Atypical radiological manifestations of thoracic sarcoidosis: A review and pictorial essay

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Abstract:
Thoracic sarcoidosis is a common disease, with well-described and recognizable radiographic features. Nevertheless, most physicians are not familiar with the rare atypical often-confusing manifestations of thoracic sarcoid. Although these findings have been previously reviewed, but more recent advances in imaging and laboratory science, need to be incorporated. We present a review of literature and illustrate the review with unpublished data, intended to provide a more recent single comprehensive reference to assist with the diagnosis when atypical radiographic findings of thoracic sarcoidosis are encountered. Thoracic involvement accounts for most of morbidity and mortality associated with sarcoidosis. An accurate timely identification is required to minimize morbidity and mortality. It is essential to recognize atypical imaging findings and relate these to clinical manifestations and histology.

Key words:
Atypical, cardiology, chest, radiology, sarcoidosis

The lungs and mediastinal lymph nodes are involved in over 90% cases with thoracic sarcoidosis, accounting for most morbidity and mortality.[1] The incidence of sarcoidosis has considerable variation and is based on geographical regions, gender race and ethnicity, but familial clustering is also described.[2] Some parts of the world report a lower incidence, with the disease probably masked by other granulomatous disease.[3–5] In general, sarcoidosis affects young adults 20–29 years of age with a slightly higher prevalence in females.[6] Approximately, half of the patients are asymptomatic usually present with non-specific symptoms including cough, dyspnea, fatigue, night sweats and erythema nodosum. However, 50% of patients are asymptomatic, with incidental findings on chest radiographs (CXR).[7] Pulmonary function tests generally exhibit a restrictive ventilatory defect with decreased volumes and decreased carbon monoxide diffusing capacity.[8] Endobronchial sarcoidosis, may present with an obstructive ventilatory pattern, which carries a poor prognosis and is associated with increased morbidity, greater incidence of respiratory symptoms and a radiographic stage 4 diseases.[9] Diagnosis is based on compatible clinical and radiological findings and histological finding of non-caseating epithelioid cell granulomas and the elimination of other granulomatous disease.[6,10] Siltzbach devised a radiographic staging system 42 years ago, which is still used because of its prognostic value. Siltzbach divides pulmonary sarcoidosis into five stages: Stage 0, normal appearance at CXR; stage 1, with lymphadenopathy only; stage 2, with lymphadenopathy and lung parenchymal lung; stage 3, lung parenchymal disease only; and stage 4, with pulmonary fibrosis.[10] Radiological findings are atypical in, 25–30% of cases. These atypical findings include unilateral or asymmetric lymphadenopathy, necrosis or cavitation, large opacity, ground glass opacity opacity [Figure 2a and b, Figure 3c and d and Figure 4a and c], an airway abnormality and pleural effusion.[11]

Radiologists and Pulmonologist need to familiarize themselves with the wide range of imaging findings in sarcoidosis, crucial in arriving at an accurate diagnosis, which may be unfamiliar to most Radiologists, causing difficulty for making a correct diagnosis.[12]

Radiological Manifestations

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology associated with a wide spectrum of clinical and imaging manifestations. Diagnosis is made on compatible clinical presentation and radiological manifestations supported by histologic findings. Familiarity with the clinical and radiologic features of sarcoidosis plays a pivotal role in achieving a diagnosis. The clinical course and prognosis of sarcoidosis is highly variable, often correlating with the mode of onset.
Imaging plays a decisive role in the management of intrathoracic sarcoidosis and often-histological diagnosis are not required when imaging findings are characteristic. Thoracic radiologic abnormalities occur in over 90% in patients with sarcoidosis at some stage of the disease, whilst 20% develop chronic lung disease leading to pulmonary fibrosis. A CXR is usually the first imaging technique employed in diagnosis in suspected intrathoracic sarcoidosis, computed tomography (CT) is more sensitive in the detection of lymphadenopathy and subtle parenchymal disease. A number of radiological abnormalities have been described in pulmonary sarcoidosis and include bilateral hilar lymphadenopathy and interstitial lung disease. High resolution computed tomography (HRCT) typically shows micronodules with a perilymphatic distribution, fibrotic changes and bilateral perihilar opacities [Figure 1].

