Eur Radiol (2014) 24:807–816
DOI 10.1007/s00330-013-3088-3

CHEST

Imaging aspects of the diagnosis of sarcoidosis

Paolo Spagnolo · Nicola Sverzellati · Athol U. Wells · David M. Hansell

Received: 2 September 2013 / Revised: 27 November 2013 / Accepted: 12 December 2013 / Published online: 8 January 2014
© European Society of Radiology 2014

Abstract Sarcoidosis is a systemic granulomatous disorder of unknown aetiology with a wide spectrum of radiological appearances and almost invariably pulmonary involvement. Lung involvement accounts for most of the morbidity and much of the mortality associated with sarcoidosis. Imaging contributes significantly to the diagnosis and management of patients with sarcoidosis. In typical cases, chest radiography may be sufficient to establish the diagnosis with little margin of error and CT is not necessary. However, CT can play a critical role in several clinical settings: atypical clinical and/or radiographic findings; normal or near-normal chest radiograph but clinical suspicion of sarcoidosis; and detection of complications. Moreover, in many patients, CT findings are atypical and unfamiliar to most radiologists (e.g. sarcoidosis mimicking other lung diseases and vice versa), and in these cases histological confirmation of the diagnosis is recommended. CT is also useful in assessing disease extent and may help to discriminate between reversible and irreversible lung disease, thus providing critical prognostic information. This review concentrates on the more difficult imaging aspects of sarcoidosis, in particular differential diagnosis and disease complications.

P. Spagnolo (✉)
Center for Rare Lung Diseases, Respiratory Disease Unit, Department of Oncology Haematology and Respiratory Diseases, University of Modena and Reggio Emilia, via del Pozzo 71, 41124 Modena, Italy
e-mail: paolo.spagnolo@unimore.it

N. Sverzellati
Department of Surgical Sciences, section of Radiology, University of Parma, via Università 12, Parma, Italy

A. U. Wells
Interstitial Lung Disease Unit, Royal Brompton Hospital, Sydney Street SW3 6NP, London, UK

D. M. Hansell
Department of Radiology, Royal Brompton Hospital, Sydney Street SW3 6NP, London, UK

Key points
- *Sarcoidosis is characterized by a wide spectrum of radiological appearances.*
- *In typical cases, imaging substantially contributes to the diagnosis of sarcoidosis.*
- *CT plays a critical role in atypical and complicated cases.*
- *CT may discriminate between reversible and irreversible lung disease.*

Keywords Sarcoidosis · Computed tomography · Differential diagnosis · Atypical manifestations · Complications

Introduction

Sarcoidosis is a systemic disorder of unknown aetiology characterised histologically by the presence of non-caseating granulomatous inflammation. The diagnosis also requires supportive clinical and radiological features, and the exclusion of known causes of granulomatous inflammation [1]. Clinical presentation and disease behaviour are highly variable but lung involvement is almost universal [2, 3]. Between 30 % and 60 % of patients present with incidental, yet typical, features of sarcoidosis on chest radiography [4]. Sarcoidosis has a wide spectrum of radiological manifestations and may mimic other lung diseases; conversely, several diseases can resemble classical sarcoidosis. This article focuses on the more challenging radiological aspects of sarcoidosis, with emphasis on differential diagnosis, atypical features and disease complications.

Role of chest radiography versus HRCT

The precise role of imaging in sarcoidosis has not been clearly defined. Pulmonary sarcoidosis is frequently classified according to appearances on chest radiography. A radiographic system, developed more than five decades ago, defines the

following stages: stage 0 (normal appearances); stage I (bilateral hilar lymphadenopathy); stage II (bilateral hilar lymphadenopathy with pulmonary infiltrates); stage III (parenchymal infiltrates); stage IV (irreversible fibrosis with parenchymal distortion or bullae). This classification scheme is purely descriptive and does not indicate disease activity [5]. Most patients with suspected sarcoidosis have a chest radiograph for diagnostic purposes and in the correct clinical context (i.e. a patient presenting acutely with erythema nodosum or ankle swelling, fever and uveitis), it can be sufficient to establish a diagnosis of sarcoidosis rapidly and with little margin of error [6, 7]. In such cases, CT is not required. However, CT plays a key diagnostic role in patients presenting with atypical clinical or radiographic findings, or in patients with a normal or near-normal chest radiograph but clinical suspicion of sarcoidosis. In addition, for patients requiring tissue confirmation of the diagnosis, CT can identify potential high-yield sites for transbronchial or surgical lung biopsy.

Once the diagnosis has been made, CT offers little obvious advantage over chest radiography in monitoring uncomplicated cases [8]. Moreover, the cost and radiation hazard of repeated CT, particularly in young patients, should be kept in mind. The role of CT in identifying disease activity and reversible abnormalities is controversial [9, 10]. However, some patients have unarguably irreversible disease (e.g. architectural distortion, traction bronchiectasis, honeycombing and bullae), and knowledge of this may help to define treatment goals and strategies—for instance, initiating or continuing potentially toxic treatments. CT may also be useful in evaluating disease extent in patients with near-normal lung function, especially when respiratory symptoms are disproportionately severe. Finally, unexplained worsening of symptoms or haemoptysis should prompt referral for CT to detect possible complications of sarcoidosis, including mycetoma, vascular involvement or bronchial stenosis (Fig. 1).

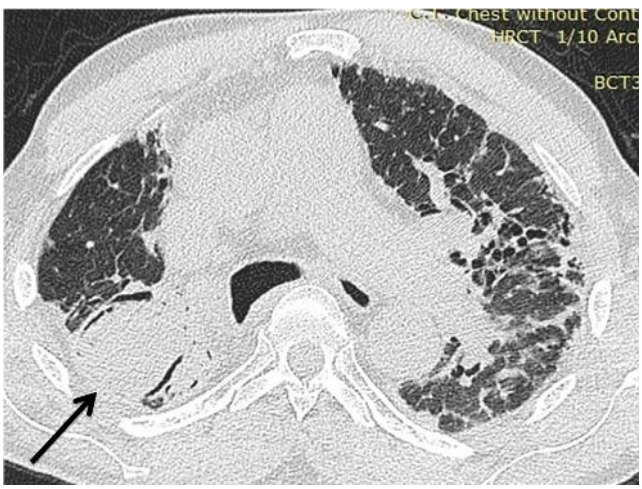

Fig. 1 Advanced fibrotic sarcoidosis with cystic lung lesion complicated by a mycetoma (appearing as a ball bordered on one side by the air crescent sign, *arrow*) in the right upper lobe

