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Letter

Two cases on primary bone marrow lymphoma

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Primary bone marrow lymphoma (PBML) is a rare lymphoma accounting for 1.23 % of non-Hodgkin lymphoma (NHL) cases. It is characterized by tumor cells invading only the bone marrow without systemic lymphadenopathy or extranodal organ involvement. Owing to the lack of standardized treatment regimens, most patients are treated using rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R–CHOP) regimens; however, their efficacy needs to be further investigated. Therefore, our study reports the diagnostic and therapeutic processes of two older patients with PBML, with the aim of improving awareness of the disease.

A 91-year-old man presented with mild anemia in April 2021. Laboratory tests showed a hemoglobin (Hb) level of 95 g/L, white blood cell (WBC) count of 4.75 $\times$ 10^9/L, and platelet (PLT) count of 227 $\times$ 10^9/L. The lactate dehydrogenase (LDH) level was elevated to 285 U/L (normal, 40–250 U/L); however, the patient was otherwise asymptomatic. Computed tomography (CT) findings of the chest, abdomen, and pelvis were unremarkable. The patient was administered strengthening nutrition, blood material supplement, and erythropoietin (EPO) injection of 10,000 international unit (IU) three times per week. However, the hemoglobin count fluctuated around 90 g/L without any obvious improvement; therefore, a bone marrow biopsy was performed. Morphological examination showed scattered and aggregated abnormal cells in the bone marrow, suggesting lymphoma or metastatic cancer. Further, a bone marrow biopsy revealed a small number of abnormal cells. Immunohistochemistry (IHC) staining showed that lymphocytes accounted for 36.51 % of the nucleated cells, of which clusters of differentiation (CDs)19+ accounted for 18.72 %. Malignant cells were positive for CD5, CD20, CD22, CD38, and CD200, but negative for CD10, CD23, CD25, CD103, CD138, secretory immunoglobulin M (sIgM), flinders medical centre 7 (FMC7), and CD43.^{18}F fluorodeoxyglucose (FDG) positron emission tomography-CT (PET-CT) revealed abnormal hypermetabolic lesions in the 5th thoracic vertebra, 3rd lumbar vertebra, and right ilium [Supplementary Figure 1]. However, based on the patient's results, bone metastases from solid tumors or lymphomas could not be excluded. Therefore, further puncture biopsy at a high metabolic site was recommended. IHC tests of the ilium puncture biopsy showed positivity for CD3 (T cells), CD20, nucleus related antigen (Ki67) (50 %), CD5, CyclinD1dim, V-myc avian myelocytomatosis viral oncogene homolog (C-myc), multiple myeloma oncogene-1 (Mum-1), CD30, B-cell lymphoma (Bcl)-6, and Bcl-2 [Figure 1]. The patient was eventually diagnosed with primary bone marrow diffuse large B-cell lymphoma (PBM-DLBCL), non-germinal center B-cell-like (non-GCB), Ann Arbor stage IVA, double-expressor lymphoma, and frailty. He received six cycles of R–CHOP every 3 weeks (R-CHOP-21) chemotherapy (rituximab 600 mg and dexamethasone 10 mg on days 1, cyclophosphamide 0.6 g, vindesine 4 mg and doxorubicin 20 mg administered on day 2, prednisolone 50 mg administered on days 1–5) and two courses of obinutuzumab monotherapy (obinutuzumab injection 1000 mg). However, after the first cycle, the patient developed tumor lysis syndrome (TLS) and lung infection, which improved with symptomatic treatment. Long-acting granulocyte colony-stimulating factor (G-CSF) treatment (pegfilgrastim 6 mg) was administered after each chemotherapy cycle and no significant bone marrow suppression was observed. Bone marrow aspirations were performed in the third, fifth, and sixth cycles and the results were normal. Following this, response to treatment was assessed as complete remission (CR). To date, the patient has not shown any signs of relapse.

