[EDITORIAL]

Knowledge of Secondary Pulmonary Alveolar Proteinosis Complicated with Myelodysplastic Syndrome

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Data collection and research on pulmonary alveolar proteinosis (PAP) in Japan has steadily progressed since Dr. Nakata and colleagues discovered anti-granulocyte/macrophage colony-stimulating factor (GM-CSF) autoantibodies in patients with PAP in 1999 (1). Between 1999 and 2017, more than 1,000 cases of PAP were diagnosed based on pathological findings and the anti-GM-CSF autoantibody titer. Ninety percent of all PAP cases were autoimmune PAP with serum anti-GM-CSF autoantibody positivity. On the other hand, very few cases of secondary PAP without serum anti-GM-CSF autoantibodies have been diagnosed. According to our registry for autoimmune PAP (2), the prevalence of autoimmune PAP was estimated to be 26.6 per million, indicating that the previous data (3) underestimated the incidence and prevalence. With regard to secondary PAP, approximately 6 patients are diagnosed with this type of PAP every year in Japan. Thus, secondary PAP is an extremely rare lung disease and there are few clinical guidelines for the condition.

Hashimoto and colleagues recently reported a case study on secondary PAP complicated with myelodysplastic syndrome (MDS) (4). There are two interesting points in this case. First, it was a rare case in which the clinical course of MDS before after the complication of secondary PAP was described in detail. In general, 80% of secondary PAP cases involve a hematological disorder, most frequently MDS (5). The prognosis of secondary PAP is very poor because the two-year survival rate after the diagnosis of secondary PAP is only 42% (6). In this case, secondary PAP developed with the progression of MDS during an azacitidine treatment and the condition of secondary PAP was improved by umbilical cord blood transplantation. This suggests that we need to control the condition of MDS to improve the development of secondary PAP. Because the indication of allogeneic hematopoietic stem cell transplantation is considered based on prognostic scoring systems such as MDS-specific comorbid-

ity index (7) and the Revised-IPSS (8), most MDS patients with secondary PAP are considered to be high-risk and cannot receive transplantation. Thus, it has been unclear whether hematopoietic stem cell transplantation really improves the prognosis of MDS with secondary PAP. There are some case reports that secondary PAP was improved by hematopoietic stem cell transplantation for MDS. However, the pathogenesis of secondary PAP remains unknown. Hence, the treatment of MDS with secondary PAP remains to be established.

Second, Hashimoto et al. performed target-capture sequencing for some oncogenic variants, known as driver genes, that are implicated in myeloid malignancies (4). Although Y591N and R592Q mutations in the *MPL* gene and a frameshift insertion in the *SH2B3* gene were detected in this case, these genes were associated with MDS rather than secondary PAP. Alveolar macrophages differentiated from abnormal hematopoietic stem cells have been reported in secondary PAP complicating MDS (9). Moreover, the relationship between the onset of secondary PAP and GATA2-deficiency has been another focus of research on the pathogenesis of secondary PAP (10). Stem cell transplantation has been proposed as a treatment for secondary PAP complicating MDS, but the outcome is not very favorable because the number of risk factors, such as infection and graft-versus-host disease, can limit its benefit for the patients. In this case, the patient also died of idiopathic pneumonia syndrome in the early phase after transplantation. In cases of MDS with secondary PAP, it is very important to diagnose secondary PAP earlier and to treat patients with hematopoietic stem cell transplantation before their general condition worsens.

Author's disclosure of potential Conflicts of Interest (COI).

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