

# A unique bone marrow lymphoma patient presenting with an isolated mass: A case report

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Received November 23, 2015; Accepted June 21, 2017

DOI: 10.3892/ol.2017.7538

**Abstract.** Bone marrow lymphoma with the onset of an isolated mass in the bone marrow is extremely rare. The present case report described a unique case of B cell lymphoblastic lymphoma (LBL) presenting with an isolated mass in the bone marrow cavity, without any organopathy or lymphadenopathy. An isolated mass in bone marrow is a rare primary manifestation of LBL. The patient in the present case report presented with pain in the right elbow, a fever, pancytopenia and splenomegaly. Additionally, no abnormality was determined in the lymph nodes, the bone marrow karyotype or a computed tomography scan of the humerus. Positron emission tomography (PET) examination revealed an increased uptake of <sup>18</sup>F-fluorodeoxyglucose in right distal humerus. An isolated mass in the bone marrow cavity was removed by surgery. Pathological findings revealed B cell LBL. The patient received an acute lymphocytic leukemia chemotherapy regimen and achieved complete remission. However, 4 months following the initial diagnosis, the patient succumbed due to a relapse. The present case highlighted the importance of PET examination and biopsy, and the requirement to identify appropriate treatments for LBL. Additionally, it is important to broaden the differential diagnosis when an isolated mass is identified in the bone marrow cavity.

## Introduction

Lymphoma originates from the lymph nodes or extra-nodal lymphoid tissue. Lymphoma is a malignant tumor that typically manifests progressive lymph nodes enlargement without pain and occasionally, the liver, bone and bone marrow may be involved (1). Lymphoma with bone marrow involvement is not rare (2). Some types of lymphoma originate directly from

bone marrow. Lymphoblastic lymphoma (LBL), marginal zone lymphoma and Burkett lymphoma typically originate from bone marrow (2-4). LBL originates from immature precursor lymphocytes, it is highly invasive and divided into B cell LBL and T cell LBL, with the majority of LBL originating from precursor T cells (2,5,6). Other types of lymphoma rarely originate from the bone marrow, including diffuse large B cell lymphoma (DLBCL) and follicular lymphoma. If these types of lymphoma present with bone marrow involvement as the only clinical manifestation, they are termed primary bone marrow lymphoma (PBML). Lymphoma originating from bone marrow typically manifests with diffuse bone marrow involvement; therefore, it is rare to present with an isolated mass (2,7,8). In the present case study, lymphoma originating from the bone marrow was termed bone marrow lymphoma (BML). The present case study describes a BML case presenting as an isolated mass and the associated literature is reviewed.

## Case report

A 29-year-old male was admitted into Peking Union Medical College Hospital (Beijing, China) on October the 12th 2013, presenting with a 6-month history of pain in the right elbow and a 4-month history of fever. Previous examinations of the patient revealed pancytopenia, no tumor cell in bone marrow aspiration (BMA) and no abnormality in a computed tomography (CT) scan of the right upper limb. The patient had received antibiotics, but no improvement was observed. The patient also had a weight loss of ~4 kg. In addition, the patient reported a seafood allergy. Physical examination revealed a fever (37.8°C), a rapid heartbeat (112 beats/min) and a low blood pressure (89/56 mmHg). No superficial lymphadenopathy was determined, and the spleen could be touched under the ribs. A complete blood count (CBC) demonstrated decreased levels of white blood cells (WBC) ( $2.0 \times 10^9$  cells/l; normal range,  $4.0-10.0 \times 10^9$  cells/l), neutrophils ( $1.2 \times 10^9$  cells/l; normal range,  $2.0-7.5 \times 10^9$  cells/l), hemoglobin (8.6 g/dl; normal range, 12.0-16.0 g/dl) and platelets ( $36 \times 10^9$  cells/l; normal range,  $100-300 \times 10^9$  cells/l). The activity of natural killer (NK) cells, determined as the activity to kill fluorescent plasmid transfected cells, was identified to be low (15.0%; normal range, 31.5-41.6%). Soluble cluster of differentiation (CD)25 was  $>44,000$  pg/ml (normal,  $<6,400$  pg/ml). An abdominopelvic

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*Key words:* bone marrow lymphoma, isolated mass

