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Pulmonary Lesions in Collagen Disease

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Summary. **Collagen disease is a group of systemic disorders involving vasculature and connective tissues. Individual collagen diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), mixed connective tissue disease (MCTD), polyarteritis nodosa (PN), and Sjögren syndrome (SjS). Since the lung contains numerous blood vessels, this organ develops lesions at a high frequency. A variety of pulmonary lesions may be seen in collagen disease; these lesions can be characterized to some extent according to the type of disease. Choice of therapy depends on the specific pathologic condition, which must be evaluated in detail before therapy. The understanding and treatment of pulmonary lesions are important for the prognosis and quality of life in patients with collagen disease.**

Key words—collagen disease, pulmonary lesion, interstitial pneumonia, Alveolar hemorrhage, bronchiolitis, pulmonary hypertension.

Pathogenesis

Collagen diseases produce lesions in various organs, but differing patterns among the organs most likely to be impaired differ characteristically between diseases. As is true elsewhere, the frequency of pulmonary lesions varies among collagen diseases[1,2]. Generally, pulmonary lesions are most frequent in systemic sclerosis (SSc), rheumatoid arthritis (RA), polymyositis/dermatomyositis (PM/DM), and mixed connective tissue disease (MCTD), and relatively infrequent in systemic lupus erythematosus. (SLE), Sjögren syndrome (SjS), and polyarteritis nodosa (PN). The number of patients with pulmonary lesions accompanying RA was highest, perhaps due to the frequency of other underlying collagen diseases (overlap syndromes).

Pulmonary lesions appear either simultaneously with the onset of collagen disease or slightly later in most cases; in some, however, pulmonary lesions occur initially and collagen disease becomes evident only later[3]. Indeed, many patients already have developed a pulmonary lesion accompanied by advanced fibrosis at the apparent time of onset of collagen disease. Although detection of specific autoantibodies suggests collagen disease, evidence of collagen disease may be suppressed due to therapy for pulmonary lesions in some patients. The proportion of cases where a pulmonary lesion precedes overt collagen disease may be higher than generally believed.

As the pathogenetic mechanisms of collagen disease have not yet been clarified, mechanisms causing the associated pulmonary lesions also are incompletely understood[4]. Various autoantibodies and abnormal immunities observed in collagen disease may be involved, as well as monocytes, macrophages, lymphocytes, T cells, other inflammatory cells, and various cytokines.

Pathophysiology

A variety of pulmonary lesions may be seen in collagen disease[1,2]. Since pleural lesions frequently develop in addition to intrapulmonary lesions, involvement often may be considered pleuropulmonary. Respiratory disorders in collagen disease also can arise from disorders of the extrathoracic upper airway, the chest wall, respiratory muscles including the diaphragm, or nerves innervating these structures, as well as disorders in swallowing and respiratory regulation.

With regard to intrathoracic lesions, interstitial pneumonia may occur due to alveolitis, showing a

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Fig. 1. A high-resolution computed tomographic image of the chest of a patient with a mixed connective tissue disease shows a "ground-glass" attenuation pattern, which may represent alveolar wall thickening.

Fig. 2. A high-resolution computed tomographic image of the chest of a patient with systemic sclerosis shows honeycombing.

thickening and inflammatory cell infiltration of the alveolar septum; this is the interstitium as narrowly defined (Fig. 1). These changes can progress to pulmonary fibrosis accompanied by alveolar collapse and the appearance of a "honeycomb lung" (Fig. 2). Although these processes exhibit varying degrees of inflammation and fibrosis from case to case, many instances appear temporally uniform within each case. Some cases are accompanied by severe exudation and organization in air spaces (Fig. 3), while others have severe lesions involving perivascular and peribroncho-bronchiolar tissue, interlobular interstititum, and pleura; this can be broadly defined as interstitium (Fig. 4). Extensive alveolar hemorrhaging lesions in the airway system such as in the bronchus and bronchiole[5-7] (Fig. 5), and lesions of the pulmonary vascular system also exist.

Classification

Pulmonary lesions can be characterized to a certain extent according to the type of collagen disease.

