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Imaging Findings of Fibrosis in Pulmonary Sarcoidosis

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Abstract. *Background:* In pulmonary sarcoidosis, respiratory tract lesions almost always appear, and residual lung shadows require treatment in about 20% of cases. Pulmonary fibrosis is among the three leading causes of death. Treatment strategies are urgently needed to inhibit the progression of pulmonary fibrosis by combining antifibrotic drugs and immunosuppressive drugs such as corticosteroids. Establishing consensus on the process of pulmonary fibrosis progression is important for determining the most effective treatment. *Our review:* Among more than 2500 cases of sarcoidosis treated at our hospital, cases that led to chronic respiratory failure were analyzed for CT findings of pulmonary fibrosis. Early in sarcoidosis, granulomatous lesions appeared along the bronchovascular bundle. As pulmonary fibrosis progressed, a central consolidation developed on the central side in the direction of lymph flow, a peripheral consolidation developed on the pleural side, and a central-peripheral band developed connecting the two. Infiltrative or wedge-shaped shadows sometimes formed in the immediate subpleural area, appearing as a pleuroparenchymal fibroelastosis-like lesion. Traction bronchiectasis may form cysts at the periphery or may congregate to form a honeycomb lung-like structure. Combination of these lesions led to shrinkage of the upper lobe. Patients with multiple peripheral cysts/bullae had a unique disease course characterized by wheezing and concomitant pulmonary hypertension and pulmonary aspergillosis. *Conclusion:* Further understanding of the process of pulmonary fibrosis progression is needed. Summarizing imaging findings and understanding their contribution to respiratory impairment will contribute to comprehensively evaluating the stages of pulmonary fibrosis progression and establishing an optimal treatment strategy.

Key words: sarcoidosis, fibrosis, honeycombing, stage IV, non-caseating epithelioid granuloma, fibrosis, pleuroparenchymal fibroelastosis

1. Introduction

Sarcoidosis is a granulomatous disease that produces a variety of lesions in the respiratory tract and other organs. It is speculated that causative antigens, such as *Propionibacterium acnes*, enter the body via the respiratory tract or percutaneous route and latently infect the mediastinal hilar lymph nodes and lungs (1, 2). Then, the bacteria proliferate in response to changes in environmental factors, inducing an excessive T helper type 1 (Th1)-type granuloma response and onset of sarcoidosis (3, 4). Respiratory lesions appear in almost all cases of sarcoidosis (5, 6). Initial lesions include bilateral hilar lymphadenopathy and multiple granular/nodular shadows along the bronchovascular bundle (BVB). Granular, nodular, and ground-glass shadows tend to appear transiently and then disappear, although about 20% of cases require treatment for residual lung shadows.

Because pulmonary fibrosis occurring in the chronic course of the disease is known to be closely

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associated with the prognosis, there is an urgent need to establish a treatment strategy for inhibiting the progression of pulmonary fibrosis by combining antifibrotic drugs and immunosuppressive drugs such as corticosteroids. However, it has been difficult to establish optimal treatment guidelines in clinical practice. Japanese clinical practice guidelines recommend the use of moderate- to high-dose corticosteroids for patients with significant shortness of breath, cough, significant worsening of imaging findings, and significant respiratory impairment, at a starting dose equivalent to 30 mg of prednisolone (PSL) in line with Western guidelines, although it has been suggested that lower doses are also effective. Furthermore, antifibrotic drugs for progressive fibrosing interstitial lung disease have been introduced in the treatment of a wide range of diseases, including sarcoidosis, although evidence on the specific usage of these drugs is lacking. One of the factors preventing the establishment of treatment guidelines is a lack of strict indicators for the stages of lung lesion progression because of difficulty in building consensus on the imaging findings and progression process of pulmonary fibrosis in sarcoidosis. One reason for this may be that sarcoidosis is a relatively rare disease and requires several years to several decades to follow the progression of pulmonary fibrosis, making it difficult to conduct a comprehensive analysis. Against this background, we conducted an analysis of Computed tomography (CT) findings in pulmonary sarcoidosis, focusing on cases that led to chronic respiratory failure.

2. Pulmonary Fibrosis in Sarcoidosis

From the clinical records of more than 2500 patients with pulmonary sarcoidosis, we identified 10 cases (3 male, 7 female) that required oxygen therapy due to chronic respiratory failure and analyzed their CT data (8). The major findings of pulmonary fibrosis included clustering of traction bronchiectasis (Figure 1), formation of peripheral cysts/bullae (Figure 2) (7), central and peripheral consolidations and a central-peripheral (C-P) band connecting the two (Figure 3a-g), and shrinkage of the upper lobe (SUL).

