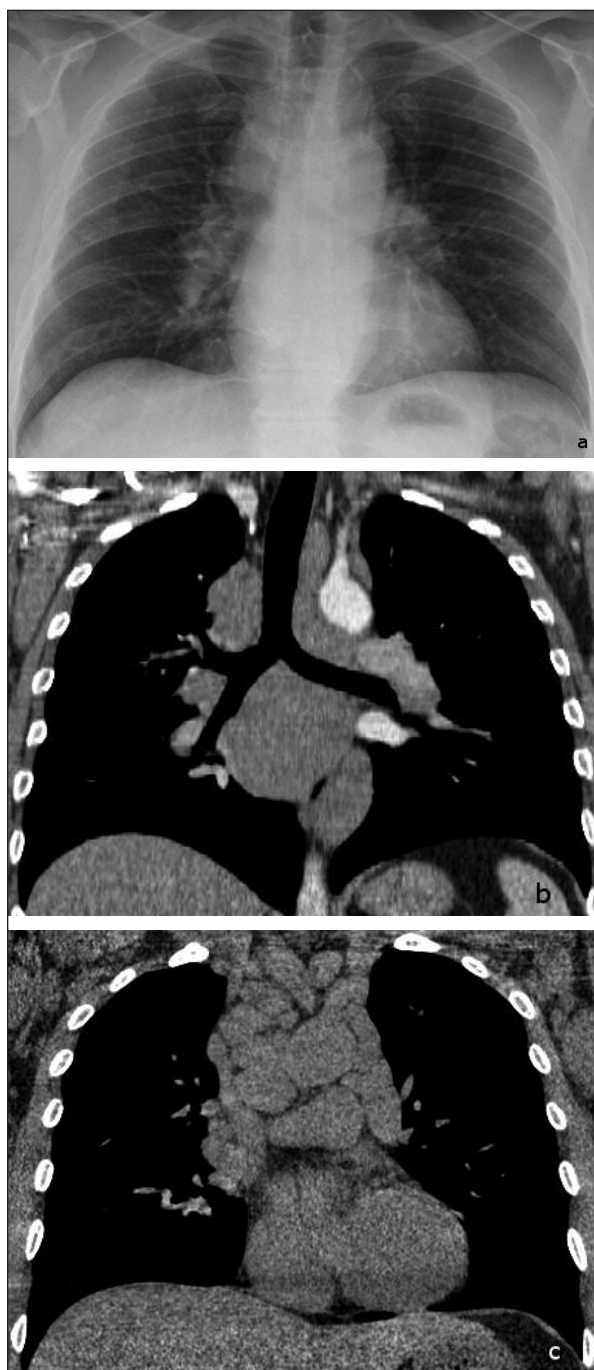
vestigation to suggest the diagnosis (10).

*Stage 0:* CT may show subtle pulmonary abnormalities, such as ground glass opacity or fine perilymphatic nodules that cannot be detected by chest radiograph (Figure 1).

*Stage I:* Thoracic lymph node enlargement is evident on chest radiography in up to 90% of cases (11). Specifically, chest radiograph is sensitive in pointing out the most commonly affected lymph nodes such as the hilar, right paratracheal, subcarinal and those located at the aorto-pulmonary window. Lymph node enlargement ranges from barely detectable to massive, while borders may be smooth or lobulated (12). Unilateral hilar lymphadenopathy is exceptional and should raise the possibility of alternative diagnoses (infection including tuberculosis and histoplasmosis, lymphoma, or bronchogenic or extra-thoracic carcinoma (12,13,14) (Figure 2).