In RA[8-10], rheumatoid nodules similar to those observed in the skin are formed in the lung, especially just beneath the pleura. The histologic findings are specific to RA, but the frequency of occurrence is not particularly high in Japan. Caplan's syndrome, in

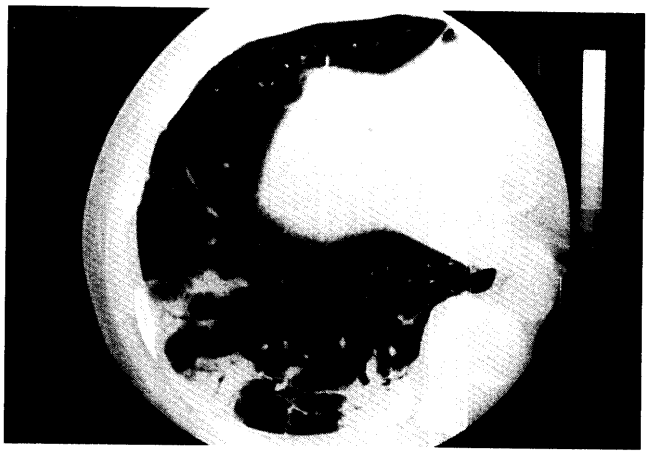

Fig. 3. A high-resolution computed tomographic image of the chest of a patient with polymyositis/dermatomyositis shows air-space consolidation with an air-bronchogram pattern, which may reflect intraalveolar exudation and organization.

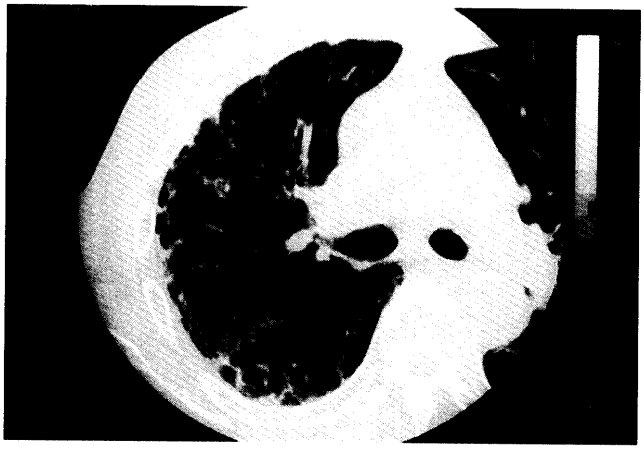

Fig. 4. A high-resolution computed tomographic image of the chest of a patient with polymyositis/dermatomyositis shows a thickemng of bronchovascular bundles and interlobular septa.

which pneumoconiosis accompanies RA and multiple nodules are formed, is also rare in Japan, where chronic interstitial pneumonia/pulmonary fibrosis is the most frequent form of involvement. Pleural lesions including effusions, thickening, and aseptic empyema also are frequent[11,12]. Positivity for rheumatoid factor (RF) and a low glucose concentration in pleural fluid are characteristic. Interstitial pneumonia cannot be differentiated from idiopathic interstitial pneumonia (IIP) in some cases, but advanced cases frequently involve connective tissues related to the vessels and airways. Lesions often are most prominent in the upper lung field. In cases of a relatively rapid onset and these showing "wandering shadows". pulmonary lesions frequently are accompanied by exudates and organization in air spaces[13,14]. Follicular bronchitis with an overgrowth of lymphoid follicles[5,6] (Fig. 6) and obliterating bronchiolitis showing a narrowing of bronchioles are relatively common on histologic examination. Although its frequency is low, bronchiolitis obliterans[7,15] (Fig. 7) showing only airway lesions without interstitial lesions can be observed in patients treated with D-penicillamine and patients who also have SjS.

Fig. 5. A high-resolution computed tomographic image of the chest of a patient with rheumatoid arthritis shows bronchiolar lesions, which resemble findings in diffuse panbronchiolitis.

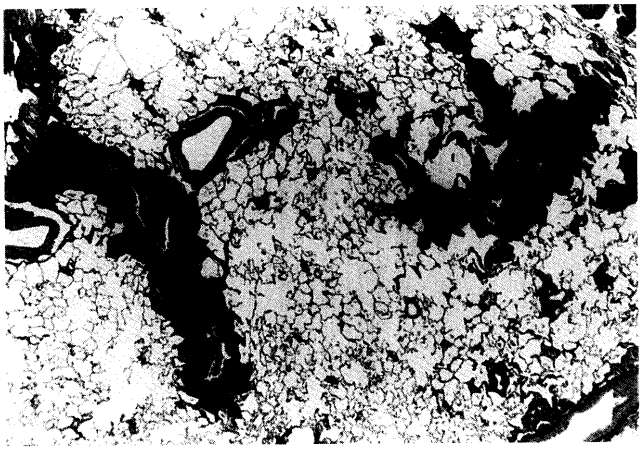

Fig. 6. A thorachoscopic lung biopsy specimen obtained from a patient with primary Sjogren's syndrome reveals follicular bronchiolitis. (Hematoxylin and eosin stain, original magnification: ×4)

Pulmonary vasculitis and pulmonary hypertension in patients with malignant rheumatoid arthritis also have been reported, but with very low frequency.

