CASE REPORT

Pulmonary findings without the influence of therapy in a patient with rheumatoid arthritis : an autopsy case

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Abstract : We report the autopsy findings of a 40- year- old woman with lung complications of rheumatoid arthritis. She has been suffering from rheumatoid arthritis and interstitial pneumonia without satisfactory therapies because of her poor compliance. At autopsy, diffuse pleural adhesions and many protruding cysts were observed. The cut surfaces had rich fibrous changes and honey-comb like appearances dominantly in the left lower lobe. Microscopically, remarkable fibrous changes were observed with destruction of the alveolar structure. These fibroses were temporally homogeneous and lacked prominent fibroblastic foci. The histological pattern was consistent with fibrous non- specific interstitial pneumonia. In peripheral pulmonary arterioles, some thrombi were detected with much recanalization. Systemic amyloidosis was observed in the submandibular gland, thyroid, heart, and arterioles of the lung, kidney, and digestive tract. In the left pulmonary artery, a large embolus was detected. This embolism was the direct cause of death. Her pulmonary findings, except for the embolism, were considered sober states of lung complications of rheumatoid arthritis without the influence of therapy. J. Med. Invest. 54 : 340-344, August, 2007

Keywords **:** *pulmonary findings, rheumatoid arthritis, interstitial pneumonia, autopsy*

INTRODUCTION

The lung is a vulnerable target in collagen vascular diseases (CVDs) represented by rheumatoid arthritis (RA) because of its abundant vasculature and large content of connective tissue (1). Pulmonary involvements of CVD are various, for example, pleuritis, interstitial pneumonia (IP) and vasculitis. IP especially is common to various CVDs, and has a great influence on patients' prognosis. The frequency of IP associated with CVD (IP- CVD) varies depending on the histological pattern : usual IP (UIP), nonspecific IP (NSIP), organizing pneumonia (OP), diffuse alveolar damage (DAD), lymphoid IP (LIP), as well as on the underlying CVD. Patients with pulmonary fibrosis associated with CVD have an improved prognosis compared to idiopathic pulmonary fibrosis (IPF) (2, 3). However, in CVD patients, other histological patterns of IP are often observed. Although such patients have been considered to have more favorable prognosis than patients with idiopathic interstitial pneumonia (IIP) who have the same histological patterns, there is currently no clear proof.

To the best of our knowledge, there is no report of detail pulmonary findings of RA without the influence of therapy. Here, we report a case with natu-

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ral pulmonary findings of RA.

CASE REPORT

A 40- year- old woman was admitted to the hospital because of her mental derangement attendant on hypoxemia. When she was 30- year- old, she was diagnosed as RA by orthopedists. Moreover, she had been suffering from IP for 12 years. Although she was recommended to take disease modifying antirheumatic drugs (DMARDs) or internal steroids several times, they had not been taken continuously because of her poor compliance. Lung transplantation was also impossible because of her mental and circumstantial problems. Pulmonary hypetension (PH) was very severe. Two years before her death, pulmonary pressure was 40 mmHg, rising to 100 mmHg just before her death. Figure 1A and 1B show the findings of chest high resolution computed tomography (HRCT) just before her death. Multiple cystic lesions and fibrous changes were observed in the bilateral lung fields. Honey-comb like appearances were found dominantly in the left and back side. Figure 1A also shows the dilatation of the right pulmonary artery. These HRCTs presented no definite rheumatoid nodules.

Recovering her mental derangement and beginning rehabilitation, she suddenly complained of dyspnea and lost her consciousness, breathing, and heart beat, leading to death without avail of cardiopulmonary resuscitation. The direct cause of death was clinically regarded as pulmonary embolism. We performed an autopsy with the permission of her family.

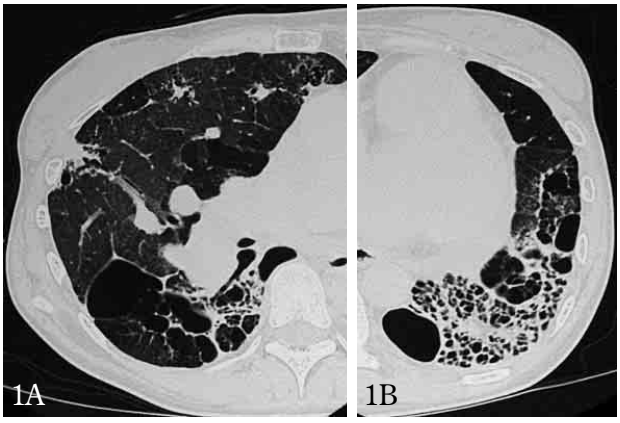


Figure 1. Chest high resolution computed tomography (HRCT) shows multiple cystic lesions and interstitial fibrotic changes in the bilateral lung fields. Honey-comb like appearance is observed in the left and back side.

