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진단혈액학 LMO

진단상의 어려움: 전신성 자가면역 질환의 증상을 모방하는 원발성 골수 광범위큰B세포림프종 진단

Diagnostic Challenge: Primary Bone Marrow Diffuse Large B-cell Lymphoma Mimicking Systemic Autoimmune Diseases

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Dear Editor,

Primary bone marrow lymphoma (PBML) is a rare entity of non-Hodgkin's lymphoma (NHL) [1] with aggressive disease progression and poor prognosis. Although PBML has been documented in the literature since 1977, its diagnostic criteria or clinical features are not clearly defined. With poor survival of less than 1 month when not treated and less than 2 years when treated [2], timely and accurate diagnosis of PBML is essential. Atypical symptoms in the absence of a tumor mass and lymphadenopathy can make the diagnostic procedure extremely challenging, leading to missing the window of opportunity. Here, we present a patient with PBML exhibiting systemic inflammatory symptoms mimicking autoimmune disorders.

A 53-year-old man visited the outpatient clinic of the neurosurgery department because of lower back pain that initiated 15 days ago. He presented with symptoms of spinal cord compression such as left leg weakness, urinary urgency, urge incontinence, constipation, and erectile dysfunction. Initial spine magnetic resonance imaging (MRI) showed a T2 hyperintense lesion in the cornus medullaris, and spinal myelitis (SM) was first suspected. After 2 weeks, his neurologic symptoms expanded to right leg weakness and sensory changes in the left leg. His initial laboratory test results were unremarkable, including complete blood count (CBC) (leukocytes 7.09×10^9/L, hemoglobin 16.1 g/dL, and platelets 206×10^9/L), routine chemistry, and C-reactive protein level (3.2 mg/L). He was immediately admitted to the neurologic department and treated with steroids based on a cerebrospinal fluid (CSF) study revealing an inflammatory condition with lymphocytic pleocytosis. Brain MRI showed no abnormality, and positron emission tomography–computed tomography revealed systemic inflammatory status involving the spinal cord, lungs, spleen, renal cortex, and prostate. Peripheral lymphadenopathy was not noted based on imaging studies. Among systemic autoimmune markers, antinuclear antibody and anti-Ro/SSA antibody were detected. However, the patient did not meet the diagnostic criteria of Sjögren syndrome, namely symptoms lasting less than 3 months, no lymphocytic infiltration on labial salivary gland biopsy, positive anti-Ro antibody, positive Schirmer's test result, and normal salivary flow.

A bone marrow (BM) study for newly developed thrombocytopenia revealed a mature B-cell neoplasm, which was most likely diffuse large B-cell lymphoma (DLBCL). Microscopic examination of the BM revealed that the atypical cells (14.7% of all nucleated cells) were large, with irregular nuclear contours and cytoplasmic vacuolations (Fig. 1A). CBC findings indicated thrombocytopenia (leukocytes 4.16×10^9/L, hemoglobin 15.6 g/dL, and platelets $59\times$