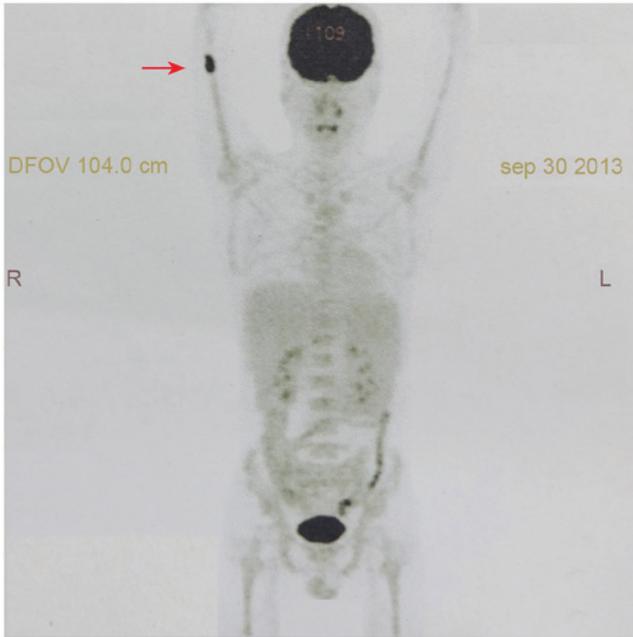


Figure 1. An increased uptake of <sup>18</sup>F-fluorodeoxyglucose as indicated by positron emission tomography examination. The red arrow indicates a standardized uptake value of 9.3 in the bone marrow cavity of the right distal humerus. DFOV, display field of view; R, right; L, left.

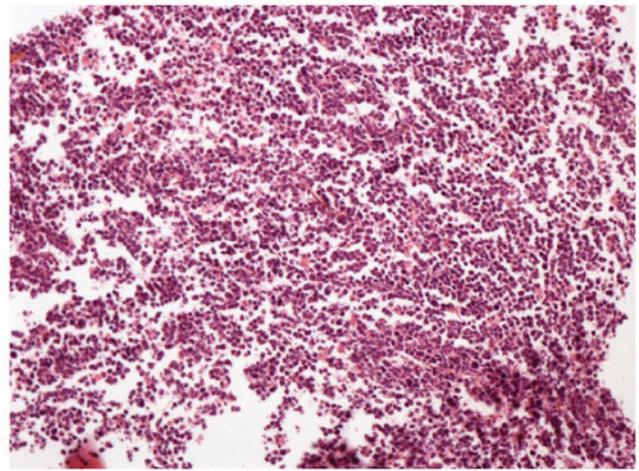


Figure 3. Biopsy of the mass in the bone marrow cavity of the right distal humerus revealed abnormal lymphoid cells gathering in clusters and hemosiderin pigment (hematoxylin and eosin staining; optical microscope; magnification, x100). Antigen Ki-67 index was 60%. The cells were positive for CD5, CD3, CD20, mutated melanoma-associated antigen 1 and CD99, and negative for anion exchanger 1/3, B cell lymphoma 6, CD10, myeloperoxidase, terminal deoxynucleotidyl transferase and cyclin D1. CD, cluster of differentiation.

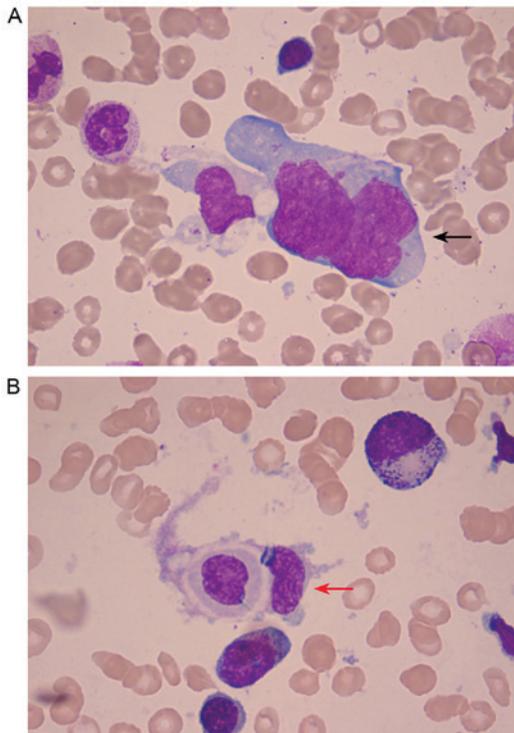


Figure 2. Bone marrow aspiration revealed (A) lymphoma cell (black arrow) and (B) phagocyte engulfing hemocyte (red arrow) (Wright-Giemsa staining; optical microscope; magnification, x1,000).

CT revealed splenomegaly (9.0x23.0 cm; normal, 4.0x12.0 cm). An <sup>18</sup>F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan demonstrated an increased uptake of FDG in medullary space of the right distal humerus (maximum standardized uptake value, 9.3) without evidence of dissemination

