Typical radiological manifestations of sarcoidosis: a review of three cases

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Abstract
Introduction: Sarcoidosis is a multisystemic granulomatous disease of unknown etiology. The lungs are the primary organ involved. It is known as the great mimicker since it exhibits a variety of symptoms, mimicking other inflammatory, infectious, and neoplastic conditions such as tuberculosis and lymphoma. Objective: Present the typical radiological manifestations of pulmonary sarcoidosis in three patients with varying pattern and severity. Clinical cases: Three Asian women, two of which complained of a history of chronic cough and ocular symptoms, the third case complaining of cutaneous lesions. All cases presented mediastinal lymphadenopathy and pulmonary infiltrates on imaging studies. Two out of the three cases showed granulomata in spleen and liver. One case had regression of lymphadenopathy while the other two persisted with pulmonary involvement. Conclusion: Diagnosing sarcoidosis can be a challenge but combining clinical symptoms with radiological manifestations can aid in the diagnosis. Hallmark signs of this disease include the presence of mediastinal lymphadenopathy along with respiratory symptoms.

Key words
Sarcoidosis, granulomata, lymphadenopathy, radiology

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■ INTRODUCTION

Sarcoidosis is an idiopathic systemic granulomatous disorder with a wide spectrum of clinical manifestations and prognosis. The lungs are involved in most patients and pulmonary symptoms can be the telltale of the disease in about 40 % of the cases. The incidence rate of sarcoidosis is highest in the Black Americans, which triples that among whites (35.5 vs 10.9 per 100,000 inhabitants) after adjusted for age. (2) White people are also less symptomatic compared to more severe multisystem involvement in blacks. (3,4) The pathogenesis of sarcoidosis is believed to be an inflammatory response to various environmental triggers, resulting in T cell activation and proinflammatory cytokine release. (5)

As non-specific as its pathogenesis is, its diagnosis, which requires compatible clinical, radiologic, and histologic findings, is as well challenging. (6) In this case series, we presented three cases of typical pulmonary sarcoidosis of varying pattern and severity. The goal is to familiarize physicians and radiologists to the typical findings of pulmonary sarcoidosis as early diagnosis and treatment is associated with an excellent long-term prognosis. (3,7)

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■ CASE PRESENTATION

Case 1

A 54-year-old Asian woman complaining of chronic cough since 2012. In March of 2021 she presented visual complaints of flashing lights, floaters and dry sensation in both eyes. Fundoscopy revealed uveitis, with visual symptoms recurring in May 2021. She denied any other pre-existing conditions. Lab tests were done due to clinical suspicion of rheumatoid disease since patient also complained of mild proximal interphalangeal pain, persistent left flank soreness and history of vesicles over hands and feet.

Lab tests only revealed elevated IgG. ANA, CRP, ANCA, and ESR tests were within normal limits. In June, 2021 she presented right facial paralysis which improved with treatment. Chest x ray was ordered in September 2021 which revealed thickened right paratracheal stripe and bilateral hilar enlargement, suspicious for lymphadenopathy. Further investigation with contrasted chest CT scan revealed bilateral perilymphatic nodular distribution, interlobular septal thickening, and multiple perifissural nodules, predominantly in hilar regions (Figure 2). There was also the presence of splenomegaly with hypoattenuating nodules (Figure 4), multiple mild

enhancing lymphadenopathy in mediastinum, bilateral hila, celiac axis and abdominal para-aortic region (blue arrows in Figure 3). Patient was treated with steroids and follow up chest x ray done in two months later revealed regression of bilateral hilar lymphadenopathy (Figure 1: A, B).