In SLE[16-18], pleuritis and pleural thickening occur most often. Lupus erythematosus (LE) cells, an antinuclear antibody, and an anti-deoxyribonucleic acid antibody sometimes may be detected in pleural fluid[9,20]. Acute and chronic interstitial pneumonia have long been reported. The acute type, called lupus pneumonitis, is relatively common, but the chronic type is rare. Alveolar hemorrhage with rapid onset[21,22] is occasionally observed. Pulmornary vasculitis, pulmonary hypertension[23], and bronchiolitis obliterans[24] have been seldom reported. Discoid atelectasis caused by dysfunction of the diaphragm[25] is relatively frequent.

In SSc[26-28], interstitial pneumonia/pulmonary fibrosis similar to the chronic type of IIP occurs more frequently than in other collagen diseases. Fibrous pleural thickening also is often observed, representing lesions of the interstitium as broadly defined. Pulmonary hypertension[29,30] occurs relatively commonly, often secondarily to pulmonary fibrosis; pulmonary vascular lesions without interstitial lesions are rare, in contrast to MCTD. Aspiration pneumonia may occur secondarily to esophageal dysmotility[31,32].

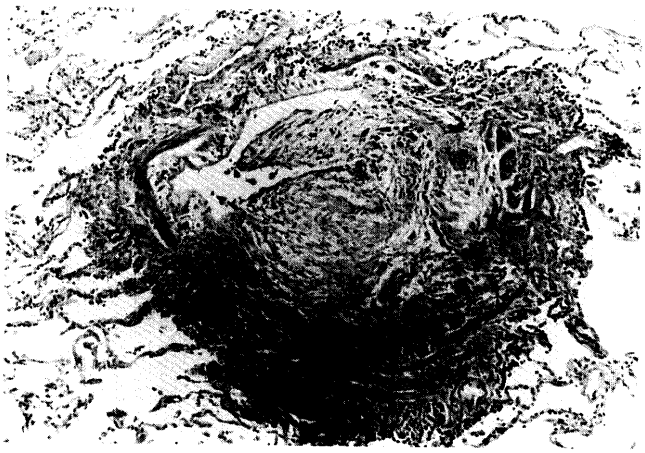

Fig. 7. A thorachoscopic lung biopsy specimen obtained from a patient with rheumatoid arthritis demonstrates bronchiolitis obliterans. (Hematoxylin and eosin stain, original magnification: ×20)

Pulmonary lesions accompanying PM/DM[33-35], especially interstitial pneumonia, may be more frequent than previously reported. Involvement that contains a temporally uniform mixture of inflammation and fibrosis tends to occur acutely or subacutely, and is accompanied by exudates and organization in air spaces. Some patients have a fulminant form[36] that begins and progresses very rapidly. A chronic type, with few respiratory symptoms, is rarely detected despite thorough clinical examination. Although frequencies are low, respiratory failure and atelectasis due to respiratory myopathy, as well as aspiration pneumonia due to an ineffective cough can occur. The frequency of coexisting lung carcinoma is significantly high, particularly in elderly men with DM[37,38].

In MCTD[39], pulmonary hypertension[40,41] from lesions of the vascular system without pulmonary parenchymal lesions is characteristic. Pulmonary hypertension is steadily progressive, and the prognosis is poor. Interstitial pneumonia or pulmonary fibrosis also can occur, with secondary pulmonary hypertension. Interstitial pneumonia often forms advanced lesions of the interstitium as broadly defined. Pleuritis and pleural thickening also are fairly common. Alveolar hemorrhage occurs rarely.

In PN, generalized arterial vasculitis occurs; vasculitis involving the pulmonary arteries is rare, while vasculitis involving bronchial artery is relatively common. Pleuritis and diffuse interstitial pneumonia have been reported, but the frequencies are low.

Many cases of SjS[42-45] complicate other collagen diseases. Although many affected patients have diffuse interstitial pneumonia and pleuritis, SjS is difficult to isolate as the cause in the presence of other collagen diseases. As a pulmonary lesion limited to primary sicca syndrome, repeated airway infection can complicate the tracheobronchial secretory disorder[46,47], frequently resulting in airway lesions such as bronchiectasis. Although the incidence is low, patients with a pulmonary lymphoproliferative disorder such as lymphocytic interstitial pneumonia[48] and pseudolymphoma progressing to pulmonary malignant lymphoma[49] have been reported, as has pulmonary amyloidosis[50].

