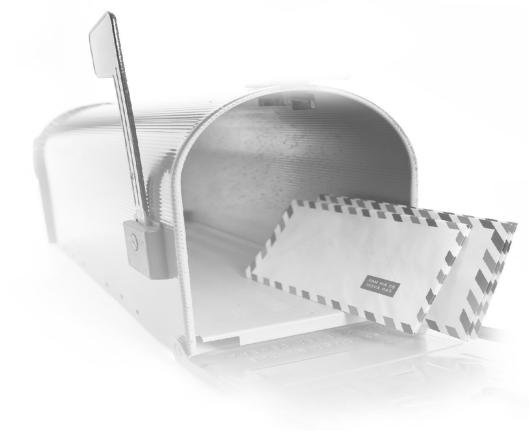

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Letters to the Editor

High-grade nodal marginal zone lymphoma with diffuse bone marrow involvement and IgM-type monoclonal paraproteinemia: a case report and review of the literature

TO THE EDITOR: Immunoglobulin M (IgM)-type monoclonal paraproteinemia is reportedly present in patients with various subtypes of lymphoma, but approximately 60% and 20% of cases are found in patients with lymphoplasmacytic lymphoma (LPL)/Waldenström's macroglobulinemia (WM) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), respectively [1-3]. Other types of non-Hodgkin lymphoma with serum monoclonal IgM paraprotein occur rarely, and we report here a case of nodal marginal zone lymphoma (NMZL) with diffuse bone marrow (BM) involvement and IgM-type monoclonal paraproteinemia.

A 60-year-old woman visited our institution in December 2018 with the symptoms of fever, cough, and epigastric pain lasting for one week. Computed tomography (CT) showed the presence of mild hepatosplenomegaly without definite evidence of a splenic mass and multiple lymphadenopathies involving the bilateral cervical, axillary, and upper mediastinum lymph nodes (LNs). Whole-body positron emission tomography-CT scan results showed diffusely increased metabolism with marrow expansion and multiple hypermetabolic LNs in the bilateral cervical, axillary, mediastinal, and abdominal areas, but there was no definite evidence of increased metabolism in other extranodal lesions, such as the stomach or other intestines. Her hemogram results at the first visit were as follows: white blood cells, 14.6×10^9/L; hemoglobin, 9.8 g/dL; and platelets, 73×10^9/L. The peripheral blood smear (PBS) revealed the presence of medium-sized to large neoplastic lymphoid cells exhibiting the absence of villous projection in their cytoplasm at a frequency of 32% (Fig. 1A).

The BM aspiration showed normocellular marrow with increased infiltration of large neoplastic lymphoid cells (8.5%) (Fig. 1B–D) and plasma cells (4.5%), and BM biopsy showed normocellular marrow (cellularity 60%) with diffuse infiltration of large neoplastic lymphoid cells (Fig. 1E, F). Subsequently performed immunohistochemical (IHC) staining of BM biopsy sections showed the presence of large neoplastic lymphoid cells with strong membranous positivity for cluster of differentiation (CD)20 (Fig. 1G), negativity for both CD3 and CD10 (Fig. 1H, I), but nuclear positivity for both B-cell lymphoma (BCL)-6 and multiple myeloma oncogene 1 (Fig. 1J, K). In addition, increased plasma cells showed positivity for CD138 (Fig. 1L). Interestingly, serum electrophoresis/immunofixation results showed the presence of monoclonal gammopathy, IgM kappa type with M-protein of 5.6 g/L.

Excisional biopsy specimens obtained from the left axillary LN showed an increase in reactive T cells with positivity for CD3, CD4, and CD8 on IHC staining and the presence of small neoplastic lymphoid cells with transformed large cells exhibiting positive results on CD20, BCL-2, and Ki-67 (40%) IHC staining, but negative results on CD10, Cyclin D1, and Epstein–Barr virus in situ hybridization IHC staining. Based on these results, the pathologic diagnosis of high-grade NMZL was made, and she was planned to receive intravenous methylprednisolone at 1 mg/kg for every 12 hours at first, followed by rituximab and bendamustine-based chemotherapy.

