Lung Disease in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) affects respiratory system including airway, parenchyma, pleura or vasculature [1]. Among RA-related lung diseases, interstitial lung disease (ILD) is the most common lung disease contributing to the morbidity and mortality in RA patients [2]. Airway diseases such as bronchiectasis are also prevalent. Previous studies have shown clear association between RA and lung disease in epidemiological aspects. Increasing number of recent articles dealing with ILD of RA patients reflects growing interest of rheumatologists on this field [3-7]. In a previous issue of The Journal of Rheumatic Disease, Kim et al. [8] investigated around five-hundred RA patients to reveal prevalence and risk factors relevant to airway disease and ILD in RA. The result of this study is interesting as it compares RA patients with airway disease or ILD and those without lung disease simultaneously.

Lung diseases were usually recognized as one of extra-articular manifestations of RA. However, there are some perspectives that lung plays active role in pathogenesis of RA. For example, autoimmune response with emergence of anti-citrullinated protein antibodies (ACPAs) was observed in bronchiectasis patients [9]. Relationship between bronchiectasis and RA can be a model of tolerance breakdown induced by chronic bacterial infection. ILD is also regarded as a process of autoimmune reaction because RA patients with ILD have higher titer and broader repertoire of ACPAs than those without ILD [10]. As respiratory system is exposed to several environmental agonists such as smoking and microbes, lung can be a first site of inflammation igniting autoimmune reaction. Smoking, a well-known environmental risk factor of RA, increased concentration of peptidylarginine deiminase which citrullinates arginine in the lungs [11]. Therefore, the lung might be most active site of citrullination and no more innocent victim in pathogenesis of RA.

Therapeutics for RA should be considered as another variable in patients with lung disease. Most generally used disease-modifying antirheumatic drugs (DMARDs), methotrexate (MTX), is suspicious for causal agent of lung disease. According to recent meta-analysis of randomized controlled trials, MTX increased the risk of lung disease significantly compared to other DMARDs and biologic agents [12]. But the amount of risk increase was very small (10%) and the scope of lung diseases in this meta-analysis included all adverse respiratory events including infection. On the other hand, results from the other two meta-analysis dealing with risk of lung disease contributed by MTX and leflunomide, showed no increased risk of lung disease in MTX users [6,13]. Although those meta-analysis using randomized controlled trials compass large number of patients, the results have to be interpreted with caution because most clinical trials excluded ILD patients at enrollment. For biologic agents in RA, serious ILD events were reported in anti-tumor necrosis factor (TNF) drugs but still they are not strictly contraindicated in patients with preexisting ILD or other lung diseases [14]. Tocilizumab which is blocking interleukin-6, tends to be used in RA-ILD patients more frequently than anti-TNF drugs. However, acute exacerbations of ILD was also reported in tocilizumab users [7]. As ILD exacerbation may result in fatal event in RA patients, choice of medication and appearance of respiratory events should be tracked thoroughly by both patient and physician.

Diagnosis in early stage is very important to remove definite aggravating factors of RA related lung disease and
several genetic and biologic markers are under investigation. Oka et al. [5] suggested HLA-DQB1*03:01 as risk alleles of bronchiectasis or emphysema in RA. For biomarkers, matrix metalloproteinases-7, CXCL10, pulmonary and activation-regulated chemokine, and surfactant protein D were increased in RA with ILD patients compared to RA without ILD [15,16]. Tumor markers such as CA15-3, CA125, and CA19-9 were specifically increased in the sera of RA-ILD patients [3]. The most important thing is to have high level of suspicion in patients who complain new or changed respiratory symptom and detect early stage ILD in RA patients, enabling to predict prognosis. Retrospective study provided by Kim and colleagues [8] showed important information in Korean RA-lung disease patients and prospective cohort study of RA-ILD patients is needed in terms of proper choice of therapeutics and prediction of prognosis in both joint and lung.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES