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Case Report

Primary Bone Marrow Large B-cell Lymphoma Presenting with Hemophagocytic Lymphohistiocytosis

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Abstract.

Primary bone marrow lymphoma is an extremely rare disease. Its unusual clinical manifestations, such as hemophagocytic syndrome, frequently delay correct disease diagnosis, thus postponing treatment. Here, we reported a 76-year-old woman presenting with intermittent night fever and jaundice for 2 weeks, accompanied with hepatosplenomegaly and pancytopenia. Despite antibiotics treatment, the patient's fever persisted. Computed tomography showed hepatosplenomegaly without lymphadenopathy, and bone marrow aspiration and biopsy revealed a large B-cell lymphoma (LBCL) with hemophagocytic lymphohistiocytosis (HLH). After chemotherapy with rituximab, cyclophosphamide, vincristine, and prednisolone, both jaundice and pancytopenia recovered to normal. After 6 cycles of chemotherapy, the patient remained in complete remission for 18 months after diagnosis. Our experience indicates that clinicians should consider performing a timely bone marrow examination on patients with unknown fever and pancytopenia, particularly given that delayed diagnosis of primary bone marrow lymphoma can make treatment of this rare disease substantially more challenging.

Keywords **:** primary bone marrow large B-cell lymphoma, non-Hodgkin's lymphoma, hemophagocytic lymphohistiocytosis, hemophagocytic syndrome

病例報告

以噬血淋巴組織球增生症表現之原發骨髓大 B 細胞淋巴癌

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中文摘要

原發骨髓淋巴癌是一種罕見的淋巴癌，合併噬血症候群等少見的臨床表現經常延誤正確即時的診斷和治療。我們報告一名 76 歲女性因間斷發燒、黃疸、肝脾腫大、貧血及血小板低下兩週前來就診，經給予抗生素後仍持續發燒，全身電腦斷層顯示肝脾腫大，但無異常淋巴結腫大情形。骨髓檢查確診為大 B 細胞淋巴癌(large B cell lymphoma)併噬血症候群，經使用標靶併化學治療(rituximab, cyclophosphamide, vincristine, prednisolone)，發

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燒、黃疸、血球異常等症狀均恢復正常，病患經完成六次化學治療及追蹤十八個月後，目前疾病仍處於完全緩解狀態。在不明原因發燒合併血球低下的病患，臨床醫師應即時進行骨髓檢查，並懷疑有原發骨髓淋巴癌之可能。

關鍵字: 原發骨髓大 B 細胞淋巴癌、原發骨髓淋巴癌、非何杰金氏淋巴癌、噬血症候群、噬血淋巴組織球增生症

INTRODUCTION

Large B-cell lymphoma (LBCL) is the most common subtype of non-Hodgkin's lymphoma in adults, and several LBCL variants had been defined in the World Health Organization classification system [1]. The involvement of bone marrow in LBCL usually indicates systemic dissemination of lymphoma. However, several recent reports have defined a distinctive entity of primary bone marrow LBCL, where lymphoma cells primarily involve bone marrow rather than lymph nodes [2-9]. The inclusion criteria used in each study differ. Consequently, without uniform or similar criteria, it is difficult to understand the exact incidence, clinical presentation, optimal treatment, and prognosis of primary bone marrow LBCL. In the case series of Chang et al., primary bone marrow LBCL accounted for 1.23% of non-Hodgkin's lymphoma, and 2.65% of diffuse LBCL [6]. Most case series report that this subtype of LBCL usually presents with aggressive disease pattern. Nearly all patients are treated with chemotherapy regimen against aggressive B-cell lymphoma, but the overall outcome is poor [2-4, 6-9]. Here, we report a patient with primary bone marrow LBCL presenting with hemophagocytic lymphohistiocytosis.

CASE REPORT

A 76-year-old woman presented to the emergency room (ER) with symptoms of intermittent night fever, general weakness, progressive jaundice, tea-colored urine, and epigastric discomfort of 2 weeks duration. The patient had no history of medical illness, and her travel and contact history were also unremarkable.

On arriving in the ER, the patient was bedridden, febrile with body temperature 38°C, tachycardic with a pulse rate of approximately 100 beats per minute, and tachypnic with a respiratory rate of 20 breaths per minute. Blood pressure and oxygenation were both normal. Physical examination revealed icteric sclera, pale conjunctiva, and vague tenderness upon knocking over the right upper quadrant (RUQ) of the abdomen. The patient's liver and spleen were both enlarged, with border palpable 2 finger spans below the costal margin. There were no palpable lymph nodes in the neck, axillary, and inguinal areas.

