Chapter 2
The Pulmonary Manifestations of Sarcoidosis

Marcel Veltkamp and Jan C. Grutters

Abstract The pulmonary manifestation of sarcoidosis has a great variability and is notorious for mimicking many other interstitial lung diseases. Knowledge of pulmonary manifestations is important in diagnosing saroidosis because thoracic involvement is present in over 90 % of patients. In this chapter, classical findings on chest X-ray and HRCT are described as well as multiple uncommon findings in radiology. The most common findings are bilateral hilar lymphadenopathy, reticulonodular pattern, perilymphatic distribution of nodules, and predominant upper- and middle lobe parenchymal abnormalities. Uncommon findings are unilateral lymphadenopathy, reticular pattern, excessive ground glass opacities, pleural disease, solitary mass, and predominant lower lobe parenchymal abnormalities. Furthermore, the appearance of pulmonary hypertension and necrotizing sarcoid granulomatosis will be described. Finally, imaging of pulmonary sarcoidosis with positron emission tomography with ^{18}F-Fluordeoxyglucose (^{18}F-FDG PET) will be discussed.

Keywords Sarcoidosis • Intrathoracic manifestations • Lymphadenopathy • Parenchymal involvement • Pulmonary fibrosis • Chest X-ray • HRCT • PET

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Abbreviations

BHL	Bilateral hilar lymphadenopathy
COP	Cryptogenic organizing pneumonia
HRCT	High resolution computed tomography
LIP	Lymphocytic interstitial pneumonia
NSG	Necrotizing sarcoid angiitis and granulomatosis
PET	Positron emission tomography
SPL	Secondary pulmonary lobule
SURT	Sarcoidosis of the upper respiratory tract

Introduction

Clinical Manifestations

The clinical manifestations of sarcoidosis are highly variable and often nonspecific. Every organ can be affected, but thoracic involvement occurs in more than 90 % of patients. It is important to state that an estimated 40 % of sarcoidosis patients are asymptomatic, with incidental findings on chest radiographs [1–3]. Dyspnea, dry cough, or chest pain occurs in approximately 50 % of all patients. Massive hilar and/or mediastinal lymphadenopathy is often asymptomatic, but may cause fatigue, retrosternal pain, or dysphagia in some patients [4, 5]. In pulmonary sarcoidosis, chest physical findings are usually minimal. Even in patients where radiographic abnormalities are extensive, crackles are present in less than 20 % of sarcoidosis patients. Finger clubbing is also uncommon in sarcoidosis [2].

Radiographic Scoring Systems: Scadding Staging

Sarcoidosis is commonly staged according to its appearance on the chest radiograph following the Scadding criteria (Table 2.1) [6]. Stage 0 indicates no visible intrathoracic findings. Stage I represents bilateral hilar lymphadenopathy, which may be accompanied by paratracheal lymphadenopathy. Stage II represents bilateral hilar lymphadenopathy accompanied by parenchymal infiltration. Stage III represents parenchymal infiltration without hilar lymphadenopathy. Stage IV consists of advanced fibrosis with evidence of honeycombing, hilar retraction, bullae, cysts, and emphysema. Despite the nomenclature, patients do not all progress through stages I–IV and these stages have no sequential order. For example, a patient may present with stage III which normalizes during follow-up. Also, it can be seen that a patient who initially presents with stage I disease that normalizes can present later on with parenchymal disease only (stage III) [7]. Hillerdal and colleagues found

Table 2.1 Radiographic staging of sarcoidosis patients at presentation according to the Scadding criteria. The estimated frequency at presentation is given as well as the probability of spontaneous resolution during disease course [8–10]

Radiographic stage	Chest X-ray	Frequency (%)	Resolution (%)
0	Normal	5–15	
I	BHL	25–65	60–90
II	BHL and pulmonary infiltrates	20–40	40–70
III	Pulmonary infiltrates without BHL	10–15	10–20
IV	Advanced pulmonary fibrosis	5	0

BHL bilateral hilar lymphadenopathy

that in a cohort of patients presenting with stage I disease 9 % progressed to stage II compared to 1.6 % who progressed to stage III or IV. Of patients presenting with stage II disease only 5.5 % progressed to stage III or IV disease [1].

An interesting feature of the above mentioned Scadding criteria is the fact that is gives prognostic information [8–10]. In stage I disease, spontaneous resolution occurs in 60–90 % of patients. Spontaneous resolution occurs in 40–70 % of patients with stage II disease and in 10–20 % of patients with stage III disease. The majority of spontaneous remissions occur within the first 2 years of disease presentation. There is no spontaneous resolution in patients with stage IV pulmonary sarcoidosis. An important limitation of the Scadding criteria is the great interobserver variability, especially between stages II and III, and III and IV [7].

Pulmonary Function Test

All varieties of abnormalities in pulmonary function tests can be seen in sarcoidosis: obstructive, restrictive, diffusion impairment, or combinations of these. However, in sarcoidosis patients with abnormal lung function testing, a decreased diffusion capacity and a restrictive ventilatory defect are most often seen. Almost 50 % of patients also have obstructive airway disease [9]. Furthermore, bronchial hyper responsiveness is seen in up to 20 % of patients and is associated with the presence of microscopic non-necrotizing granulomas in the endobronchial mucosa [11–13].