The second patient was a 66-year-old man who presented with a >10-year history of elevated blood immunoglobulin (Ig) Kappa (KAP) light-

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chain levels and a 1-month history of lumbar trauma. On admission, the patient's laboratory results were as follows: Hb 111 g/L, WBC 5.46 × 10^9/L, PLT 168 × 10^9/L, IgA <26.8 mg/mL, Ig KAP 1210 mg/dL; and Ig lambda (7.2 mg/dL). The patient had concurrent monoclonal gammopathy of undetermined significance (MGUS), with no other diseases. Furthermore, physical examination and imaging studies on admission did not reveal lymph nodes, liver, or splenic enlargement. However, non-marrow morphology showed 44.8 % abnormal cells, suggesting a high possibility of bone marrow infiltration or PBML. FDG PET/CT revealed multiple hypermetabolic lesions in the left 3rd anterior rib, bilateral 6th ribs, right 7th posterior rib, left accessory of the 7th thoracic vertebra, 11th thoracic vertebra, and right ilium, with diffusely increased metabolism of the skeletal system in the field of view [Supplementary Figure 2]. Multiple non-metabolic lymph nodes were also found in the neck, axillary, and retroperitoneal regions. Subsequently, the patient underwent percutaneous thoracic vertebral puncture biopsy and vertebral molding surgery. Pathological results confirmed the diagnosis of B-cell NHL (B-NHL) with indolent features. IHC tests were positive for CD5, CD19, CD20, CD23, Mum-1 (individual cells positive), paired box-5 (PAX-5), and kappa but negative for CD3, CD38, CD138, Bcl-6, CyclinD1, lambda [Figure 2]. Therefore, the patient underwent a repeat bone marrow biopsy at sites of high metabolic activity, as determined by the PET-CT results. Bone marrow morphology revealed that the bone marrow space was almost entirely replaced by diffuse medium/small lymphocytes, with a few scattered large cells that were relatively mature. Based on the IHC results, B-NHL was suspected, considering the source of the germinal center cells. IHC result showed that B cells were characterized as CD20 (+), CD10dim, Bcl-6 (−), Ki67 (+10 %), C-myc (−), terminal deoxynucleotide transferase (TdT) (positive for stove expression, consistent with CD10 positive distribution); lymphocytes were characterized as PAX-5 (+), CD19 (+), Bcl-2 (+), CD23 (+), CD10 (+), Bcl-6 (−), CD5 (−), CyclinD1 (−), SRY-related HMG-box 10 (SOX-10) (−), Mum (−), kappa (+), lambda (−), TdT (−), Ki67 (majority+<10 %, specific areas + 50 %). Based on the above results, the patient was diagnosed with NHL, indolent B-cell lymphoma, stage IVA with the International Prognostic Index (IPI) score of 3, and a high intermediate-risk group. The patient started immunotherapy (IO)-based therapy (obinutuzumab injection 1000 mg on days 1, 8, 15, q3w + ibrutinib 280 mg/day) on June 28, 2022, and completed four cycles of chemotherapy. During the first cycle, the patient developed an allergic reaction that manifested as high fever and chills. After symptomatic treatment, the patient's condition improved without any discomfort. The patient is currently stable and shows no signs of recurrence.

Approximately 10–20 % of patients diagnosed with diffuse large B-cell lymphoma (DLBCL) develop bone marrow infiltration, which can result in anemia and even a decrease in blood cell lines. Lymphomas primarily originating from the bone marrow are rare. Moreover, PBML can be classified into five types based on its pathological features: Hodgkin's lymphoma (HLH), DLBCL, peripheral T-cell lymphoma, anaplastic lymphoma kinase (ALK) negative anaplastic large cell lymphoma, and follicular lymphoma (FL). Among PBMLs, DLBCL is the most common pathological subtype.[1] Patients with PBML usually exhibit rapid disease progression, poor prognosis, and difficult diagnosis. Therefore, a combination of imaging and early bone marrow biopsy is necessary to make a diagnosis of exclusion.

