

[CASE REPORT]

Progression of Central-peripheral Band and Traction Bronchiectasis Clusters Leading to Chronic Respiratory Failure in a Patient with Fibrotic Pulmonary Sarcoidosis

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Abstract:

We herein report a rare case of pulmonary sarcoidosis leading to chronic respiratory failure with restrictive ventilatory impairment during a 53-year-long observation period. Nine years after the histological diagnosis of stage I sarcoidosis on chest X-ray in a woman in her 20s, she developed bilateral reticular and granular opacities on chest computed tomography and was started on prednisone for 18 years. Seven years after prednisone withdrawal, these persisting opacities around the bronchovascular bundle, including a central-peripheral band, had progressed, forming traction bronchiectasis clusters and peripheral cysts, some of which developed continuously at the distal side of these clusters, with eventual upper lobe shrinkage.

Key words: sarcoidosis, fibrosis, cyst, chronic respiratory failure, traction bronchiectasis

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Introduction

Sarcoidosis is a granulomatous disease that causes various lesions in organs throughout the body. Respiratory involvement, characterized by bilateral hilar-mediastinal lymphadenopathy (BHL) and granular/nodular shadows along the lymphatic vessels, especially in the upper lung zones, is found in most patients with sarcoidosis.

Most such patients enter remission and have good long-term outcomes, but patients with advanced, active organ lesions comprise about 20% of cases, and cardiac lesions, central nervous system lesions, and pulmonary fibrosis are the three major causes of death associated with sarcoidosis. However, the mechanisms underlying the distortion of the lung architecture resulting in chronic respiratory failure are still unknown, and further studies on the morphology of se-

vere fibrotic pulmonary sarcoidosis need to be conducted (1-3).

To understand the correlation between the findings and disease prognosis and to determine the proper indications for anti-fibrosis treatment, such as nintedanib (4), there is an urgent need for the computed tomography (CT) findings of fibrotic pulmonary sarcoidosis to be clarified. A clinical trial in patients with progressive fibrosing interstitial lung diseases with not only the usual interstitial pneumonia pattern but also other fibrotic patterns has demonstrated the efficacy of this treatment (4).

In a previous study (5), we extracted 10 consecutive patients who required oxygen therapy for chronic respiratory failure from among more than 2,500 pulmonary sarcoidosis inpatients/outpatients treated at our 3 hospitals between 2000 and 2018 and analyzed their CT images. We described the areas of consolidations around the bronchovascular bun-

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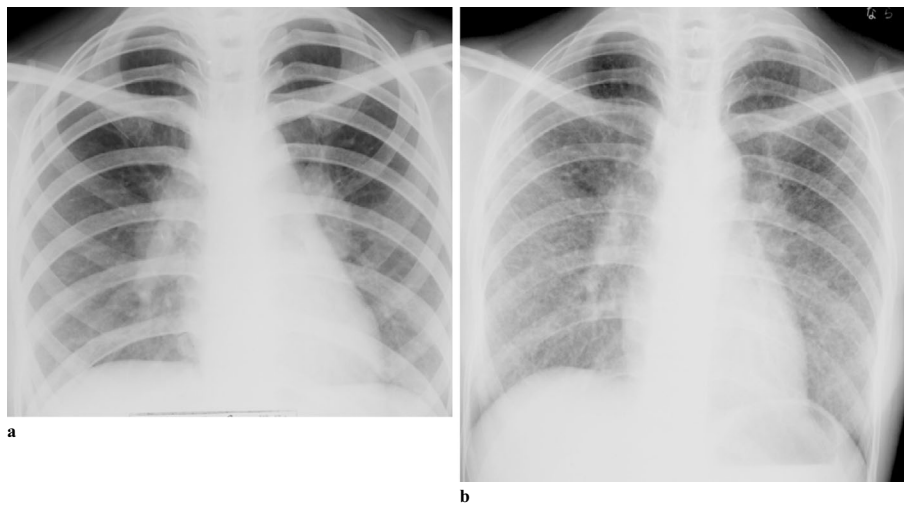


Figure 1. (a) Chest X-ray in December 1964 showing stage I sarcoidosis (bilateral hilar lymphadenopathy only) on chest X-ray staging. (b) Chest X-ray in December 1973 showing reticular and granular opacities in both lungs.