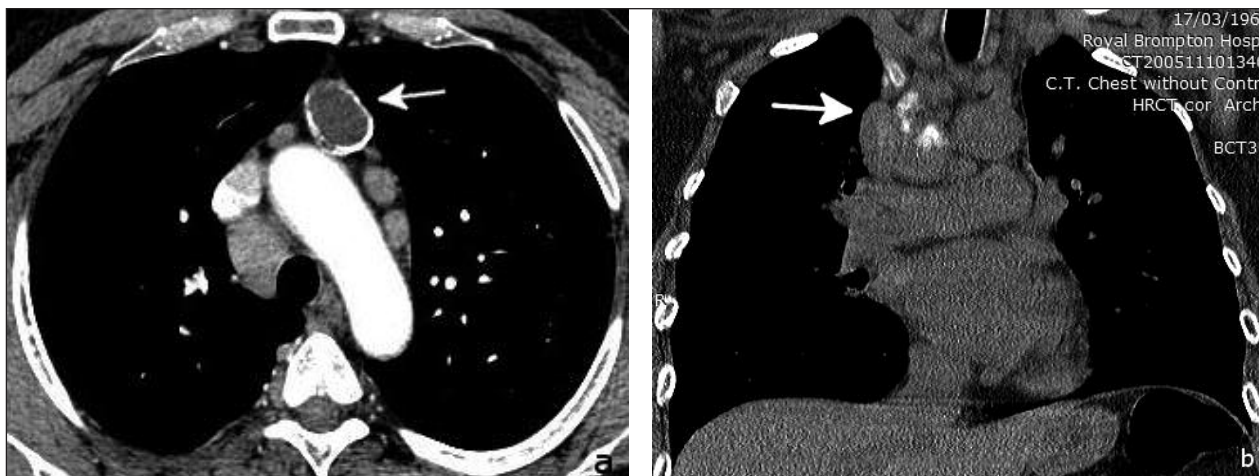
CT may also disclose the presence of enlarged lymph nodes in uncommon sites that cannot be adequately explored by chest radiograph (e.g. internal mammary, retrocrural and posterior mediastinum lymph nodes). Finally, as compared to chest radiograph, CT is more sensitive in detecting lymph node enlargement and characterize their calcification pattern, such as egg shell or “icing sugar” (12,15,16) (Figure 3).

*Stage II-III-IV:* In 30-40% of sarcoidosis patients chest radiograph shows both lymphadenopathy and parenchymal infiltrates (Stage II). Parenchymal disease varies from moderately increased linear shadowing to nodular densities; alveolar opacities resembling fluffy “cotton wool” patches may also occur. In half the patients, radiographic changes resolve while in the other half remain static or progresses to Stage III or IV. About 15% of patients present with parenchymal infiltration without hilar lymphadenopathy (Stage III). In such cases, reticulonodular infiltration is common and tends to spare the extreme apices and the bases. Alveolar opacities are occasionally seen and unilateral infiltrates are rare. Parenchymal fibrosis (Stage IV) is present on the initial chest radiograph in 25% of patients, and develops in 10% to 15% of patients presenting with stages 0-III chest radiographs (15). Fibrotic changes, which take years to develop, range from minimal localised scarring to severe (gross) fibrosis. Typical findings consist of coarse linear opacities radiating from the hilum into the adjacent middle and



**Fig. 2.** A 50 year old man presents to the emergency room with fever and erythema nodosum of the lower limbs. On the frontal chest radiograph, both hila are markedly enlarged (a), CT-scan with contrast confirms mediastinal and hilar lymphadenopathy (Löfgren's syndrome) (b). Many other conditions (tuberculosis, histoplasmosis, lymphoma, or bronchogenic or extra-thoracic carcinoma) are characterized by enlarged lymph nodes but are generally more asymmetrical. However, some overlap exists and the differential diagnosis becomes challenging in some instances as shown in figure 2c displaying multiple enlarged lymphnodes related to lymphoma.