The total and direct serum bilirubin levels were 3.0 and 2.3 mg/dL, respectively. Besides direct hyperbilirubinemia, laboratory tests also showed elevated alkaline phosphatase (467 U/L), γ-glutamyl transpeptidase (98 U/L), and lactic dehydrogenase (533 U/L). Both alanine and aspartate aminotransferase were not elevated. A routine hemogram revealed normal white blood cell (WBC) count with left shifting (WBC 6.7 K/μL, segment neutrophil 84%, band form neutrophil 2%), normocytic anemia (hemoglobin 6.2 g/dL, MCV 85 fL), and thrombocytopenia (platelet 79 K/μL). No fragmented or nucleated red blood cells were observed in the blood smear. Whole body computed tomography showed hepatosplenomegaly without lymphadenopathy. The patient was initially managed as a case of biliary tract infection based on her fever, RUQ abdominal knocking tenderness, and jaundice. Despite

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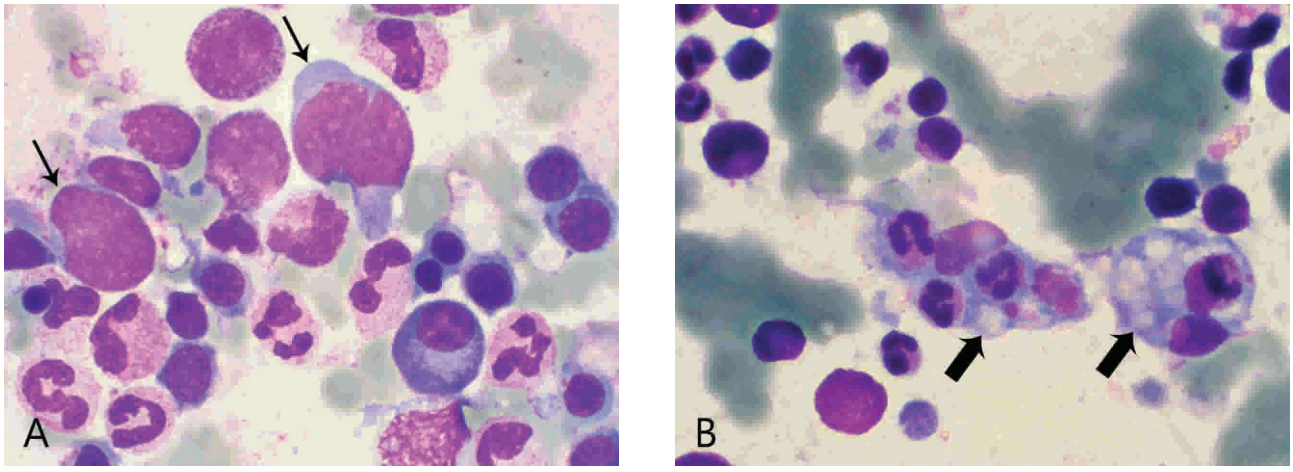

Figure 1. Smear of bone marrow aspiration. (A) Large size bizarre cells with large nucleus with several prominent nucleoli (arrows). (B) Hemophagocytosis with several band-from neutrophils being engulfed by histiocytes (fat arrows) (A&B: Liu's stain, 1000X)

antibiotics use for 5 days, the patient's fever persisted with progressively worsening direct hyperbilirubinemia, cytopenias, lactic acidosis, and deterioration of consciousness. Levels of fasting triglyceride, fibrinogen, and ferritin were 310 mg/dL, 4.28 g/dL, and 4670 μg/L, respectively.

Bone marrow aspiration revealed infiltration of abnormal large lymphoid cells (Figure 1A) and evident histiocytic hemophagocytosis (Figure 1B). Bone marrow biopsy showed patchy infiltrate of large lymphoma cells (Figure 2A, 2B), which were positive for CD20, bcl-6, MUM-1 and negative for CD3, CD5, cyclin-D1, CD10, and bcl-2 immunohistochemically (Figure 2C, 2D). No lymphoma cells were observed in the sinusoids. In situ hybridization for Epstein-Barr virus-encoded small RNA (EBER) was negative. Arising from the findings of bone marrow pathology and whole body CT, the diagnosis of primary bone marrow large B-cell lymphoma, non-germinal center (non-GC) type was made.