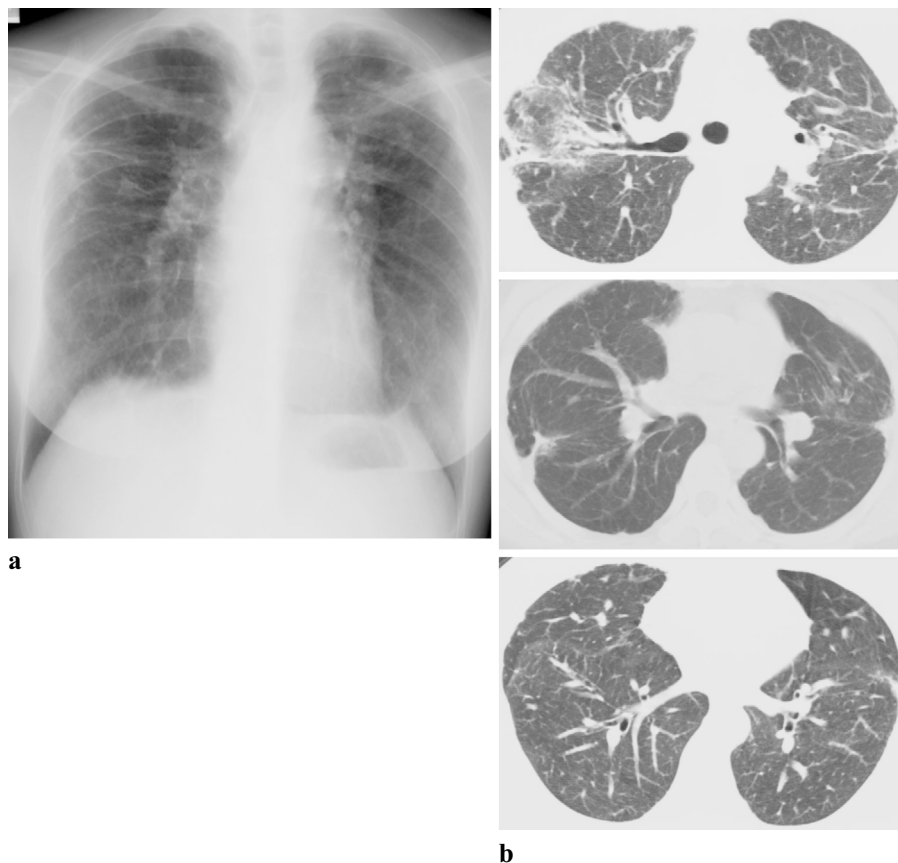


Figure 2. (a) Chest X-ray in October 1991 after 18 years of prednisone use showing the improvement of reticular and granular opacities. (b) CT still shows persistent opacities around the bronchovascular bundle, comprising a central-peripheral band.

dle that progressed towards the mediastinum and the pleura as a central-peripheral band (5) that likely reflects the lymphatic flow through which inhaled antigen-laden antigen-presenting cells move. Findings possibly associated with the progression of fibrosis and respiratory failure were shown to be consolidations comprising a central-peripheral band, trac-

tion bronchiectasis clusters that distorted the airways secondary to mechanical traction on the bronchi from fibrosis of the surrounding lung parenchyma, peripheral cysts, and eventual upper lobe shrinkage.

