Typical and atypical radiological manifestations of thoracic sarcoidosis with their pathologic correlation.

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Learning objectives

1. Describe typical and atypical radiological features of sarcoidosis in chest radiograph and CT and their pathological correlation.


3. Perform sarcoidosis staging on the basis of the chest radiograph.
Background

Sarcoidosis is a systemic granulomatous disease of unknown aetiology. Although it may involve any organ, thoracic manifestation is most common and is responsible for most of mortality and morbidity[1]. Despite high prevalence of pulmonary involvement, most patients are asymptomatic or present with nonspecific symptoms. Thus a radiologist plays a vital role in establishing early diagnosis and further management.
Findings and procedure details

Diagnosis of Sarcoidosis

In general, according to the international 1999 consensus, sarcoidosis should be diagnosed on the basis of correlating clinical symptoms as well as histologic and radiologic findings. Biopsy should be obtained whenever possible. Usually transbronchial biopsy is recommended as primary biopsy site. Biopsy of other affected body regions may be useful, excluding erythema nodosum which does not contain granulomas. It should be stressed that histological findings alone are not diagnostic for sarcoidosis. Similar pathology manifestation can be seen in other granulomatous diseases. Moreover, if biopsy is contraindicated or patient refuses to receive one, diagnosis in some cases can be made on the basis of clinicoradiological correlation alone. In a setting of typical clinical presentation, reliability of diagnosis established in such a way depends on radiological stage of the disease. It is highest in stage I (98%) and stage II (89%) but is much worse in stages III (52%) and stage 0(23%)[1].

Histologic Findings

The most prominent pathologic finding in the sarcoidosis is presence of the granulomatous inflammation. Granulomas(Fig. 1 on page 11) are composed of a central core of monocyte derived epithelioid histiocytes, multinucleated giant cells. The inner part is encircled by lymphocytes, mostly CD4+ T helper cells, but also occasional CD8+ T cells, regulatory T cells, B cells and fibroblasts are present. The multinucleated giant cells may display inclusions such as asteroid bodies and Schaumann bodies. Granulomatous inflammation may completely resolve, however minor residual fibrotic changes are often seen. Fibrous tissue is usually initially formed at the periphery of a granuloma next to the adjacent normal connective tissue. Gradually it extends inward, leading to the complete granuloma fibrosis. Granulomas in the lung have a distinctive distribution - they are most prominent in the airway mucosa, perivascularly, in the interstitial tissue of the interlobular septa and pleura[1,2].

Diagnostic Imaging in Sarcoidosis

Thoracic radiological manifestations of sarcoidosis are observed at some stage of the disease in up to 90% of patients(Table 1 on page 11, Table 2 on page 12). Chest radiograph in most cases is the first imaging study performed and in some cases provides enough information to indicate the diagnosis. CT studies are more sensitive and allow to detect subtle parenchymal and lymph nodes abnormalities[3].

Chest radiograph
Pathologic chest radiograph findings are reported in 60% to 70% of patients with sarcoidosis. The pattern of these chest radiographic abnormalities is a basis of classic sarcoidosis staging system (Fig. 2 on page 13).

In 1961 Scadding presented his classic work describing staging system based on chest radiograph findings [4]. Even though this classification is now more than 50 years old, it is still used because of its prognostic value.

Stage I is described as isolated bilateral hilar lymphadenopathy which may be accompanied by paratracheal lymph node enlargement. Stage II is lymphadenopathy with parenchymal lung disease. Stage III is parenchymal involvement without hilar adenopathy. Stage IV consists of fibrosis.

At time of presentation, most patients (up to 50%) have stage I disease. More advanced stages are increasingly infrequent at time of presentation, stage II is seen in 25-30% of cases, stage III in 10-12% and stage IV in 0%. Chest radiograph stage correlates well with disease prognosis. Spontaneous remission is observed in 60%-90% of patients with stage I disease, in 40%-70% with stage II, in 10%-20% with stage III and in 0% with stage IV. It is important to notice that correlation between stage of the disease and the prognosis is only valid for the chest radiograph findings. CT due its superior sensitivity can detect even minute parenchymal abnormalities in patients with no such changes detectable on chest radiographs [5].

CT

According to American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders Consensus Statement on Sarcoidosis, HRCT is indicated in 3 cases [1]:

1 Verifying diagnosis in patients with atypical chest radiograph or clinical findings

2 Clinical suspicion with normal chest x ray

3 Detecting pulmonary complications

In case of normal and atypical chest radiograph findings CT provides superior sensitivity in detecting subtle, small nodular and reticular opacities allowing to narrow the differential diagnosis list.