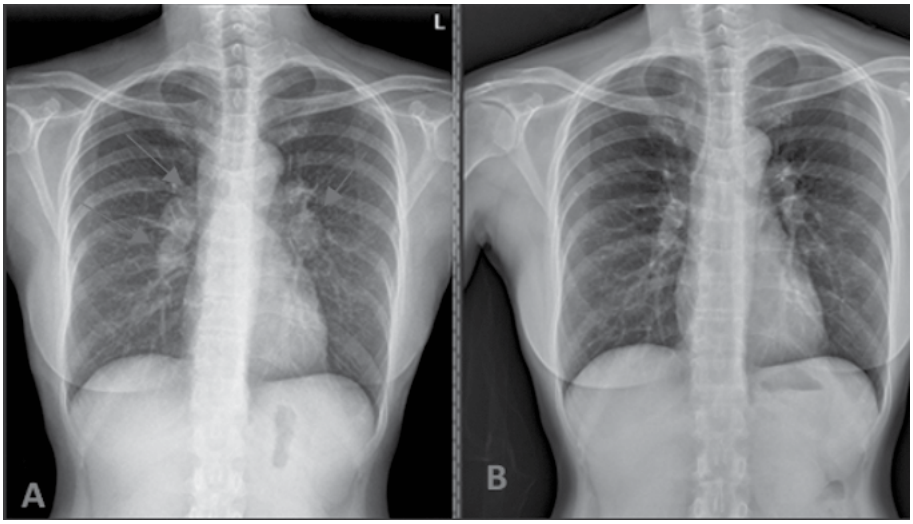

Figure 1. A- Chest x ray showing typical right lower tracheal and bilateral hilar lymphadenopathy. B- Chest x ray repeated two months later regression of bilateral hilar lymphadenopathy.

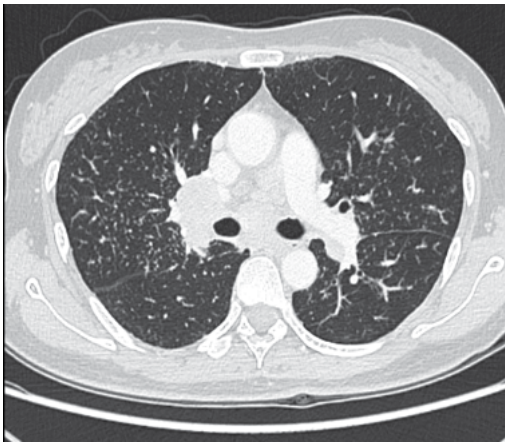

Figure 2. Chest CT scan shows typical perilymphatic distribution of micronodules.

Case 2

A 62-year-old Asian woman who visited the outpatient Ophthalmology Department of our institution in May of 2019 complaining of progressive blurred vision for the past two months. Further ophthalmological exams concluded hypertensive granulomatous uveitis. The patient had also recently been diagnosed with Hepatitis B. No other previous medical history of chronic diseases was reported but previous clinical notes did reveal a chronic intermittent cough since September, 2014. Chest x ray taken in 2014 was non remarkable but lab tests showed altered results for IgG: 1610 mg/dl (normal range <700-1600) and elevated serum angiotensin converting enzyme (ACE): 30.9 IU/L (normal reference rage at <22.5 IU/L).

Within that same month non contrasted chest CT scan was done which informed peribronchovascular ground glass opacities, small consolidations in the bilateral lungs and a few tiny nodular opacities in the bilateral lower lungs. Lymphadenopathy was present in bilateral pulmonary hila, subcarinal, bilateral lower paratracheal, right upper paratracheal, preaortic regions (arrows in Figure 6). Also clustered lymph nodes were present around celiac axis and abdominal para-aortic regions (arrows in Figure 6). Primary diagnosis was compatible with pulmonary and mediastinal involvement of sarcoidosis. Differential diagnosis included metastatic lymphadenopathy and lymphoma. Chest x rays done one month before shows presence of interstitial disease with reticulonodular pattern which has maintained relatively stationary until 2021 (Figure 5).

In June of 2019 endobronchial ultrasound biopsy with transbronchial needle aspiration (TBNA) of the mediastinal lymphadenopathy was done which concluded presence of granulomatous tissue inflammation without evidence of acid-fast stain or fungi infection. Sarcoidosis was favoured. The patient received treatment with oral steroids and regression of lymphadenopathy noted after 5 months with