AUTOPSY FINDINGS

Extensive and hard pleural adhesions were detected in the bilateral thoracic cavities (Figure 2A). Many protruding cysts (max : 7.5 cm in diameter) were also observed. The cut surfaces (Figure 2B) had the pleural thickness, many cysts of various size, remarkable proliferation of fibrous tissue, and honey-comb like appearances dominantly in the left lower lobe. Microscopically, comparatively loose interstitial fibroses that were temporally homogeneous and lacked prominent fibroblastic foci were demonstrated (Figure 3A and 3B). This histological pattern was NSIP, because no temporal heterogeneity of fibrosis was seen despite the lack of steroidal or immunosuppressive therapy (4). Dense fibroses were also observed in the alveoli and alveolar

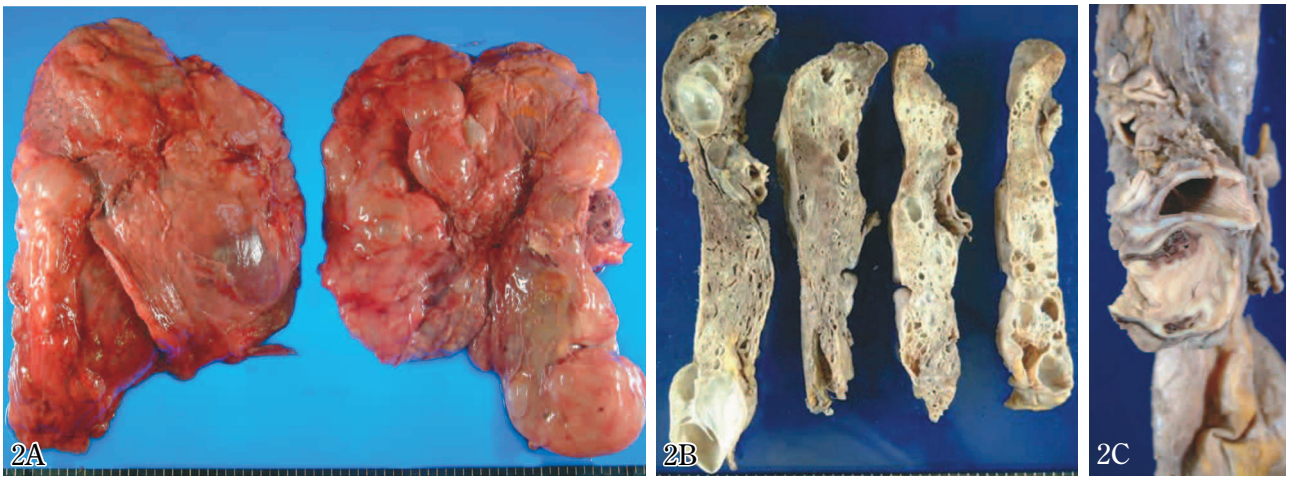


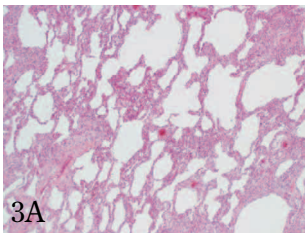
Figure 2A. Pleural adhesions and many cysts are seen on the surface of the bilateral lungs.
Figure 2B. The cut surfaces of the left lung have the pleural thickness, many cystic lesions and remarkable fibrous changes.
Figure 2C. The left pulmonary artery is filled up by an embolus.

walls with moderate infiltration of lymphoid cells especially around the small airways (Figure 4A and 4B). The original structures of alveolar walls were destroyed with fragmentation of elastic fibers (Figure 4B). Samples from the left lower lobe showed the pleural thickness and honeycomb-like appearance with dense fibrosis histologically (Figure 5). This fibrosis was temporally homogeneous and lacked fibroblastic foci. Although the lumens of airspaces were partially covered by bronchiolar metaplastic epithelial cells, complete bronchiolization was never observed. Smooth muscle filaments were not increased so much. In the peripheral arterioles, fibrous wall thicknesses with poor infiltration of lymphoid cells were noted especially in the intima. Some arterioles were filled up by organized thrombi with much recanalization (Figure 6A and 6B).