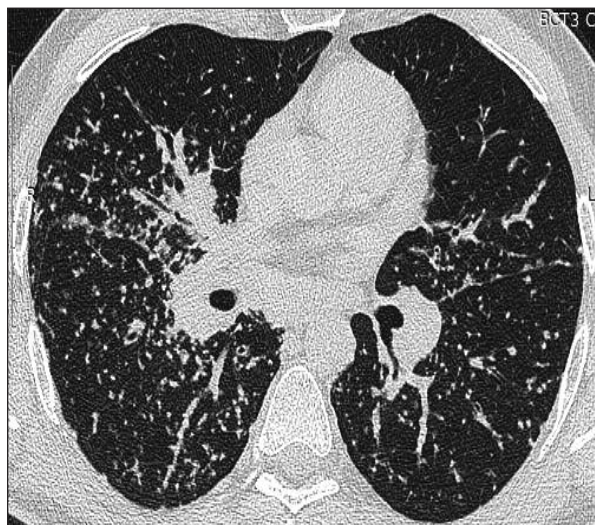
**Fig. 3.** CT is very sensitive in detecting lymph node enlargement and characterizing their calcification pattern such as egg shell (a) or “icing sugar” (b).

upper zones associated with hilar lymphadenopathy. This combination of radiographic features is virtually diagnostic of pulmonary sarcoidosis (17). The hila, vessels and fissures are distorted upwards and outwards (18). These appearances are strongly predictive of irreversible disease and can be associated with translucency of the upper zone due to cyst and bullae formation, and lower zone due to compensatory hyperinflation. When fibrotic changes are advanced, they can give rise to massive para-hilar opacities in the middle and upper zones. Thin-walled ring opacities in the upper zones are also common in severe fibrotic disease (19) and are caused by severe traction bronchiectasis or bullae. Conversely, thick-walled ring opacities usually represent infected bullae or concurrent tuberculosis. Mycetoma develops in more than 50% of patients with stage IV and apical bullous disease (20) but is more readily visualized on CT. In cases of advanced fibrosis, secondary pulmonary hypertension (PH) may ensue, and enlarged central pulmonary arteries may be visible on the chest radiograph, although PH is not exclusively found in advanced pulmonary disease reflecting considerable pathophysiologic heterogeneity.

Parenchymal involvement encompasses a wide spectrum of CT abnormalities that can be broadly divided into two categories: reversible and irreversible.

#### REVERSIBLE CHANGES

*Nodules:* typically well defined, they may have smooth or irregular margins, and commonly measure 2-5 mm; because of their typical lymphatic predilection, on CT nodules appear mainly clustered along the bronchovascular bundles, interlobular septa, interlobar fissures, and subpleural regions; they usually predominate in the mid-upper lung zones (18,21) (Figure 4).



**Fig. 4.** CT image of pulmonary sarcoidosis with micronodules (2-5mm) with perilymphatic distribution along the bronchovascular bundles, interlobular septa, interlobar fissures, and subpleural regions; they usually predominate in the mid-upper lung zones.

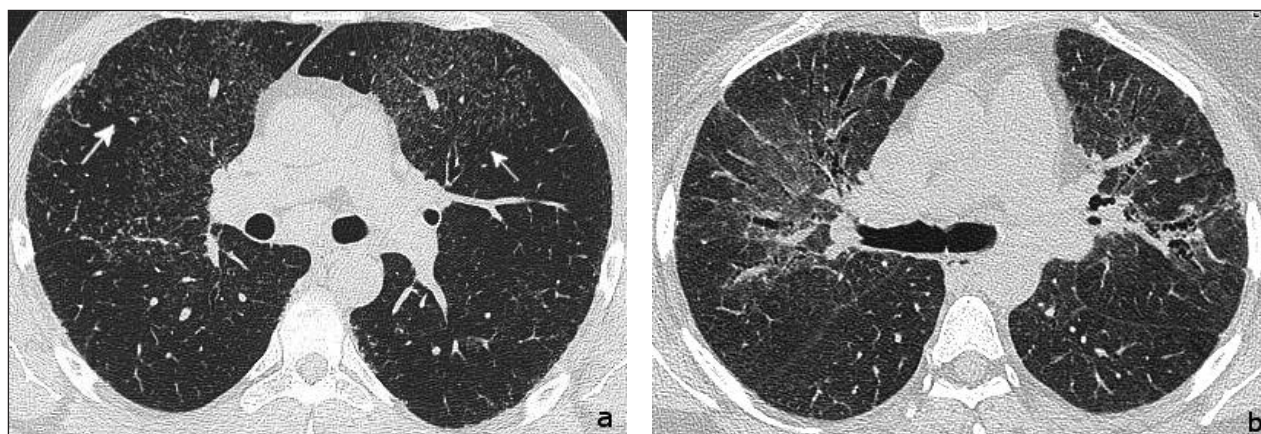
*Ground-glass*: it is observed in up to 40% of CT from patients with sarcoidosis. Ground glass opacity (GGO) is usually multifocal rather than extensive and is often overlaid on a background of subtle micronodularity and associated with enlarged lymph nodes(22,23) (Figure 5). The reversibility of ground-glass opacities, visible only on CT, is more difficult to predict as this pattern may represent either underlying pulmonary microgranulomas or initial fine fibrosis. (22,24-26). In this regard, longitudinal studies have shown that GGO may either resolve or progress to fibrosis(27).