Atypical Manifestations

Atypical manifestations of sarcoidosis include hemoptysis, chest pain and predominant pleural or proximal bronchial involvement. Diffuse ground glass appearance and cavitating lesions may be seen on a CXR. Atypical sarcoidosis can be definitively confirmed by showing non-caseous tuberculoid granuloma on histology.9

With atypical findings, a meticulous analysis of the clinical presentation often combined with histological examination of the involved tissue is necessary to achieve a diagnosis. Unusual findings include predominant ground glass opacity, excavated consolidation or masses, honeycombing, pleural involvement or necrotizing sarcoidosis. Other manifestations that may pose diagnostic challenges include stage IV sarcoidosis, pulmonary hypertension, bronchial stenosis and pulmonary aspergillosis.10

Park et al. studied patients with atypical radiological findings in pulmonary sarcoidosis. According to the authors, radiological findings are atypical in, 25-30% of cases, which may be unfamiliar to most Radiologists, causing difficulty for making a correct diagnosis.11 These atypical findings include unilateral or asymmetric lymphadenopathy, necrosis or cavititation, large opacity, ground glass opacity [Figures 2, 3c and 4] an airway and pleural abnormalities. Radiologists need to familiarize themselves with the wide range of imaging findings in sarcoidosis, which is crucial in arriving at an accurate diagnosis.11

Rockoff and Rohatgi using the information derived from a systematic review of the literature and clinical material from their institutions have determined and tabulated the relative incidence and a classification of unusual thoracic manifestations of sarcoidosis.12 These include lesions of the osseous, pleural, mediastinal, hilar, bronchial, pulmonary parenchymal, vascular and cardiac structures [Figures 5-11].

Rubinstein and associates analyzed the CXR of 85 Jewish patients with biopsy-proven pulmonary sarcoidosis to review the frequency of unusual findings. In 29% patients, the initial CXR revealed the following: Large pulmonary nodules in 11, an acinar pattern in 10 and right hilar lymphadenopathy in 3 and a large pericardial effusion in one patient. Biopsy material was available in all, which include an open lung biopsy in 13 patients, by anterior mediastinoscopy in four,
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by transbronchial lung biopsy in three, by skin biopsy in three and the liver and splenic tissue examination in two patients.\(^{[13]}\)

Criado et al.\(^{[16]}\) reported unusual manifestations, of pulmonary sarcoidosis. Example of such manifestation includes mass-like or alveolar opacities [Figures 2, 3 a-c, 12], honeycomb [Figure 13], miliary shadowing [Figures 14 and 15], mosaic attenuation [Figures 4 and 16], tracheobronchial involvement, pleural disease [Figures 17 and 18] and aspergillomas [Figures 19 and 5].
Avital et al.[17] analyzed the radiographic thoracic findings in 100 consecutive patients with biopsy-proven sarcoidosis over a 10 years period. Mediastinal adenopathy occurred in 89% whilst lung parenchymal involvement occurred in 60% of the patients. The lung parenchymal changes showed a variety of patterns: Ground-glass attenuation (39%), multiple small nodules in (44%) and irregular thickening of the interlobular septa (16%). Larger lung masses/nodules measuring 1-3 cm (12%) patients and frank consolidations (12%) [Figure 20] is an example of air space consolidation. Pleural thickening with subpleural nodules occurred in 17% patients [Figures 21 and 22].

