Early View

Research letter

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LETTER TO THE EDITOR

Expansion of ST2-expressing macrophages in a patient with bronchiolitis obliterans syndrome

Toyoshi Yanagihara1,3*, Kentaro Hata1,3, Kunihiro Suzuki1, Keisuke Matsubara2, Kazufumi Kunimura2, Kazuya Tsubouchi1, Daisuke Eto, Hiroyuki Ando, Maki Uehara1, Satoshi Ikegame1, Yoshinori Fukui2, Isamu Okamoto1

1 Department of Respiratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
2 Division of Immunogenetics, Department of Immunobiology and Neuroscience, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan
3 These authors contributed equally to this work and share the first authorship

* Corresponding author: Toyoshi Yanagihara
E-mail: yanagihara.toyoshi.759@m.kyushu-u.ac.jp

Dear Editor,

Bronchiolitis obliterans syndrome (BOS) is a major complication of hematopoietic stem cell transplantation (HSCT) that affects the lungs and has limited treatment options[1]. BOS after HSCT is considered a manifestation of chronic graft-versus-host disease (GVHD). T-cells play a crucial role in its onset[2], while the contribution of myeloid cells has been largely unknown.

Here, we report a case of a 29-year-old woman with acute myeloid leukemia (AML-M2) who developed BOS five months after receiving an allogeneic peripheral blood stem cell transplant. The patient presented with symptoms of dry cough and dyspnea, and a chest computed tomography scan revealed mosaic attenuation, mild bronchial thickening, small nodules, and faint ground glass opacity with hyperinflation in both lungs (Figure 1A).

Pulmonary function tests indicated severe obstructive disease compared to the results before HSCT, with a forced expiratory volume in one second of 0.98 L (33.6% of predicted), a forced vital capacity of 1.90 L (56.4% of predicted), and an FEV1/FVC ratio of 0.52, as well as a diffusing capacity of the lungs for carbon monoxide of 62.4% of predicted (Figure 1B). Bronchoalveolar lavage (BAL) was conducted in the right B4b lung
area using 150 mL of saline solution, resulting in the collection of 87 mL of bronchoalveolar lavage fluid (BALF). Analysis of BALF revealed 95.2% of macrophages, 0.6% of neutrophils, and 4.2% of lymphocytes, with no evidence of infection. Transbronchial lung biopsy showed mild chronic inflammation without any signs of specific infection or malignancy. The patient was subsequently diagnosed with BOS.

Mass cytometry analysis of BALF cells revealed distinct patterns of immune cell populations compared to other lung diseases, such as sarcoidosis, connective tissue disease-related interstitial lung diseases (CTD-ILDs), and cytotoxic drug-induced ILDs (Figures 1C and 1D). The macrophage population was prevalent, as indicated by the cytological data, and there was a significantly increased proportion of ST2+ CD64+ macrophages in the BALF of the patient with BOS. These ST2+ CD64+ macrophages were CD11b+ CD11c+ CD16+ HLA-DRlo CCR2– CCR5– CD36– CD163hi CD223–, possibly representing an alternatively activated macrophage phenotype[3]. This is the first demonstration of the increased proportion of ST2+ macrophages in BALF from a patient with BOS. ST2 is a receptor for IL-33, a cytokine released by damaged epithelial cells, and is expressed on various cell types, including innate lymphoid cell type 2 and macrophages[4]. During epithelial damage, airway macrophages are activated to support epithelial repair and display IL-33-ST2 activation during their differentiation[5]. Continuous epithelial damage by allo-reactive T cells[2] may aberrantly stimulate these ST2+ macrophages to produce excessive growth factors and extracellular matrix, resulting in airway remodeling and obstruction. Soluble ST2 levels in plasma have been identified as a marker for the risk of therapy-resistant GVHD,[6] suggesting a link to our hypothesis, although we did not assess plasma ST2 levels in the patient. ST2+ macrophages may thus be a potential therapeutic target, particularly for treatment-refractory BOS.[1]

We also observed a reduction in the proportion of CCR2+CD14+ monocytes compared to other lung disorders. These monocytes were characterized as CD64+ CD11b++ CD11c++ CD16+ HLA-DR+ CCR5+ CD32++ CD36+ CD163– CD206lo. Recent evidence suggests that CCR2+ monocytes accumulating in the lung can stimulate tissue-resident CD8+ T cell activation, leading to airway epithelial cell apoptosis in a mouse model of BOS after lung transplantation.[7] The precise reason for the reduction of CCR2+CD14+ monocytes, which were previously observed to be increased in a mouse model of BOS, in the present case remains unclear. Possible explanations include variations in the conditions of BOS (lung transplantation versus hematopoietic stem cell transplantation), limitations in model
replication, or disparities in timing from disease onset.

The study has limitations. First, only one case was investigated due to its rarity, and validation is required. Second, we have used BALF samples from sarcoidosis, CTD-ILDs, and DI-ILDs as disease controls. Given that BOS mainly affects “small airways,” it would have been ideal to use other airway diseases, such as bronchial asthma or COPD, that exhibit small airway lesions as disease controls. The remaining BALF obtained as part of clinical testing was used in our study. It is not common to perform BAL in these patients as part of clinical practice, which led to the unavailability of BALF samples from small airway diseases as disease controls. Last, the BALF analysis lacks spatial information on the lung. Muranushi et al. recently reported monocyte and lymphocyte accumulation around bronchioles in human GVHD characterized by BO, although precise analysis of peribronchial macrophages was not conducted.[8] Since BALF can reflect peribronchial components as well as alveolar ones, these ST2+ macrophages could be from the peribronchiole, the main inflammation site of BOS. Immunohistochemistry analysis of these macrophages in BOS would provide additional insights into the pathogenesis of BOS. Further research for validation, spatial investigation, and measurement of plasma ST2 levels is warranted to fully understand the precise mechanisms of immune dysregulation in BOS.

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Figure 1. (A) A chest CT image and (B) a flow volume curve on spirometry of the patient. (C) t-stochastic neighborhood embedding (tSNE) plots visualizing cell population, distribution, and intensity of ST2 and CCR2 in CD45+ gated BALF cells from patients with BOS (n = 1), sarcoidosis (n = 11), CTD-ILD (n = 8), cytotoxic drug-ILD (n = 5). For sarcoidosis, CTD-ILD, and cytotoxic drug-ILD, individual data were concatenated into one file per disease group. Alveolar macrophages are characterized by CD64+CD14−CD11bhiCD11chiHLA-DRhi expression, neutrophils by CD64−CD11b+CD16+CD11c−HLA-DR− expression, B cells by CD19+ expression, and T cells defined by CD3+ expression. (B) The proportion of cell populations in CD45+ gated BALF cells as determined by tSNE analysis. The methodology has been previously described[9].

References