We herein report a rare case of fibrotic pulmonary sarcoidosis that led to chronic respiratory failure during disease

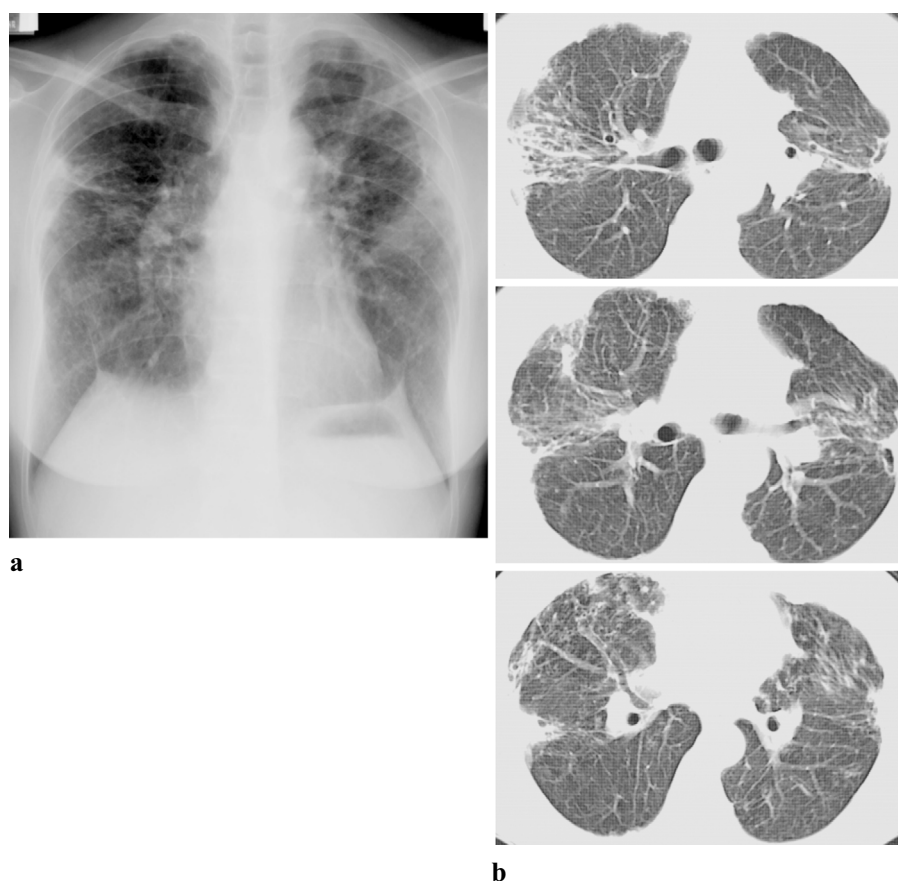


Figure 3. After 18 years of prednisone use, (a) chest X-ray and (b) CT in August 1998 at 7 years after prednisone withdrawal, showing progression of the opacities around the bronchovascular bundle, which resulted in mild central and peripheral traction bronchiectasis.

progression over a period of 53 years. This case was included in the abovementioned study (5) and is considered to show morphological changes as fibrotic pulmonary sarcoidosis progression based on the crucial involvement of the central-peripheral band and traction bronchiectasis clusters.

Case Report

A 21-year-old woman visited the respiratory center of a regional hospital in December 1964 for uveitis and BHL detected on a physical examination. She was a nonsmoker diagnosed with sarcoidosis on detection of noncaseating epithelioid granulomas at a scalene lymph node biopsy. Thus, the definitive diagnosis was sarcoidosis classified as stage I (bilateral hilar lymphadenopathy only) on chest X-ray (Fig. 1a). In December 1973, reticular and granular opacities appeared in both lungs (Fig. 1b), and she was started on prednisone 30 mg daily.

In 1987, the dose of prednisone was gradually tapered to 5 mg daily. Chest X-ray in October 1991 showed improvement of reticular and granular opacities (Fig. 2a). CT still showed persisting opacities around the bronchovascular bundle, comprising a central-peripheral band (Fig. 2b). Prednisone was stopped at her request, and she continued to visit the hospital periodically as an outpatient with almost no

symptoms. In February 1996, her pulmonary function test results showed the following: vital capacity (VC), 1.93 L (%VC 76.9%); forced expiratory volume 1 (FEV1), 1.47 L; FEV1% (G) 76.6%; and diffusing capacity of the lungs for carbon monoxide (DL_{co}), 14.2 mL/min/mmHg (%DL_{co} 88.2%).

