EDITORIAL

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Lung injury as an extra-intestinal manifestation of inflammatory bowel disease

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Inflammatory bowel disease (IBD), represented by ulcerative colitis and Crohn's disease, is a refractory chronic gastrointestinal (GI) disorder characterized by various degrees of inflammation of the GI tract. The prevalence and incidence of IBD in Asia have increased dramatically over the last two decades [1]. Although the pathophysiology of IBD is not completely understood, abnormal activation of the GI immune system and resulting production of proinflammatory cytokines are the main pathophysiological mechanisms [2]. Because these inflammatory processes can occur in many other organ systems, IBD is considered a systemic disorder not confined to the GI tract. Therefore, it may present various extraintestinal manifestations (EIMs) [3]. Up to 50% of all patients with IBD suffer from EIMs, and about 25% have more than one [1,2]. These EIMs may involve nearly any organ system and can potentially impair the patient's quality of life and functional status [4]. Frequently affected sites of EIMs include peripheral or axial joints, the hepatobiliary tract, skin, and eyes. As a result, various arthropathies, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, episcleritis, and uveitis can develop. Although infrequently, the heart, pancreas, or vascular system can also be affected in patients with IBD [3,4].

The relationship between EIMs and intestinal disease activity in patients with IBD varies [4,5]. The development of episcleritis or several EIMs, such as pauciarticular arthritis, erythema nodosum, oral aphthous ulcers, usually implies increased intestinal disease activity. On the other hand, uveitis or ankylosing spondylitis is less likely related to intestinal disease activity. Pyoderma gangrenosum and primary sclerosing cholangitis may or may not be related to intestinal disease activity in patients with IBD.

In addition, pulmonary involvement has risen steadily in patients with IBD since the first report by Kraft et al. [6], in 1976. Involvement of the lungs is not unexpected, considering the embryological origin of the GI and pulmonary system and that IBD is a systemic disease. Various types of pulmonary manifestations, such as tracheal stenosis, bronchitis, peribronchiolitis, alveolitis, bronchiectasis, and interstitial pneumonia, have been reported [7-9]. Studies on pulmonary pathology are difficult to find, although several reports on clinical aspects, including subjective symptoms, respiratory function, and X-ray findings, are available.

In this issue of the *Korean Journal of Internal Medicine*, the presence of abnormal pulmonary pathology in an IBD animal model was investi-

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gated, and the relationship between the degree of tissue inflammation and tissue concentrations of two important cytokines in IBD, i.e., tumor necrosis factor α (TNF-α) and vascular endothelial growth factor (VEGF), were evaluated [10]. The authors discovered extensive alveolar hemorrhage in the pulmonary tissues of most rats with trinitrobenzene sulfonic acid (TNBS)- and dextran sulfate sodium (DSS)-induced colitis, and pulmonary tissue concentrations of TNF-α and VEGF increased in these animals. They concluded that the inflammatory process caused by these proinflammatory cytokines was associated with increased alveolar epithelial permeability and may affect the development of IBD-associated pulmonary manifestations.

In this experiment, 83.3% of rats with colitis developed an alveolar hemorrhage, unlike in previous clinical studies in which only 1% to 6% of patients with IBD showed pulmonary involvement. A bias due to the experimental process itself when producing the colitis model cannot be excluded. It is possible that ingested foreign material, such as TNBS or DSS, directly injured the pulmonary tissues regardless of injury to the colon. Or, as the authors mention in the manuscript, a lack of exposure (only 7 days), which is applicable to the acute colitis stage, could produce this discordance because there may be some differences in the degree of inflammation between acute colitis and IBD (chronic disease). Moreover, the number of rats per group in this study was too small to obtain sufficient results, including the independent etiologic risk factors for pulmonary involvement. Experiments with other IBD models, such as interlukin-10 knock-out mice, along with a sufficient sample size may generate more robust results and conclusions.

Another limitation of this study is that the authors could not elucidate the acceptable mechanism for alveolar hemorrhage. They suggested that the VEGF-associated increase in alveolar epithelial permeability may have played a role in the etiopathogenesis of IBD-associated pulmonary involvement. However, it is unclear whether the increase in pulmonary VEGF was induced by pulmonary involvement of IBD.

In summary, the authors concluded that serious pulmonary histopathological changes directly related to colitis frequently occur as an EIM in IBD and that increases in the levels of TNF-α and VEGF may play a role in the development of this pulmonary involvement. Despite several limitations, this study has value as the first report on the relationship between pulmonary pathology and IBD.

Conflict of interest

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

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