Adenopathy
Bilateral hilar lymphadenopathy is the most common presentation of sarcoidosis. Such a pattern may also occur in other granulomatous disease. In the absence of symptoms or signs, sarcoidosis is the most common cause of bilateral lymph node enlargement.[18]

Atypical lymphadenopathy includes unilateral hilar adenopathy and adenopathy in unusual locations such internal mammary, paravertebral and retrocrural regions, also it may calcify. With such findings other pathology such as lymphoma or tuberculosis need exclusion [Figures 23-27]. Isolated unilateral hilar lymph node enlargement particularly on the right is seen in less than 5% of cases. Enlargement of mediastinal lymph nodes without hilar lymph node enlargement is even less common, atypical patterns of lymphadenopathy occur more frequently in patients older than 50 years, unilateral hilar adenopathy usually appears in early stage sarcoidosis, which eventually become bilateral and may extend to other mediastinal lymph nodes.[14,19-23]

Pulmonary nodules and masses
Atypical parenchymal lung nodules and lung masses are seen in up to a quarter of patients with sarcoidosis.[22-25] These multiple parenchymal nodules/masses are bilateral and usually peripheral and the peripheral regions on CT [Figures 2 and 3]. An air-bronchogram is seen in some nodules and less than 3% of the opacities may cavitate. Often, peripheral small satellite nodules producing surround these masses, an appearance, termed the “galaxy sign.”[25] This sign is non-specific and has been described with other granulomatous diseases and neoplasms.

Wegener mimics
Armengol et al. described a 21-year-old non-Caucasian who presented with pulmonary nodular infiltration and sinonasal involvement revealing sarcoidosis suggestive of Wagener’s disease. Thoracic and sinus CT scan showed multiple large cavitating large lung nodules and micro nodules, hilar lymphadenopathy and sinus mucosal thickening. Angiotensin-converting-enzyme (ACE) levels were raised at 120 UI/L. Patient responded to corticosteroids; at 8-month-follow-up, patient was asymptomatic while receiving prednisone 22.5 mg/day.[26]

Pseudo-tumoral manifestations
Intrathoracic pseudo-tumors have been described as a rare

![Figure 10](attachment:cardiac_sarcoidosis.png)

**Figure 10:** Atypical presentation of cardiac sarcoid in a 62-year-old woman with history of heart block: (a) Short axis phase sensitive inversion recovery sequence show a full thickness transmural enhancement in the mid-part of antero- and inferoseptal segments. (b) Short axis phase-sensitive inversion recovery sequence shows wall thickening and transmural enhancement in the mid-inferolateral and inferior segments. Although the enhancement patterns are suggestive of an infarct, the patchy in a non-vascular distribution is suggestive of non-ischemic pattern of enhancement. Biopsy showed cardiac sarcoidosis

![Figure 11](attachment:cardiac_sarcoidosis2.png)

**Figure 11:** Unusual appearances of cardiac sarcoidosis in a 63-year-old man with biopsy confirmed pulmonary sarcoidosis: (a) Axial HASTE-MR image shows enlarged lymph nodes in the paratracheal and hilar regions. (b) 4-chamber delayed enhancement image shows near full thickness transmural enhancement in the basal lateral wall and patchy areas of enhancement in the septal segments. In addition, there is also patchy enhancement in the right ventricular myocardium. There is relatively low signal intensity in the blood pool. These appearances are suggestive of diffuse sarcoidosis

![Figure 12](attachment:stage_4_sarcoidosis.png)

**Figure 12:** (a) (1) A chest radiographs on a 44-year-old woman with stage 4 sarcoidosis disease. (b) (2 and 3) CT shows confluent alveolar opacities. Note small nodules mostly along the bronchovascular bundles, giving the bronchi and vessels a beaded appearance, traction bronchiectasis and cyst formation mainly mid-zones
manifestation of pulmonary sarcoidosis. Louzir et al. reported three cases including two with multiple lesions, which mimicked pulmonary metastases in women, aged 31 years and 30 years. A third, 51-year-old male smoker had opacity in the upper left lobe on a CXR then developed endobronchial

![Image](Figures/Al-Jahdali_atypical_radiological_manifestation_of_sarcoidosis.png)

**Figure 13:** Axial CT scans on a 58-year-old woman with chronic fibrotic sarcoidosis (1 and 2) reveal bronchial distortion pattern with bronchovascular deformation, predominantly peripheral. The bronchi are angulated and irregularly dilated. Note the honeycomb – appearance at the lung bases. Unlike the typical subpleural cysts in sarcoidosis, this distribution is atypical and mainly the lung bases are involved. This distribution of honeycomb pattern may cause confusion with idiopathic pulmonary fibrosis.