Typical features of pulmonary sarcoidosis on HRCT

In the appropriate clinical setting, a combination of mediastinal and parenchymal abnormalities on HRCT is virtually diagnostic of sarcoidosis. This is particularly the case when lymph nodes show subcarinal and symmetrical hilar enlargement with the typical perilymphatic distribution of nodules. The nodules, typically well defined, may have smooth or irregular margins, and most commonly measure 2–5 mm [11, 12]. Nodules are identified in 80–100 % of cases on HRCT [13, 14]. Because of their typical lymphatic predilection, the nodules are mainly clustered along the bronchovascular bundles, interlobular septa, interlobar fissures and subpleural regions [15]. The nodules predominate in the mid to upper lung zones and may coalesce or clump into larger opacities [11, 16] (Fig. 2). The distribution of granulomas (peribronchiolar or intraluminal) may account for regional air trapping (i.e. areas of low attenuation interspersed with larger areas of normal lung parenchyma) that reflects small airways involvement more easily identifiable on expiratory CT [16]. Air trapping on expiratory CT is present in nearly all cases of sarcoidosis irrespective of radiographic staging [17–19]. Consolidation and ground-glass opacity are other features that may occur with or without the more typical pattern of perilymphatic nodules [12, 20], and have been reported on CT in 15–27 % [21, 22] and 16–83 % [4, 14, 17] of cases, respectively. Innumerable small interstitial granulomas beyond the resolution of HRCT may account for a faint texture within what is otherwise amorphous ground-glass opacification [23]. Symmetrical hilar lymphadenopathy with subcarinal involvement, even as an isolated finding, is also highly suggestive of sarcoidosis [24]. Lymph node enlargement is commonly seen in the right paratracheal, aortopulmonary, tracheobronchial, distal bronchopulmonary and, characteristically, subcarinal regions [25, 26]. A cloud-like or an "icing sugar" pattern of nodal calcification is also typical of sarcoidosis, as it is not

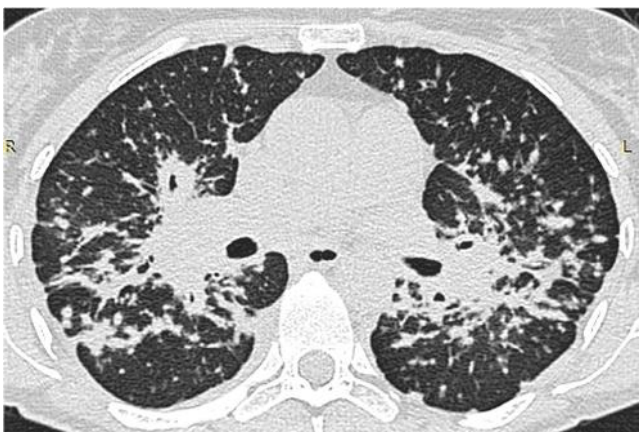

Fig. 2 Classical manifestations of pulmonary sarcoidosis: hilar and mediastinal lymphadenopathy and perilymphatic nodules (with bronchovascular and interlobular septal beading, centrilobular and subpleural nodules)

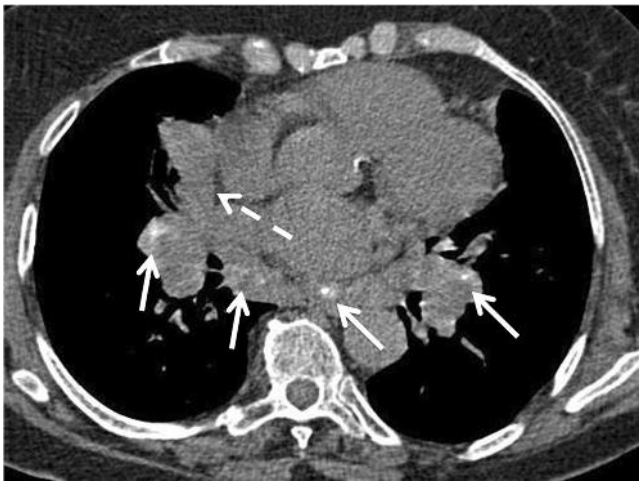

Fig. 3 CT scan showing hilar and subcarinal enlarged lymph nodes containing amorphous calcification (*arrows*). This pattern of amorphous ("icing sugar") calcification is highly suggestive of sarcoidosis. Lymph nodes enlargement also caused partial right middle lobe collapse (*dashed arrow*)

usually associated with other forms of granulomatous disease, notably tuberculosis [25] (Fig. 3). Pulmonary fibrosis occurs in approximately 20–25 % of cases [1, 27]. Classic fibrotic changes include linear opacities (radiating laterally from the hilum), fissural displacement, bronchovascular distortion (bronchiectasis) and honeycombing concentrated in the upper zones of the lungs (Fig. 4).

Conditions that sarcoidosis can mimic

The gross appearance of pulmonary sarcoidosis on HRCT depends on the distribution of granulomas, which may be responsible for several less common radiological presentations [28].

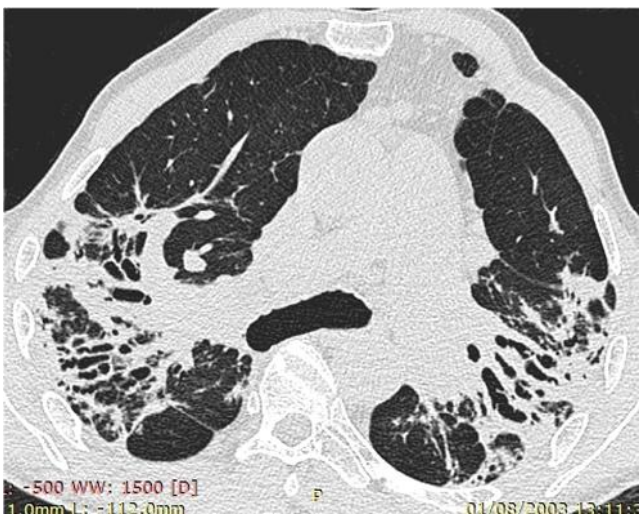

Fig. 4 Classic appearance of advanced fibrotic sarcoidosis: dense conglomerate perihilar fibrosis with severe traction bronchiectasis that radiate from the hilum toward the dorsal regions of the upper lobes

Lymphangitic carcinomatosis In sarcoidosis, nodules are more profuse in the subpleural regions and along the fissures than those associated with lymphangitic carcinomatosis (LC) [29]. Conversely, when septal thickening is present in sarcoidosis (in up to 50 % of cases), it is usually less extensive and does not outline the secondary pulmonary nodules forming polygonal structures, which instead would be more typical of LC (Fig. 5). Other findings that favour sarcoidosis are the upper lobe predominance and the lack of pleural effusion and nodular thickening ("cuffing") of segmental and subsegmental bronchi.