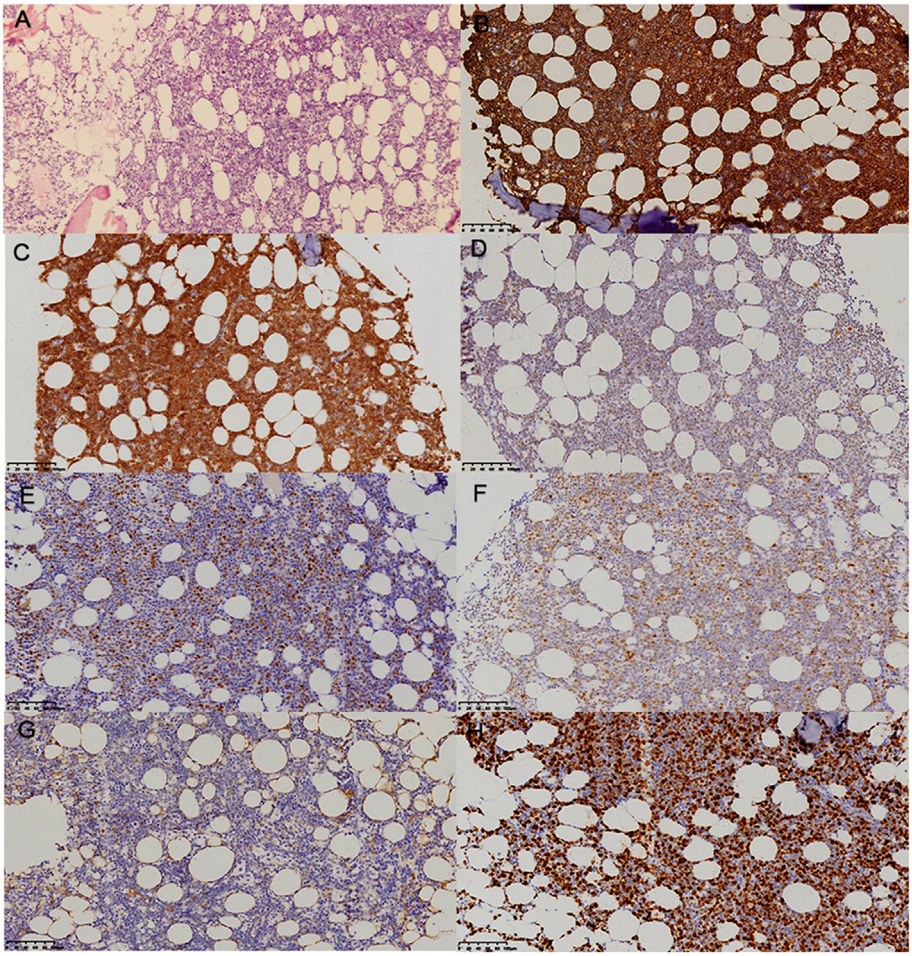

Figure 1. Microscopic features of the bone marrow with IHC for the first patient. (A) Bone marrow core biopsy, hematoxylin and eosin (H&E) stain, 100 × . (B) Positive for CD20, IHC stain, 100 × . (C) Positive for Bcl-2, IHC stain, 100 × . (D) Partial positive for Bcl-6, IHC stain, 100 × . (E) 30 % positive for C-myc, IHC stain, 100 × . (F) Partial positive for Mum-1, IHC stain, 100 × . (G) Negative for CD10, IHC stain, 100 × . (H) Positive for Ki67, IHC stain, 100 × . Bcl: B-cell lymphoma; CD: Cluster of differentiation; C-myc: V-myc avian myelocytomatosis viral oncogene homolog; H&E: Hematoxylin and eosin; IHC: Immunohistochemistry; Ki67: Nucleus related antigen; Mum-1: Multiple myeloma oncogene-1.

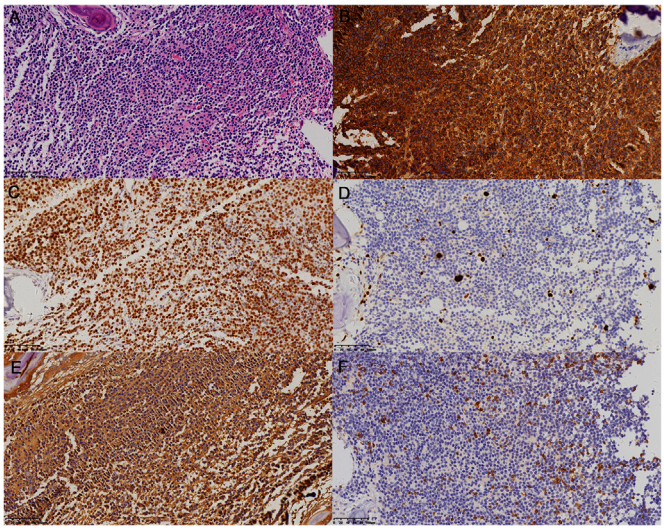

Figure 2. Microscopic features of the bone marrow with IHC for the second patient. (A) Bone marrow core biopsy, H&E stain, 200 × . Positive for CD20 (B), PAX-5 (C), and Kappa (E). Negative for Ki-67 (D) and CD5 (F) (IHC stain B–F, 200 ×). CD: Cluster of differentiation; H&E: Hematoxylin and eosin; IHC: Immunohistochemistry; Ki-67: Nucleus related antigen; PAX-5: Paired box-5.