In patients with advanced sarcoidosis or preexisting conditions it may be hard to detect subtle complications on chest radiograph. CT increases detection rate of superimposed infections and coexisting malignancy.

Another role of CT in sarcoidosis management is distinguishing active inflammation from irreversible fibrosis. Imaging findings that indicate potentially reversible granulomatous inflammation include small nodules, ground-glass and alveolar opacities. On the other
hand, volume loss, honeycombing, traction bronchiectasis and architectural distortion suggests irreversible fibrosis.

**Typical and atypical lymphadenopathy patterns.**

The most typical chest radiograph lymphadenopathy pattern(Fig. 3 on page 14), occurring in 85-95% of diagnosed patients, is bilateral, symmetric, well-defined hilar lymph node enlargement. Right paratracheal lymph nodes are enlarged in 75% of cases. Together they form a sign named Garland's triad or a 1-2-3 sign. Lymphadenopathy in other localizations is less frequent, it is found in 50-75% in the aortopulmonary window, 20% in the subcarinal region, 10-15% in the anterior mediastinum, <5% in the posterior mediastinum, <5% intramammary. Lymph node enlargement usually resolves in 2 years' time, however it may persist for many years. Recurrence following resolution is uncommon. Lymph node calcifications are reported in chest X-rays of up to 20% of patients with sarcoidosis lasting for 10 years or more[6].

CT is particularly useful in detecting lymph nodes abnormalities in patients with prominent pulmonary fibrosis which can impede chest radiograph reading. Due to its superior sensitivity CT displays a different pattern of lymphadenopathy in patients who have sarcoidosis(Fig. 4 on page 15). Right lower paratracheal lymph nodes are enlarged in 100%; subaortic and paraaortic lymph nodes (lymph nodes of aortopulmonary window) in 95%; hilar in 90%, prevascular in 65%; in posterior mediastinum in 15%. Calcifications are observed in CT in 25-50% of patients, and its prevalence increases with disease duration(Fig. 4 on page 15). In contrast to densely calcified lymph nodes characteristic for tuberculosis, sarcoid lymph nodes often display a hazy or eggshell calcification pattern[3].

Even though lymphadenopathy in sarcoidosis is often prominent, it rarely causes any symptoms.

In fact, sarcoidosis is most common cause of asymptomatic bilateral hilar lymph node enlargement. Differential diagnosis of such finding includes infection, malignancy and pneumoconiosis however, they usually are present with some clinical symptoms.

Pathologic manifestation of lymph node involvement is characterized by diffuse replacement of normal tissue by granulomas(Fig. 5 on page 16). At the beginning granulomas are discrete and active but with disease progression they coalesce together and display progressive fibrosis. Finally leading to replacement of entire lymph node with fibrotic tissue.

**Typical and atypical parenchymal manifestations.**

The most characteristic CT abnormality in patients with pulmonary sarcoidosis consists of small (typically 2-4 mm), relatively well defined, rounded nodules, displaying a
perilymphatic distribution (Fig. 6 on page 17, Fig. 7 on page 18). Nodules can be visible most often in the subpleural (including fissures) and peribronchovascular interstitium, but can also be present adjacent to parahilar vessels and bronchi, in the centrilobular regions as well as in the interlobular and intralobular septa. There is a considerable variation in the involvement of these structures among individual patients. They are most frequently bilateral and symmetric, predominantly seen in upper and middle lung zones. However, nodules can also display focal or asymmetric pattern. In that case patchy abnormal areas of lung can coexist with unaffected lung tissue. In case of patients with extensive disease, micronodules rarely can appear to be randomly distributed. This pattern is seen in less than 1% of patients and should raise a question of different disease diagnosis. Miliary tuberculosis, fungal infections and metastatic disease must be excluded prior to making diagnosis of sarcoidosis. Other rarely seen distribution is pseudo tree-in-bud pattern. It is present in case of clusters of nodules arising in proximity of the branching centrilobular artery mimicking small airways disease [7].

Occasionally nodules can calcify which can coexist with lymph nodes calcification or be an isolated finding.