Large Airway Involvement

Sarcoidosis of the upper respiratory tract (SURT) may involve the nose, sinuses, larynx, oral cavity, ear, trachea, and bronchi [14, 15]. The incidence of SURT is approximately 5 % [16]. During bronchoscopy common lesions in the trachea as well as in the bronchi are erythema, thickening of the mucosa, and a “cobblestone appearance” (Fig. 2.1), which yields a high number of granulomas on biopsy. In a small study by Shorr and colleagues it was shown that 71 % of sarcoidosis patients

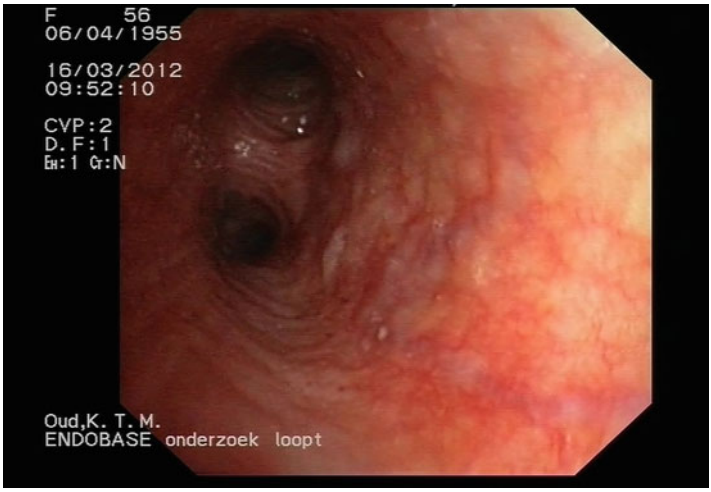

Fig. 2.1 Endobronchial "cobblestone" appearance in a 57-year-old sarcoidosis patient. Biopsy proved multiple non-necrotizing granulomas. Courtesy of Dr. A.C. Verschoof, Hospital Gelderse Vallei, Ede, The Netherlands

undergoing bronchoscopy had bronchial abnormalities [17]. Severe endoluminal stenosis of the trachea or main bronchi is rare in sarcoidosis, estimated to be less than 1 % [18]. It is important to state when diagnosing sarcoidosis that even in patients with a normal appearing airway, granulomas can be identified in almost 30 % of patients [17].

Mediastinal and Hilar Lymphadenopathy

Lymphadenopathy is the most common intrathoracic manifestation of sarcoidosis occurring in approximately 80 % of patients during their illness, irrespectively of radiographic staging [19–25]. An overview of common and uncommon sites of thoracic lymphadenopathy in sarcoidosis is given in Table 2.2. In most cases bilateral hilar lymphadenopathy is present (Fig. 2.2), with unilateral hilar adenopathy occurring in only 3–5 % of patients [19, 26, 27]. When present, unilateral hilar lymphadenopathy is more common on the right side as on the left side. Furthermore, besides the hilar region, lymphadenopathy in sarcoidosis is also seen in the right paratracheal, aortopulmonary window, and tracheobronchial regions [22–25, 28]. A typical example of bilateral lymphadenopathy and right paratracheal lymphnode enlargement in sarcoidosis is known as Garland's triad or 1-2-3 sign.

The groups of Niimi and Patil demonstrated that the most commonly involved nodal stations are Naruke 4R (right lower paratracheal), Naruke 10R (right hilar), Naruke 7 (sub-carinal), Naruke 5 (aortopulmonary window), Naruke 11R (right interlobular), and Naruke 11L (left interlobular) [23, 24] (Table 2.2).

Table 2.2 Classical versus more uncommon features of pulmonary sarcoidosis at HRCT. The features are also divided in potentially reversible versus irreversible

Classical findings, potentially reversible
Lymphadenopathy: bilateral hilar, mediastinal, right paratracheal, subcarinal, aortopulmonary
Reticulonodular pattern: micronodules (2–4 mm, well defined, bilateral distribution)
Perilymphatic distribution of nodules (peribronchovascular, subpleural, interlobular septal)
Predominant upper- and middle zones parenchymal abnormalities
Uncommon findings, potentially reversible
Lymphadenopathy: unilateral, isolated, anterior and posterior mediastinal, paracardiac
Reticular pattern
Isolated cavitations
Isolated ground glass opacities without micronodules
Mosaic attenuation pattern
Pleural disease (effusion, pleural thickening, chylothorax, pneumothorax)
Mycetoma
Macronodules (>5 mm, coalescing). Galaxy sign and cluster sign
Classical findings reflecting irreversible fibrosis or chronic disease
Reticular opacities, predominantly middle and upper zones
Architectural distortion
Traction bronchiectasis
Volume loss, predominantly upper lobes
Calcified lymphnodes
Fibrocystic changes
Uncommon findings reflecting irreversible fibrosis or chronic disease
Honeycomb-like changes
Reticular opacities in predominantly lower lobes

The differential diagnosis of hilar and mediastinal lymphadenopathy is broad, with the major diagnostic alternatives being lymphoma, metastatic disease, and infections (especially tuberculosis). An important feature of lymphadenopathy in sarcoidosis is the symmetrical distribution, being rather unusual in the abovementioned diagnostic alternatives. Lymphadenopathy can also be seen in other interstitial lung diseases such as (idiopathic) interstitial pneumonitis and hypersensitivity pneumonitis. However, in diseases other than sarcoidosis, usually only one or two nodes are enlarged and their maximal short axis diameter is mostly <15 mm [24]. Mediastinal lymphadenopathy without hilar involvement is uncommon and a biopsy-proven diagnosis is warranted.