No studies have suggested the possible mechanism or hypothesis of IgM-type monoclonal paraproteinemia in B-cell lymphoma. However, in the association between the development of B cells and specific lymphoma subtypes, previous studies have demonstrated the association between monoclonal paraproteinemia and diffuse large B-cell lymphoma (DLBCL) with non-germinal center B cell (GCB) subtype with an explanation summarizing that DLBCL with non-GCB subtype develops from post-GCB and is associated with an up-regulation in Blimp-1, which is a master regulator of plasma cell differentiation [4, 5].

A previous study showed that in 430 patients with serum IgM-type monoclonal paraproteinemia, 56.3% of the cases were of monoclonal gammopathy of undetermined significance (MGUS) and 16.5% were of WM, followed by other lymphomas, CLL, and primary amyloidosis with frequencies of 6.5%, 4.9%, and 1.4%, respectively [1]. Another

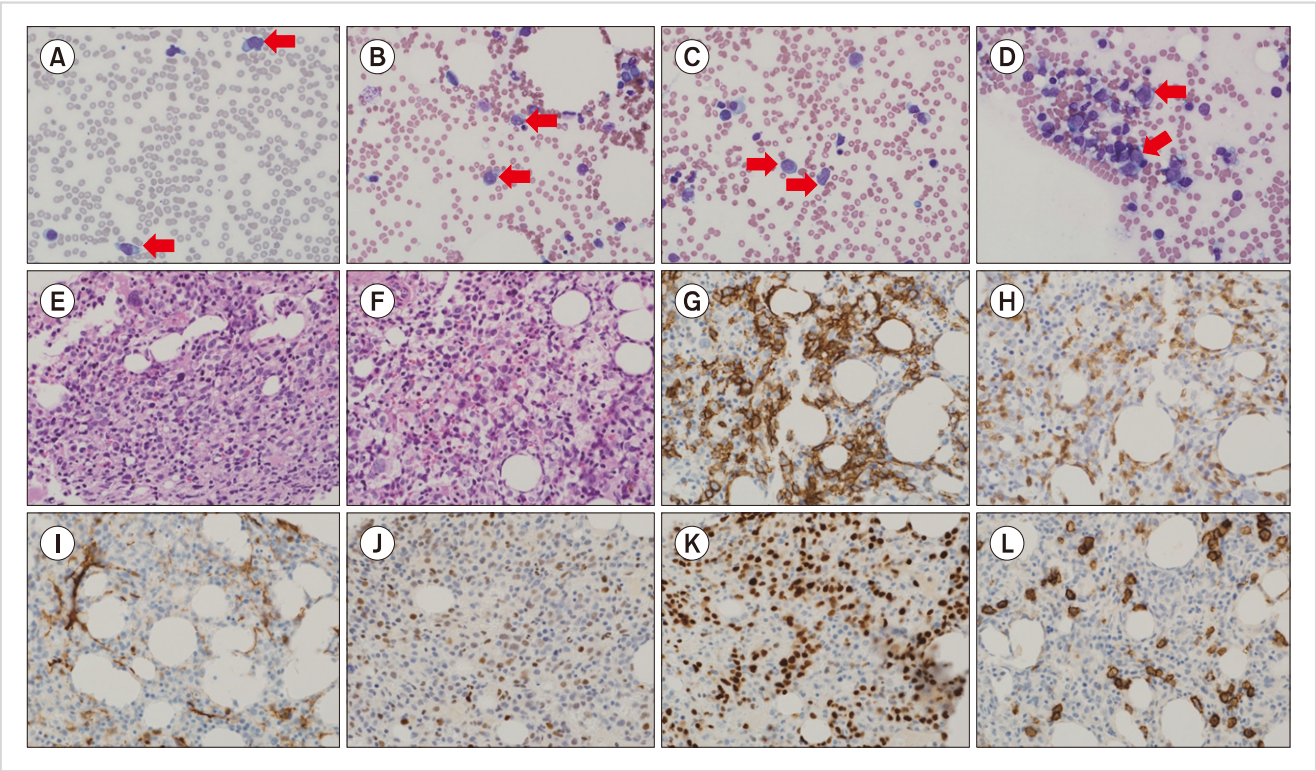

Fig. 1. Peripheral blood smear, bone marrow aspiration and biopsy, and immunohistochemical staining results of the patient. The peripheral blood smear **(A)** revealed the presence of medium-sized to large neoplastic lymphoid cells (indicated with red arrows, Wright stain, ×400). The bone marrow aspiration **(B, C)** and touch print **(D)** showed normocellular marrow with increased infiltration of large neoplastic lymphoid cells (indicated with red arrows, Wright stain, ×400) and plasma cells. The bone marrow biopsy **(E, F)** showed normocellular marrow with diffuse infiltration of large neoplastic lymphoid cells (Hematoxylin & Eosin stain, ×400). Subsequently performed immunohistochemical staining showed the presence of large neoplastic lymphoid cells with strong membranous positivity for CD20 **(G)** and negativity for both CD3 and CD10 **(H, I)**, but nuclear positivity for both BCL-6 and MUM1 **(J, K)**. In addition, increased plasma cells showed positivity for CD138 **(L)**.
Abbreviations: CD, cluster of differentiation; BCL-6, B-cell lymphoma 6; MUM1, multiple myeloma oncogene 1.