Although sarcoid granulomas arise as micronodular lesions, they may coalesce over time, forming larger lesions - macronodules. Such changes, observed in 15-25% of patients, take appearance of irregular consolidation measuring 1-4 cm which may have air bronchogram (Fig. 8 on page 19). On periphery of consolidation individual small nodules can be spotted - an image named "galaxy sign" (Fig. 9 on page 20). Even though these consolidations are commonly called "alveolar sarcoidosis", in fact they are the result of numerous interstitial micronodules coalescing together. Occasionally sarcoidosis may display reversed halo sign (atol sign). It initially was thought to be pathognomonic for cryptogenic organizing pneumonia but now is known to occur in number of other diseases including sarcoidosis.

In about 10-20% of individuals with parenchymal abnormalities, patchy ground glass opacities are seen on CT scans (Fig. 10 on page 21). They are result of interstitial granulomas inflammation and fibrotic changes causing small airways compression. Groundglass opacities are seen simultaneously with other parenchymal findings and are often superimposed on perilymphatic nodules.

Infrequently sarcoidosis can manifest as isolated mass-like opacity (Fig. 11 on page 22). In such context smaller accompanying nodules may imitate metastases while small perilymphatic nodules could be mistaken for lymphangitis carcinomatosa.

Pathologic findings in pulmonary disease are similar to those found in the lymph nodes. Granulomas are most commonly found in perivascular, pleural and interlobular septal interstitial tissue as well as airway mucosa. Initially discrete with disease progression they become confluent and associated with fibrosis. Since disease is not uniform in whole lung and local severity varies greatly it results in nodular thickening of interstitium which can be appreciated in the low magnification microscopy as well as HRCT (Fig. 12 on page...
23). It should be stressed that lung parenchyma is relatively spared. Usually only small foci of granulomatous inflammation can be seen in it. However in rare cases parenchymal involvement may be more extensive resulting in relatively big masses which can measure even several centimeters.

Cystic and Cavitary Disease

True cavitary sarcoidosis is exceedingly rare, more often pseudocavity lesions are seen. They are often reported in patients with fibrotic changes and represent bullae or bronchiectasis.

True cavities are present in only about 0.8% of cases. Thus such finding should rise question of superimposed infectious disease capable of cyst formation - especially tuberculosis or fungal infections. Mycetoma formation may be a result of invasive fungal infection but in most cases it is seen in patients with super infected bullae or cysts in fibrotic stage of the disease(Fig. 13 on page 24, Fig. 14 on page 25)[5].

Fibrotic Changes

In most patients, parenchymal abnormalities resolve over time. However, approximately 20% of patients, develop some degree of fibrosis. Since fibrosis develops in areas previously affected by granulomatous inflammation, it is usually patchy and predominantly localized in upper and middle lung zones(Fig. 15 on page 25).

There are three main types of lung fibrosis[7]:

1 bronchial distortion

2 linear scarring

3 honeycombing

Each type tends to be associated with distinctive pulmonary function abnormality. Obstructive lung function is associated with bronchial distortion, while restrictive lung disease coexists with honeycombing. Reticular scarring can be asymptomatic or show only mild lung function abnormalities.

Common sign of early fibrosis in sarcoidosis is coexistence of reticular opacities, distortion of pulmonary fissures and posterior displacement of main and/or upper lobe bronchi. This is due to increasing loss of upper lobes volume.

Progression of fibrosis results in central distortion of parahilar bronchi and vessels associated with conglomerates of fibrous tissue(Fig. 16 on page 26).
Subsequent advancement of fibrosis causes increasing bronchial distortion, manifesting as sharp angle of central airways division associated with traction bronchiectasis. Coexistence of fibrous central conglomerates and bronchial distortion is characteristic for small group of diseases including: sarcoidosis, tuberculosis, and pneumoconiosis.

Honeycombing can be seen in patients with long standing fibrosis. They most frequently are located in subpleural areas of the middle and upper lung zones. Typically there is lower lung zone sparing. However, if honeycomb like cysts are present in basal regions, they can be mistaken for usual interstitial pneumonia(Fig. 17 on page 27)[5].

Extensive fibrosis can lead to pulmonary arterial hypertension which in turn can cause right heart failure. In CT it can manifest as enlargement of: main pulmonary artery, right and left pulmonary arteries and right ventricular.

**Airway Involvement**

Airway involvement in sarcoidosis is relatively common, seen in approximately 65% of patients. In vast majority of cases it is asymptomatic, only 2%-8% of patients have any related symptoms. The most common manifestations of airway involvement include bronchial wall thickening and endobronchial lesions. In case of small bronchi endobronchial granulomas and accompanying fibrosis can lead to their obstruction which may result in CT image of a mosaic attenuation pattern on inspiratory images and air trapping on expiratory studies[5].