Silicosis and other pneumoconiosis In sarcoidosis, nodules may be scant, large and mainly distributed in the subpleural regions mimicking the pseudoplaques sometimes seen in silicosis (Fig. 6) [30]. Similarly, eggshell lymph node calcification may be seen in both sarcoidosis and silicosis [31]. Furthermore, in as many as 25 % of cases of sarcoidosis, late-stage fibrosis can be so marked that conglomerate parahilar opacities, resembling progressive massive fibrosis (PMF) observed in silicosis, coal workers' pneumoconiosis or talcosis, develop. An important distinguishing feature is the way "massive fibrosis" in sarcoidosis streams directly off the hila (often trending posteriorly); by contrast, PMF is usually seen as large mass-like upper lobe predominant conglomerates of dense fibrosis often associated with radiating strands.

Lymphoproliferative disorders In sarcoidosis, lymph node enlargement may occasionally be asymmetrical, unilateral and limited only to the mediastinum or unusually located [32]. This makes it difficult, if at all possible, to differentiate sarcoidosis from lymphoproliferative disorders solely on the basis of nodal morphology and distribution. Lymphoproliferative disease may also display peribronchovascular nodules, similar to those associated with sarcoidosis (Fig. 7) [29]. Patchy airspace consolidation with or without air bronchograms (which is more typical of cryptogenic organizing pneumonia) and, more rarely, solitary mass-like opacities (resulting from the coalescence of individual granulomas and mimicking a neoplastic process) may also be observed in sarcoidosis [12]. The presence of accompanying imaging findings typical of sarcoidosis (e.g. symmetrical hilar lymph node enlargement and profuse nodules distributed along the bronchovascular bundles, interlobular septa and interlobar fissures with a mid to upper lung zones predominance) usually allows the correct diagnosis to be made in these cases [33]. However, histological confirmation of the diagnosis is strongly recommended if uncertainty persists.

Chronic hypersensitivity pneumonitis and other fibrosing lung diseases Chronic fibrotic sarcoidosis may resemble chronic

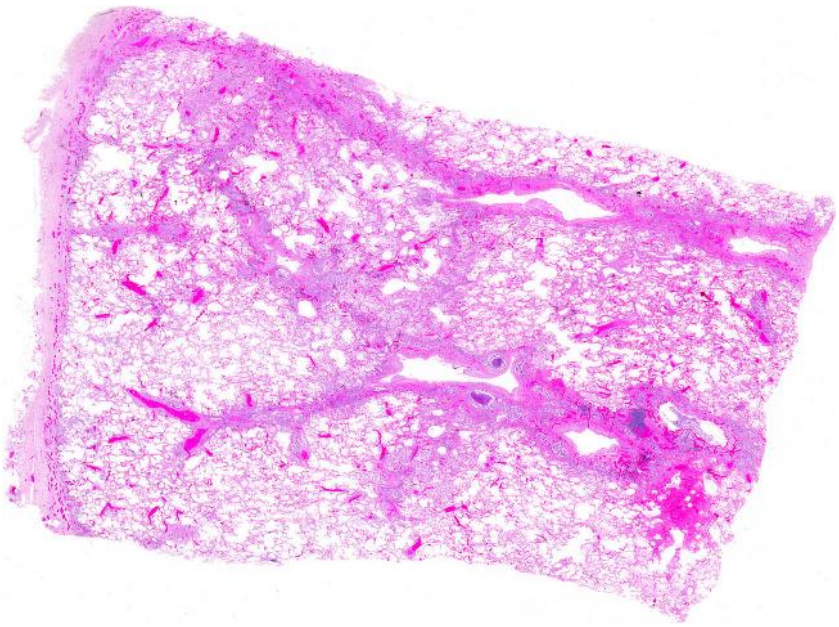

Fig. 5 Lymphangitic carcinomatosis. Aggregates of neoplastic cells filling the lymphatics and causing secondary oedema with smooth thickening of lymphatic vessels (haematoxylin–eosin, ×20. Courtesy Dr Alberto Cavazza, Reggio Emilia, Italy)

hypersensitivity pneumonitis on HRCT as both are characterized by a combination of interstitial fibrosis and lobules of decreased attenuation (the latter reflecting small airways obliteration) [34]. Other fibrosing lung diseases that predominantly affect the upper lobes and may occasionally be confused with fibrotic sarcoidosis include idiopathic pleuroparenchymal fibroelastosis (Fig. 8) [35]. However, in sarcoidosis, reticular abnormalities and traction bronchiectasis both tend to radiate dorsolaterally from the hilum and are associated with perilymphatic nodules [27]. Exceptionally, sarcoidosis may also display an usual interstitial pneumonia pattern (subpleural, basal-predominant honeycombing and reticular abnormality, with or without traction bronchiectasis) that is indistinguishable from the pattern typical of idiopathic pulmonary fibrosis (IPF) (Fig. 9a and b) [36]. However, unlike in IPF, the honeycomb change observed in sarcoidosis mostly affects the upper and perihilar regions. In advanced fibrotic disease, cystic destruction, bullae and paracicatricial emphysema may be encountered with a mid-upper zone predilection [34]. The presence of either multiple lymph node calcification or conspicuous interlobular septal thickening may help to suggest the diagnosis of sarcoidosis in such cases.

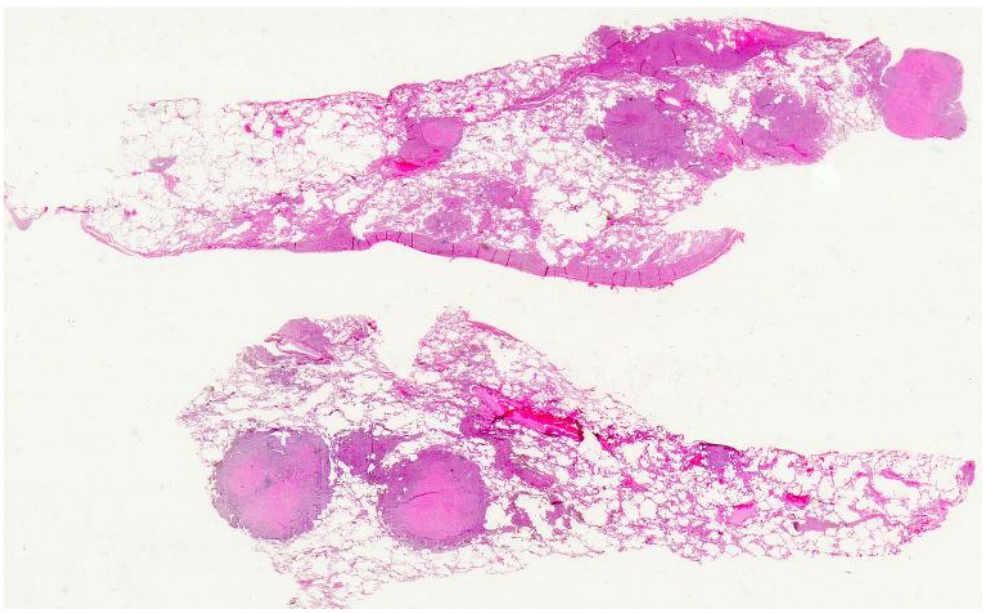

Fig. 6 Silicosis. "Dirty" macrophages in a subpleural perilymphatic and peribronchovascular distribution associated with bronchiolocentric fibrotic nodules (haematoxylin–eosin, ×20. Courtesy Dr Alberto Cavazza Reggio Emilia, Italy)