*Alveolar opacities*: they are due either to interstitial granulomas producing alveolar collapse or endobronchial granulomas occluding bronchioles(28). On CT alveolar opacities are distributed in a peribronchovascular fashion with upper and middle zone pre-

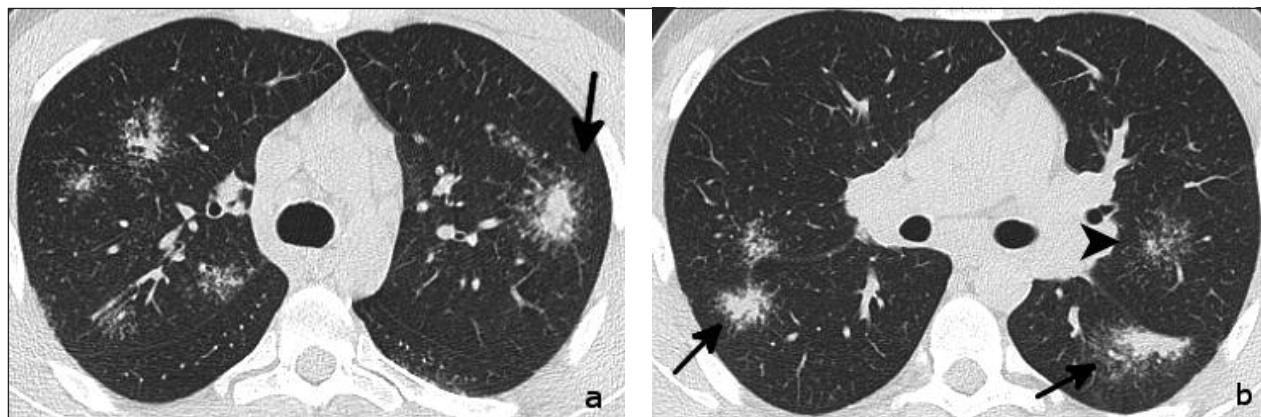
dominance. A large nodule, usually with irregular boundaries, encircled by a rim of numerous tiny satellite nodules is referred to as the “galaxy sign”. The “sarcoid cluster sign” also refers to a multitude of small nodules close each other but, in contrast to the “galaxy sign” they are not confluent (29). These opacities have been reported to resolve with or without steroidal therapy in 31% to 66% of cases but they may also persist and progress to peri-hilar fibrotic masses (12) (Figure 6).

#### IRREVERSIBLE CHANGES

Signs of advanced lung fibrosis can be clearly recognized on chest radiography. Reticular opacities and consolidation usually radiate from the hilar to-



**Fig. 5.** CT shows extended ground glass opacities due to presence of innumerable small interstitial granulomas, beyond the resolution of CT (fig a arrows). Other times it is generated by fine fibrosis with or without parenchymal distortion. In this case is irreversible (b).