Autopsy also revealed remarkable thickness of right ventricular wall (8 mm) (not shown). Phenomenons of right ventricular dysfunction were also observed, for example, subcutaneous edema, pericardial effusion (80 ml), ascitis (850 ml), and congestive changes of the liver, kidney, and spleen.

Systemic amyloidosis was detected in the submandibular gland, thyroid, coronary arteries and arterioles of the lung, kidney and digestive tract, showing immunoreactions against only AA protein, but not against Aλ, Aκ, transthyretin, and beta2-microglobulin in immunohistochemistry (not shown).

A large embolus was found in the left pulmonary artery (Figure 2C), filling up its lumen. It consisted of reddish coagulations and white organizations.



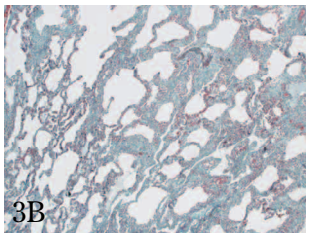
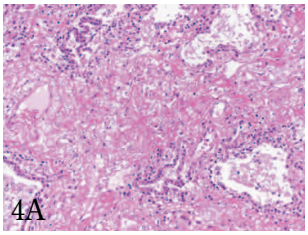


Figure 3A. Comparatively loose interstitial fibrosis that is temporally homogeneous and lacks prominent fibroblastic foci is demonstrated in the sample from the right lower lobe (hematoxylin-eosin, original magnification ×40).
Figure 3B. Proliferated collagen fibers are greenly stained in the same sample as Figure 3A (the combination Verhoeff's elastic and Masson's trichrome : Elastica-Masson, original magnification ×40).



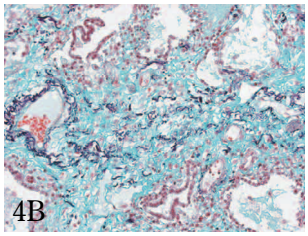


Figure 4A. The collagen fibers are remarkably increased in the left upper lobe with moderate infiltration of lymphoid cells around the small airways (hematoxylin-eosin, original magnification ×200).
Figure 4B. The alveoli are replaced by fibroses (green staining) with fragmentations of elastic fiber of the alveolar walls (black staining) in the same sample as Figure 4A (Elastica-Masson, original magnification ×200).

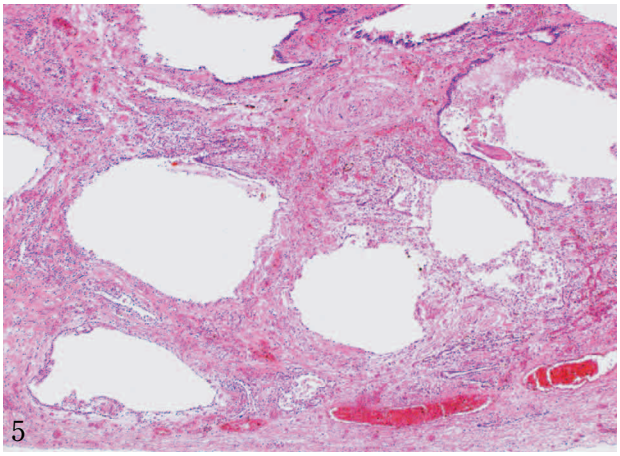


Figure 5. A sample from the left lower lobe shows the pleural thickness and honeycomb-like appearance with dense fibrosis. The fibrosis is temporally homogeneous (hematoxylin-eosin, original magnification ×40).