Diagnostic procedures

The presence of pulmonary lesions is disclosed in the course of evaluating patients diagnosed with collagen diseases. Importantly, all collagen diseases may cause pulmonary lesions. Inquiries about respiratory symptoms and physical examination are carried out, and two-directional chest radiography, electrocardiography, and spirometry are performed as screening examinations. As more sensitive evaluations, specialized respiratory function tests including diffusing capacity for carbon monoxide (DLco), lung volumes, blood gas analysis, chest computed tomography (CT), and echocardiography can be used. Chest CT, especially high-resolution CT[6,28,35,44], is very useful for the analysis of intrapulmonary lesions. Echocardiography by the color Doppler method can diagnose pulmonary hypertension. Thoracentesis is performed in patients with pleural effusion. In patients with interstitial lesions and airway lesions, gallium scintigraphy, ventilation/perfusion scintigraphy, bron-

choalveolar lavage[51-55], and transbronchial lung biopsy are of value. Thoracoscopic lung biopsy or open lung biopsy is considered if necessary[8,30,34]. In patients with pulmonary hypertension, right-sided cardiac catheterization should be performed to examine the pathophysiology before therapy.

When a patient demonstrates a pulmonary lesion, particularly the interstitial pneumonia that is frequent in collagen disease, the presence of underlying collagen disease must be considered and investigated. Examination often will detect extrapulmonary lesions, especially of the joints, skin, muscle, kidney, and heart. Sicca symptoms may be present. Various autoantibodies shoud be assessed. In pleuritis of an unknown cause, RE and LE cell testing in pleural fluid[11,19,20] may lead to the diagnosis of collagen disease. Finally, although the cause of the lesion may be unknown at the time of initial examination, careful observation during the clinical course is important, considering that pulmonary lesions may precede other evidence of collagen disease.

Differential diagnosis

Pulmonary lesions that develop secondarily to collagen diseases require careful attention in diagnosis. Various infections may complicate abnormal immune states resulting from collagen disease itself as well as immunocompromise caused by treatment for collagen disease. In addition to bacterial pneumonia, pulmonary tuberculosis, and pulmonary mycosis, *Pneumocystis carinii* pneumonia or cytomegalovirus pneumonia may occur; these can rapidly cause respiratory failure and require differentiation from acute interstitial pneumonia. Detection of protozoa or viral intranuclear inclusion bodies in bronchoalveolar lavage specimens is useful in many cases[56]. A diagnosis using polymerase chain reaction also has been studied in recent years[57], and shows promise. Since antirheumatic drugs themselves occasionally cause pneumonitis[58-61], consideration of a drug reaction is important. Gold-induced pneumonitis is particularly frequent, and interstitial pneumonias caused by D-penicillamine, methotrexate, cyclophosphamide, and bucillamin have been reported. Concurrently administered drugs such as antibiotics and non-steroidal anti-inflammatory drugs also must be kept in mind. Since pulmonary edema may accompany collagen disease-induced renal and cardiac lesions, examination of other organs is essential.

Treatment

No single overall therapeutic approach to pulmonary lesions in collagen disease has been established. Choice of therapy depends on the specific pathologic condition[62-64], which must be evaluated in detail before therapy. Progressive and active lesions require treatment, usually with corticosteroids. Among interstitial lesions, cases showing abnormal foci on gallium scintigraphy, cases with increased lymphocytes in bronchoalveolar lavage specimens, and cases showing intense cell infiltration with little fibrosis accompanied by changes in air spaces on histologic examination generally are considered highly active; these usually require treatment with large doses of steroid. Pleuritis is evident as pleural thickening in many cases; on the other hand, pleuritis may spontaneously subside although a pleural effusion has accumulated. Cases where pleural effusion persists or increases require intermediate-dose steroid treatment.

Acute or subacute interstitial pneumonia accompanying PM/DM, SLE, and MCTD often responds to steroid therapy, and a high dose is indicated. However, pneumonia sometimes progresses very rapidly and does not respond to maximal steroid therapy including intravenous "pulse" therapy. A combination regimen with immunosuppressive drugs such as cyclophosphamide and azathioprine has been attempted, but its effectiveness has yet to be clearly established. Concurrent administration of cyclosporine A may be effective for fulminant interstitial pneumonia accompanying DM. Although a patient may respond to high-dose steroid treatment, reduction of steroid dose often causes a relapse, so careful dose reduction and long-term treatment with a maintenance dose are necessary. Since the interstitial pneumonia or pulmonary fibrosis accompanying SSc and RA is chronic and often gradually progresses despite steroid therapy, steroids often are not indicated; when steroid therapy is employed, the starting dose should be low. D-penicillamine has been effective for some cases of SSc.

Prognosis

Prognoses of pulmonary lesions associated with different pathologic conditions have not been prospectively investigated in a large number of patients because of the variety of pulmonary lesions in collagen disease. At least in interstitial pneumonia, some cases progress to acute respiratory failure or to

pulmonary fibrosis and chronic respiratory failure, and the prognoses for these cases are poor. In patients who respond to steroids, interstitial pneumonia may improve, unlike IIP; in these responders the prognosis may be relatively good. The prognosis is good in many patients with only pleural lesions, while prognoses of patients with alveolar hemorrhage, bronchiolitis obliterans, or pulmonary hypertension usually are poor.

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