In the early stages of sarcoidosis, granulomatous lesions appeared along the BVB, and as pulmonary fibrosis progressed, a central consolidation developed on the central side in the direction of lymph flow, a peripheral consolidation developed on the pleural side, and a C-P band developed connecting the two (Figure 3a-e) (8). In some cases, a peripheral consolidation developed into infiltrative or wedge-shaped shadows in the immediate subpleural area, which were recognized as a pleuroparenchymal fibroelastosis (PPFE)-like lesion (Figure 3f-h) (9). Traction bronchiectasis may form cysts at its periphery or may cluster to form a honeycomb lung-like structure (8, 10, 11). The combination of these lesions led to the development of SUL (8).

Patients with multiple peripheral cysts/bullae had a unique disease course characterized by wheezing and concomitant pulmonary hypertension and

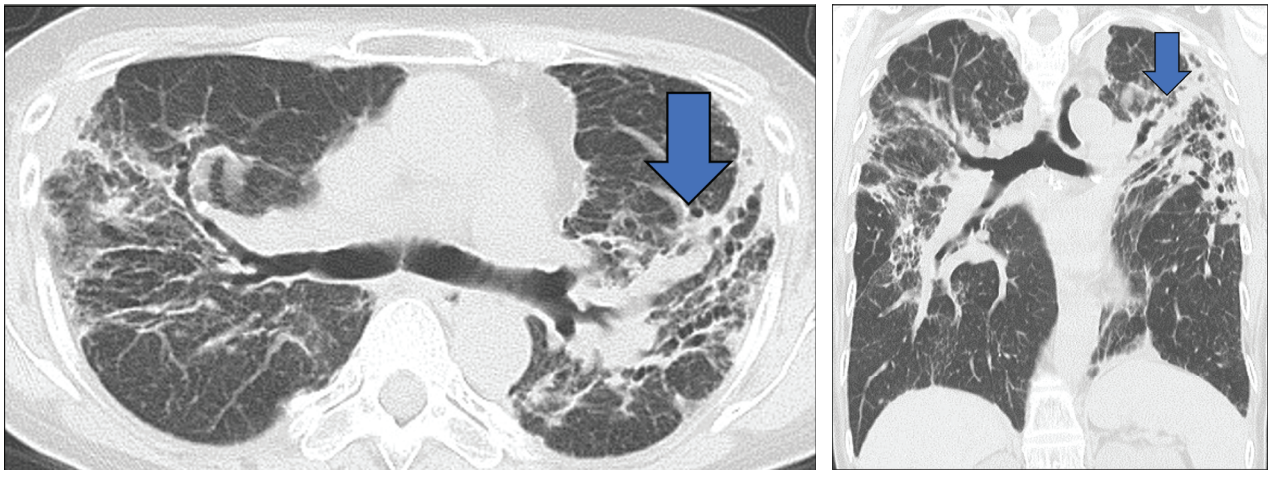

Figure 1. Clustering of traction bronchiectasis.
Traction bronchiectasis was defined as irregular bronchial dilatation within or around areas with parenchymal abnormality.