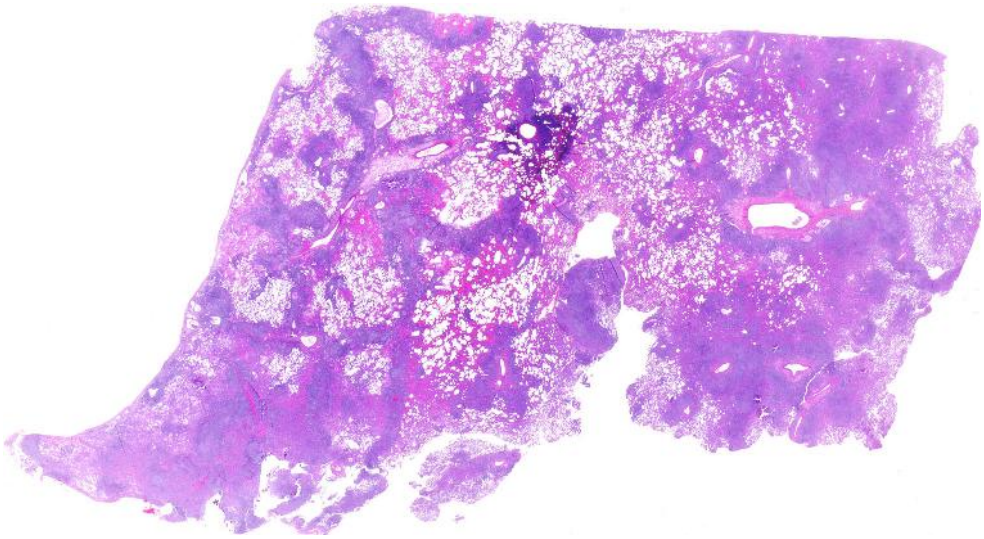

Fig. 7 T cell lymphoma. Neoplastic proliferation of T lymphocytes with a perilymphatic and peribronchovascular pattern of infiltration (haematoxylin–eosin, ×20. Courtesy Dr Alberto Cavazza, Reggio Emilia, Italy)

Situations in which the "diagnosis" of sarcoidosis should be challenged

Common variable immunodeficiency Common variable immunodeficiency (CVID), the most common clinically relevant of the primary immunodeficiency disorders, is a syndrome that is characterized by low serum antibody levels, poor antibody responses and recurrent bacterial infections [37]. Although CVID has long been known to be associated with recurrent bacterial infections and bronchiectasis, granulomatous disease has also been reported [38–40]. The spectrum of granulomatous disease in CVID ranges from isolated granulomas in a single organ to widespread granulomatous inflammation at several sites (e.g. lungs, skin, spleen, liver, lymph nodes and eyes), and may make it difficult to distinguish CVID from sarcoidosis, particularly when granulomas precede the onset of the immune deficiency [39, 41–45]. On CT, ill-defined nodules, either centrilobular or randomly distributed, and with a mid-lower lobe predominance are present in over 50 % of CVID cases [44, 45] (Fig. 10). Such findings overlap with those of sarcoidosis. Furthermore, well-defined nodules with a perilymphatic distribution, irregular thickening of the pleura and interlobular septa as well as hilar and mediastinal lymphadenopathy that are indistinguishable from those typically observed in sarcoidosis have also been described [41, 46]. As is the case for sarcoidosis, the histology of granulomas in CVID reveals non-necrotizing granulomas composed of epithelioid cells, multinucleate giant cells and lymphocytes; however, areas of organizing pneumonia and follicular bronchiolitis, which are not encountered in "pure" sarcoidosis, are also frequently seen. Several clinical and laboratory features may help distinguish between the two conditions [46].

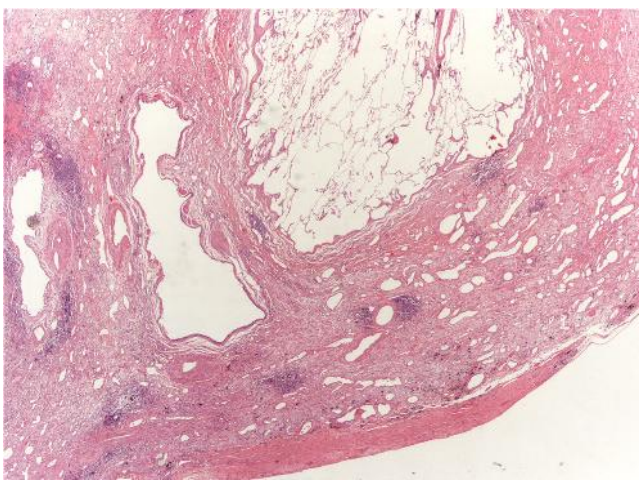

Fig. 8 Pleuroparenchymal fibroelastosis. Markedly thickened visceral pleura and prominent subpleural fibrosis (haematoxylin–eosin, ×40. Courtesy Dr Alberto Cavazza, Reggio Emilia, Italy)

Infection Apart from sarcoidosis, the most common granulomatous disease affecting the lungs is tuberculosis (TB) (including non-tuberculous mycobacterial) infection; other less common causes of granulomatous lung disease include actinomycosis, aspergillosis and infections caused by *Nocardia*, *Histoplasma* or *Cryptococcus*. In general, sarcoidosis does not present acutely nor does it progress rapidly, and it is unlikely to be confused with the clinical presentation of most infections. However, TB should always be in the differential diagnosis in patients born in high-risk countries (especially if recent immigrants) and in those with impaired T cell immunity secondary to either concomitant diseases (HIV, malignancies) or therapy (corticosteroids, anti-TNF-α). There is little overlap between the radiological manifestations of typical sarcoidosis and reactivation or miliary TB: the key feature of reactivated TB is exudate, in the form of consolidation, acinar nodules or a tree-in-bud pattern—none of which are expected findings in sarcoidosis. In miliary TB, the micronodules are