Seven years after withdrawal of prednisone, chest X-ray (Fig. 3a) and CT (Fig. 3b) in August 1998 showed that the opacities around the bronchovascular bundle had progressed, which resulted in mild central and peripheral traction bronchiectasis. Moderate calcification of the hilar mediastinal lymphadenopathy was also observed. Restrictive ventilatory impairment developed, and in March 2002, her pulmonary function test results were VC 1.69 L (%VC 70.1%), FEV1 1.28 L, FEV1% (G) 79.0%, and DL_{co} 14.2 mL/min/mmHg (%DL_{co} 94.0%). In June 2005, the results were VC 1.59 L (%VC 67.1%), FEV1 1.21 L, FEV1% (G) 76.6%, and DL_{co} 14.5 mL/min/mmHg (%DL_{co} 98.2%).

In June 2007, erythromycin was started for bronchiectasis, but chest X-ray (Fig. 4a) and CT (Fig. 4b) in April 2009 revealed central and peripheral traction bronchiectasis clusters and peripheral consolidation right under the pleura that had progressed markedly, with eventual upper lobe shrinkage.

From March 2011, she sometimes noticed bloody sputum from the bronchiectasis. In February 2014, home oxygen

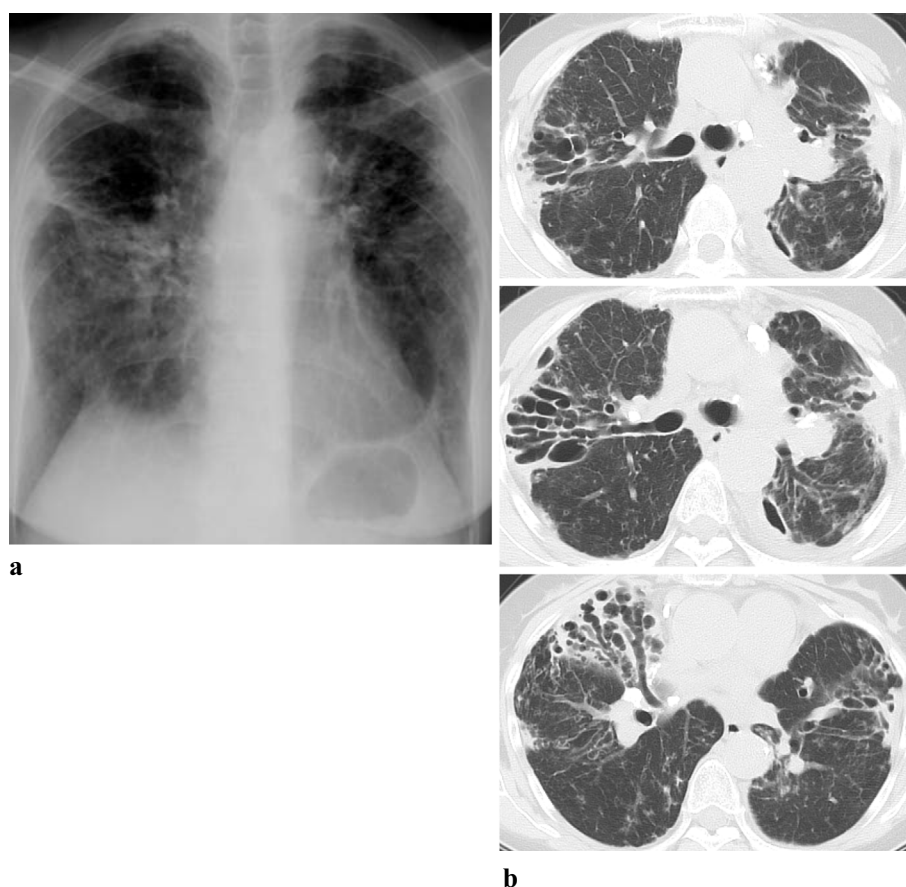


Figure 4. (a) Chest X-ray and (b) CT in April 2009 showing central and peripheral traction bronchiectasis clusters and peripheral consolidation right under the pleura that progressed markedly with eventual upper lobe shrinkage.

therapy was started. Chest X-ray (Fig. 5a) and CT (Fig. 5b) in May 2017 showed severe central and peripheral traction bronchiectasis clusters, which had increased in size compared with those seen on CT in April 2009. Some cysts were found to have developed continuously at the distal side of the peripheral traction bronchiectasis (Fig. 5c). Severe calcification of hilar mediastinal lymphadenopathy was also detected.