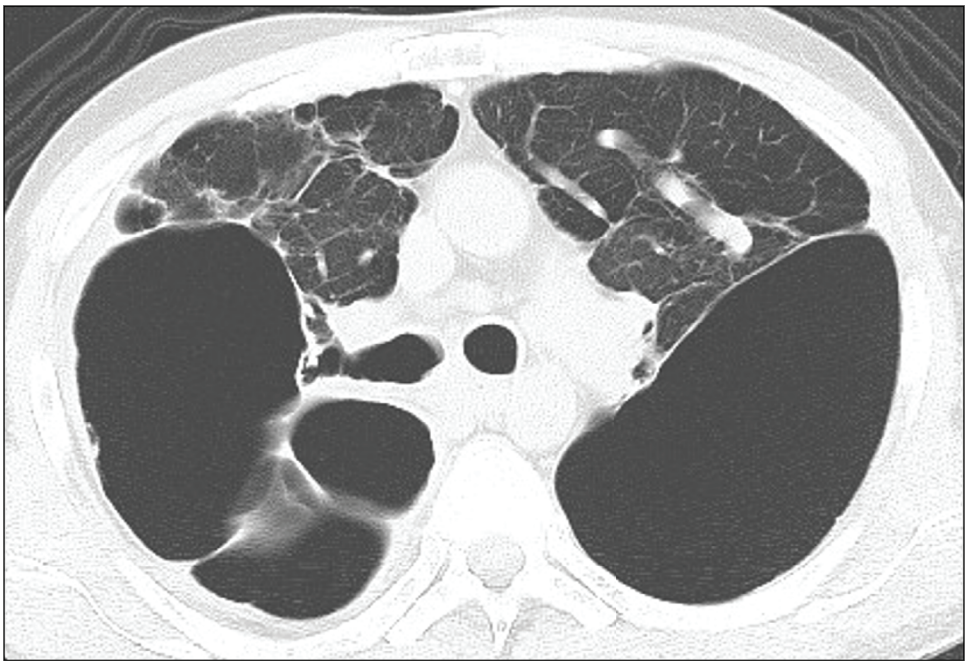

Figure 2. A case of multiple peripheral cysts/bullae.
Multiple peripheral cysts/bullae, wheezing, concomitant pulmonary hypertension, and pulmonary aspergillosis.

pulmonary aspergillosis. Calcification of hilar mediastinal lymph nodes (Figure 4) was often observed in the chronic stage.

Clustering of traction bronchiectasis

Traction bronchiectasis detected on chest CT (Figure 1) formed from granular/nodular shadows or infiltrative shadows around the BVB (8). Pathologically, this lesion represents fused granulomas and resulting fibrosis in the BVB, accompanied by atelectasis (12).

We reported 2 cases showing that the honeycomb lung-like structure formed as a lung lesion of sarcoidosis consisted of clusters of traction bronchiectasis (10, 11). In the first case, infiltrating shadows detected on chest CT, from which granuloma was sampled, were observed to form a cluster of traction bronchiectasis and appeared as a honeycomb lung-like shadow during the long-term course (10). In the second case, a honeycomb lung-like structure contiguous with dilated bronchioles observed on chest CT, which was sampled by video-assisted thoracic surgery, and granulomas were detected in the membranous bronchiolar wall (11). The honeycomb lung-like structure contiguous with dilated bronchioles observed on the chest CT scans of sarcoidosis patients were pathologically characterized by membranous bronchioles with sparse granulomas on the walls and dilated and cystic intralobular bronchioles involving the peripheral alveoli, unlike the honeycomb lung of idiopathic pulmonary fibrosis/usual interstitial pneumonia. These cases radiologically and pathologically demonstrate the possibility that bronchiectasis/bronchioloectasis clusters can develop into cysts to form a honeycomb lung-like structure as the fibrosis of sarcoidosis-related lung lesions progresses (10, 11).

Formation of peripheral cysts/bullae

Bronchial/bronchiolar narrowing and fibrosis of the surrounding tissue, as well as the resulting check-valve mechanism may be involved in peripheral cyst/bulla formation. This is supported by the fact that peripheral cysts can form in some cases of traction bronchiectasis (6), and that a transient decrease in cyst size can be observed. Furthermore, an experimental study in mice showed that impaired lymphatic flow resulted in features of emphysema-like

