KL-6 as a Serum Marker for Amiodarone-induced Pulmonary Toxicity

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Amiodarone hydrochloride is a class III anti-arrhythmic agent. It is often used to treat intractable and life-threatening arrhythmias (1). This compound is also well known for its pulmonary toxicity (amiodarone-induced pulmonary toxicity: APT), which restricts the clinical use of amiodarone. It occurs 0.8–17% of patients, with up to 30% mortality (2). However, concomitant conditions such as congestive heart failure or infection, from which the patients taking amiodarone often suffer, frequently mask non-specific symptoms, signs, and radiological changes of APT (3). Microscopic findings of APT include hyperplasia of respiratory epithelium, thickening and edema of the pulmonary interstitium and variable degrees of inflammation involving neutrophilic and mononuclear cells (2). These histological findings indicate that APT is a drug-induced interstitial pneumonia (IP) in nature.

IP is a general term for more than 150 kinds of inflammatory lung diseases in which pulmonary interstitium is mainly damaged. Recently, high resolution computed tomography (HRCT) has been technically progressing and facilitating better clinical care of IP. Serum levels of lactate dehydrogenase (LDH) have been recommended as a handy marker for IP. As a matter of course, however, its specificity and sensitivity for diagnosis are quite low. In this context, the circulating level of KL-6, a high molecular weight glycoprotein (MUC1), is proved to be a much more specific and sensitive marker for IP (4). KL-6 is strongly expressed on type II pneumocytes and regenerative alveolar epithelial cells. Even in healthy persons, KL-6 levels are very high (about 5,000 U/ml) in epithelial lining fluids. Serum level of KL-6 is considered to be controlled by the amount of production mainly by regenerative alveolar epithelial cells and the alveolar-capillary permeability brought from the damage of alveolar epithelium.

Serum levels of KL-6 are less than 500 U/ml in healthy and patients with bacterial pneumonia, mycoplasma pneumonia, and inflammation of the respiratory tract. On the other hand, abnormally high serum levels of KL-6 are noted in most patients (70 to 100%) with idiopathic pulmonary fibrosis, hypersensitivity pneumonia, radiation pneumonia, collagen vascular disease-associated interstitial pneumonia, drug-induced pneumonia, or pulmonary alveolar proteinosis (5–7). Thirty to seventy percent of patients with diffuse panbronchiolitis are positive. In sarcoidosis, a few patients without lung lesions show high levels of KL-6, but most with lung lesions show abnormal high levels (8). Although serum levels of KL-6 do not increase in bacterial pneumonia, fibrosing lung infections such as Legionella pneumonia, Pneumocystis carinii pneumonia (PCP), and tuberculosis with widespread lesion show a high KL-6 level (9). Some reports show that KL-6 levels are increased in patients with Cytomegalovirus pneumonia, however, they may be due to usual complication of PCP. There are many reports that indicate KL-6 is also a useful marker for drug-induced pneumonia. However, the patients with drug-induced eosinophilic pneumonia do not usually show abnormal levels.

In the case of APT, histological findings indicate a drug-induced interstitial pneumonia. In fact, there was a report describing 2 patients with fulminant APT, whose KL-6 levels were 2,100 and 3,100 U/ml, respectively (10). In this issue of Internal Medicine, Nakajima et al (11) confirmed that circulating KL-6 could be a marker for APT.

See also p 1097.

Serum KL-6 of their patient showed a slightly increased level (988 U/ml) when APT was diagnosed. It is also noted that there was a correlation between the improvement of APT and decrease of KL-6 level. These reports may also indicate that the serum level of KL-6 reflects the activity of APT.

Hereafter, if KL-6 is proved to be a good marker for APT, and especially to be useful for preclinical diagnosis of APT, amiodarone could be prescribed more safely.

Nobuoki Kohno, MD, Akihito Yokoyama, MD and Keiichi Kondo, MD
The 2nd Department of Internal Medicine, Ehime University School of Medicine, Shitsukawa, Sigenobu-cho, Onsen-gun, Ehime 791-0295

References