Honeycomb lung-like structures resulting from clustering of traction bronchiectasis distally in sarcoidosis

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Keywords
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Abstract
Gene expression profiles of patients with progressive sarcoidosis, most of whom had evidence of fibrosis on imaging, have been reported to be similar to those of patients with inflammatory hypersensitivity pneumonitis, while expression profiles in progressive sarcoidosis did not resemble those of idiopathic pulmonary fibrosis. However, it is not known whether specific parenchymal features discerned on computed tomography (CT) imaging can predict development of fibrosis in pulmonary fibrosis. We herein describe a rare case of pulmonary sarcoidosis with honeycomb lung-like structures developing as a result of concentration of traction bronchiectasis distally, predominantly in both lower lung fields, which developed through shrinkage of consolidations comprising a “central–peripheral band” detected in a woman in her 60s, with non-caseating epithelioid granuloma. To our knowledge, this is the first case demonstrating the distinctive morphology and developmental process of honeycomb lung-like structures in fibrotic pulmonary sarcoidosis.

Introduction
The number of reports that have examined pulmonary sarcoidosis patients with honeycomb lung-like structures is increasing. Some reports suggest that we cannot rule out the possibility that we are seeing honeycomb lung-like structures of interstitial pneumonia such as idiopathic interstitial pneumonia [1] and collagen disease-associated interstitial pneumonias complicating sarcoidosis, rather than those of pulmonary sarcoidosis itself.

We herein describe a rare case of fibrotic pulmonary sarcoidosis with honeycomb lung-like structures leading to chronic respiratory failure, which was included in our previous computed tomography (CT) image analysis [2]. Honeycomb lung-like structures developed as a result of concentration of traction bronchiectasis distally, which developed through shrinkage of consolidations comprising the “central–peripheral band” with detection of non-caseating epithelioid granuloma.

Case Report
A 62-year-old woman with skin lesions and uveitis visited the dermatology department of a regional hospital in January 2002, where skin biopsy revealed scattered non-caseating epithelioid granulomas. She was diagnosed as having sarcoidosis and her chest X-ray in January 2002 showed stage II (bilateral hilar lymphadenopathy with pulmonary infiltration) at chest X-ray staging (Fig. 1A). She had a 16.5 pack-year smoking history and was referred to a specialist respiratory centre for further management. The findings on laboratory examination were as follows: angiotensin-converting enzyme 29.0 IU/L (normal level ≤ 23.7), lysozyme 18.3 IU/L (normal level ≤ 11.5), bronchoalveolar lavage fluid lymphocytes 19.0%, and CD4/CD8 ratio 3.27. Ga scintigraphy showed abnormal accumulation in the bilateral parotid and lacrimal glands, intrathoracic lymph nodes, and bilateral lung fields.
Pulmonary function test results were as follows: vital capacity (VC) 2.39 L (%VC: 101.3%), forced expiratory volume in 1 sec (FEV₁) 1.91 L, FEV₁% (G) 86.8%, and diffusion capacity of the lung for carbon monoxide (DLCO) 19.03 mL/min/mmHg (%DLCO: 110.4%). Chest CT in March 2003 revealed consolidations around the bronchovascular bundles comprising the "central–peripheral band" (B). Chest X-ray (C) and CT (D) in November 2006 showed that the central–peripheral band detected in March 2003 had shrunken, resulting in the formation of traction bronchiectasis and peripheral cysts. The patient’s pulmonary function values were found to have deteriorated to VC 1.79 L (%VC: 76.8%), FEV₁ 1.42 L, FEV₁% (G) 82.1%, and DLCO 9.38 mL/min/mmHg (%DLCO: 58.5%). Therefore, inhaled budesonide therapy (800 mg/day) was started.

Chest X-ray (Fig. 2A) and CT (Fig. 2B) in September 2008 revealed that the clusters of central and peripheral traction bronchiectasis had progressed, although her restrictive ventilatory impairment improved to VC 2.08 L (%VC: 92.4%). Enlarged peripheral cysts and mild calcification of the hilar mediastinal lymphadenopathy were also

**Figure 1.** Chest X-ray in January 2002 showed stage II (bilateral hilar lymphadenopathy with pulmonary infiltration) at chest X-ray staging (A). Chest computed tomography (CT) in March 2003 revealed consolidations around the bronchovascular bundles comprising the "central–peripheral band" (B). Chest X-ray (C) and CT (D) in November 2006 showed that the central–peripheral band detected in March 2003 had shrunken, resulting in the formation of traction bronchiectasis and peripheral cysts.
detected. She was started on treatment with prednisolone and methotrexate in May 2012. However, her pulmonary function values in May 2013 deteriorated to VC 1.91 L (% VC: 88.4%), FEV₁ 1.58 L, FEV₁% (G) 81.4%, and DLCO 6.23 mL/min/mmHg (%DLCO: 42.3%). On further chest X-ray (C) and CT (D) in December 2015, several enlarged cysts have shrunken, followed by honeycomb lung-like structure formation as a result of concentration of traction bronchiectasis and small cysts distally, predominantly in both lower lung fields. In March 2019, she was started on home oxygen therapy. As of May 2019, she is alive and visits a respiratory physician regularly. Neither pulmonary hypertension nor chronic progressive pulmonary aspergillosis was detected during the chronic course of development of fibrosis.

**Discussion**

This case report demonstrates for the first time the distinctive morphology and developmental process of honeycomb lung-like structures in fibrotic pulmonary sarcoidosis on the basis of the following key observations. First, honeycomb lung-like structures formed as a result of clustering of traction bronchiectasis and small cysts distally. Second, traction bronchiectasis...
arose from consolidations around the bronchovascular bundles comprising the central–peripheral band.

Concerning the first observation, a similar pattern is frequently seen in chronic hypersensitivity pneumonitis and rheumatoid arthritis-associated interstitial pneumonia [3]. This notion is compatible with recent results supporting the hypothesis that fibrosis results from unbridled inflammation where gene expression profiles of patients with progressive sarcoidosis, most of whom had evidence of fibrosis on imaging, were similar to those with inflammatory hypersensitivity pneumonitis; expression profiles in progressive sarcoidosis did not resemble those of idiopathic pulmonary fibrosis [4].

Concerning the second observation, we previously described the areas of opacities around the bronchovascular bundle progressing towards the mediastinum and the pleura as a central–peripheral band, a characteristic finding detected in the early stage of fibrotic pulmonary sarcoidosis [2]. The distribution of central–peripheral band consolidations in chest CT of March 2003 may reflect the lymphatic flow through which inhaled antigens travel. The pulmonary lymphatic flow is known to move along the pleura in addition to a flow towards the pulmonary hilum along with the pulmonary artery and vein and the bronchi. This lymphatic flow moves continuously from the visceral pleura to the mediastinal lymph nodes. Moreover, this central–peripheral band had shrunken and formed traction bronchiectasis clusters on the chest CT of September 2008, whose concentration distally with small peripheral cysts eventually formed honeycomb lung-like structures. This notion is supported by a pathological study of 66 autopsy cases [5] in which bronchovascular bundle fibrosis was frequently observed (58%) with accompanying peribronchial atelectasis. These parenchymal features, which can be best discerned on CT imaging, may predict eventual development of a pulmonary fibrosis in sarcoidosis.

In conclusion, we presented the distinctive developmental process of honeycomb lung-like structures in fibrotic pulmonary sarcoidosis. CT findings possibly associated with the progression of respiratory failure need to be analyzed comprehensively to gain a proper understanding of their pathology, association with prognosis, and indications for optimal use of anti-fibrosis treatment.

Disclosure Statement
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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