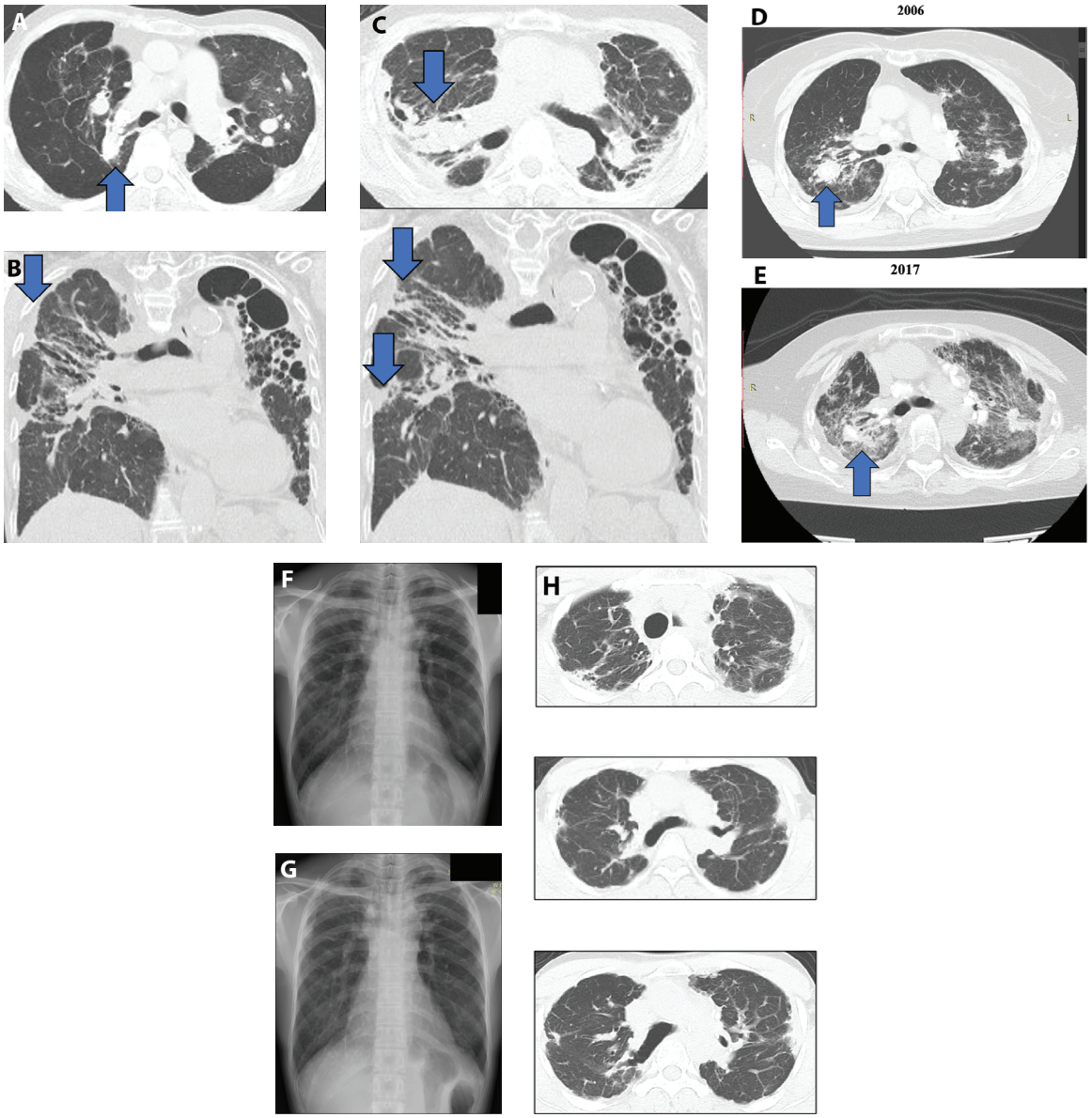

Figure 3. (a-c) Central-peripheral band. Consolidations are defined as areas of homogenous increased attenuation that obscure the pulmonary vasculature. The spatial distributions of abnormalities were designated as *central consolidation* (a), defined as the region from around the trachea to the fifth bronchus, and *peripheral consolidation* (b), defined as the region from the sixth bronchus to the area immediately under the pleura. In addition, we defined areas of consolidations around the bronchovascular bundle that progress toward the mediastinum and pleura as a *central-peripheral band* (c) (7); d, e) Formation process of central consolidation. Pulmonary sarcoidosis is characterized by lesion formation around the bronchovascular bundle (d, arrow). As this lesion develops, the pathogenic agents flow into the bronchial root of the upper lobe, mainly through the centrally directed lymphatic flow, and form a granuloma, which is seen as a mass-like lesion on chest CT (central consolidation) (e). However, these pathogenic agents can also be carried by the lymphatic flow toward the periphery, which results in the formation of a lesion seen as a peripheral consolidation or a PPFE-like lesion on chest CT; f-h) A case with a pleuroparenchymal fibroelastosis-like lesion. In 2007, the patient received a definitive diagnosis of sarcoidosis at the age of 39 years. In September 2008, shrinkage of the upper lobe (SUL) was already noted on chest X-ray (f). Pulmonary function test results showed a force vital capacity (FVC) of 1.71 L (%FVC 64.8%) and a diffusing capacity for carbon monoxide (%DLCO) of 61.5%. In December 2012, chest X-ray (g) and chest CT (h) revealed a wedge-shaped shadow and internal bronchiolar radiolucency, in addition to SUL, which were regarded as a PPFE-like lesion. Pulmonary function test results showed a FVC of 1.60 L (%FVC 62.0%) and a %DLCO of 56.8%.