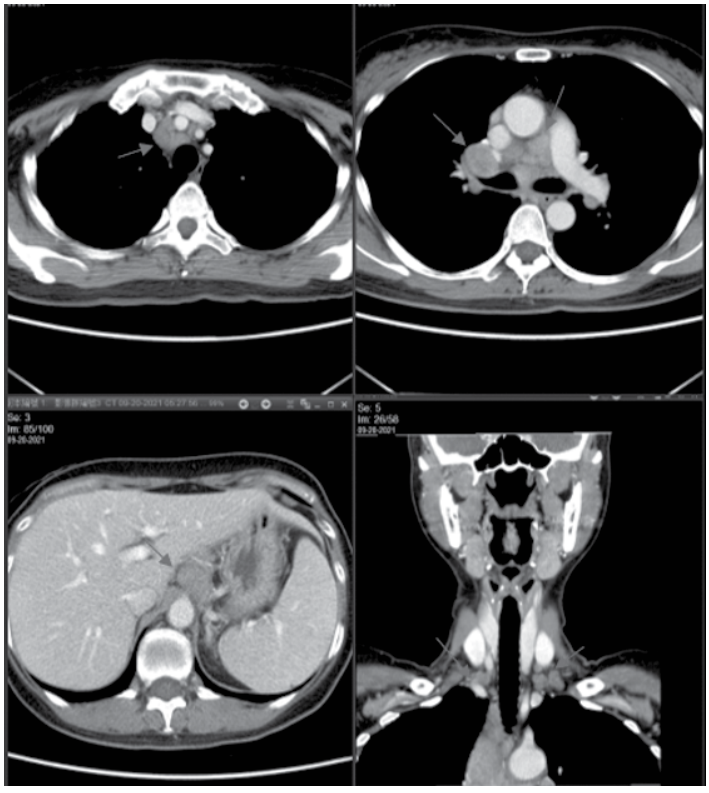

Figure 3. Chest CT Scan axial and coronal views showing lower paratracheal, right hilar, celiac axis and lower cervical lymphadenopathy.

chest CT follow up study (Figure 7). Chest CT done 2 years after initial diagnosis shows progression to pulmonary fibrosis with presence of architectural distortion, ground glass opacities.

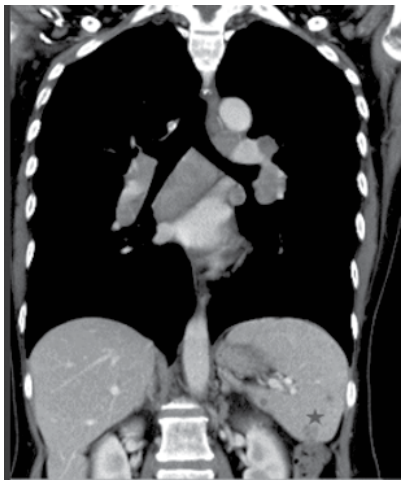

Figure 4. Contrasted Chest CT in coronal view showing mild splenomegaly with several hypoattenuating nodules known as granulomata (star).

Case 3

A 53-year-old Asian woman with previous medical history of Systemic Lupus Erythematosus, Rheumatoid Arthritis and Sjogren's syndrome was received in the outpatient clinic in August 2014 complaining of new onset of firm, 2-5 mm papules around her nose, translucent, red brown in appearance. Skin biopsy was done that same month which informed diagnosis compatible with sarcoidosis.