**Fig. 6.** many small nodules can coalesce into a large nodule with irregular boundaries, encircled by a rim of numerous tiny satellite nodules configuring the “galaxy sign” (arrows). The “sarcoid cluster sign” also refers to a multitude of small nodules close each other but they are not confluent (arrow head).



wards the dorsal regions of the lung determining upper lobes volume reduction with compensatory hypertransradiancy of the lung bases (Figure 7). Upper lobes radiolucency may also be observed in case of coexistence of large cysts and bullae that, in turn, may be complicated by fungal infection.

Radiologists should look carefully for signs of architectural distortion (e.g. bronchiectasis) in the context of GGO in order to sort out whether it is generated by innumerable small interstitial granulomas or by fine fibrosis without parenchymal distortion (Figure 5b).

Honeycomb change, bronchovascular distortion, gross peri-hilar reticulation and irregular consolidation represent irreversible abnormalities on CT. (24, 30,31 )

A large percentage of patient with sarcoidosis (6-23% at rest, 43% on exertion), is suffering from pulmonary hypertension.(32) Usually, It's related to pulmonary fibrosis, but in 30% of cases is isolated. (33) In these cases, the diffusion of the granulomas in large or small pulmonary veins leads to obliteration of venous and postcapillary pulmonary arterial hypertension with a similar mechanism to veno-occlusive disease. (34,35)

## AIRWAYS

Trachea and main bronchi may be directly infiltrated by submucosal granulomas that may cause nodu-

lar wall thickening and lumen reduction. In addition, the airways may be compressed by mediastinal and hilar enlarged lymph nodes (Figure 8a).

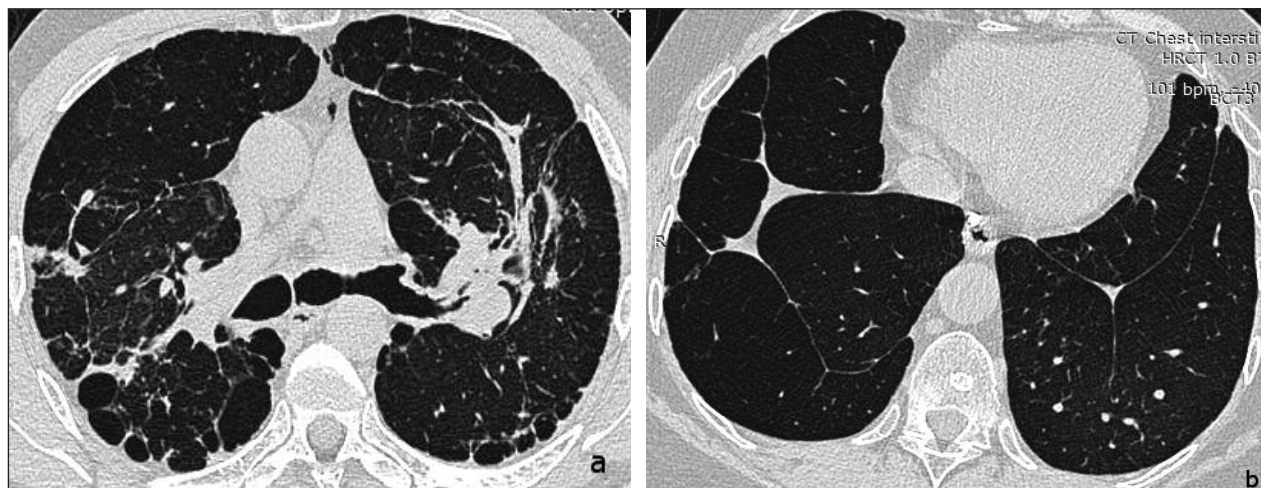
CT signs of small airways involvement consist of patchy areas of decreased attenuation that increase on expiratory CT scanning (i.e. air trapping) (Figure 8b). This is a very common finding being observed in 83% to 98% of the patients, although rarely represents the predominant pattern in sarcoidosis (32,33).