Air trapping( Fig. 18 on page 27) is a very common but nonspecific manifestation of sarcoidosis reported in up to 95% of patients. In about 10% of cases it is reported to be the only finding. There is no difference in the extend of the air trapping among stages of disease. Most patients with sarcoidosis show air trapping in CT in locations suggestive of small airways disease. However, some studies have showed air trapping present at the level of the secondary lobule and patterns suggestive of sublobular, subsegmental, or even segmental involvement. Air trapping may be the only persisting manifestation seen even after regression of parenchymal and lymph node abnormalities[7].

In the rare cases enlarged peribronchial lymph nodes or endobronchial lesions can lead to bronchial obstruction(Fig. 19 on page 27)leading to atelectasis(Fig. 20 on page 28). Right middle lobe bronchus is most frequently affected because of its acute angle of origin, significant length, relatively narrow diameter and proximity of lymph nodes draining whole right lung.

**Pleural Disease**

Pleural involvement in sarcoidosis patients is rare, present in 1%-4% of cases. It most commonly manifest as a pleural thickening(Fig. 21 on page 29, Fig. 22 on page 29). Pleural effusion(Fig. 22 on page 29) are second most common pleural
finding they usually are exudative or transudative, hemothorax or chylothorax are rarely reported. Usually pleural effusions are minimal and resolve spontaneously within 2-3 months. However, there have been singular reports of massive pleural effusions. Pleural calcifications can only occasionally be seen[5].

**Pleural Plaquelike Opacities**

Pleural plaquelike opacities are well defined, subpleural opacities with irregular border usually found in upper and middle lung zones. Sometimes simultaneous pleural effusion can be seen.

Pleural plaquelike opacities are not pathognomonic for sarcoidosis and can be present in silicosis, and coal-worker's pneumoconiosis[5].
Fig. 1: Sarcoid granuloma is a well-defined collection of epithelioid histiocytes (Ep) and multinucleated giant cells (MGC), surrounded by lymphoid cells (Lym) and/or concentric fibrosis (Fib). Giant cells sometimes contain so-called "asteroid bodies" (As) but this finding is not specific for sarcoidosis. Sarcoid granulomas are usually non-necrotizing but necrosis does not exclude sarcoidosis! (Hematoxylin & eosin staining, magn. X 400).

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### CT manifestations of early Sarcoidosis

<table>
<thead>
<tr>
<th>Most common</th>
<th>Less common</th>
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<tbody>
<tr>
<td>Small, well-defined nodules in perilymphatic distribution</td>
<td>Random distribution of small nodules</td>
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<tr>
<td>Symmetric hilar lymph node enlargement</td>
<td>Isolated nodules</td>
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<td></td>
<td>Parahilar predominance of nodules in the upper lobes</td>
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<td></td>
<td>Nodules &gt;1 cm, masses, or areas of consolidation</td>
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<tr>
<td>Galaxy sign</td>
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<tr>
<td>Focal, patchy ground-glass opacity</td>
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<td></td>
<td>A patchy distribution of abnormalities</td>
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<tr>
<td>Hazy or eggshell lymph node calcifications</td>
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<tr>
<td>Thickening or nodularity of airways walls</td>
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<tr>
<td>Narrowing of airways</td>
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<td>Mosaic perfusion or air trapping</td>
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**Table 1: CT manifestations of early Sarcoidosis**

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### CT manifestations of Fibrotic Sarcoidosis

<table>
<thead>
<tr>
<th>Description</th>
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<tbody>
<tr>
<td>Peribronchovascular interstitial thickening – reticular changes</td>
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<tr>
<td>Interlobular septal thickening</td>
</tr>
<tr>
<td>Honeycombing in upper and middle lung zones</td>
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<tr>
<td>Partial or complete regression of nodular opacities</td>
</tr>
<tr>
<td>Conglomerate parahilar masses associated with bronchiectasis</td>
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<tr>
<td>Posterior displacement of main and/or upper lobe bronchi</td>
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<tr>
<td>Fissures distortion</td>
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<tr>
<td>Thickening or nodularity of airways walls</td>
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<td>Narrowing of airways</td>
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<td>Mosaic perfusion or air trapping</td>
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</table>

**Table 2: CT manifestations of fibrotic sarcoidosis**

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Fig. 2: Frontal chest radiographs of patients with: A - Stage I - bilateral hilar and paratracheal lymph node enlargement. B - Stage II - diffused, multiple small nodular opacities predominantly located in the upper lung lobes and bilateral symmetric hilar lymph node enlargement. C - Stage III - diffused, multiple small nodular opacities predominantly located in the upper lung lobes D - Stage IV - prominent upper zones fibrosis and volume loss.