previous study analyzed 106 patients with lymphoma and IgM-type monoclonal paraproteinemia and showed that although LPL/WM were the most common disease subtypes, 24 patients showed other lymphoma subtypes such as 10 patients with CLL, 5 patients with DLBCL, and 3 patients with extranodal MZL of mucosa-associated lymphoid tissue (MALT) lymphoma, follicular lymphoma (FL), and mantle cell lymphoma (MCL), respectively [2]. Another study analyzed 382 patients with IgM-type monoclonal paraproteinemia and lymphoma and revealed the diagnoses of LPL/WM, CLL/SLL, FL, MALT lymphoma, splenic MZL, MCL, and DLBCL with frequencies of 58.9%, 20.2%, 4.7%, 3.9%, 2.9%, 2.9%, and 1.8%, respectively [3]. This study demonstrated only one case of NMZL with IgM-type monoclonal paraproteinemia, representing a frequency of 0.003% [3], and to date, no cases have been reported except for a case study performed in China that presented two cases of NMZL with IgM-type monoclonal paraproteinemia [6]. Therefore, it can be speculated that although some cases of MZL with IgM-type monoclonal paraproteinemia have been reported, most cases are of the extranodal and splenic subtypes, and cases of NMZL are extremely rare. The mechanism or hypothesis that explains the rarity of IgM-type monoclonal paraproteinemia in NMZL and possibility in MZL of extranodal and splenic subtypes has not been suggested in a previous study, and this issue should be further analyzed in a more comprehensive future study. In summary, we report here a rare case of NMZL with diffuse BM involvement and IgM-type monoclonal paraproteinemia.

Sang Hyuk Park[1], Jaewook Kim[1], Joseph Jeong[1], Seon-Ho Lee[1], Hee Jeong Cha[2], Seol Hoon Park[3], Yunsuk Choi[4], Jae-Cheol Jo[4], Ji-Hun Lim[1]
Departments of [1]Laboratory Medicine, [2]Pathology, [3]Nuclear Medicine, [4]Hematology and Cellular Therapy, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea

Correspondence to: Ji-Hun Lim
Department of Laboratory Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Bangujin-sunhwandoro 877, Dong-gu, Ulsan 44033, Korea
E-mail: limjh@uuh.ulsan.kr

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No potential conflicts of interest relevant to this article were reported.