**Figure 14:** Two different patients presenting with miliary sarcoidosis. (1) The CXR shows of the first patient shows very subtle miliary shadowing, confirmed on HRCT (2). (3) The CXR of the second patient shows extensive miliary shadowing. Work up for other causes of miliary shadowing in both cases include tuberculosis were negative, and bronchoscopic biopsies in both cases revealed non-caseating granulomas and both responded to treatment with steroid.

![Image](Figures/Al-Jahdali_atypical_radiological_manifestation_of_sarcoidosis.png)

**Figure 15:** HRCT in a young patient shows uniformly small, bilateral nodules in a miliary pattern. The patient also had mediastinal and hilar adenopathy. This is stage II disease (Courtesy eMedicine Khan et al.)

**Figure 16:** Axial CT through the mediastinum show mosaic attenuation.

![Image](Figures/Al-Jahdali_atypical_radiological_manifestation_of_sarcoidosis.png)

**Figure 17:** (a) (1) (CXR) of 49 years old man with known sarcoidosis performed in 2007 shows a right-sided pleural effusion. (2) CXR 5 years later showed a persistent effusion. (b) (3) Axial CT images confirms the right basal effusion. (4) HRCT scans show lung parenchymal changes suggestive of sarcoidosis. (c) (5 and 6) Oblique ultrasound images, the thick walled right pleural cavity with almost solid/necrotic contents suggestive of blood. Images through the liver show periporal echogenicity characteristically described for hepatic sarcoidosis. Ultrasound guided-biopsy revealed periporal non-caseating granulomas. (d) (7-9) confirms the pleural effusion and small pericardial effusion. Note the pleural effusion is insinuating through the intercostal space (arrow). (e) (10) Axial HRCT images show features of stage 4 disease.
hemorrhage suggestive of a primary bronchogenic cancer. In most cases, bronchial or transbronchial biopsies are sufficient for diagnosis.[27]

**Predominantly lower lobe involvement**
Sarcoidosis predominantly affecting the lower lung fields is rare; Matsui et al. report nine cases of pulmonary sarcoidosis, which predominantly involved the lower lung fields.[28] Over a 13 years period, the authors treated 119 patients. Among these, nine patients (3 men, 6 women, mean age 62 years) had pulmonary lesions predominantly affecting the lower lung fields. The authors concluded that patients with sarcoidosis affecting the lower lung fields often had symptoms of dyspnea and lesions affecting the eyes and/or on the skin and elevated serum KL-6 levels, but not ACE levels. CT showed findings typical of sarcoidosis, with lymphatic distribution, but also showed unusual findings such as ground-glass opacities, curvilinear shadows, patchy shadows, traction bronchiectasis and pleural effusions.[29]

**Eosinophilic pleural effusion, peripheral eosinophilia, pleural thickening and hepatosplenomegaly in sarcoidosis**
Vafiadis et al. present a case of a 32-year-old male of an atypical sarcoidosis. Patient had an unusual combination of clinical and laboratory findings. He presented with a 3 months history of chest pain with dyspnea. Laboratory examination, a CXR and CT scans of the chest and abdomen revealed eosinophils of pleural effusion and blood, pleural thickening, hepatosplenomegaly and bronchiolitis obliterans. A mediastinal lymph node biopsy revealed non-caseating epithelioid granulomas, characteristic of sarcoidosis.[29]