Lymph node calcification is visible at presentation in approximately 20 % of patients, increasing to 44 % during disease course [29]. The morphology of calcified lymph nodes is variable and nonspecific. Sometimes, the calcification can have an

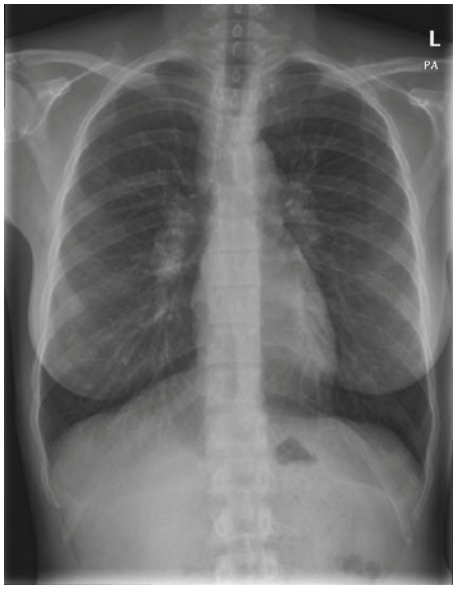

Fig. 2.2 Characteristic distribution of bilateral hilar lymphadenopathy in stage I sarcoidosis on a chest X-ray

eggshell appearance [30]. Calcification of lymph nodes is linked to the duration of disease and can be seen in other granulomatous disorders like tuberculosis or histoplasmosis as well. When comparing calcified lymph nodes in sarcoidosis and tuberculosis it was found that in sarcoidosis their diameter was significantly larger, calcium deposition more focal, and hilar distribution more bilaterally (65 % vs. 8 %) [25].

Parenchymal Involvement

Basic Anatomic Patterns in Interstitial Lung Disease

When interpreting a chest X-ray or HRCT in interstitial lung disease, knowledge of microscopic lung anatomy is essential. In microscopic lung anatomy there are primary as well as secondary pulmonary lobules. A primary pulmonary lobule is defined as the area of the lung distal to the respiratory bronchioles. It is smaller than an acinus and is composed of alveolar ducts, alveolar sacs, and alveoli. The primary pulmonary lobule is rarely used in HRCT imaging, but is the reason the secondary pulmonary lobule (SPL) has its name. The SPL is the smallest part of the lung that is surrounded by connective tissue septa. (Fig. 2.3a). It measures 1–2.5 cm in diameter and is made up of approximately 12 pulmonary acini [31]. Interpretation of HRCT in interstitial lung diseases depends, among other things, on the type of involvement of the SPL. The center of each SPL is named the centrilobular area and contains a small terminal bronchiole, a pulmonary artery branch, and pulmonary

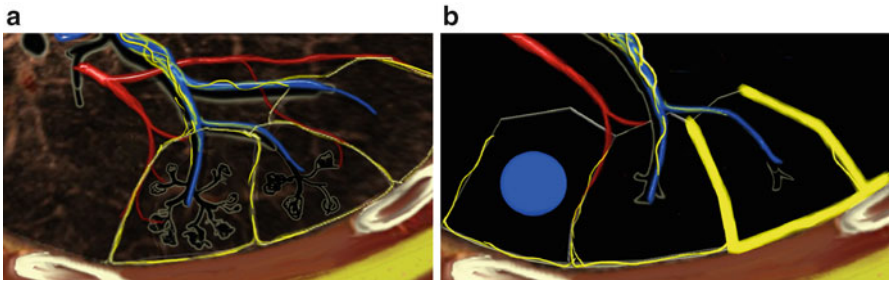

Fig. 2.3 Overview of the pulmonary secondary lobule. (**a**) The terminal bronchiole in the center divides into respiratory bronchioles with acini that contain alveoli. Branches of the pulmonary artery are in *blue*, branches of pulmonary veins are colored *red*. Lymphatic vessels are depicted in *yellow*. (**b**) The *blue circle* indicates the centrilobular area (*left*). The perilymphatic area is shown in *yellow* (*right*). Publication with permission from http://www.radiologyassistant.nl

lymphatics. The margins of the SPL are made up of the interlobular septa containing connective tissue, a pulmonary vein, and pulmonary lymphatics (Fig. 2.3b). The term perilymphatic defines the distribution of lymphatics along the peribronchovascular bundles, the centrilobular area, the interlobular septa, and the subpleural interstitium including the fissures. Within the SPL there are also intralobular septa, which are delicate strands of connective tissue separating adjacent pulmonary acini and primary pulmonary lobules. They are continuous with the interlobular septa.

Radiological Patterns in Parenchymal Sarcoidosis

The HRCT appearance of pulmonary sarcoidosis has a great variability and is notorious for mimicking many other interstitial lung diseases. The most important two radiological patterns in sarcoidosis with involvement of the lung parenchyma are the nodular pattern and the reticulonodular pattern. The distribution of nodules on HRCT can follow three different patterns; random distribution, centrilobular distribution, and perilymphatic distribution (Fig. 2.4).