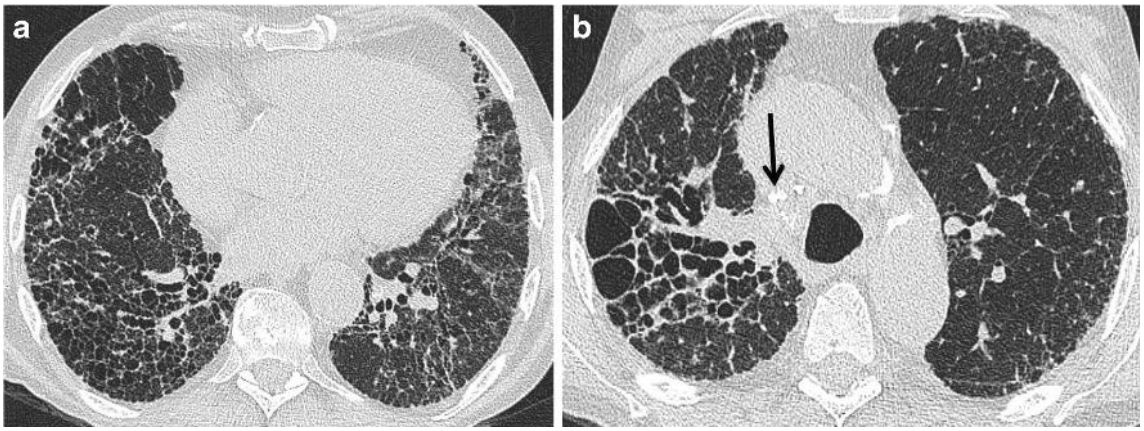

Fig. 9 Sarcoidosis mimicking idiopathic pulmonary fibrosis. Although present in the subpleural basal regions (**a**), the honeycombing is due to large cysts that are evident also in the perihilar regions of the upper lobes (**b**). Partially calcified hilar nodes suggesting the correct diagnosis are also present (*arrow*)

randomly distributed unlike in sarcoidosis where they are typically (although not necessarily) localized along the lymphatics, i.e. bronchovascular bundles, interlobular septa, major fissures and subpleural regions [12]. However, the rare *necrotizing* form of sarcoidosis can be mistaken for infection, and *micronodular* sarcoidosis may be completely random in distribution and indistinguishable from miliary TB, pneumoconiosis, endemic fungal infections or metastatic lesions (Fig. 11). In patients with isolated mediastinal lymph node enlargement, radiology does not conclusively distinguish sarcoidosis from TB. Calcification of lymph nodes is detectable on CT in around 45 % of sarcoidosis cases, and the extent of calcification seems to correlate with the duration of disease [25]. Calcification is also common in TB. However, two features help to discriminate between sarcoidosis and tuberculosis lymph nodes: first, sarcoidosis tends to produce a delicate appearance that has been likened to sprinkled icing sugar (at least in the earlier stages of calcification) as opposed to TB which more commonly produces denser calcifications [25]; second, the calcified nodes in sarcoidosis tend to be bilateral, as expected for a systemic disease, whereas in TB they are more often unilateral, following the path of lymphatic drainage. Finally, eggshell calcification has been reported to occur in sarcoidosis but is relatively uncommon [47]. However, sarcoidosis and tuberculosis may coexist; thus, a diagnosis of TB should be vigorously reconsidered if the clinical course is atypical for sarcoidosis even in the presence of imaging features fairly suggestive of sarcoidosis [48].

Chronic beryllium disease and aluminosis Chronic beryllium disease (CBD) is a rare systemic granulomatous disorder resulting from an immunological response to long-term exposure to beryllium. The appearance of CBD on imaging can be

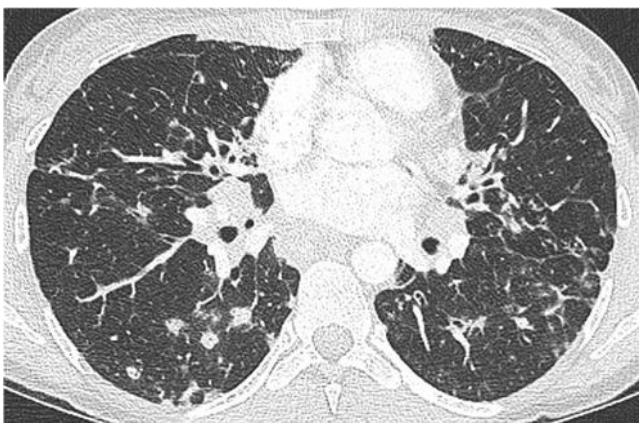

Fig. 10 A 33-year-old female with combined variable immunodeficiency. Contrast-enhanced HRCT showing subcarinal and bilateral symmetrical hilar lymphadenopathy. There are widespread nodules ranging in size from a few millimetres to approximately 1 cm in diameter, slightly more profuse in the lower lobes. Thickening of the interlobular septa is also evident. Although non-specific, this concatenation of features resembles sarcoidosis

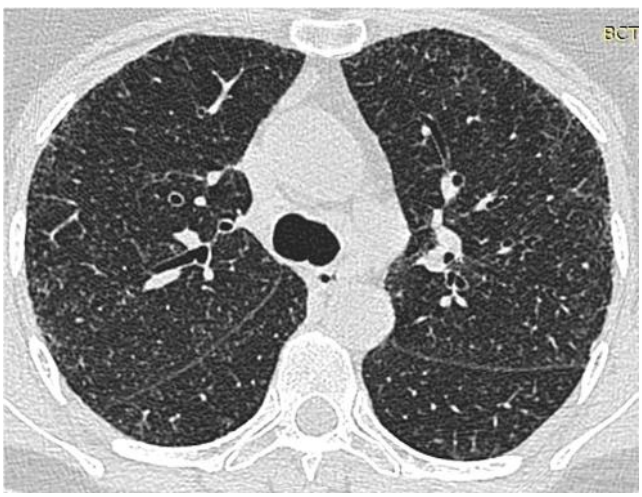

Fig. 11 Sarcoidosis. CT scan showing small pulmonary nodules of homogeneous size and without an obvious perilymphatic distribution, thus mimicking miliary tuberculosis. However, a more careful inspection allows one to identify a subtle fissural involvement, a pattern of nodules distribution more in keeping with sarcoidosis

indistinguishable from that of sarcoidosis, although CBD is usually confined to the lungs and occurs in subjects who have been occupationally exposed to beryllium (Fig. 12) [49, 50]. In addition, the large hilar nodes seen in sarcoidosis are infrequent in CBD.

Aluminosis is a rare occupational lung disease induced by aluminium dust [51]. In the early stages of the disease, small, rounded and ill-defined centrilobular opacities (usually resembling subacute hypersensitivity pneumonitis more than sarcoidosis) with or without thickened interlobular septa and mainly located in the upper lobes are the predominant findings on CT, whereas subpleural bullae and parenchymal distortion are usually seen in advanced stages of the disease [52]. Contrary to sarcoidosis, hilar lymphadenopathy is an uncommon finding.