**Airway compression, venous obstruction and direct pericardial and myocardial involvement**
Extensive studies in thoracic sarcoidosis suggest that close attention should be paid to a number of unusual manifestations of the disease including airway compression, venous obstruction and direct pericardial and myocardial involvement.[30]

**Role of HRCT sudden death cardiac involvement**
Staging of thoracic sarcoidosis, which classifies patients according to their probability of spontaneous remission, is based on the plain chest film findings. However, HRCT is more sensitive at detecting lymphadenopathy and involvement of lungs or bronchi. HRCT findings can be characteristic, but atypical features occur in some cases. HRCT provides information on the activity of disease and early signs of fibrosis and other complications. Cardiac involvement can cause sudden death. The diagnosis of cardiac involvement remains difficult and is based on a variety of other imaging modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET).[31]

**Role Ultra Sound Guided Biopsy**
A total of 90% patients with sarcoidosis have pulmonary
involvement. Isolated extrapulmonary disease is rare. Giovinale et al. report on two patients with systemic sarcoidosis with the onset with splenic and hepatosplenic disease and one patient with splenic disease with no pulmonary involvement.[32] A 53-year-old woman patient presented with mild abdominal pain underwent sonography and CT, which revealed hypoechoic/hypodense splenic lesion. Laboratory tests were normal. A staging laparotomy was performed and a splenectomy undertaken to exclude a lymphoma. Histology of the spleen revealed a sarcoid granuloma.

The second patient described was that of a 66-year-old woman that had lost 8 kg in weight over 2 months. The liver function tests were deranged with a raised Alkaline phosphatase. As patient had a history of familial colonic cancer, abdominal ultrasound (US), CT scan and MRI were performed, which showed aortocaval lymphadenopathy and multiple hepatic and splenic lesions, but no primary cancer was identified. Gastrointestinal (GI) endoscopy and gynecological work-up and tumor markers, bone marrow biopsy was all negative for neoplastic disease. The CXR and CT revealed small pulmonary infiltrates, but cytology and Broncho Alveolar Lavage (BAL) were normal. There were no stigmata of infection. At laparotomy, whitish peritoneal, hepatic and splenic nodules were identified. Histologically examination revealed sarcoid granulomas.

The third patient was a 32-year-old woman with mild epigastric pain after meals. A neck-thoracic CT, bone scintigraphy and upper GI endoscopy were negative. An abdominal US and MRI revealed splenomegaly with the multiple splenic lesions. A splenectomy was undertaken and histological exam showed typical chronic sacroid granulomatous lesions. All laboratory tests were normal, except for ACE (66 UI/L). Following surgery the ACE levels returned to normal.

The authors concluded that liver and spleen involvement are rarer than thought. Splenic and liver involvement are present with few and non-specific symptoms and laboratory abnormalities. Diagnosis remains elusive as laboratory tests for sarcoid are negative. Ultrasonography and CT are useful, but diagnosis can only be reached by histology of suspected lesions.[32]

Sartori et al. reported two cases where sonography played a useful role in diagnosing sarcoidosis with early...
nodular hepatosplenic manifestations. In the first case of an asymptomatic woman with raised liver enzymes, an abdominal US revealed multiple hypoechoic nodules within the liver and spleen. CT confirmed the US findings, but also showed micro nodular infiltrates of both lung fields, without hilar/mediastinal lymphadenopathy. The second case of a woman presented with cough, dyspnea and raised liver enzyme, thoracic CT revealed a right pleural effusion causing passive atelectasis and mediastinal lymphadenopathy. In both patients, bronchoscopy, bronchial and bronchoalveolar lavages and transbronchial and mediastinal biopsies were negative results. US-guided biopsies of the liver nodule were undertaken, which revealed sarcoid granulomas in the portal areas. Thus, US-guided biopsy of liver nodules may play a pivotal role in diagnosis of atypical sarcoidosis.