Nodular and Reticulonodular Pattern

The nodular pattern is seen in almost 90 % of sarcoidosis patients with parenchymal involvement [32, 33]. Sarcoid granulomas are microscopic in size but can aggregate to form small nodules which can be seen on HRCT. These small nodules are 1–10 mm in diameter, usually have irregular margins, and are predominantly present in the mid and upper zones of the lungs. The nodules are frequently found along the bronchovascular bundles and in the subpleural region (Fig. 2.5) following a perilymphatic distribution. Aggregated subpleural nodules account for the fissural

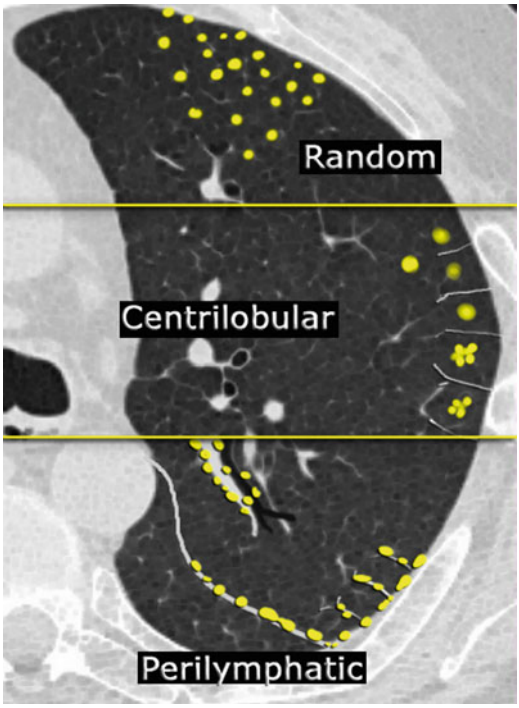

Fig. 2.4 Different nodal distribution patterns in interstitial lung diseases. In most cases, small nodules can be placed into one of three categories: random, centrilobular, or perilymphatic distribution. In sarcoidosis, small nodules typically follow a perilymphatic distribution. *Random distribution*: Randomly distributed nodules do not follow a particular pattern of involvement with respect to the pulmonary architecture and the secondary pulmonary lobule. These nodules affect the fissures, peribronchovascular structures, and the center of the secondary pulmonary nodules. However they lack a predominance in any of these areas since they are randomly distributed. *Centrilobular*: Centrilobular nodules exist predominantly in the center of the secondary lobule around the small airways. Centrilobular nodules spare the subpleural surface. They are typically at least 5–10 mm away from the pleural surfaces. *Perilymphatic*: Nodules that are distributed with a perilymphatic predominance are seen near the fissures, subpleural location, and the peribronchovascular structures. Publication with permission from http://www.radiologyassistant.nl

thickening that can be seen on HRCT. The nodules adjacent to interfaces of vessels, airways, and septa give these structures an irregular or beaded appearance, implicating to be pathognomonic for sarcoidosis. This pattern is also seen in histological specimens, where granulomas are found in association with lymphatics along vessels, airways, and in the subpleural area [34]. This distribution of granulomas can also explain the high rate of success in diagnosing sarcoidosis by bronchial and transbronchial biopsy. Frequently, sarcoidosis causes nodular septal thickening defining the reticulonodular pattern. A reticular pattern is a descriptive term (reticulum meaning network) with several morphological variations ranging from generalized thickening of interlobular septa to honeycomb lung destruction. A pure reticular pattern is rarely seen in sarcoidosis [35].

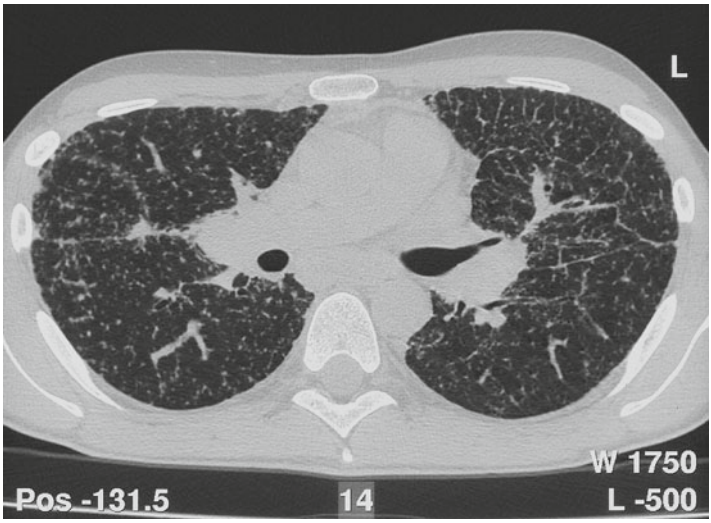

Fig. 2.5 HRCT with the classical perilymphatic distribution of nodules in a patient with sarcoidosis. Note the occurrence of small nodules along subpleural surface and fissures, along interlobular septa and the peribronchovascular bundles giving these structures a "beaded" appearance. This is thought to be pathognomonic for sarcoidosis

Large Nodules and Alveolar Sarcoidosis

Sarcoid nodules can aggregate into pulmonary nodules (no greater than 3 cm in diameter) or large masses (Fig. 2.6). Such a presentation is uncommon in sarcoidosis and estimated to be 2.4–4 % [19, 27, 36–38]. In a retrospective analysis in African-American patients, it was found that 82 % had multiple masses/nodules and only 18 % had a solitary lesion [39]. An air bronchogram was seen in 58 % of the cases and the nodules tend to be more peripheral. The margins of the nodules are often irregular and hazy [37]. The nodules can remain stable for years; however, partial or complete regression has been described [36]. Cavitation is rarely seen in large pulmonary masses and is usually benign, however, hemoptysis can occur [40, 41]. In approximately 10–20 % of patients, massive consolidation with air bronchograms develops [42–45] (Fig. 2.7). The pathologic mechanism is loss of alveolar air due to compression of the alveoli by coalescent granulomas in the interstitium [26]. The alveolar opacities are usually present in the peripheral middle zones of the lung [26, 37].