Considering her age and performance status, chemotherapy with R-COP regimen, consisting of rituximab 375 mg/m^2 day 1, cyclophosphamide 750 mg/m^2 day 1, vincristine (Oncovin) 1.4 mg/m^2 day 1, and prednisolone 100 mg/day days 1~5, was initiated right after the diagnosis was confirmed. The patient's fever subsided on the second day after chemotherapy started, and improvements were observed in follow-up hemogram, bilirubin, and lactate level. Thereafter, she regained clear consciousness on the fifth day of chemotherapy. Overall, the patient had received 6 cycles of R-COP chemotherapy, and remained in complete remission 18 months after diagnosis.

DISCUSSION

We reported a case of primary bone marrow LBCL, presenting with hemophagocytic lymphohistiocytosis (HLH) with no lymph node involvement. There are differences between the criteria used in reported case series of primary bone marrow LBCL. Some include LBCL with isolated bone marrow involvement, some include LBCL without lymphadenopathy, and others include LBCL with bone marrow involvement as the first manifestation [3-4,7-9]. The presentation of this patient was LBCL with bone marrow involvement but without lymph node involvement, which fulfilled the criteria applied in most series of primary bone marrow lymphoma, and was also compatible with the "bone marrow-liver-spleen (BLS) type LBCL", which was defined by Yeh et al. as lymphoma limited entirely to