The currently recognized diagnostic criteria were used to define PBML: (1) isolated or localized bone marrow infiltration; (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 trabecular structure on bone marrow biopsy; and (5) exclusion of known leukemia/lymphoma cases with primary bone marrow infiltration.[2] In addition to meeting the diagnostic criteria mentioned above, confirmation of the morphological diagnosis and IHC or fluorescence *in situ* hybridization (FISH) is required to establish the diagnosis of DLBCL.[3] Based on these results, the two older patients in this study were diagnosed with PBML. One case was of DLBCL and the other was classified as indolent B-cell lymphoma. In a study by Kajiura et al., 10 of 37 patients (27 %) with PBM-DLBCL expressed CD5. CD5+ B cells, which have progenitor functions, are increased in older individuals and are associated with event-free survival (EFS) and overall survival (OS), suggesting that they could be poor prognostic factors for DLBCL; however, the role of CD5 in the disease requires further investigation.[4,5] In our study, both patients were CD5-positive. Martinez et al. conducted a retrospective analysis of data from 12 research institutions in seven countries over 25 years, focusing on patients with lymphoma. They found that only 21 patients met the PBML diagnostic criteria mentioned above, including four with FL, 15 with DLBCL, and two with peripheral T-cell lymphoma.[6] Among the 15 cases of DLBCL, eight showed diffuse tumor cell infiltration, six showed nodal infiltration, and one presented with focal sinusoidal interstitial infiltration. The bone marrow biopsy results of the two patients in this study suggested diffuse tumor cell infiltration at different sites, consistent with previous reports.

Studies have shown that the median survival time (MST) for PBM-DLBCL is 14.9 months, and approximately 70 % of patients with PBML die within 2 years of chemotherapy.[7] Moreover, there is no standard treatment regimen for patients with PBML, especially in older patients. Chang et al.[1] found that only 15 (20 %) of 75 patients who met the diagnostic criteria survived short-term follow-up. However, the long-term survival time of patients is unknown, suggesting that PBML is characterized by a high degree of malignancy and a short survival period. This study suggests that patients with PBML have a more aggressive disease than those with other types of lymphoma and that the combination of targeted drugs can significantly improve patient prognosis. Previous reports have suggested that the treatment regimen for young patients with PBML should increase the drug dose and decrease the treatment interval. Autologous hematopoietic stem cell transplantation (HSCT) can be performed if the patient's physical state and financial circumstances permit. In older patients, newly targeted drugs can be used to improve outcomes.

The main mechanisms by which rituximab acts are antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). However, current rituximab-based chemotherapeutic regimens present problems such as drug resistance, refractory/relapse, and disease progression.[8] Studies have shown that the main causes of resistance include weak CD20 expression, decreased binding capacity to CD20, genetic polymorphisms of Fc receptors (FCRs) that mediate the binding of effector cells to the Fc portion of the antibody, and increased negative impact of complement-dependent cytotoxicity (CDC) on ADCC.[9] To avoid these problems and improve patient outcomes, we selected a novel anti-CD20 monoclonal antibody, obinutuzumab, for the first time in combination with chemotherapy in clinical settings. This drug has advantages such as low immunogenicity, high affinity between antibodies and FCR, and a strong cytotoxic effect. However, in this study, the two patients achieved CR after receiving an obinutuzumab-based regimen and are currently undergoing consolidation therapy. Thus, our results suggest that the obinutuzumab-based regimen can benefit patients with PBML with minimal adverse effects. This study is also rare in China, thus, providing novel treatment ideas.

In conclusion, we reviewed the diagnosis and treatment of two older patients with PBML and the first use of the monoclonal antibody, obinutuzumab, in the treatment of PBML, resulting in disease remission. These findings provide new insights for future clinical studies.

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Authors contribution

Zining Wang performed the data collection and statistical analyses and wrote the manuscript. Lu Sun collected the pathological data from two patients and wrote the manuscript. Yue Wang conceived and revised the manuscript. Haoran Chen participated in patient enrollment and revised the manuscript. Hongbin Pu collected the imaging data from two patients. Bo Yang and Xuechun Lu supervised the study and revised the manuscript. All authors have approved the final submitted version.

Ethics statement

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 *Declaration of Helsinki* and its later amendments or comparable ethical standards. Written informed consent for the publication of their details was obtained from all patients.

Data availability statement

Data used in this study are available from the corresponding author upon request.

Conflict of interest

None.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2023.10.001.

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