Galaxy Sign, Cluster Sign, and (Reversed) Halo Sign

Recently, three CT signs have been reviewed in sarcoidosis involving a more atypical distribution of large and small nodules [46]. The "sarcoid galaxy sign" represents a large pulmonary nodule or mass surrounded by many small satellite nodules

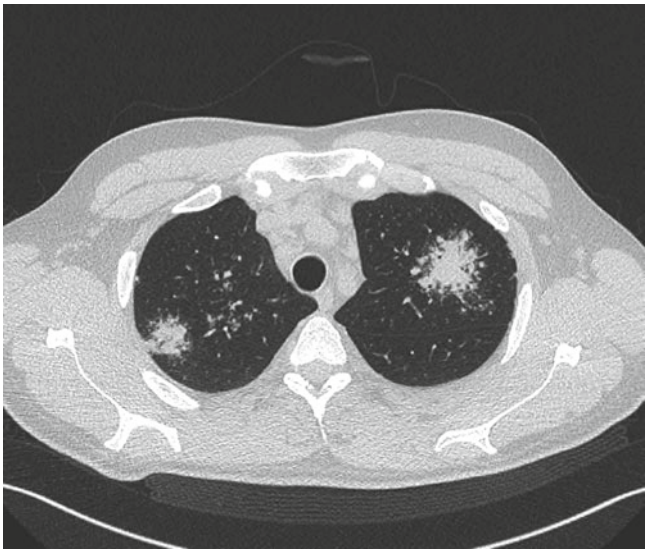

Fig. 2.6 Pulmonary mass with sarcoid galaxy sign in both left and right upper lobe in a 28-year-old sarcoidosis patient. In both upper lobes the mass is surrounded by multiple small satellite nodules. Courtesy of Dr. K. Cuppens, University Hospital Leuven, Belgium

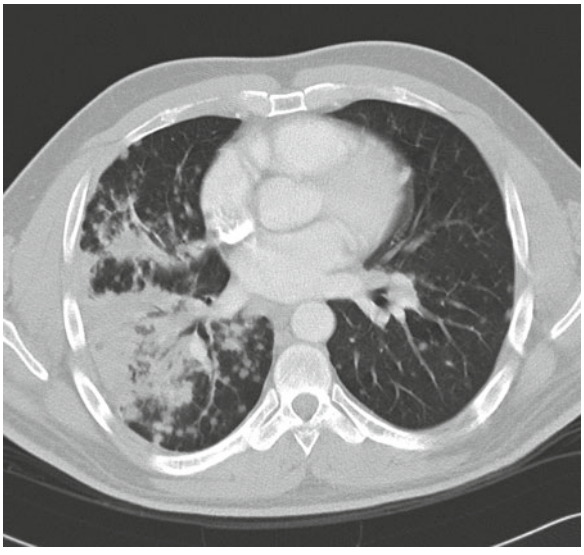

Fig. 2.7 Alveolar consolidation in the middle and right lower lobe of a sarcoidosis patient. Note the presence of air bronchograms in the major consolidation in the right lower lobe. Furthermore, multiple nodules with a mildly irregular outline are seen bilaterally

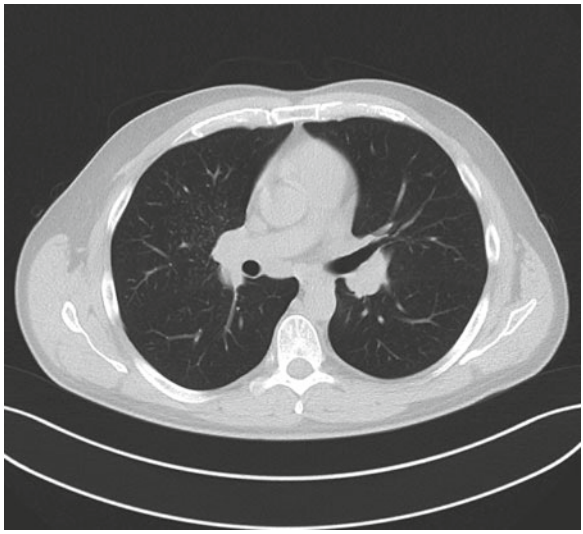

Fig. 2.8 Sarcoid cluster sign in sarcoidosis. Note the subtle clustering of micronodules without confluence in the right parahilar region. Courtesy of Prof. dr. J. Verschakelen and Prof. dr. W. Wuyts, University Hospital Leuven, Belgium

(Fig. 2.6). It is named after a galaxy, where the stars are known to be more concentrated to the galactic center than in the periphery. The "sarcoid cluster sign" is also characterized by clusters of multiple small nodules forming a pulmonary mass but, in contrast to the galaxy sign, the nodules do not tend to coalesce in the center (Fig. 2.8). The most important differential diagnosis for "sarcoid galaxy sign" or "sarcoid cluster sign" is tuberculosis. However, clusters of small nodules can also be seen in cryptococcus infection and silicosis [46]. The "reversed halo sign" is a far more nonspecific sign and describes a focal area of ground glass opacity surrounded by an almost complete ring of consolidation (Fig. 2.9). It was first described as a specific finding in patients with cryptogenic organizing pneumonia (COP) [47]. Later on, multiple authors described the "reversed halo sign" in various diseases such as tuberculosis, aspergillosis, Wegener's granulomatosis, and adenocarcinoma in situ (formerly known as bronchoalveolar carcinoma) [48]. The "reversed halo sign" is also known as the "atoll sign" due to its resemblance of a ring shaped coral reef that encloses a lagoon with shallow water [49]. A true "halo sign," describing a pulmonary mass with a surrounding area of ground glass has been rarely described in sarcoidosis [50].

