Various systemic diseases or disorders involve the lungs but the initial involvement does not always reveal abnormal findings of chest radiograph or pulmonary function. The early stage of lung injury (interstitial pneumonia (or fibrosis), viral pneumonia, hypersensitivity pneumonia, etc.) may not be detected by routine chest radiograph or pulmonary function tests. Pulmonary granulomatous lesions in lung fields are sometimes overlooked by routine, noninvasive diagnostic tools. For example, a chest radiograph characterized by hilar lymphadenopathy without any interstitial infiltrates is seen in approximately 90% or more of Japanese patients with pulmonary sarcoidosis, and their pulmonary function is normal. Despite the absence of radiographic infiltrates by chest radiograph or CT, 67Ga-scintigraph, bronchoalveolar lavage fluid (BALF) and lung biopsy (i.e., transbronchial lung biopsy; TBLB) show diffuse uptake in lung fields, markedly-increased lymphocytes and granulomatous lesions, respectively, in patients with pulmonary sarcoidosis (1), indicating diffuse granulomatous lesions in the lungs. Although almost all patients with sarcoidosis show a spontaneous remission of the disease, in some patients, pulmonary fibrosis develops. It is still unknown what types of factor(s) are involved in the development of pulmonary fibroses. Detection at such an early stage of pulmonary disorders or diseases is necessary for preventing deterioration in pulmonary function; for example, granulomatous lesions sometimes lead to interstitial fibrosis resulting in respiratory failure. In addition, investigations of the initial stages of pulmonary disorders will give us important clues for not only understanding the pathophysiology (and/or pathogenesis) but also for developing new therapeutic tools. Many diffuse alveolar and interstitial lung diseases produce severe pulmonary fibrosis at the end-stage, and clinical or laboratory investigations of such lungs damaged by severe fibrosis provide little useful knowledge for understanding the pathogenesis of pulmonary (interstitial) diseases or disorders.

In this issue, Kawabata et al (2) reported abnormal cell differentials in BALF and granulomatous lesions in TBLB samples from patients with the rare inherited disease, cerebrotendinous xanthomatosis, who showed no abnormal findings in chest radiograph or pulmonary function.

See also p 922.

Nieman-Pick’s disease and Gaucher’s disease are well-known lipid storage diseases which involve pulmonary tissues (3). These diseases and cerebrotendinous xanthomatosis are classified as lipid storage diseases. Although the viscera and central nervous system have been extensively studied in these diseases, comparatively little attention has been paid to the lungs. Since there have been some reports describing diffuse interstitial shadows in chest radiographs of patients with this disease (4), their study should have dealt with the initial event or early stage of the disease. Foreign-body granulomas and a significantly-increased level of neutrophils are reported to be observed in TBLB samples and BALF from these patients, respectively (2). The increased number of neutrophils in BALF is in contrast to the markedly increased number of lymphocytes in BALF from patients with pulmonary granulomatous diseases such as hypersensitivity pneumonitis, or sarcoidosis etc. (1). Two types of granuloma are known to occur in the lungs, and both immune responses and foreign-body stimulation in the lungs induce granulomatous lesions of the alveolar region.

We can speculate on the mechanism of foreign-body granuloma in lungs of cerebrotendinous xanthomatosis patients as follows. Oxidation of low density lipoprotein (LDL) is a major risk factor for atherosclerosis, and an increase in the activity of macrophage oxidized LDL receptors induces the formation of atherosclerosis (5). Exposure to lipoproteins increases the expression of macrophage scavenger receptors, suggesting that accumulated lipoproteins can further contribute to foam cell development in atherosclerosis (6). Similar mechanism(s) may be also active in the formation of lipid or cholesterol-containing foamy cells and granuloma since cerebrotendinous xanthomatosis is characterized by the accumulation of cholesterol and cholestanol in various tissues. There has been growing evidence for this, although the receptors responsible for avid alveolar macrophage phagocytosis of unopsonized environmental particulates have not been well defined. Northern blot analysis in recent reports (7) revealed the presence of VLDL receptor mRNA in rabbit resident alveolar macrophages. Further, foreign bodies are reported to be phagocytosed by alveolar macrophages through the activity of their scavenger receptors (8) that are known to play a key role in the LDL-phagocytosis and formation of foamy cells in atherosclerosis. Namely, scavenger receptors or LDL receptors in alveolar macrophages may play roles in the development of pulmonary granulomatous disorders or diseases.

In conclusion, normal chest radiograph and pulmonary function do not always mean normal lungs but sometimes represent the initial stage of pulmonary disorders or involvement. Detection of such an early event or initial stage of the disease may not be revealed by non-invasive methods. In such
a case, the “informed consent” will be another important issue. There has been a growing awareness and respect for patients’ rights, and informed consent has become a major topic in Japan in recent years (9). Both BAL and, especially, TBLB sometimes produce serious complications (10). The invasive diagnostic methods should be carefully considered, especially when patients suffer from mental disorders because it is difficult to obtain informed consent from such patients. Kawabata et al (2) addressed this issue by obtaining the informed consent not only from the patients themselves but also from their relatives. In the future, the issues of what kinds of patients should undergo such invasive diagnostic examinations, and also how and when they are to be requested are likely to be more frequently discussed at medical meetings and/or ethical committees.

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References