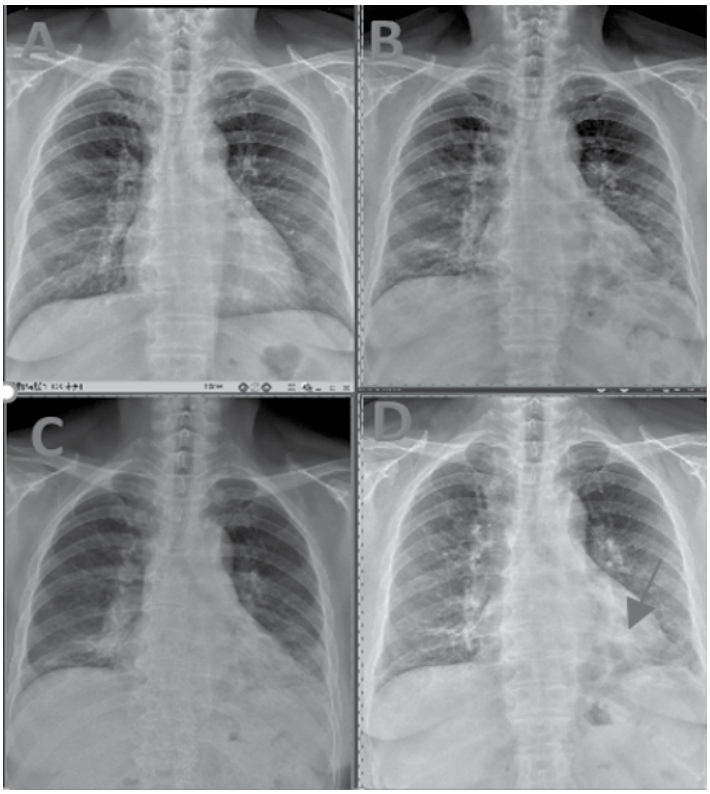

Figure 5. Serial chest x rays shows normal findings in 2014 (A) with progression of reticular interstitial pattern in 2016(B) and has maintained relatively stationary from 2019 to 2021 (C,D). Some fibrotic bands can be noted in left lower lung zone (arrows in D).

Chest x ray done in August 2014 informed right hilar enlargement (Figure 7 A). CT scan done that same month reported enlarged lymphadenopathy at right paratracheal region, subcarinal and bilateral pulmonary hilar regions with perilymphatic micronodules (Figure 8). Also, there were clustered smaller lymph nodes at the bilateral axilla. No hepatosplenomegaly was present.

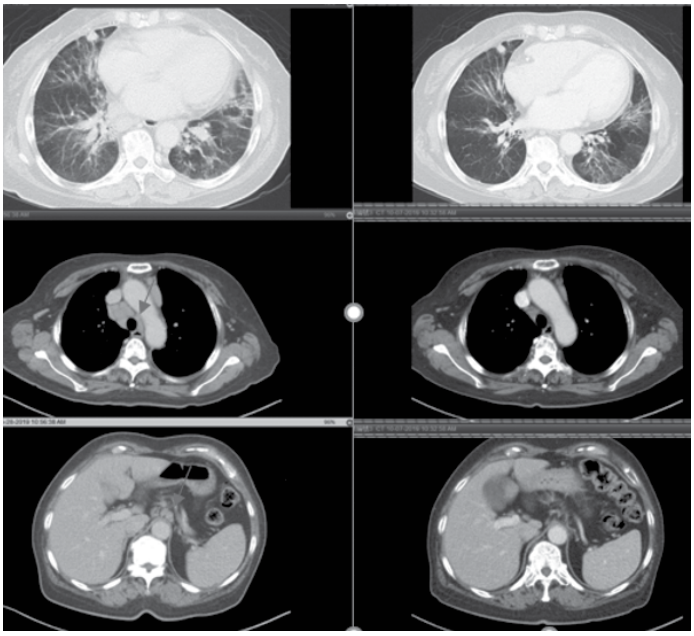

Figure 6: A- Chest CT axial view including upper abdomen range shows peribronchovascular ground glass opacities, consolidations and nodular opacities. There is lymphadenopathy in lower paratracheal and around celiac axis (blue arrows). B- Chest CT axial view including upper abdomen repeated 5 months later shows regression of mediastinal and celiac axis lymphadenopathy.

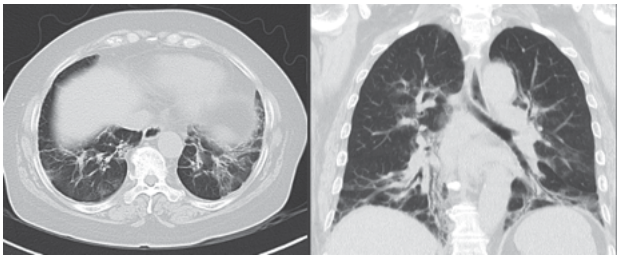

Figure 7: Chest CT axial and coronal views shows reticulation with architectural distortion, ground glass opacities and fibrotic bands in lower lung zones on follow up CT 2 years later.