Ground Glass Opacities

Ground glass attenuation in HRCT is defined as areas of hazy increased attenuation with preservation of bronchial and vascular margins. In sarcoidosis patients, the prevalence of ground glass opacities is estimated to be 40 % ranging from 16 to 83 % [29, 42, 45, 51, 52]. Historically, it was believed to represent active alveolitis, but now it is thought to be caused by small interstitial granulomas or fibrotic lesions

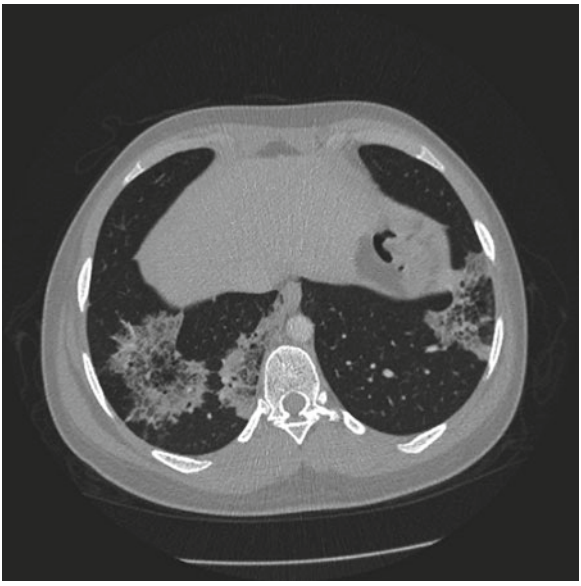

Fig. 2.9 Reversed halo sign in both lower lobes in a 32-year-old patient clinically and radiologically suspected of sarcoidosis. There is a focal area of ground glass opacity surrounded by an almost complete ring of consolidation. Lung biopsy of the mass in the right lower lobe revealed a histopathological diagnosis of lymphocytic interstitial pneumonia (LIP)

beyond the resolution of CT [34]. Ground glass is multifocal and often accompanied by subtle micronodularity [53]. Furthermore, it is most frequently seen at disease presentation [43]. The response to steroids depends on the presence of underlying fibrosis, with clearance being more likely if it is of short duration [45].

Fibrotic Sarcoidosis

At presentation, approximately 5 % of sarcoidosis patients have fibrotic changes on their chest X-ray [9, 10]. However, in an estimated 10–20 % of patients fibrosis develops or becomes more prominent during disease course [54]. On the chest X-ray, linear opacities radiating laterally from the hilum into the middle and upper zones is a characteristic finding [26]. The hila are shifted upward and vessels and fissures are distorted (Fig. 2.10) [19]. Due to compensatory hyperinflation, the lower lobes are sometimes transradiant. On HRCT, fibrotic changes are represented by fibrous bands, hilar retraction, displacement of fissures, traction bronchiectasis, honeycomb cysts, bullae, and irregular reticular opacities including intralobular lines and irregular septal thickening. Fibrosis is seen predominantly in the upper and middle lobes in a patchy distribution. A common feature of fibrotic sarcoidosis is the presence of conglomerated masses surrounding and encompassing vessels and bronchi. It occurs in 60 % of fibrotic sarcoidosis and is associated with bronchial distortion [44].

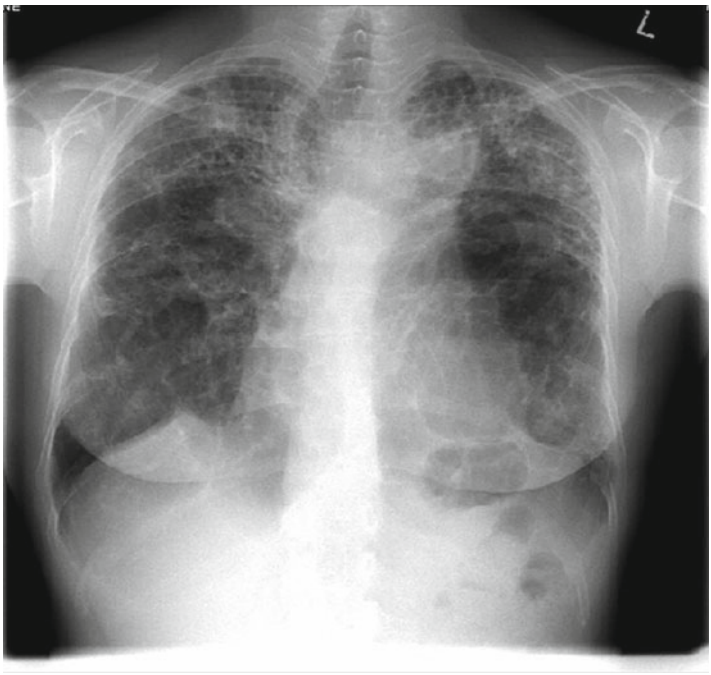

Fig. 2.10 Pulmonary fibrosis on a chest X-ray in a 46-year-old sarcoidosis patient. Note that the hila are shifted upward

Fibrotic cysts, bullae, traction bronchiectasis, and paracicatricial emphysema (air space enlargement and lung destruction developing adjacent to areas of pulmonary scarring) represent advanced fibrotic sarcoidosis (Fig. 2.11). Cystic abnormalities are particularly common in the upper lobes in advanced fibrotic sarcoidosis [55]. Honeycombing (subpleural clustering of cystic airspaces) is thought to be less common in sarcoidosis compared to other end-stage lung diseases [56]. If present, honeycomb-like cysts are most commonly found in the upper lobes but can also be seen in the lower lobes mimicking idiopathic pulmonary fibrosis [35].