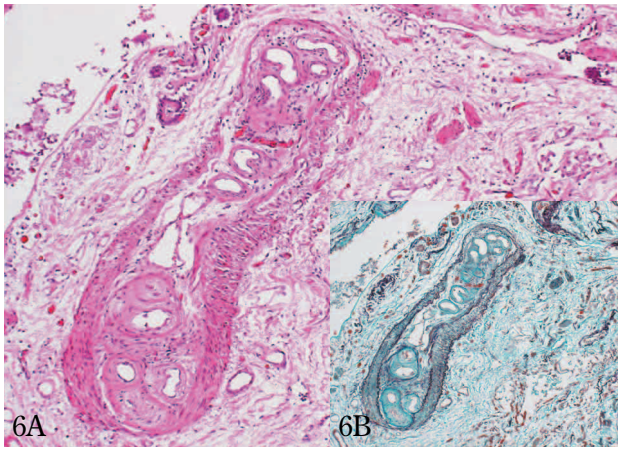


Figure 6A. Thrombus with many recanalizations is observed in a lung peripheral arteriole of the right lower lobe (hematoxylin-eosin, original magnification ×100).
Figure 6B. This indicates that the lumen is filled up by the thrombus with organizations (green staining) and many recanalizations in the same sample as Figure 6A (Elastica-Masson, original magnification ×100).

DISCUSSION

The pulmonary manifestation of RA has traditionally been considered under the following 5 categories : pleuritis with or without effusion, necrobiotic

nodules (nonpneumoconiotic intrapulmonary rheumatoid nodules), Caplan's syndrome (rheumatoid pneumoconiosis), pulmonary arteritis and hypertension, and IP (1). Although the rheumatoid necrobiotic nodule is comparatively specific, the others are not so specific to RA (5). Therefore, we should diagnose the case without rheumatoid nodule as RA lung disease, being supported by the clinical systemic diagnosis of RA. Pulmonary findings of this case corresponded to lung complications of RA, showing pleuritis, IP, arteriolar thrombi probably caused by the arteriolitis, but not the rheumatoid nodule. We finally diagnosed her lung as RA lung disease, being supported by her clinical diagnosis.

Kim *et al.* summarized previous reports, showing that IP- CVD was diverse and included UIP, NSIP, OP, DAD, LIP, and apical fibrosis (6). They also described that the histopathologic findings of IP-CVD were correspondent to those of their idiopathic counterparts, however, lymphoid hyperplasia (follicular hyperplasia) and prominent plasma cell infiltration in interstitial inflammation were comparatively specific to that. Also in this case, we could detect moderate lymphoid hyperplasia especially around the small airways.

It has been considered that UIP was the most frequent histological pattern in IP associated with RA (IP- RA) (7). However, Tansey, *et al.* recently reported NSIP was more frequent pattern than UIP (8). In this case, with some distributive heterogeneity, no temporal heterogeneity of fibrosis was observed. Therefore, we diagnosed the histological pattern of this case as fibrous NSIP rather than UIP. Because this case was not influenced by DMARD or steroid, we do not have to consider the possibility that the characteristics of UIP, for example, the temporal heterogeneity of fibrosis, were blotted out by drugs. In IIPs, NSIP has been reported as a distinct clinicopathological entity, having more favorable prognosis than UIP (9). On the other hand, in IPs- CVD, it was described that the prognosis of patients with NSIP pattern might not be different from that with UIP pattern (10). More investigations are required to reveal the prognosis of each histological pattern of IP- CVD.

Although many thrombi were observed in the peripheral arterioles with remarkable recanalizations, the infiltration of lymphoid cells was poor in the arteriolar walls. These findings indicated that the thrombi had been formed by insensible degrees. Therefore, we considered that these thrombi were caused by chronic inflammation with RA, not by emboli. The histological patterns of primary PH were not observed, for example, glomoid, plexiform and angiomatoid lesions. We also considered that this thrombosis was one of the causes of her progressive PH.

This case had been considered as possible LAM, clinically, because of its remarkable cystic changes of bilateral lungs. However, the smooth muscle filaments were not histologically increased so much. We excluded the possibility of LAM according to this autopsy finding. We regarded the cause of diffuse cystic changes as fibrous NSIP associated with RA.

Amyloidosis of this case showed immunoreactions against only AA protein. This fact was consistent with secondary amyroidosis associated with RA.

The direct cause of death was massive pulmonary embolism. Autopsy findings did not indicate the coronary events or congestive heart failure caused by secondary amyroidosis in the heart.

We experienced a case with lung complications of RA. Unfortunately, it was impossible to achieve either satisfactory drug therapies or lung transplantation because of her poor compliance and circumstantial problems. However, this was a valuable case to observe natural and sober pulmonary findings in a patient with RA.

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