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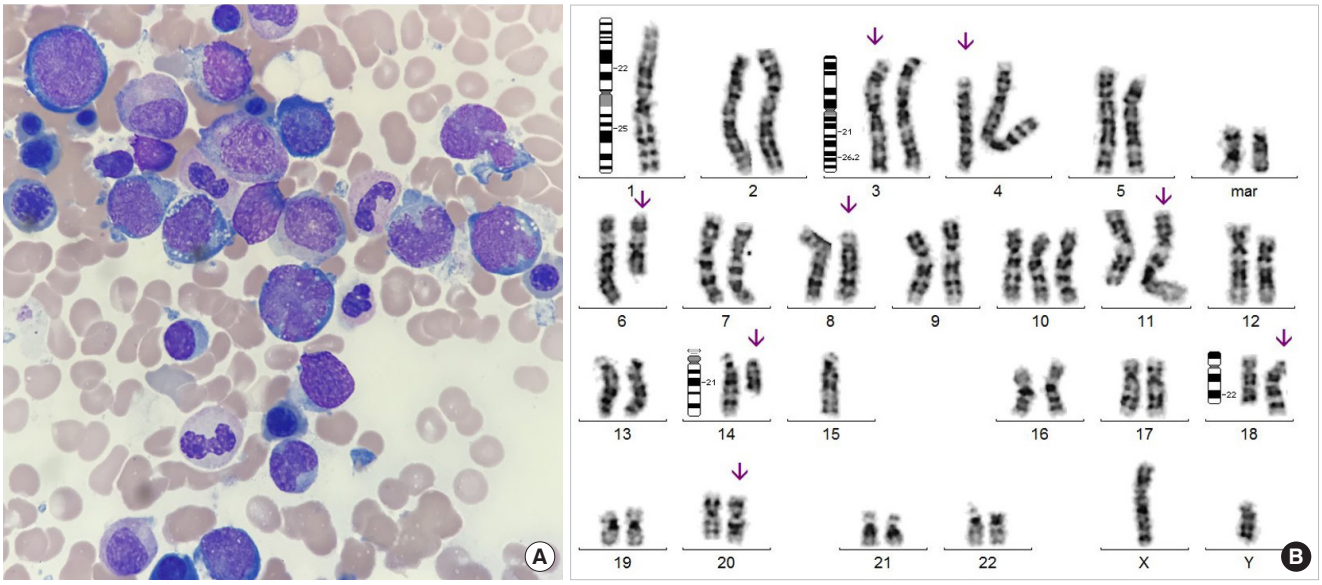

Fig. 1. Cytomorphology of bone marrow and G-banded karyotype result. (A) Bone marrow aspirate smear showed that the atypical cells were large with irregular nuclear contours and cytoplasmic vacuolations. (B) G-banding revealed complex structural and numerical abnormalities; 47~51,Y,-X,-1,t(1;21)(q25;q22),inv(3)(q21q26.2),del(4)(p13),der(4)t(1;4)(q25;q34),del(6)(q13q23),del(8)(p12),+10,der(11)t(1;11)(p22;q21),+12,-13,t(14;18)(q21;q22),-15,add(18)(q22),add(20)(q12),+mar1~3[cp16]/46,XY[4].

10^9/L). A peripheral blood smear test revealed leukoerythroblastosis with 1% immature cells. The atypical population from the BM comprised CD19+ (kappa restricted), CD20+, cCD22+, cCD79a+, CD3-, CD7-, CD10-, CD34-, and TdT- in flow cytometry analysis (Navios, Beckman Coulter, CA, USA). Immunohistochemistry showed aggregation of CD20+ B cells, occupying 50% of the nucleated cells. A complex BM karyotype was observed in a chromosomal study (Fig. 1B). B-cell clonality was confirmed through the detection of immunoglobulin heavy chain and immunoglobulin κ light chain gene rearrangements. Two days after the BM diagnosis was confirmed, the patient developed metabolic acidosis, hypotension, and respiratory failure, and he expired.

We reviewed recent literature and documented clinical presentations of primary BM DLBCL. The most common features of primary BM DLBCL are the lack of evidence of lymphoma involvement of lymph nodes, elevated lactate dehydrogenase levels, absence of organomegaly, and clinical symptoms of fatigue and fever of unknown origin (Table 1). Our patient had no typical clinical symptoms of lymphoma, but presented with SM, which has never been reported in the patients with this disease entity. All the previous cases of primary BM DLBCL involved cytopenia in at least one lineage at initial presentation. Our case did not involve cytopenia until SM progressed to systemic inflammation when isolated mild thrombocytopenia appeared.

