Monoclonal B-cell Lymphocytosis in a Patient with Wegener Granulomatosis: A Case Report and Update on 2016 World Health Organization Classification

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The association between autoimmune disease and risk of monoclonal malignancy is well studied. However, monoclonal B-cell lymphocytosis (MBL) in patients with autoimmune diseases has rarely been reported. The newly published 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms has officially accepted MBL as an independent disease entity.¹ Herein, we present a case of Wegener granulomatosis (WG) with MBL. Through this case, the diagnosis and management of MBL as a less known condition to rheumatologists, especially under the background of an autoimmune disorder, is reviewed. Moreover, the association between autoimmune disease and risk of monoclonal malignancy is discussed.

A 70-year-old Chinese man presented with a 2-month history of hearing loss, intermittent fever, and diffuse myalgia. Physical examination was almost normal. Laboratory examination indicated Hb 108 g/L, white blood cell (WBC) 19.44 × 10⁹/L (Neutrophils 82.2%, Lymphocyte 7.4%, Eosinophil 2.1%), and platelet 214 × 10⁹/L; albumin 29.1 g/L and globulin 48.1 g/L; aspartate aminotransferase 37 IU/L, alanine aminotransferase 31 IU/L, and creatinine 133 μmol/L; erythrocyte sedimentation rate 96 mm/h, C-reactive protein 133 μmol/L, C-reactive protein 136 mg/L, procalcitonin 0.28 ng/ml, and ferritin 1111 ng/ml. Serum protein electrophoresis and immunofixation electrophoresis revealed no monoclonal immunoglobulin, urine protein 0.21 g/24 h, and WBC 8/HP. Magnetic resonance imaging (MRI) of the brain revealed paranasal sinusitis and bilateral otitis media. Chest computed tomography (CT) revealed scattered infiltration and small patches. The results of purified protein derivative skin testing and Mycobacterium tuberculosis interferon-γ release testing were negative. Cultures of fiber bronchoscopic bronchial alveolar lavage (BAL) fluid yielded Staphylococcus aureus. The antineutrophil cytoplasmic antibody (ANCA) testing revealed low-positive anti-myeloperoxidase (MPO) by enzyme-linked immunosorbent assay (ELISA) (1.5 units; reference range, 0–1.0 units). The result of ANCA testing by indirect immunofluorescence on ethanol-fixed neutrophils was suspiciously positive. Serologic testing for rheumatoid factor, anticitrullinated cytoplasmic antibodies, and anti-extractable nuclear antigen autoantibody profiles were negative. There were no atypical cells on cytological examinations of the bone marrow (BM). Flow cytometry (FCM) of BM revealed monoclonal B-lymphocyte accounting for 4.8% of the nucleated cells with an immunophenotype of Cluster of differentiation (CD)19(+), CD20(+), CD22(+), FMC7(+), CD5(−), CD10(−), CD23(−), CD103(−), and CD38(−).

At first, intravenous moxifloxacin was given for 2 weeks considering his pulmonary infection, which turned out ineffective. Thus, ANCA testing, which usually involves a stepwise approach, was repeated in this patient with increased MPO-ANCA titer of 2.9 units (reference range 0–1.0 unit) by ELISA. Lack of clinical response to antimicrobial therapy,
S. aureus in BAL fluid (commonly as a trigger for WG), and positive MPO-ANCA test result were highly suggestive of WG. Finally, nasal inflammation and otic inflammation were revealed by MRI, and infection-unexplained chest radiograph finding made our patient meet the criteria for WG published by the American College of Rheumatology in 1990. On the other hand, in consideration of the monoclonal B-cells found by FCM, positron emission tomography-CT (PET-CT) was performed with no signs of malignancy detected. Thus, a diagnosis of MBL with WG was established. A combination therapy of oral methylprednisolone 40 mg/d and cyclophosphamide 100 mg/d was initiated for WG, and oral trimethoprim-sulfamethoxazole was used to eradicate the S. aureus. Steady improvement in hearing, with resolution of fever and myalgia, was achieved after the treatment. Laboratory studies revealed improvement of anemia (Hb 108 g/L), increased albumin (34.5 g/L), decreased globulin (29.2 g/L), erythrocyte sedimentation rate (36 mm/h), C-reactive protein (12.2 mg/L), fibrinogen (3.23 g/L), and procalcitonin (0.06 ng/ml). Urine protein disappeared.

Discussion
As far as we know, this is a rare case reporting MBL in a patient with autoimmune disease. MBL was first described in 1984, and got more and more attention in the past 5 years. It was regarded as a monoclonal B-cell disorder characterized by an asymptomatic monoclonal expansion of circulating B-lymphocytes in the blood and could not fulfill any criteria for a lymphoid malignancy. Whereas, in 2008, it was unknown whether MBL was a precursor of chronic lymphocytic leukemia (CLL), we now know that MBL precedes virtually all cases of CLL. The updated WHO emphasizes that “low-count” MBL, defined as a peripheral blood monoclonal lymphocyte count of less than $0.5 \times 10^9/L$, must be distinguished from “highcount” MBL. Low-count MBL has an exceedingly small risk of progression to CLL. In contrast, high-count MBL had a 1–2% per year risk of progression to CLL.

The association between autoimmune disorders and the pathogenesis of lymphoma have been revealed by several studies. Shared pathogenesis of those two disorders may explain this association. First, activation of B-cells and T-cells was seen in both autoimmune disorder and lymphoma. Longstanding chronic inflammation and/or antigen stimulation in patients with active autoimmune disease could be the predisposing factor of lymphoma. Second, in autoimmune diseases, abnormalities in the expression of cytokines (e.g., B-cell activating factor, interleukin [IL]-6, IL-10, and tumor necrosis factor-α) are also implicated in the growth and survival of B-cell malignancies.

It is noteworthy that although the progression rate was low, MBL might make patients more susceptible to infection because of the depletion of normal B-cells due to the overexpansion of monoclonal elements. Moreover, autoimmune disorder itself is associated with an increased risk of developing malignant lymphoma. Thus, we suspect that the transformation risk in this condition is higher than healthy people due to the double effective by autoimmunity and monoclonal lymphoproliferation. Therefore, we should keep in mind that repetitive FCM analysis and/or PET-CT evaluation in the follow-up should be done in a 3–6 months interval.

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Conflicts of interest
There are no conflicts of interest.

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