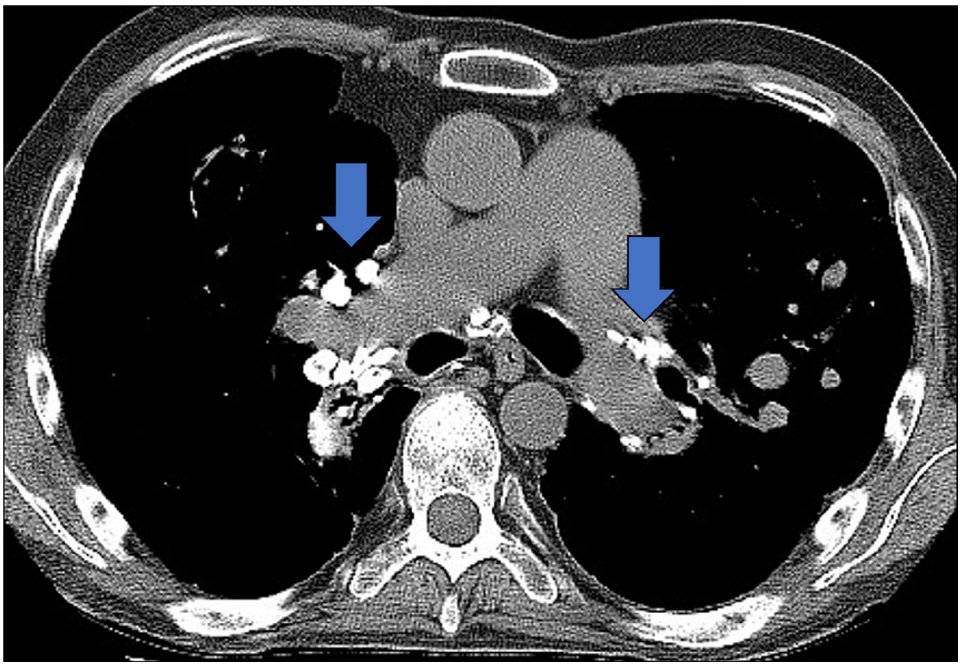

Figure 4. Calcification of lymph nodes.

lung injury in association with a pulmonary inflammatory state characterized by tertiary lymphoid organ formation (13).

We also found that some patients with chronic respiratory failure without SUL or traction bronchiectasis had a unique disease course in which multiple peripheral lung cysts/bullae occurred, as well as wheezing and concomitant pulmonary hypertension and pulmonary aspergillosis (Figure 2) (8).

Central-peripheral band

Consolidations includes airspace consolidations, defined by Felson and Heitzman as a gradual transition from dark to light shadow with indistinct margins (alveolar shadow), and discrete consolidations, which exclude masses/nodules and are assumed to be fibrotic lesions (14, 15). The latter is seen in cases of advanced pulmonary fibrosis in sarcoidosis.

We have noticed that discrete consolidations occur in the hilar area (central consolidation) and the subpleural area (peripheral consolidation) along the BVB, which is a lymphatic tract, and we refer to the connection between the two as the C-P band (Figure 3a-e) (8). This subpleural consolidation has been described as "pleural thickening" in some reviews (16), but it has not been recognized as a continuous lesion from the lung field, nor has its association with the initial lesion been suggested. We previously found that during the fading of granular/nodular shadows around the BVB, which were observed as early lung field lesions of sarcoidosis on chest CT scans when granuloma was detected by transbronchial lung biopsy, a subpleural consolidation or wedge-shaped shadow was formed in its periphery, appearing as a PPFE-like lesion (9). We believe that this association between early lung field lesions and subpleural consolidation can be explained by the following anatomical knowledge: "lymphatic flow around the BVB is mainly directed toward the hilum and partly toward the pleural surface" (17). More specifically, we speculate that macrophages phagocytosing antigens that have entered the airways (18) may enter the lymphatic flow from the BVB and lung lobules, and then form a central consolidation in the hilar region and a peripheral consolidation in the immediate subpleural region. We have also encountered several cases of pulmonary sarcoidosis with

PPFE-like lesions that eventually led to restrictive ventilatory impairment (Figure 3f-h). PPFE-like lesions are especially likely to occur when peripheral consolidation is confined to the apex of the upper lobe.

Shrinkage of the Upper Lobe

In some cases, traction bronchiectasis formed from granular/nodular shadows or infiltrative shadows around the BVB in the chronic course of sarcoidosis, resulting in a honeycomb lung-like structure. Multiple cyst formation was also observed in some cases. In other cases, a central consolidation, a peripheral consolidation, and a C-P band connecting the two formed along the lymphatic flow. SUL progressed as these lesions developed (adapted from Ref. (8)).