Specific complications

Mycetoma In a large sarcoidosis series, the incidence of *Aspergillus*-related lung disease has been reported to be around 2 % [53, 54], although this figure is much higher in patients with chronic fibrotic disease. Radiographically, mycetomas appear as a mass of soft-tissue density within a lung cavity, most commonly located in the upper lobes, separated from the cavity itself by an air crescent [55–58] (Fig. 1). Erosion of the fungal ball into the hypervascular cavity wall causes hemoptysis, which in 5 % of patients may be life-threatening [59]. Thickening of the lateral pleural surface adjacent to the cavity wall is an early sign of mycetoma formation and may be detected on a radiograph or CT [60].

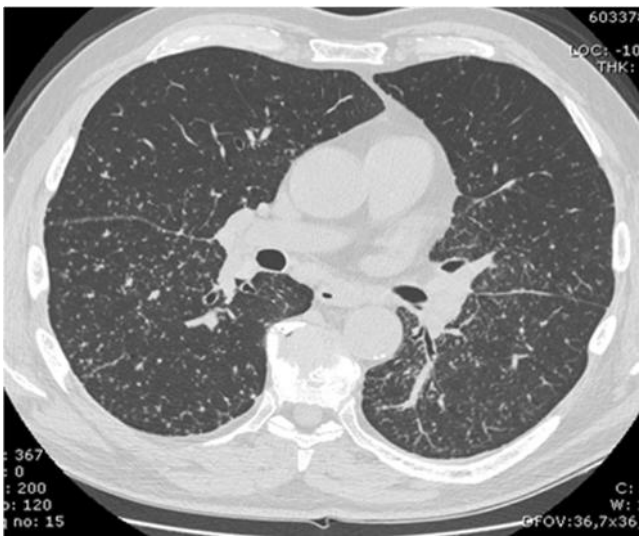

Fig. 12 Chronic beryllium disease in a dental mechanic. Thin-section CT scan reveals diffuse nodules predominantly distributed along the pleura and septa. The diagnosis of CBD was confirmed by a blood beryllium lymphocyte proliferation test

Pulmonary hypertension Pulmonary hypertension (PH) is particularly common in patients with advanced pulmonary disease, most of whom will also have fibrotic disease and a significantly impaired pulmonary function test [61, 62]. Nevertheless, PH is not exclusively found in the context of advanced pulmonary fibrosis, reflecting its considerable pathophysiological heterogeneity. Indeed, extrinsic compression of the central pulmonary vessels by lymphadenopathy or mediastinal fibrosis, destruction of the pulmonary vascular bed, intrinsic pulmonary vasoreactivity, pulmonary veno-occlusive disease and intrinsic sarcoid vasculopathy have all been proposed to contribute to PH pathophysiology in sarcoidosis [61, 62]. Chest radiography is relatively insensitive for the detection of PH [63]. Radiographic signs, when present, include dilatation of the pulmonary trunk and main pulmonary arteries with peripheral "pruning" [64]. CT signs of PH are more sensitive and specific than those detected by radiography. A ratio greater than 1 for the diameter of the main pulmonary artery at the level of its bifurcation to the ascending aorta and dilatation of segmental pulmonary arteries have been reported to correlate with the presence of PH regardless of the presence of fibrotic changes, although this observation has been made from patients with a spectrum of diseases associated with PH [65, 66]. CT may also provide additional information such as compression or obstruction of the pulmonary vessels by mediastinal lymphadenopathy or fibrosis (e.g. fibrosing mediastinitis) as well as findings suggestive of pulmonary veno-occlusive disease (PVOD) (dilated central

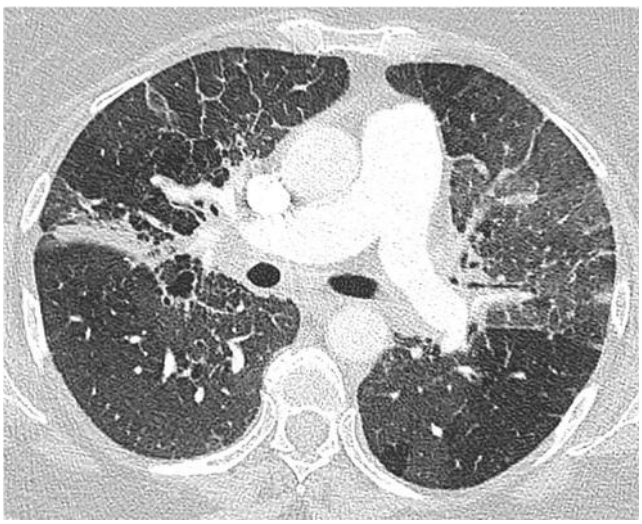

Fig. 13 Pulmonary veno-occlusive disease associated with sarcoidosis. This 62-year-old female with long-standing sarcoidosis then deteriorated over a few weeks. Contrast-enhanced CT showing a slightly enlarged main pulmonary artery. Compared with a previous CT, the fibrotic perihilar changes were stable but the thickening of the interlobular septa (anterior segment of the right upper lobe) and ground-glass opacification (left upper lobe) were new. These changes progressed over the following 12 months and echocardiography confirmed severe pulmonary hypertension. A presumptive diagnosis of sarcoidosis-related veno-occlusive disease was made

pulmonary arteries accompanied by widespread, smoothly thickened interlobular septa, ground-glass opacification and pleural effusion) [67]. In a study of 22 subjects with sarcoidosis and associated PH, CT features of PVOD were observed in 86 % of patients with non-fibrotic sarcoidosis [61] (Fig. 13). Furthermore, veno-occlusive disease was histologically confirmed in 4 out of 5 patients who underwent transplantation [61].

Sarcoidosis-associated PH is usually mild to moderate and survival is primarily linked to the severity of lung disease. Nevertheless, in patients with advanced disease, PH is an independent malignant prognostic determinant, with a 5-year survival of approximately 60 % [61, 68–70].

Disease monitoring and prediction of outcome

Once the diagnosis of sarcoidosis has been established, serial CT is not necessary for disease monitoring in most patients. Furthermore, although no study has systematically evaluated the additional information provided by serial CT over lung function tests and chest radiography, CT may be too sensitive in some cases, revealing changes of limited, if any, clinical relevance. Nevertheless, CT may help discriminate between generally reversible (nodules, septal lines, consolidation) and reliably irreversible abnormalities (irregular coarse lines, cysts, honeycombing, traction bronchiectasis, parenchymal distortion), thus providing crucial prognostic information. CT is also more sensitive than pulmonary function tests in capturing the development of fibrotic abnormality, and thus has the potential to influence disease management [71]. In this regard, functional improvement on treatment is more likely in patients with predominant peribronchovascular thickening than in those with predominant bronchial distortion [72]. Yet, even in the case of advanced fibrotic disease, a trial of steroids might be warranted if a potentially reversible component is still visible on CT [27].

At present, serial CT cannot be recommended for routine use for monitoring disease or staging severity, both of which are multidisciplinary evaluations, although CT is able to identify early fibrotic changes that would be undetected on chest radiography. On the other hand, CT does have a major role in reconciling lung morphology and function in the many instances where there is clinically important discordance between symptomatic changes, pulmonary function trends and serial chest radiography.