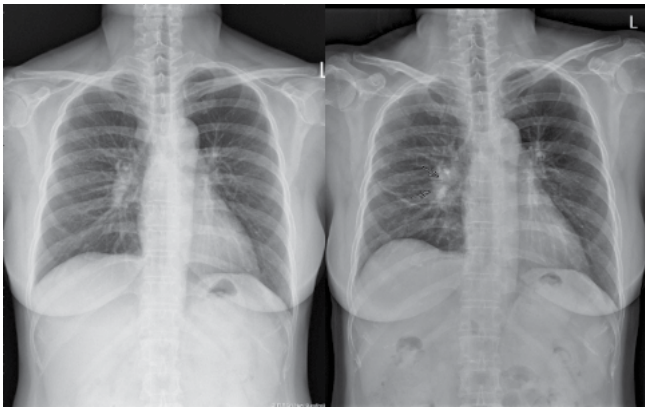

Figure 8: A-Initial posteroanterior chest x ray at time of diagnosis. B- chest x ray after treatment shows progressive enlargement of right hilar lymphadenopathy with increased infiltrates in right lower lung field (yellow arrows).

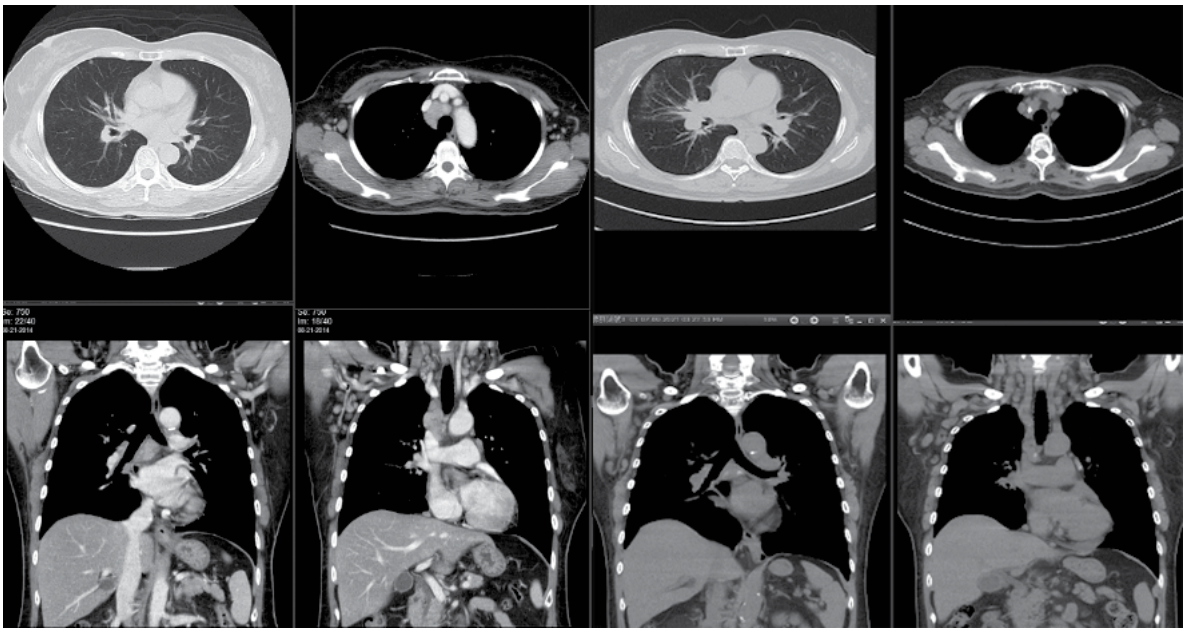

Figure 9: A- Chest CT scan axial and coronal views shows mediastinal lymphadenopathy. B- Follow up CT done 7 years later shows mild regression of lymphadenopathy with calcifications indicating chronicity.

Further study one month later with whole body inflammation scan informed: "1. Active inflammatory process at the right paratracheal, and subcarinal lymph nodes, probably consistent with sarcoidosis changes. 2. Active local inflammation process of the skin over the left thigh and bilateral lower legs, DDx: sarcoidosis with skin involvement, or muscular uptake." Follow up chest X ray done seven years later shows progressive enlargement of right hilar lymphadenopathy (Figure 8B). Chest CT without IV contrast done in July 2021 shows mild regression of lymphadenopathy, several of which have calcifications (Figure 9). Hypoattenuating lesions in right hepatic lobe and spleen are suspicious for hepatosplenic involvement (Figure 10).