3. Problems Associated with Progression of Pulmonary Fibrosis

Respiratory impairment

In pulmonary sarcoidosis, obstructive ventilatory impairment is often observed from early stages due to peripheral airway involvement, and as fibrosis develops, it can further progress to restrictive ventilatory impairment (8). An important future task is to investigate the relationship between each of the aforementioned chest CT findings and respiratory impairment.

Complications (pulmonary hypertension, pulmonary aspergillosis, pneumothorax)

In the process of fibrosis development, concomitant pulmonary hypertension also contributes to the progression of chronic respiratory failure, which is important from a prognostic standpoint. Pulmonary hypertension develops not only due to pulmonary fibrosis and the resulting parenchymal destruction and capillary occlusion, but also due to non-pulmonary pathologies, such as cardiac, vascular, and hepatic lesions. For this reason, pulmonary hypertension in sarcoidosis is classified as Group 5 of the Nice Classification (pulmonary hypertension due to complex factors). Pulmonary aspergillosis is caused by the growth of *Aspergillus* spp. in multiple cysts formed during the process of pulmonary fibrosis development in the upper lung fields. This condition tends to become refractory to antifungal therapy and can be complicated by pneumothorax. (8).

4. Treatment of Sarcoidosis: Aiming to Inhibit the Progression of Pulmonary Fibrosis

About half of sarcoidosis cases go into spontaneous remission within 2 years, and more cases go into remission within 5 years. Disappearance of lung lesion shadows in sarcoidosis is strongly associated with age, and the recent trend toward lower rates of shadow disappearance compared with previous reports may reflect the increasing age of patients in an aging society (19).

Given the underlying idea that granulomatous inflammation promotes the elimination of causative antigens and favors spontaneous remission, the indications for treatment need to be carefully determined. There is an urgent need to establish a treatment strategy for preventing the progression of pulmonary fibrosis by combining antifibrotic drugs and immunosuppressive drugs such as corticosteroids. The purpose of using systemic drugs in the acute phase is to inhibit the progression of organ damage and reduce symptoms, with corticosteroids being the first choice. In Japan, the main indications for systemic steroid therapy include extensive pulmonary lesions associated with significant symptoms (shortness of breath, cough) and respiratory impairment, eye lesions refractory to local treatment, cardiac lesions, neurological lesions, and renal lesions/hypercalcemia. The standard treatment protocol is to start with 0.5 mg/kg/day of PSL, reduce the dose by 5–10 mg/day every 4–8 weeks to 2.5–5 mg/day if possible, and determine the duration of treatment while monitoring the treatment effect. Japanese clinical practice guidelines recommend that the therapy be introduced at a dose equivalent to 30 mg of PSL in line with Western guidelines, although evidence for this is lacking. Evidence has also suggested that when introducing steroid therapy in pulmonary sarcoidosis, lower doses than those specified in the treatment guidelines may be sufficient (20). When systemic steroid therapy needs to be continued, immunosuppressants can be added to reduce the use of corticosteroids or to enhance the treatment effect. The immunosuppressants used include methotrexate (MTX) and azathioprine, with MTX being the first choice as an adjunct or alternative to corticosteroids.

Because sarcoidosis is associated with increased airway hyperresponsiveness, inhaled corticosteroids may be a treatment option for patients with chronic cough, although clear evidence has not been established. Inhaled corticosteroids alone often lead to improvement in patients with significant cough who have extensive pulmonary involvement but granular or cotton-like shadows as the predominant imaging findings.

5. Conclusion and Future Issues

We demonstrated that SUL progresses with the clustering of traction bronchiectasis, formation of peripheral cysts/bullae, and development of a C-P band. Continued efforts are needed to understand the process of pulmonary fibrosis progression in sarcoidosis, to build consensus on imaging findings, and to understand the level of contribution of each imaging finding to different aspects of respiratory impairment. Through these efforts, it will be possible to comprehensively evaluate the stages of pulmonary fibrosis progression and establish an optimal treatment strategy.

Conflict of Interest: All authors declare that he or she has no commercial associations that might pose a conflict of interest in connection with the submitted article

Abbreviations: Th1=T helper type 1; BVB=bronchovascular bundle; PSL=prednisolone; CT=Computed tomography; C-P band=central-peripheral band; SUL=shrinkage of the upper lobe; PPFE=pleuroparenchymal fibroelastosis; MTX=methotrexate

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