## PLEURA

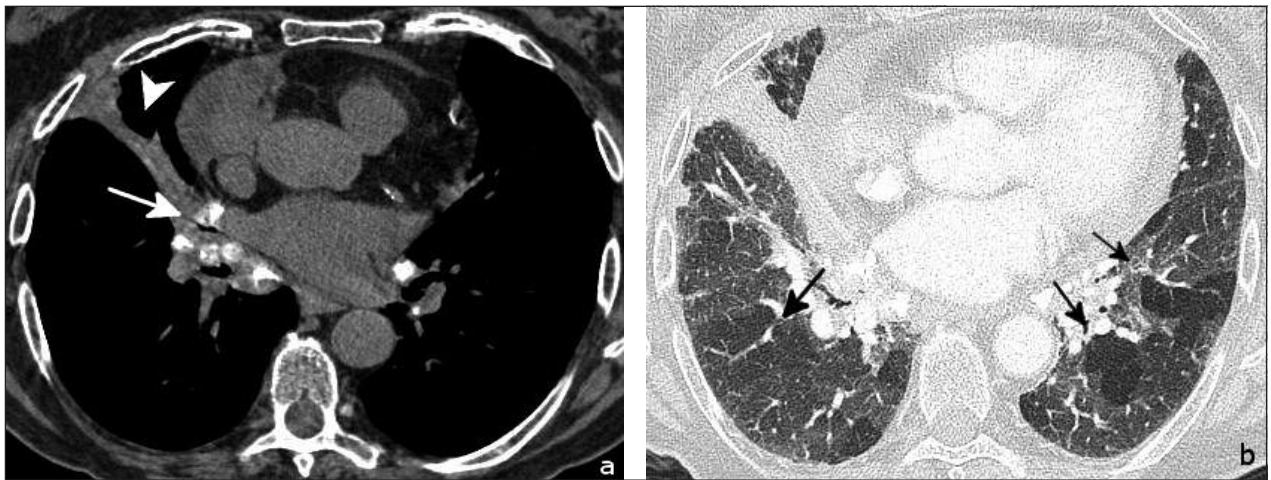
Owing to their perilymphatic distribution, sarcoid granulomas can infiltrate both the parietal and visceral pleura. Pleural effusion, a very uncommon finding, usually resolves in week or months regardless of therapy whereas pleural thickening frequently persists (12,18,34).

## DIFFERENTIAL DIAGNOSIS

Hilar and mediastinal lymph nodes enlargement constitutes a typical (and often diagnostic) feature of sarcoidosis, although it can be also observed in a number of conditions, including infections (mycobacterial, fungal, and viral), neoplasms (lymphoma, metastases, leukemia) and occupational disorders(silicosis, chronic beryllium disease), amongst others. The differential diagnosis between sarcoido-



**Fig. 7.** Advanced lung fibrosis. CT of upper lung shows a parahilar reticulation with associated bronchial distortion and scattered subpleural nodules (a). These abnormalities determine upper lobes volume reduction with compensatory hypertransradiancy of the lung bases (b).



**Fig. 8.** 69-year-old female with calcified right hilar nodal enlargement leading to bronchostenosis (a-arrow) and atelectasis of the middle lobe (a- arrow head). Some patchy areas of decreased attenuation are also visible (i.e. air trapping - arrows) (b), akin to CT signs of small airways involvement.

sis and pulmonary infections may be challenging as enlarged lymph nodes, miliary nodules and alveolar opacities can be observed in both conditions. Metastases may also display a miliary pattern. In this latter case, the distribution is random and the nodules are of variable size whereas sarcoid micronodules are preferentially distributed in the upper lobes. Similarly, the “sarcoid galaxy” sign may also be observed in other granulomatous disease (e.g., tuberculosis and neoplasm), although in sarcoidosis it is typically accompanied by lymphadenopathy.