Conclusion

Imaging makes a significant contribution to the diagnosis and management of patients with sarcoidosis. Conversely, its role in disease monitoring and prediction of outcome has not been conclusively established. CT is not necessary in all cases but may be decisive in atypical cases and for detecting pulmonary complications. Patterns of involvement and disease extent on CT appear to correlate with disease activity, but the clinical relevance of such correlations is unclear and requires further study.

References

1. (1999) Statement on sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 160:736–755
2. Baughman RP, Teirstein AS, Judson MA et al (2001) Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 164:1885–1889
3. Baughman RP, Culver DA, Judson MA (2011) A concise review of pulmonary sarcoidosis. Am J Respir Crit Care Med 183:573–581
4. Lynch JP 3rd, Ma YL, Koss MN, White ES (2007) Pulmonary sarcoidosis. Semin Respir Crit Care Med 28:53–74
5. Scadding JG (1961) Prognosis of intrathoracic sarcoidosis in England: a review of 136 cases after five years' observation. BMJ 2:1165–1172
6. Mañá J, Gómez-Vaquero C, Montero A et al (1999) Löfgren's syndrome revisited: a study of 186 patients. Am J Med 107:240–245
7. Spagnolo P, Grunewald J (2013) Recent advances in the genetics of sarcoidosis. J Med Genet 50:290–297
8. Mana J, Teirstein AS, Mendelson DS, Padilla ML, DePalo LR (1995) Excessive thoracic computed tomographic scanning in sarcoidosis. Thorax 50:1264–1266
9. Remy-Jardin M, Giraud F, Remy J, Wattinne L, Wallaert B, Duhamel A (1994) Pulmonary sarcoidosis: role of CT in the evaluation of disease activity and functional impairment and in prognosis assessment. Radiology 191:675–680
10. Leung AN, Brauner MW, Caillat-Vigneron N, Valeyre D, Grenier P (1998) Sarcoidosis activity: correlation of HRCT findings with those of ^{67}Ga scanning, bronchoalveolar lavage, and serum angiotensin-converting enzyme assay. J Comput Assist Tomogr 22:229–234
11. Nishino M, Lee KS, Itoh H, Hatabu H (2010) The spectrum of pulmonary sarcoidosis: variations of high-resolution CT findings and clues for specific diagnosis. Eur J Radiol 73:66–73
12. Criado E, Sanchez M, Ramirez J et al (2010) Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. Radiographics 30:1567–1586
13. Brauner MW, Grenier P, Mompoint D, Lenoir S, de Crémoux H (1989) Pulmonary sarcoidosis: evaluation with high-resolution CT. Radiology 172:467–471
14. Müller NL, Kullnig P, Miller RR (1989) The CT findings of pulmonary sarcoidosis: analysis of 25 patients. AJR Am J Roentgen 152:1179–1182
15. Raoof S, Amchentsev A, Vlahos I, Goud A, Naidich DP (2006) Pictorial essay: multinodular disease: a high-resolution CT scan diagnostic algorithm. Chest 129:805–815
16. Nunes H, Uzunhan Y, Gille T, Lamberto C, Valeyre D, Brillet PY (2012) Imaging of sarcoidosis of the airways and lung parenchyma and correlation with lung function. Eur Respir J 40:750–765
17. Hansell DM, Milne DG, Wilsher ML, Wells AU (1998) Pulmonary sarcoidosis: morphologic associations of airflow obstruction at thin-section CT. Radiology 209:697–704
18. Davies CW, Tasker AD, Padley SP, Davies RJ, Gleeson FV (2000) Air trapping in sarcoidosis on computed tomography: correlation with lung function. Clin Radiol 55:217–221