■ DISCUSSION

Sarcoidosis is a chronic multisystemic inflammatory disorder that classically involves the lungs but can affect any organ. Its etiology is still unknown. Over half of patients can be asymptomatic. Sarcoidosis is characterized by non-caseating granulomas in the lungs and intrathoracic lymph nodes. (1) Since it primarily affects the lungs, chief complaints include dyspnea, dry cough, chest pain and bronchial hyperreactivity. Constitutional symptoms include fatigue, night sweats, weight loss, and erythema nodosum. Other complaints include ocular symptoms (e.g., pain, visual change), and musculoskeletal symptoms (e.g., joint pains, myalgias). It is of unknown etiology, and it is referred to as the great mimicker due to its varied presentations. Abnormal findings are usually detected as an incidental finding on chest x ray.

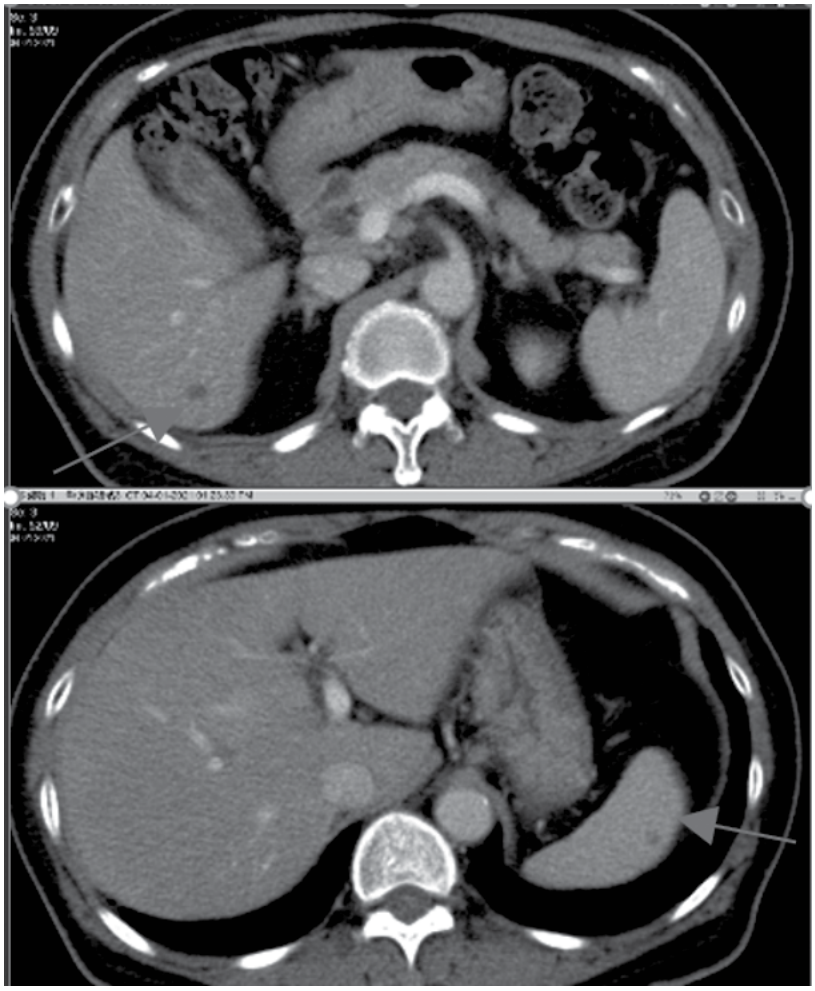

Figure 10: Chest CT scan including upper abdomen shows hypoattenuating lesions in right hepatic lobe and spleen, suspicious for granulomata (blue arrows).

