Monocytosis and High Serum Macrophage Colony-Stimulating Factor in Waldenström's Macroglobulinemia

To the Editor:

Waldenström's macroglobulinemia (WM) is a clonal lymphoid disorder characterized by the lymphoplasmacytic proliferation in the bone marrow (BM) and the elevation of serum monoclonal IgM.1 Several cytokines were reported to be involved in the clonal proliferation of lymphoid neoplasia. For example, in patients with myeloma, malignant plasma cells constitutively produce interleukin-6 (IL-6) and promote their autocrine proliferation.2 Serum IL-1β and IL-6 are elevated in the patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome, suggesting a role of both cytokines in its pathogenesis.3 We report a case of macroglobulinemia with high serum concentration of macrophage colony-stimulating factor (M-CSF) and IL-6, which presented marked monocytosis and severe pulmonary hypertension.

A 56-year-old man was admitted to our hospital because of fatigue and dyspnea on exertion. Physical examination showed mild hepatomegaly and holosystolic murmur at the left sternal margin. Serum IgM was markedly elevated to 7,120 mg/dL, shown to be monoclonal IgM (κ) by immunoelectrophoresis. The leukocyte count was 5,300/μL with 34% of neutrophils, 25% lymphocytes, and 37% monocytes. The hemoglobin was 7.9 g/dL and the platelet count was 207 × 10⁹/μL. He had no lytic bone lesions. BM examination showed the proliferation of abnormal lymphoplasmacytoid cells (up to 14%).

Chest radiograph disclosed enhanced pulmonary vascular shadow and cardiomegaly. Echocardiography showed marked right ventricular enlargement and massive tricuspid regurgitation. The estimated systolic pulmonary artery pressure was about 60 mm Hg. Based on these findings, he was diagnosed as having WM with monocytosis and pulmonary hypertension. The observed monocytosis in this patient was transiently normalized in response to chemotherapy (cyclophosphamide and prednisolone) and returned to the pretreatment level after 3 weeks. Thus, we suspected its correlation to macroglobulinemia. To clarify the cause of monocytosis, we measured serum M-CSF concentration by enzyme-linked immunosorbent assay (ELISA). It was remarkably elevated to 2,319 U/mL (mean ± SD serum level of M-CSF was 756 ± 147 U/mL in 634 healthy individuals). Serum IL-6 was also elevated to 41.8 pg/mL (normal: <4.0 pg/mL). Next we attempted to clarify which cell populations produced high level of M-CSF in this patient. For this purpose, the peripheral blood mononuclear cells (PBMCs) from the patient as well as a normal control were stained with anti-M-CSF antibody in combination with anti-CD20. The cells were then run on a laser confocal scanning microscopy. It has been shown that the PBMCs from the patient were double-stained by anti-CD20 and anti-M-CSF (Fig 1A), whereas those from a normal control were not (Fig 1B). These results strongly indicate that CD20⁺ B lymphocytes in this patient produce M-CSF.

There are few reports describing serum cytokine concentration in patients with macroglobulinemia. Solary et al4 reported high serum IL-6 in 2 of 20 patients with macroglobulinemia. Gherardi et al5 also found one patient with high serum IL-6, but no case with high serum IL-1β among five patients they studied. It is reported that serum M-CSF concentration is elevated in some cases with lymphoplasmacytoid malignancy such as lymphoma, chronic lymphocytic leukemia (CLL), and myeloma6; however, macroglobulinemia was not included in this study. To our knowledge, this is the first report of high serum M-CSF in patient with macroglobulinemia.

The major production sites of M-CSF are monocytes, fibroblasts, endothelial cells, and placenta. However, Epstein-Barr virus (EBV)-

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transformed or mitogen-activated B lymphocytes are also reported to express M-CSF mRNA by Northern blotting analysis. These results suggest that M-CSF mRNA is negatively regulated in resting B lymphocytes, but could be induced by stimulation from the cell interior or exterior. Thus, it is likely that M-CSF was produced by the malignant and/or activated B lymphocytes in this patient. Although it is difficult to determine which is the predominant population to produce M-CSF, the malignant B cells could have a central role in this setting either by producing M-CSF as an autocrine growth factor, or producing some mitogenic substances that activate normal B lymphocytes.

The etiology of pulmonary hypertension is unclear because there was no evidence of organic heart and pulmonary diseases. Vascular intimal smooth muscle cells from the atherosclerotic lesions are reported to proliferate in response to M-CSF, and these phenomena contribute to the atherosclerotic process in the arterial wall. Thus, high serum M-CSF level may have some role in pulmonary hypertension through promoting arteriosclerosis of the pulmonary arteries.

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