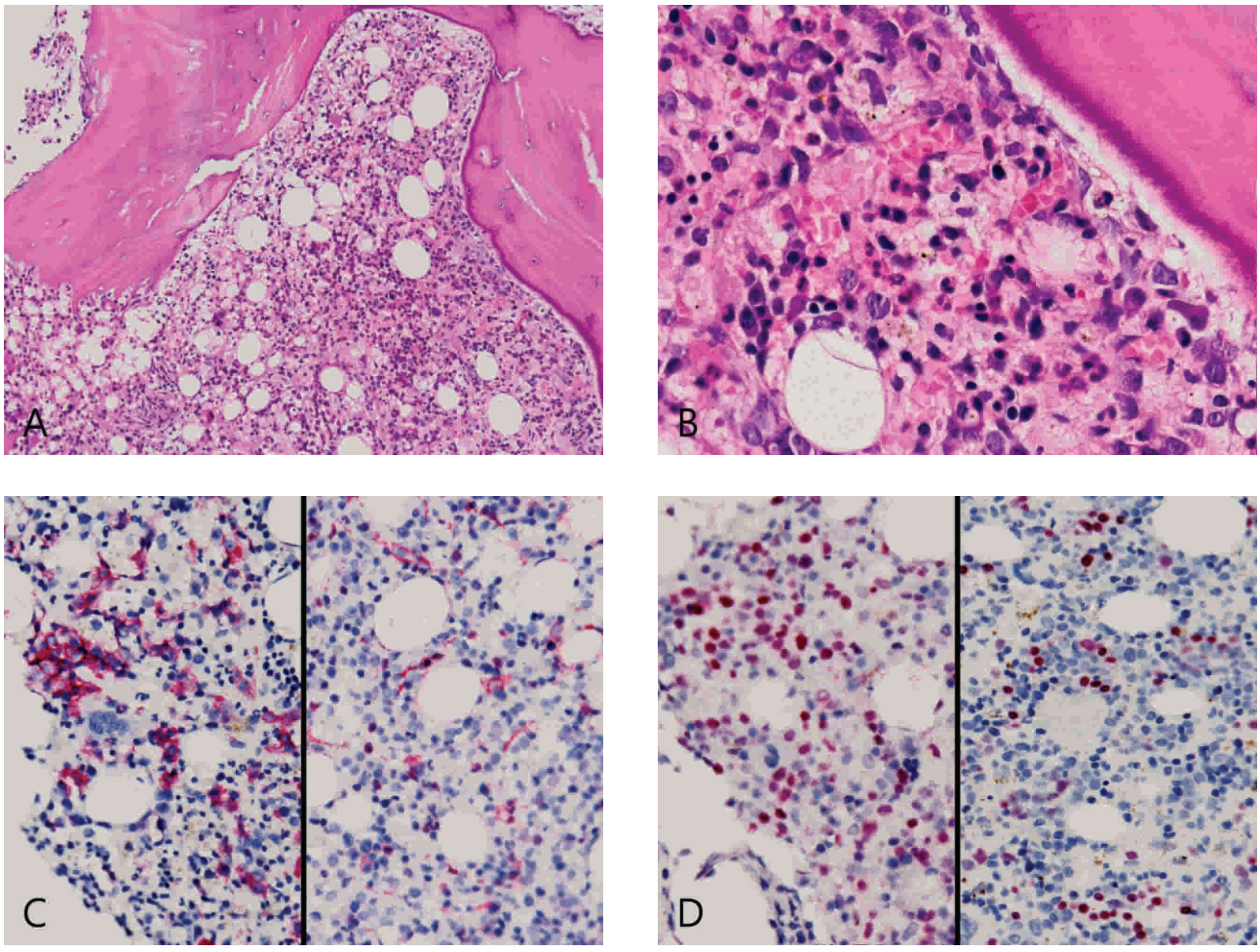

Figure 2. Pathological findings of bone marrow biopsy. (A) Patchy infiltration of tumor cells in bone marrow [haematoxylin and eosin (H&E), 100X]. (B) Tumor cells are large with several prominent nucleoli. No intravascular involvement of tumor cells is found (H&E, 400X). (C) Immunohistochemically, the tumor cells are positive for CD20 (left), and negative for CD10 (right) (200X). (D) Tumor cells are additionally positive for bcl-6 (left) and MUM-1 (right) (200X), imparting an activated B-cell phenotype

the bone marrow, liver and/or spleen without any lymph node involvement [2]. Common initial presentations include fever, fatigue, anorexia, weight loss, and hepatosplenomegaly. As in our patient, these clinical presentations usually mimic infection with multiorgan failure, and make early diagnosis difficult. The disease course was usually aggressive. Bone marrow examination is mandatory to make the diagnosis of primary LBCL, and should be performed early in patients with unexplained fever, hepatosplenomegaly, jaundice, and cytopenia.

HLH, also called as hemophagocytic syndrome , is a life-threating syndrome characterized by fever, cytopenia, hepatosplenomegaly, and hyperbilirubinemia [10]. According to the HLH-2004 diagnostic and therapeutic guidelines, the diagnosis of HLH can be made with either molecular diagnosis or diagnostic clinical criteria, including fever, splenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogemia, hemophagocytosis, ferritin level, soluble CD25 level, and NK-cell activity [11]. In adults, HLH is mostly secondary, and may be related to infection of various

pathogens, autoimmune diseases, and malignancies. Hematological malignancies, especially lymphomas, accounted for 22 to 57% of adult HLH in the reported case series [12,13]. HLH could be observed in 35% (13/37) and 63% (7/11) of patients with primary bone marrow LBCL in the series of Kajiura et al. [9] and Yeh et al. [2], respectively. However, HLH was not observed in another series using similar inclusion criteria [6]. The exact prevalence of HLH in primary bone marrow LBCL remains unclear.

In our case, the phenotype of LBCL can be determined as non-GC type by immunohistochemical staining using the decision tree proposed by Hans et al. [14]. It is compatible with the finding that most LBCLs involving bone marrow, liver, and spleen are of the non-GC phenotype. Positivity of CD5 in LBCL had been found to be a poor prognostic factor [15]. The successful treatment in our patient also supported this finding in addition to the cause of early diagnosis. Most cases of primary bone marrow LBCL are also negative on CD5 [2,3,6,8].

Patients with the Asian variant of intravascular LBCL may also present with hepatosplenomegaly, bone marrow involvement, pancytopenia, and HLH [1]. Although they share common clinical features with primary bone marrow LBCL, these diseases can be differentiated by the presence of intravascular proliferation of lymphoma under pathological study [2].

Since primary bone marrow LBCL is rare, there is no standard treatment to date. Most patients were treated with anti-lymphoma chemotherapy in combination with rituximab [2,6]. A large proportion of patients have been managed with supportive care only, mainly due to their poor general condition at the time of diagnosis. The prognosis of patients with primary bone marrow LBCL was usually poorer than those with systemic diffuse LBCL with bone marrow involvement [2]. In our case, the patient was successfully treated with R-COP chemotherapy. Considering her advanced age, hematopoietic stem cell transplantation (HSCT) was not planned. Patients successfully treated with allogeneic and autologous HSCT had been reported in the literature [2,6]. Contamination of autograft by lymphoma cells was a concern in patients with primary bone marrow LBCL. A recent case report from Japan had demonstrated a case of primary bone marrow LBCL treated successfully with high dose chemotherapy and rescued by in vivo rituximab-purged autologous stem cells [5]. Further studies are needed to investigate the role of HSCT in primary bone marrow LBCL.

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