Sarcoidosis can affect patients of any age, sex, or race, and it is typically more common before the 4th decade of life with peak incidence in the 3rd decade of life. Studies have showed it is more prevalent among women, disregarding racial and ethnic groups. (2) Familial clustering has also been shown. (3) Prevalence is higher in Afro-americans and the Scandinavian race. This disease may be underdiagnosed in other parts of the world due to lack of organized screening for chest diseases. Usually, similar pulmonary diseases in other parts of the world are attributed to more common causes of granulomatous lung diseases such as tuberculosis, leprosy, and fungal infections. (4)

Abdominal viscera may also be involved. Liver and spleen are the most frequently affected, usually presenting as organomegaly. Hypodense or hypoattenuating nodules known as granulomata ranging in size from 5-20 mm may be seen on CT scan. This is present in 40-70 % of patients. (5) This presentation is noted in Case 1 where hypoattenuating nodules were present in the spleen, as well as splenomegaly indicating systemic involvement of sarcoidosis.

Typical histopathologic finding is a granuloma without caseous necrosis. (6) Diagnosis is confirmed when associated with clinical and radiological manifestations. Similar differential diagnosis includes tuberculosis which is usually characterized by caseous necrosis. Other entities with similar histopathological findings include chronic berylliosis, histoplasmosis, coccidioidomycosis, lymphoma, Hodgkin's disease, bronchogenic carcinoma, foreign body granuloma, schistosomiasis, syphilis, and leprosy. (7)

Knowledge of the clinical and radiologic features of sarcoidosis plays a pivotal role in achieving the diagnosis. Diagnosis relies on three criteria: (I) a compatible clinical and radiologic presentation, (II) pathologic evidence of noncaseating granulomas, and (III) exclusion of other diseases with similar findings, such as infections or malignancy. (8)

Bilateral hilar lymphadenopathy is distinctive and usually accompanied by paratracheal lymphadenopathy. There are other multiple causes of noncaseating granulomatous diseases presenting with mediastinal lymph nodes. Besides tuberculosis and histoplasmosis, which may be present without a caseous component, other alternative diagnoses include common variable immune deficiency, granulomatous lesions associated with past or concomitant carcinoma and lymphomas. (1,9,10) Middle mediastinal nodes at the paratracheal level, subcarinal level, and level of the aortopulmonary window, prevascular nodes, or both are involved in approximately 50 % of patients. (11)

Conventional chest x ray is usually the first investigation that would suggest the diagnosis of sarcoidosis. Abnormalities are present in over 90 % of cases. (12) The most typical finding is known as Garland's triad (or Pawnbroker's sign) which consists of enlarged right paratracheal nodes, and right and left hilar nodes. Hilar lymphadenopathy tends to be symmetrical, non-compressive and may be massive. Unilateral lymphadenopathy should raise the suspicion for alternative diagnoses. Lymphadenopathy tends to regress within two years but in long standing disease calcification may occur after 10 years. Pulmonary infiltrates are present in 25-50 % of cases and tend to involve the mid-upper lung fields showing a micronodular pattern. (12) The Siltzback (Scadding) classification was developed more than 40 years ago and defines the five stages of sarcoidosis (Figure 10). It is widely used because of its great prognostic value.

Indications for chest CT, according to the American Thoracic Society/European Respiratory Society/ World Association of Sarcoidosis and Other Granulomatous Disorders expert

Staging of Sarcoidosis on the Basis of Chest Radiographs

STAGE 0	No abnormalities	5%–10%
STAGE 1	Lymphadenopathy (fig. A)	50%
STAGE 2	Lymphadenopathy + pulmonary infiltration (fig. B)	25%–30%
STAGE 3	Pulmonary infiltration (fig. C)	10%–12%
STAGE 4	Fibrosis	5% (up to 25% during the course of the disease)

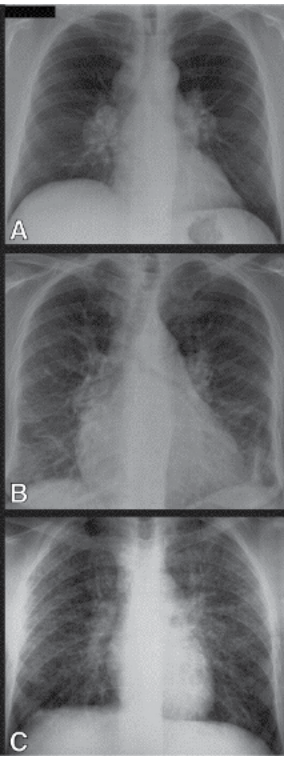

Figure 11. Imaging of pulmonary sarcoidosis based on the pattern of chest radiographic findings. Percentages indicate the proportion of the population with this stage of sarcoidosis at presentation diagnosis.