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**Fig. 3**: Frequency of lymphadenopathy in patients with sarcoidosis 1) Hilar lymph nodes 95% 2) Right paratracheal lymph nodes 75% 3) Aortopulmonary window lymph nodes 50% 4) Subcarinal lymph nodes 20%

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Fig. 4: Typical (a, b) and atypical (c, d) lymphadenopathy patterns in two patients with sarcoidosis. (a,b) Axial contrast enhanced CT scans show typical bilateral and symmetric hilar and subcarinal lymphadenopathy(blue arrows). (c) Axial unenhanced CT scan shows calcifications in hilar lymph nodes(red arrows). (d) Coronal reformation of unenhanced CT shows bilateral eggshell-like calcifications of hilar and mediastinal lymph nodes(red arrows).

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**Fig. 5:** Lymph node involvement - confluent aggregates of sarcoid granulomas (Gr) effaced the structure of a lymph node, only a couple of lymphoid follicles (LF) left intact (Hematoxylin & eosin staining, magn. X 40).

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Fig. 6: Aggregates of granulomas (Gr) concentrated around bronchovascular bundles containing bronchioles (Br) and small pulmonary arteries (PA) - characteristic distribution of lesions (Hematoxylin & eosin staining, magn. X 40).

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Fig. 7: Axial CT scan and coronal reconstruction show typical perilymphatic distribution of micronodules with upper lung zones domination.

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Fig. 8: Enhanced axial CT scan showing areas of consolidations (blue arrows) resulting from confluence of multiple small nodules.

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Fig. 9: Axial CT scan showing area of consolidation (blue arrow) with surrounding multiple small satellite nodules - appearance of "galaxy sign".

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**Fig. 10**: Axial CT scan showing patchy areas of ground glass attenuation (blue arrows).

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Fig. 11: Axial CT scan showing mass mimicking lung cancer (blue arrow) in patient with sarcoidosis.

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Fig. 12: Aggregates of granulomas (Gr) are separated by unchanged lung tissue (Lung) - characteristic microscopic distribution in less advances stages of the disease (Hematoxylin & eosin staining, magn. X 40).

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**Fig. 13:** Axial CT scan and coronal reconstruction showing thick wall cavity with mycetoma (blue arrows) in the right upper lung lobe.

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**Fig. 14:** Fungal (consistent with Aspergillus spp.) colony. The hyphae show frequent septation and branch at acute angles (Grocott staining, magn. X 100 and 600).

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Fig. 15: Axial CT scan and coronal reconstruction show prominent typical pattern of fibrosis. There is severe upper zone volume loss associated with architectural distortion, cystic spaces (blue arrows) and traction bronchiectasis.

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**Fig. 16:** Fibrotic area (Fib) in more advanced stages of sarcoidosis surrounded by aggregates of granulomas (Gr) (Hematoxylin & eosin staining, magn.x 40).

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![Fig. 16](image1.png)

**Fig. 17:** Axial CT scan and coronal reconstruction show atypical pattern of fibrosis in sarcoidosis - most prominent in lower lung zones.

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![Fig. 17](image2.png)

**Fig. 18:** Axial CT scans show extensive air trapping (blue arrows).

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![Fig. 18](image3.png)
**Fig. 19:** Axial CT scan shows narrowing of right upper lobe bronchus (blue arrow).

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**Fig. 20:** Axial CT scan and coronal reconstruction show atypical finding of right upper lobe atelectasis (blue arrows).
**Fig. 21:** Axial CT scan shows right pleural effusion (blue arrows) and subtle left pleural thickening.
Fig. 22: Pleural involvement - sarcoid granulomas are seen in thickened pleura (asterisks) and in a subpleural region - characteristic distribution of lesions (Hematoxylin & eosin staining, magn. x 40).

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Conclusion

Sarcoidosis is often asymptomatic and clinical presentation in majority of cases is not specific thus a radiologist plays a vital role in its diagnosis.

Sarcoidosis can manifest in a variety of different patterns, it is necessary to recognize both typical and atypical presentations.

Similar radiological changes may occur in other diseases (Table 3 on page 32), hence correlation of imaging features with pathologic findings aid to establish final diagnosis.
<table>
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**Table 3:** Sarcoidosis stage dependent differential diagnosis.

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References