Role of fluorodeoxyglucose PET
Braun et al. evaluated the role of 18F-fluorodeoxyglucose (18F-FDG) PET/CT and 67Ga scintigraphy 20 consecutive patients with biopsy-proven sarcoidosis retrospectively. Included in this group were 13 patients with thoracic and seven patients with and extra-thoracic sarcoidosis. Five patients were re-examined by 18F-FDG PET/CT to assess response to corticosteroid treatment. The authors concluded that 18F-FDG PET/CT allow a complete morphological and functional imaging of active disease, particularly in atypical, complex and multisystem involvement. It also allows assessment of therapeutic measures.

Cardiac Sarcoidosis
Symptoms from cardiac sarcoidosis occur in only 5% of patients; although, autopsy series show 20-50% of patients with non-caseating granulomatous infiltration of the myocardium. Presentations include arrhythmias including sudden death (most common) heart block, congestive cardiac failure angina pectoris.
ventricular and aneurysm formation. Although, involvement of the pericardium is rare, constrictive pericarditis occurs.[35]

Despite the low incidence of symptoms from cardiac sarcoidosis, early diagnosis can be life-saving. Sudden demise accounts for ≤60% of the fatalities from cardiac sarcoidosis. Early initiation of corticosteroid therapy prevents malignant arrhythmia, which can cause sudden death. Steroid therapy also improves left ventricular function. A definitive diagnosis requires a cardiac biopsy. However, cardiac biopsy is an invasive technique carries several risks and includes a false-negative biopsy as infiltration can be patchy. No study prospectively has an established accuracy of each of the techniques used to assess myocardial involvement in cardiac sarcoidosis.[35] Cardiac MRI has been shown to have a sensitivity of 100% and specificity of approximately 80% and positive predictive value of approximately 55% in diagnosing cardiac sarcoidosis [Figures 5-11]. MRI and FDG-PET are more sensitive than the established clinical criteria. MRI is an established imaging modality in the diagnosis of various other cardiomyopathies.[36]

The value of T2-weighted and gadopentetate dimeglumine enhanced MRI for diagnosing cardiac sarcoidosis has been recently established.[31,37,38] The sensitivity and specificity of other imaging techniques such as echocardiography and thallium myocardial scanning is limited.

**MRI Features of Cardiac Sarcoid**

Increased signal intensity on T2-weighted gadopentetate dimeglumine-enhanced images may mimic hypertrophic cardiomyopathy. Increased signal intensity may occur on delayed gadopentetate dimeglumine-enhanced inversion-recovery prepared gradient-echo acquisitions. There is often myocardial thickening and the thickening may extend to the septum. Myocarditis due other causes can show similar MRI pattern.[31,37,38]

Focal increased myocardial signal may occur on T2-weighted images in cardiac sarcoid without myocardial thickening and gadolinium uptake. This pattern may occur on follow-up cardiac MRI scans in patients already receiving corticosteroids. In advanced cases of cardiac sarcoid at post-inflammatory stage and replacement scarring, a delayed enhancement can
Sarcoidosis may involve the pericardium. Cardiac MRI is not specific sarcoid related pericarditis, but diagnosis may be suggested by associated myocardial involvement.

Conclusions

Sarcoidosis may mimic many disease entities and has a variety of imaging features. Thoracic sarcoidosis has a wide differential, which includes other granulomatous disease, lymphoma and many other causes of lung parenchymal abnormalities. Severe thoracic sarcoid is associated with high morbidity and mortality.

Radiologists need to familiarize themselves with the wide range of imaging findings in sarcoidosis, crucial in arriving at an accurate diagnosis, which may be unfamiliar to most radiologists, causing difficulty at making a correct diagnosis. Diagnosis should always be made in the appropriate clinical setting to avoid serious clinical misadventures.

Imaging plays a decisive role in the diagnosis of thoracic sarcoidosis. CT and HRCT have increased diagnostic accuracy.

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