Primary BM DLBCL is a rare entity of extranodal NHL. The diagnostic challenges of this disease include overlapping features with those of intravascular large B-cell lymphoma (IVLBCL), absence of disease-specific clinical symptoms, and a lack of unified diagnostic criteria [2]. Several studies have made attempts to overcome these challenges. Ponzoni et al. suggested that a random biopsy of uninvolved organs would be a useful confirmatory strategy to distinguish IVLBCL from primary BM DLBCL [3]. Martinez et al. proposed the diagnostic criteria of PBML: (1) isolated BM infiltration regardless of peripheral blood involvement; (2) no evidence of lymph node, spleen, liver, or other extra marrow involvement on physical examination or imaging studies; (3) absence of localized bone tumors; (4) no evidence of bone trabeculae destruction on BM biopsy; and (5) exclusion of leukemia/lymphoma cases that are considered to primarily involve the BM [1].

A retrospective review of our patient revealed that his laboratory test results strongly correlated with those of primary BM DLBCL: (1) meeting all diagnostic criteria except for mild splenomegaly, which can be explained by the overall inflammatory state; (2) exclusion of central nervous system lymphoma based on CSF cytology and brain MRI; and (3) differential diagnosis from IVLBCL with negative findings on lip biopsy. However, the clinicians had

Table 1. Clinical characteristics of primary bone marrow diffuse large B-cell lymphoma reported in the literature

Study	Present patient	Staples 1977* [4]	Strauchen, 2003 [5]	Alvares, 2004 [6]	Kajiura, 2007* [7]	Martinez, 2012 [1]	Bhagat, 2016 [8]	Kim, 2017 [9]
No. of cases		6	4	3	9	15	4	1
Age, range (mean)	M/53	18–68 (median 63)	45–86 (72)	42–78 (median 73)	45–82 (59)	29–79 (median 64)	51–64 (54.8)	57
Bone marrow findings	DLBCL	NHL	DLBCL	DLBCL	DLBCL	DLBCL	DLBCL	DLBCL
Hemophagocytosis	Positive	NI	NI	NI	Positive (6/9)	NI	NI	Positive
Immunohistophenotype	CD19, CD20, cCD22, cCD79a+	NI	B-cell marker+	B-cell marker+	B-cell marker+ (9/9) CD5+ (3/9)	B-cell marker+ (15/15) CD5- (15/15)"	CD20+	B-cell marker+ CD5+
Clinical presentation	Spinal myelitis	Fatigue (1/6) Fever (1/6) Weight loss (1/6) Night sweats (1/6)	Fever (2/4) Back pain & leg weakness (1/4) Weight loss (1/4) Arthralgia (1/4)	Weight loss & night sweats (2/3) Fatigue (1/3)	NI	Fatigue (7/15) Bone pain (6/15) B symptom (5/15) Malaise (5/15)	Fatigue (4/4) BOE (4/4)	Fever Weight loss
Cytopenia (initial finding)	None	Anemia (4/6) Anemia, thrombocytopenia (1/6) Pancytopenia (1/6)	Anemia, thrombocytopenia (2/4) Pancytopenia (1/4)	Thrombocytopenia (1/3) Anemia, thrombocytopenia (2/3)	NI	Pancytopenia	Anemia (1/4) Bicytopenia (1/4) Pancytopenia (2/4)	Anemia, thrombocytopenia
Lymphadenopathy	None	Absent or inconspicuous	None	None	None	None	None	None
Extramedullary involvement	None	None	None	None	None	None	None	None
Organomegaly (n/total)	Mild splenomegaly	None	NI	None	NI	None	None	Mild splenomegaly
Survival	3 months	NI	NI	Alive (1/3) Less than 9 months (2/3)	Less than 3 years (7/9)	Median survival 1.5 years	NI	More than 10 months
Other abnormalities	Elevated LD	NI	Elevated LD	Elevated LD	Elevated LD	Elevated LD	NI	Increased levels of ferritin, soluble CD25, and LD

*True primary bone marrow DLBCL without involvement of other sites only were counted.
Abbreviations: BOE, breathlessness on exertion; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; NI, not indicated; LD, lactate dehydrogenase; NHL, non-Hodgkin's lymphoma.

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difficulty diagnosing the patient because of atypical manifestations such as spinal myelitis, lack of cytopenia, and detection of autoimmune markers. In this study, we report extremely rare clinical symptoms of primary BM DLBCL and try to draw the attention of clinicians to this disease entity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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