Sarcoidosis can be very difficult to differentiate from lymphoproliferative disorders and lymphangitis carcinomatosa, both conditions characterized by a perilymphatic distribution of nodules (Figure 9). However, in lymphangitis carcinomatosa interlobular septal thickening represents the predominant feature.

Nodal calcification, a typical finding in sarcoidosis, may also be observed in tuberculosis and silicosis). In these circumstances, the differential diagnosis on CT relies on the associated parenchymal abnormalities typical of each disease. Silicotic nodules show a random distribution and tend to coalesce in partially calcified pseudoplaques (Figure 10 a). Advanced fibrotic sarcoidosis may also be characterized by mass-like lesions very similar to those observed in fibrotic pulmonary silicosis, or other pneumoconiosis. However, gross linear opacities radiating from the hila to the adjacent upper and middle

zones and upward hilar retraction are CT features highly suggestive of sarcoidosis (Figure 10 b).

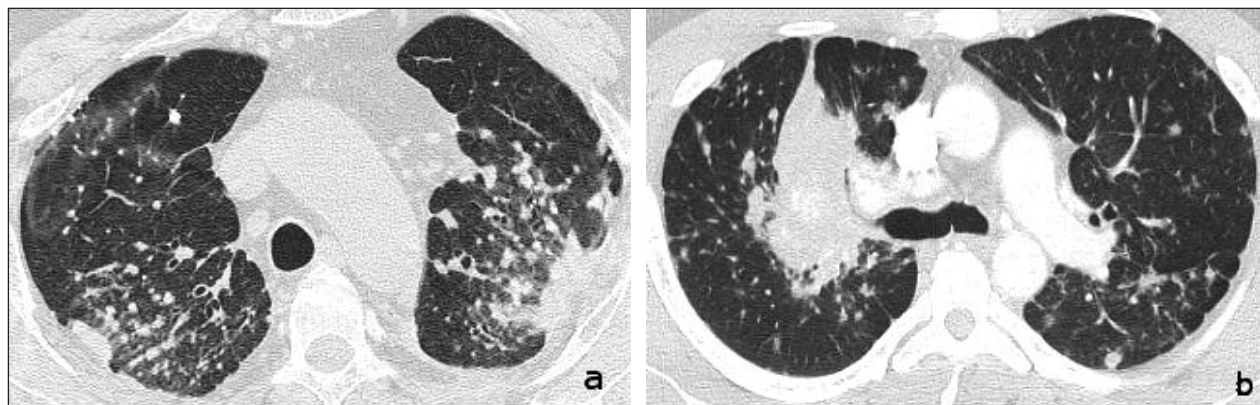
#### FINAL REMARKS

Imaging makes a major contribution to the diagnosis and management of patient with sarcoidosis. Despite substantial discrepancy regarding the recognition of radiographic stages, Scadding staging system still represents a valuable tool for predicting disease outcome. On the other hand, while not neces-



**Fig. 9.** 53 -year-old female with lymphangitis carcinomatosa in breast cancer. CT image is characterized by perilymphatic distribution of nodules and interlobular septal thickening, the latter representing the predominant CT feature.





**Fig. 10.** Differential diagnosis between sarcoidosis and silicosis. (a) 72-year-old man ex-miner. CT through the upper lobes shows well-defined nodules and subpleural pseudoplaques with streaks of connection to the nodules. (b) A 48-year-old man with history of occupational exposure to silica. CT shows parahilar mass with associated bronchial distortion, upper lobes volume reduction, and scattered nodules along the interlobular septae. A histologic diagnosis of sarcoidosis was finally obtained.

sary in all patients, CT provides crucial information when diagnostic uncertainty persists or for the detection of disease complications. In addition, CT is useful in assessing disease extent and may help discriminate between reversible and irreversible lung disease (with prognostic implications) better than chest radiograph. Conversely, its role in disease monitoring and prediction of outcome has not been conclusively established and requires further study.

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