19. Terasaki H, Fujimoto K, Müller NL, Sadohara J, Uchida M, Koga T et al (2005) Pulmonary sarcoidosis: comparison of findings of inspiratory and expiratory high-resolution CA and pulmonary function tests between smokers and nonsmokers. AJR Am J Roentgen 185: 333–338
20. Rabinowitz JG, Ulreich S, Soriano C (1974) The usual unusual manifestations of sarcoidosis and the "hilar haze" - a new diagnostic aid. Am J Roentgenol Radium Ther Nucl Med 120:821–831
21. Bergin CJ, Bell DY, Coblentz CL, Chiles C, Gamsu G, MacIntyre NR et al (1989) Sarcoidosis: correlation of pulmonary parenchymal pattern at CT with results of pulmonary function tests. Radiology 171:619–624
22. Akira M, Kozuka T, Inoue Y, Sakatani M (2005) Long-term follow-up CT scan evaluation in patients with pulmonary sarcoidosis. Chest 127:185–191
23. Muller NL, Miller RR (1993) Ground-glass attenuation, nodules, alveolitis, and sarcoid granulomas. Radiology 189:31–32
24. Winterbauer RH, Belic N, Moores KD (1973) Clinical interpretation of bilateral hilar adenopathy. Ann Intern Med 78:65–71
25. Gawne-Cain ML, Hansell DM (1996) The pattern and distribution of calcified mediastinal lymph nodes in sarcoidosis and tuberculosis: a CT study. Clin Radiol 51:263–267
26. Trisolini R, Anevlavis S, Tinelli C, Orlandi P, Patelli M (2013) CT pattern of lymphadenopathy in untreated patients undergoing bronchoscopy for suspected sarcoidosis. Respir Med 107:897–903
27. Abehsera M, Valeyre D, Grenier P, Jaillet H, Battesti JP, Brauner MW (2000) Sarcoidosis with pulmonary fibrosis: CT patterns and correlation with pulmonary function. AJR Am J Roentgenol 174: 1751–1757
28. Nishimura K, Itoh H, Kitaichi M, Nagai S, Izumi T (1993) Pulmonary sarcoidosis: correlation of CT and histopathologic findings. Radiology 189:105–109
29. Honda O, Johkoh T, Ichikado K et al (1999) Comparison of high resolution CT findings of sarcoidosis, lymphoma, and lymphangitic carcinoma: is there any difference of involved interstitium? J Comput Assist Tomogr 23:374–379
30. Grenier P, Chevret S, Beigelman C, Brauner MW, Chastang C, Valeyre D (1994) Chronic diffuse infiltrative lung disease: determination of the diagnostic value of clinical data, chest radiography, and CT and Bayesian analysis. Radiology 191:383–390
31. Gross BH, Schneider HJ, Proto AV (1980) Eggshell calcification of lymph nodes: an update. AJR Am J Roentgenol 135:1265–1268
32. Spann RW, Rosenow EC 3rd, DeRemee RA, Miller WE (1971) Unilateral hilar or paratracheal adenopathy in sarcoidosis: a study of 38 cases. Thorax 26:296–299
33. Nakatsu M, Hatabu H, Morikawa K et al (2002) Large coalescent parenchymal nodules in pulmonary sarcoidosis: "sarcoid galaxy" sign. AJR Am J Roentgenol 178:1389–1393
34. Hawtin KE, Roddie ME, Mauri FA, Copley SJ (2010) Pulmonary sarcoidosis: the 'Great Pretender'. Clin Radiol 65:642–650
35. Reddy TL, Tominaga M, Hansell DM et al (2012) Pleuroparenchymal fibroelastosis: a spectrum of histopathological and imaging phenotypes. Eur Respir J 40:377–385
36. Padley SP, Padhani AR, Nicholson A, Hansell DM (1996) Pulmonary sarcoidosis mimicking cryptogenic fibrosing alveolitis on CT. Clin Radiol 51:807–810
37. (1997) Primary immunodeficiency diseases: report of a WHO Scientific Group. Clin Exp Immunol 109(Suppl 1):1–28
38. Cunningham-Rundles C, Bodian C (1999) Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 92:34–48
39. Ardeniz O, Cunningham-Rundles C (2009) Granulomatous disease in common variable immunodeficiency. Clin Immunol 133:198–207
40. Oksenhendler E, Gérard L, Fieschi C et al (2008) Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis 46:1547–1554
41. Fasano MB, Sullivan KE, Sarpong SB et al (1996) Sarcoidosis and common variable immunodeficiency. Report of 8 cases and review of the literature. Medicine 75:251–261
42. Mechanic LJ, Dikman S, Cunningham-Rundles C (1997) Granulomatous disease in common variable immunodeficiency. Ann Intern Med 127:613–617
43. Artac H, Bozkurt B, Talim B, Reisli I (2009) Sarcoid-like granulomas in common variable Immunodeficiency. Rheumatology 30:109–112
44. Tanaka N, Kim JS, Bates CA et al (2006) Lung diseases in patients with common variable immunodeficiency: chest radiographic, and computed tomographic findings. J Comput Assist Tomogr 30: 828–838
45. Park JE, Beal I, Dilworth JP, Tormey V, Haddock J (2005) The HRCT appearances of granulomatous pulmonary disease in common variable immunodeficiency. Eur J Radiol 54:359–364
46. Bouvry D, Mouthon L, Brillet P-Y et al (2013) Granulomatosis-associated common variable immunodeficiency disorder: a case-control study versus sarcoidosis. Eur Respir J 41:115–122
47. McLoud TC, Putman CE, Pascual R (1974) Eggshell calcification with systemic sarcoidosis. Chest 66:515–517
48. Spagnolo P, Luppi F, Roversi P, Cerri S, Fabbri LM, Richeldi L (2012) Sarcoidosis: challenging diagnostic aspect of an old disease. Am J Med 125:118–125
49. Maier LA (2002) Clinical approach to chronic beryllium disease and other nonpneumoconiotic interstitial lung diseases. J Thorac Imaging 17:273–284
50. Newman LS, Buschman DL, Newell JD Jr, Lynch DA (1994) Beryllium disease: assessment with CT. Radiology 190:835–840
51. Morgan W, Dinman B (1989) Pulmonary effects of aluminum. In: Gitelman HJ (ed) Aluminum and health. Dekker, New York
52. Kraus T, Schaller KH, Angerer J, Hilgers RD, Letzel S (2006) Aluminosis - detection of an almost forgotten disease with HRCT. J Occup Med Toxicol 1:4
53. Pena TA, Soubani AO, Samavati L (2011) Aspergillus lung disease in patients with sarcoidosis: a case series and review of the literature. Lung 189:167–172
54. Hours S, Nunes H, Kambouchner M et al (2008) Pulmonary cavitary sarcoidosis: clinico-radiologic characteristics and natural history of a rare form of sarcoidosis. Medicine 87:142–151
55. Israel HL, Ostrow A (1969) Sarcoidosis and aspergilloma. Am J Med 47:243–250
56. Wollschlager C, Khan F (1984) Aspergillomas complicating sarcoidosis. A prospective study in 100 patients. Chest 86:585–588
57. Tomlinson JR, Sahn SA (1987) Aspergilloma in sarcoidosis and tuberculosis. Chest 92:505–508
58. Pesle GD, Monod O (1954) Bronchiectasis due to aspergilloma. Dis Chest 25:172–183
59. Franquet T, Müller NL, Gimenez A, Guembe P, de La Torre J, Bagué S (2001) Spectrum of pulmonary aspergillosis: histologic, clinical, and radiologic findings. Radiographics 21:825–837
60. Sansom HE, Baque-Juston M, Wells AU, Hansell DM (2000) Lateral cavity wall thickening as an early radiographic sign of mycetoma formation. Eur Radiol 10:387–390
61. Nunes H, Humbert M, Capron F et al (2006) Pulmonary hypertension associated with sarcoidosis: mechanisms, hemodynamics and prognosis. Thorax 61:68–74
62. Corte TJ, Wells AU, Nicholson AG, Hansell DM, Wort SJ (2011) Pulmonary hypertension in sarcoidosis: a review. Respirology 16:69–77
63. Weitzman S, Pocock WA, Hawkins DM, Barlow JB (1974) Observer variation in radiological assessment of pulmonary vasculature. Br J Heart 36:280–290
64. Matthay RA, Schwarz MI, Ellis JH et al (1981) Pulmonary artery hypertension in chronic obstructive pulmonary disease: determination by chest radiography. Invest Radiol 16:95–100
65. Tan RT, Kuzo R, Goodman LR (1998) Utility of CT scan evaluation for predicting pulmonary hypertension in patients with parenchymal

lung disease. Medical College of Wisconsin Lung Transplant Group. Chest 113:1250–1256
66. Devaraj A, Wells AU, Meister MG, Corte TJ, Hansell DM (2008) The effect of diffuse pulmonary fibrosis on the reliability of CT signs of pulmonary hypertension. Radiology 249:1042–1049
67. Resten A, Maitre S, Humbert M et al (2004) Pulmonary hypertension: CT of the chest in pulmonary venoocclusive disease. AJR Am J Roentgenol 183:65–70
68. Shorr AF, Davies DB, Nathan SD (2003) Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest 124: 922–928
69. Arcasoy SM, Christie JD, Pochettino A et al (2001) Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. Chest 120:873–880
70. Shorr AF, Davies DB, Nathan SD (2002) Outcome for patients with sarcoidosis awaiting lung transplantation. Chest 122:233–238
71. Gafà G, Sverzellati N, Bonati E et al (2012) Follow-up in pulmonary sarcoidosis: comparison between HRCT and pulmonary function tests. Radiol Med 117:968–978
72. Naccache JM, Lavole A, Nunes H et al (2008) High-resolution computed tomographic imaging of airways in sarcoidosis patients with airflow obstruction. J Comput Assist Tomogr 32:905–912