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Bone marrow metastasis of small cell lung carcinoma with spontaneous tumor lysis syndrome without hepatic metastasis at diagnosis: first case report in Korea and review of literature

TO THE EDITOR: Tumor lysis syndrome (TLS) is a severe metabolic and electrolytic disturbance caused by rapid lysis of neoplastic cells, and resulting in various end-organ damages. TLS is frequently encountered in tumors with high cell turnover and growth rates such as hematologic malignancies including acute leukemias, Burkitt lymphoma, and high-grade lymphomas, and is commonly observed in these patients after administration of induction chemotherapy, radiotherapy, or cytolytic antibody therapy [1, 2]. TLS unrelated to therapy is defined as spontaneous TLS (STLS), which can be observed in patients with the aforementioned hematologic malignancies, but the incidence of STLS is lower than that of TLS associated with prior therapy [3, 4]. TLS is also rarely encountered in patients with solid cancers. STLS in small cell lung carcinoma (SCLC) was first reported in 2008, and since then, only five other cases have been reported up to present time [3-7]. We report here a case of STLS associated with bone marrow (BM) metastatic SCLC without hepatic metastasis at diagnosis, and to our best knowledge, this is the first case report of STLS with BM metastatic SCLC in Korea.

A 71-year-old man visited our institution in January 2019 with increased nodule size in the right lower lobe (RLL) of the lungs. The RLL nodule was initially found five years prior, but its size had decreased at follow-up and it was regarded as an inflammatory nodule. Computed tomography (CT) showed the development of ill-defined ground-glass opacities in the right upper lobe of the lungs accompanied by multiple lymphadenopathies in the right supraclavicular, prevascular, upper paratracheal, both lower paratracheal, subcarinal, and left paraesophageal lymph nodes, but evidence of hepatic or renal metastasis of solid cancer was not found. The hemogram and peripheral blood smear results of the patient at the first visit were as follows: white blood cells, 6.09×10^9/L; hemoglobin, 10.3 g/dL; and platelets, 7.0×10^9/L. The complete blood cell differential count results of the patient at the first visit were as follows: metamyelocytes, 3%; band neutrophils, 12%; segmented neutrophils, 44%; lymphocytes, 33%; monocytes, 7%; basophils, 1%; and the presence of nucleated red blood cells (nRBCs) with a frequency of 5 nRBCs/100 white blood cells. At initial workup, the patient showed increased inorganic phosphate (6.9 mg/dL, reference range, 2.9–4.3), uric acid (11.9 mg/dL, reference range, 2.1–7.4), fibrinogen degradation product (81.99 μg/mL, reference range, <5.00), D-dimer (6.53 μg/mL, reference range, <0.50), lactate dehydrogenase (3922 IU/L, reference range, 106–230), and creatinine (1.77 mg/dL, reference range, 0.60–1.50) levels and prolonged prothrombin time (13.3 s, reference range, 9.3–13.2). The patient also showed normal potassium (4.10 mM/L, reference range, 3.50–5.30) and calcium (8.6 mg/dL, reference range, 7.8–10.0) levels and a decreased fibrinogen (146.0 mg/dL, reference range, 200.0–400.0) level. At the previous visit to another hospital 2 months prior, the patient showed normal uric acid (3.7 mg/dL, reference range, 2.5–8.3) and creatinine (0.78 mg/dL, reference range, 0.6–1.2) levels. For the pathologic diagnosis, endobronchoscopic ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and liquid-based aspiration cytology from the lymph nodes, BM aspiration, and biopsy were performed.

The BM aspiration showed hypocellular marrow due to dilution by peripheral blood with infiltration of small to medium-sized neoplastic cells at a frequency of 56.0%, which showed deeply stained nuclei, finely dispersed nuclear chromatin without distinct nucleoli, scanty amount of cytoplasm, and frequent nuclear moulding defined as conformity of adjacent cell nuclei to one another (Fig. 1A–C). BM biopsy showed hypercellular marrow (cellularity 90%) with proliferation of neoplastic cells in a diffuse and patched pattern accompanied with frequent nuclear moulding (Fig. 1D–F). Subsequently performed immunohistochemical (IHC) staining in BM biopsy sections showed the presence of neoplastic cells with positivity for cluster of differentiation (CD)56 (Fig. 1G), cytokeratin (Fig. 1H), and chromogranin (Fig. 1I). Both CD3 and CD20 IHC stains showed the presence of a few reactive T and B lymphocytes, without evidence of neoplastic lymphoid cell infiltrations. Based