Restrictive ventilatory impairment further developed, and in May 2017, the pulmonary function test results were as follows: VC 0.90 L (%VC 40.0%), and FEV1 0.66 L, FEV1 % (G) 79.6%. Her respiratory failure worsened, and in September 2017, 53 years after the diagnosis, she died. Neither pulmonary hypertension nor chronic progressive pulmonary aspergillosis had been detected during the chronic course of fibrosis development.

Discussion

This report describes a rare case of pulmonary sarcoidosis that led to chronic respiratory failure with restrictive ventilatory impairment over a long observation period of 53 years. This case is considered to demonstrate typical morphological changes as the fibrotic progression of pulmonary sarcoidosis (5) based on the following two observations: first, con-

solidations comprising a central-peripheral band, traction bronchiectasis clusters, and peripheral cysts progressed together with eventual upper lobe shrinkage; second, peripheral cysts formed at the distal edge of traction bronchiectasis, which developed along the central-peripheral band.

In sarcoidosis, the inhaled causative agent is believed to act as an antigen of granuloma and travel in the lymphatic vessels. Pulmonary lymph is known to flow toward the hilum in the direction of the pulmonary artery and vein and the bronchi as well as around the pleura, flowing directly into the mediastinal lymph nodes from the visceral pleura to the mediastinal pleura (6). Given that sarcoidosis is relatively rare and that decades of observation are necessary before pulmonary fibrosis develops, finding many patients with this condition is difficult, which is regarded as the main reason why fibrotic pulmonary sarcoidosis has not been well investigated.

When considering the first observation, consolidations comprising central-peripheral band and traction bronchiectasis clusters seem to play crucial roles in the mechanism of upper lobe shrinkage. Indeed, a pathological study of 66 autopsy cases (7) showed that bronchovascular bundle fibrosis was frequently observed (58%) and was accompanied by peribronchial atelectasis. In the abovementioned study (5), traction bronchiectasis arose from granular/nodular opacities