Mosaic Attenuation Pattern and Airtrapping

Mosaic attenuation is defined as a patchwork of regions with varied attenuation on HRCT. This pattern can represent patchy interstitial disease, vascular disease, or small airway disease. In patients with sarcoidosis, the presence of mosaic attenuation frequently results from small airway involvement by granulomas or fibrosis [57, 58]. To verify that mosaic attenuation is caused by small airway disease,

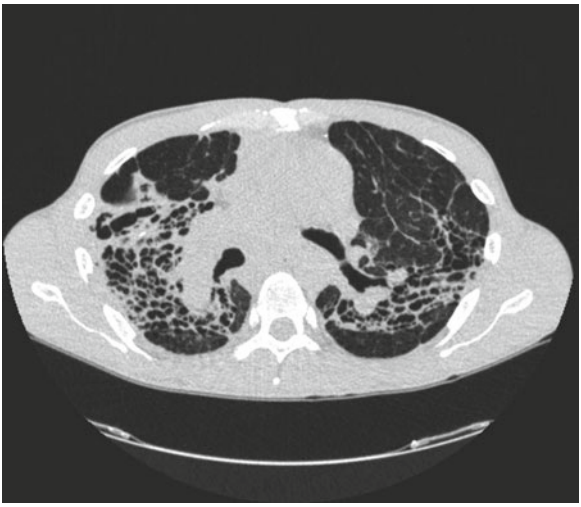

Fig. 2.11 Fibrotic pulmonary sarcoidosis on HRCT. The CT demonstrates parenchymal distortion and destruction. Multiple honeycomb cysts are noted throughout the upper lobes bilaterally

inspiratory images on CT must be compared with the parenchymal appearance on expiratory images in order to identify airtrapping. Airtrapping is a common but nonspecific feature of pulmonary sarcoidosis occurring in 95 % of patients [57, 59].

Mycetomas

The formation of mycetomas occurs in approximately 2 % of sarcoidosis patients, especially in stage IV cystic disease [60]. Fungal balls can develop in pre-existing bullae or cysts which are colonized by fungi, usually *Aspergillus* species. The characteristic appearance of a pulmonary aspergilloma consists of a mobile opacity occupying part or most of the cavity. It is surrounded by a peripheral rim of air known as the air crescent sign or Monod sign (Fig. 2.12) [61]. A common symptom in patients with aspergillomas is hemoptysis and, when massive, can be life threatening.

Pleural Involvement

Pleural Effusion

In sarcoidosis, granulomas can be found on both visceral and parietal pleura. This pleural localization as well as blockage of lymphatic channels by granulomas can result in pleural effusion. However, pleural effusion is an uncommon manifestation of sarcoidosis with an estimated incidence of 0.7–10 % on chest X-ray [62–67]. In a more recent study, the occurrence of pleural effusion was studied with ultrasonography in 181 patients with sarcoidosis presenting at the outpatient clinic of a

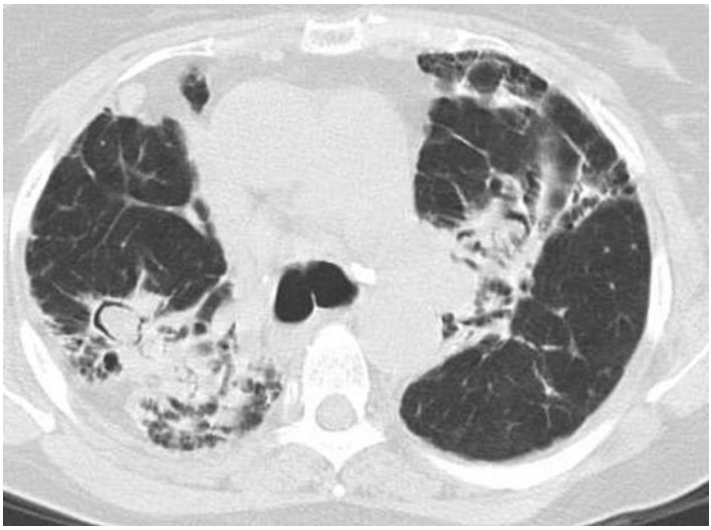

Fig. 2.12 Aspergilloma in the right upper lobe of a 57-year-old patient with advanced pulmonary sarcoidosis. The aspergilloma is surrounded by a peripheral rim of air known as the air crescent sign or Monod sign

University Hospital [68]. In 2.8 % of patients pleural fluid was detected, with some patients having a parapneumonic effusion and congestive heart failure. Therefore, in this study only 1.1 % of patients had sarcoidosis-related pleural effusion demonstrated by biopsy-proven sarcoid pleural involvement. Sarcoidosis-related pleural effusion occurs more often in the right side of the lung compared to the left (45 % vs. 33 %, respectively) [67]. It mostly resolves spontaneously within 6 months [69], sometimes leaving residual pleural thickening [26, 65].

Chylothorax

The development of chylothorax is an exceptionally rare complication of sarcoidosis, with only a few case reports in the literature [70–73]. In one case report, chylothorax was the presenting feature of sarcoidosis [71].