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consensus statement on sarcoidosis include: 1) atypical clinical and/or radiographic findings; 2) normal chest radiography but a clinical suspicion of sarcoidosis; and 3) detection of pulmonary complications. (2) Typical chest CT findings include bilateral hilar lymph node enlargement and micronodular pattern. If upper abdomen is included, granulomata can also be detected in organs such as the spleen and liver as seen in case 1 and 3.

CT also aids in predicting patient outcome and pulmonary function. Features that would be classified as reversible include micronodules, nodules and peribronchovascular thickening as seen in Case 1, which also had resolution of lymphadenopathy after 2 months. Non reversible features include architectural and bronchial distortion, honeycombing and bullae. Features of variable reversibility include ground glass opacities, linear opacities and consolidation. (13)

In reviewing the three previous cases we can find that Case 1 presented bilateral hilar and paratracheal lymphadenopathy falling under the classification of Stage 1 disease. This is also the typical presentation for Garland's triad. The CT findings including reversible features of micronodules and peribronchovascular thickening. This patient had resolution after 2 months. Sarcoidosis in this patient had ocular, pulmonary and visceral involvement.

Case 2 presented lymphadenopathy on initial plain film but did show bilateral infiltrates with reticulonodular pattern, classifying it as Stage 3 disease. CT findings for this case included presence of nodules, ground glass opacities and consolidations which are features of variable reversibility. Two years later, the patient progressed to Stage 4 disease showing presence of fibrotic bands and architectural distortion on CT scan. This is a case of ocular and pulmonary sarcoidosis progressing to pulmonary fibrosis.

Initially case 3 would be classified as Stage 1 disease due to the presence of bilateral hilar lymphadenopathy but then progressed to Stage 2,characterized by the additional presence of increased infiltration seen in right lower lung field. This would be a case of cutaneous, pulmonary and hepatosplenic involvement of sarcoidosis since granulomata were also detected in the abdominal viscera.

Stage 1 is usually associated with excellent long-term prognosis while stage 3 has less than 20 % probability of spontaneous resolution. Stage 4 indicates advanced pulmonary fibrosis and will not resolve. This case would represent cutaneous and pulmonary involvement of sarcoidosis since skin biopsies had also revealed granulomatous inflammation.

■ CONCLUSION

Radiologic diagnosis of pulmonary sarcoidosis can be challenging. It is important for radiologists to understand the typical findings, radiologic-pathologic correlations and clinical presentation of sarcoidosis in order to make an accurate diagnosis in typical cases.

Manifestaciones radiológicas típicas de la sarcoidosis: revisión de tres casos

Resumen

Introducción: La sarcoidosis es una enfermedad granulomatosa multisistémica de etiología desconocida. Los pulmones son el principal órgano involucrado. Se le conoce como el gran simulador pues exhibe una variedad de síntomas, similares a otras enfermedades inflamatorias, infecciosas y neoplásicas como la tuberculosis y el linfoma. Objetivo: Presentar las manifestaciones radiológicas típicas de la sarcoidosis pulmonar en tres pacientes con patrón y severidad variable. Casos clínicos: Tres mujeres asiáticas, dos de las cuales se quejaban de antecedentes de tos crónica y síntomas oculares, mientras que el tercer caso se quejaba de lesiones cutáneas. Todos los casos presentaron adenopatías mediastínicas e infiltrados pulmonares en los estudios de imagen. Dos de los tres casos presentaron granulomas en el bazo e hígado. Un caso tuvo regresión de las adenopatías mientras que los otros dos persistieron con afectación pulmonar. Conclusión: El diagnóstico de sarcoidosis puede ser un desafío, pero la combinación de los síntomas clínicos con las manifestaciones radiológicas puede ayudar en el diagnóstico. Los signos distintivos de esta enfermedad incluyen la presencia de linfadenopatía mediastínica junto con síntomas respiratorios.

Palabras clave

Sarcoidosis, granuloma, linfadenopatía, radiología

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