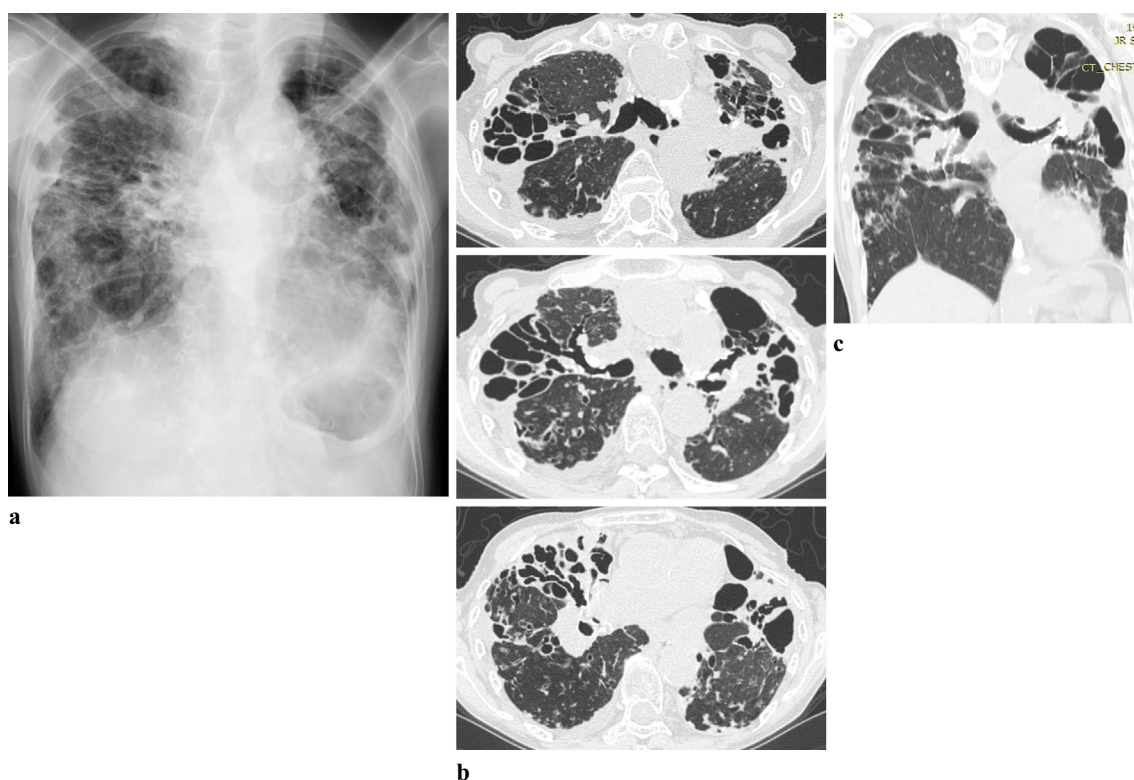


Figure 5. (a) Chest X-ray and (b) CT in May 2017 showing severe central and peripheral traction bronchiectasis clusters, which had increased in size compared with the findings observed on CT in April 2009. (c) Some cysts had developed continuously at the distal side of peripheral traction bronchiectasis.

and consolidations around the bronchovascular bundles, comprising a central-peripheral band. Clustering of traction bronchiectasis at the distal side formed a honeycomb lung-like structures in some patients (8). Until recently, obstructive ventilatory impairment rather than restrictive ventilatory impairment had been of interest in pulmonary sarcoidosis; however, the present case, as well as other cases included in the abovementioned study (5), showed progression of restrictive ventilatory impairment as fibrosis progressed. Neither pulmonary hypertension nor chronic progressive pulmonary aspergillosis, which are frequently observed in fibrotic pulmonary sarcoidosis, were detected in this case. In future studies, it will be important to investigate each CT finding in relation to each type of pulmonary dysfunction.

The steroids administered during the course seemed to have had some sort of effect on the present case in suppressing the amplified and persistent granulomatous reaction; however, after the withdrawal of the steroids, these opacities progressed, which resulted in traction bronchiectasis. The number of reports on *Cutibacterium acnes* (formerly *Propionibacterium acnes*)-associated sarcoidosis has increased, particularly in Japan, where cases are detected using immunohistochemistry with a specific monoclonal antibody against its lipoteichoic acid (PAB antibody) (9). Steroids may reactivate such antigenic intracellular bacteria endogenously, which might eventually result in progression of the disease.

Regarding the second observation, the mechanisms underlying how peripheral cysts form after the disappearance of granular/nodular opacities and consolidations around the bronchovascular bundles may include stenosis of the bronchi with granulomatous involvement and peribronchial fibrosis, and a further check-valve mechanism of bronchiolar involvement of granulomata and fibrosis (7). This notion is supported by the fact that a decrease in the size of the enlarged cysts over time is sometimes observed in fibrotic pulmonary sarcoidosis (5), as was seen in this case. Furthermore, pulmonary sarcoidosis cases have been detected with multiple severe cysts occupying more than half of the total lung volume (5), suggesting the possibility of other factors. An experimental study with mice showed that an impaired lymphatic flow resulted in hypoxia and features of emphysema-like lung injury in association with pulmonary inflammatory state characterized by tertiary lymphoid organ formation (10).

In summary, opacities comprising a central-peripheral band, traction bronchiectasis clusters, and peripheral cysts together with eventual upper lobe shrinkage led to chronic respiratory failure with restrictive ventilatory impairment over an observation period of 53 years. The CT findings need to be analyzed further for a proper understanding of the pathology and correlation with the prognosis and to clarify indications for anti-fibrosis treatment.

The authors state that they have no Conflict of Interest (COI).

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