Pneumothorax

It has been estimated that pneumothorax has a 2–3 % prevalence in sarcoidosis patients [74, 75]. Cases of spontaneous pneumothorax may develop due to rupture of a subpleural bleb, particularly in patients with advanced fibrocystic disease [67]. Bilateral pneumothorax in sarcoidosis has also been reported [76].

Necrotizing Sarcoid Granulomatosis

Necrotizing sarcoid angiitis and granulomatosis (NSG) is a rare entity and seen as a variant of sarcoidosis [77], however, with some uncertainty. It is debated whether NSG is a manifestation of systemic sarcoidosis with necrotizing granulomata or a form of necrotizing angiitis with a sarcoid-like reaction [78]. NSG is defined by a granulomatous vasculitis, confluent non-necrotizing granulomas, and foci of infarct-like necrosis with variable degrees of fibrosis [77, 79]. Since the first paper in 1973 [80], approximately 135 cases have been described [81]. The clinical features of NSG are nonspecific. The lungs are primarily affected; however, other organs can also be affected. Radiographic features are similar to the nodular presentation with large pulmonary nodules or masses as described in section "Parenchymal Involvement."

Pulmonary Hypertension

It is estimated that 1–6 % of patients with sarcoidosis have pulmonary hypertension, most patients having advanced stages on chest radiography (Scadding stages III and IV) [82, 83]. However, fibrosis or extensive parenchymal abnormalities are not always present and the absence should not exclude further evaluation for pulmonary hypertension [84]. Clinical characteristics are often atypical but some symptoms can suggest underlying pulmonary hypertension; dyspnea more severe compared to functional impairment, chest pain, and near syncope on exertion. Also, almost 25 % of sarcoidosis patients with pulmonary hypertension present with signs of right-sided heart failure [83, 84]. Diagnosing pulmonary hypertension in sarcoidosis solely with the use of CT is difficult and merely impossible. However, severe pulmonary hypertension is likely to be present when the diameter of the main pulmonary artery at the level of its bifurcation is clearly greater than that of the adjacent ascending aorta or more than 29 mm [85]. In a study by Nunes and colleagues, a higher frequency of ground glass attenuation and septal lines was found in sarcoidosis patients with pulmonary hypertension compared to sarcoidosis patients without pulmonary hypertension [84].

Positron Emission Tomography

In the last 10–15 years, positron emission tomography (PET) with ^{18}F-Fluordeoxyglucose (^{18}F-FDG PET) has emerged as a powerful tool to visualize the intensity and extent of sarcoidosis activity throughout the body [86–88]. This seems important for clinicians dealing with sarcoidosis patients with unexplained,

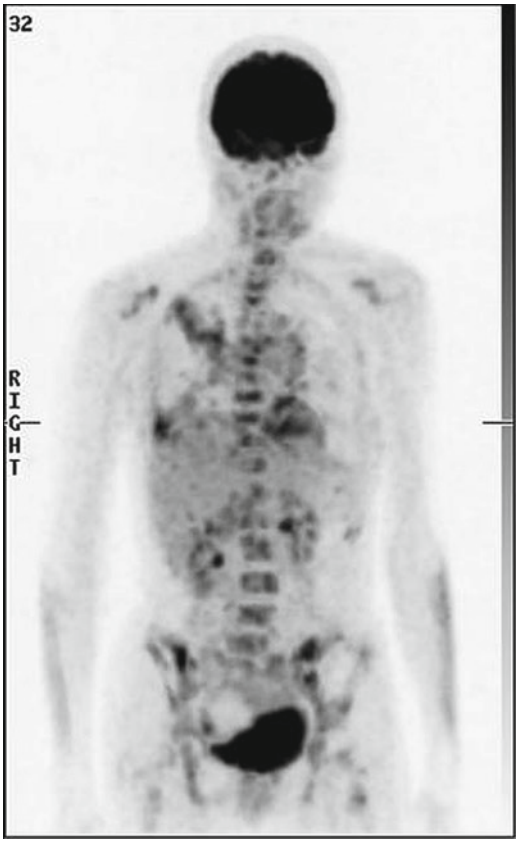

Fig. 2.13 ^{18}F-FDG PET in a 50-year-old patient with active pulmonary and extrapulmonary sarcoidosis. Note the high uptake in the right upper lobe representing a massive consolidation. Due to a high uptake in both skeleton and bone marrow a biopsy of the right crista iliaca was performed revealing multiple non-necrotizing granulomas and fibrosis

persistent, and disabling symptoms not coinciding with pulmonary function tests and radiographic features. It has been demonstrated that ^{18}F-FDG PET is a more sensitive technique in detecting disease activity in sarcoidosis compared to genotype-corrected ACE en sIL-2R [87, 89]. Pulmonary disease activity can be demonstrated with ^{18}F-FDG PET in patients with either a normal chest X-ray or signs of extensive fibrosis (Scadding stage IV). This observation has two important implications. First, when screening for pulmonary involvement in patients presenting with extrapulmonary sarcoidosis, a normal chest X-ray does not exclude pulmonary involvement. Second, in a majority of patients with Scadding stage IV persistent parenchymal disease activity can be detected using ^{18}F-FDG PET [89]. ^{18}F-FDG PET has been demonstrated to asses to possible functional improvement that can be achieved by immunosuppressive therapy [90] Therefore in some patients with stage IV disease anti-inflammatory therapy might be appropriate. An example of ^{18}F-FDG PET in active pulmonary sarcoidosis is given in Fig. 2.13.

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