at other sites (Fig. 1). BMA, using Wright-Giemsa staining, revealed 4% lymphoma cells and phagocytes engulfing hemocytes (optical microscope; magnification, x1,000) (Fig. 2). Bone marrow biopsy (BMB) was embedded with paraffin and stained with ready-to-use hematoxylin and eosin for between 30 and 40 min, and incubated between 24 and 28°C (optical microscope; magnification, x100) (Fig. 3). The proportion of hematopoietic tissue in bone marrow increased and the BMB revealed scattered and focal CD20-positive cells. According to the results of BMB, B cell lymphoma involving bone marrow was not excluded. Gene rearrangement detection, using multiplex polymerase chain reaction (IGH PCR assay; Invivoscribe, San Diego, CA, USA), identified a rearrangement in immunoglobulin κ (VkKde<sup>+</sup>INTR·Kde<sup>+</sup>). The bone marrow karyotype was 46, XY [20]. Flow cytometric (FCM) analysis revealed that CD45<sup>+</sup>CD19<sup>+</sup> cells, which were potentially abnormal B lymphocytes, expressed human leukocyte antigen-antigen d related, CD5, CD11c, CD20, CD22, CD38, limited FCM-7 antigen, no κ- or λ-polyclone, and accounted for 0.5% of nuclear cells.

Subsequently, the patient received fenestration surgery, a biopsy and bone reconstruction on the right distal humerus. In surgery, it was identified that the bone cortex of the right distal humerus became thin without periosteal reaction, and a tender, dark red, isolated mass was identified in the medullary space. Without the capsule, the size of the mass was ~4.0x2.0x2.0 cm, and it was not able to distinguish the mass from the surrounding tissue. A curettage biopsy was performed and subsequent immunohistochemistry (IHC) was performed. The IHC indicated the following: Gathering of abnormal lymphoid cells in cluster, hemosiderin pigment, anion exchanger 1/3<sup>-</sup>, CD5<sup>+</sup>, CD3<sup>+</sup> (scattered), CD20<sup>+</sup>, CD23<sup>-</sup>, mutated melanoma-associated antigen 1<sup>+</sup>, B cell lymphoma 6<sup>-</sup>, CD10<sup>-</sup>, myeloperoxidase<sup>-</sup>, antigen Ki-67 (index, 60%), terminal deoxynucleotidyl transferase<sup>-</sup>, CD99<sup>+</sup> and

Table I. Details of chemotherapy regimen.

Date	Acronym of regimen	Regimen	Notes
25/10/13	CHO	CTX, 1.3 g, day 1; epirubicin hydrochloride, 130 mg, day 1; vindesine sulfate, 4 mg, day 1	Rituximab (100 mg infusion) was ceased on day 1 due to an allergy, and the regimen did not include prednisone due to a wound in the right upper limb
06/11/13	CHOP	CTX, 1.3 g, day 1; epirubicin hydrochloride, 130 mg, day 1; vindesine sulfate, 4 mg, day 1; prednisone, 100 mg, days 1-5	Lumbar puncture and intrathecal injection (50 mg cytarabine and 5 mg dexamethasone) were performed on November 6, 2013.
28/11/13	CHOP	CTX, 1.3 g, day 1; epirubicin hydrochloride, 130 mg, day 1; vindesine sulfate, 4 mg, day 1; prednisone, 100 mg, days 1-5	N/A
19/12/13	HD-MTX/VL	MTX, 8.9 g, day 1 and 15; VDS, 4 mg, day 1 and 15; pegaspargase, 3,750 U, day 5 and 19	Lumbar puncture and intrathecal injection (50 mg cytarabine and 5 mg dexamethasone) were performed on December 19, 2013 and January 2, 2014.
23/01/14	CLEA	VP16, 100 mg, days 1-5; ara-c, 130 mg, days 1-5; pegaspargase, 3,750 U, day 1 and 15; CTX, 1.8 g, day 1	Lumbar puncture and intrathecal injection (50 mg cytarabine and 5 mg dexamethasone) were performed on January 24, 2014.

HD, high-dose; CTX, cyclophosphamide; MTX, methotrexate; VDS, vindesine; VP16, etoposide; N/A, not applicable.

cyclin D1<sup>+</sup> (Fig. 3). The patient was diagnosed with B cell LBL and secondary hemophagocytic lymphohistiocytosis (HLH). Subsequently, the patient was administered the following chemotherapy: 3 courses of cyclophosphamide (CTX), epirubicin hydrochloride, vindesine sulfate, prednisone (CHOP), a course of high-dose methotrexate, vindesine and pegaspargase (HD-MTX/VL) and a course of etoposide, ara-c, pegaspargase and CTX (CLEA) (Table I).

The patient achieved complete remission following 3 courses of CHOP and a course of HD-MTX/VL (Table I), and during treatment, the patient did not experience discomfort and cerebrospinal fluid was normal. However, 4 months following the initial diagnosis, the patient experienced disease relapse, which manifested as acute leukemia. The patient did not respond to repeated CHOP regimen and succumbed. The present case report obtained informed consent from the patient's next of kin.

**Discussion**

Lymphoma is a type of malignant tumor and originates from the lymph nodes or extra-nodal lymphoid tissue (5). A study revealed there was 36.4% extra-nodal involvement in non-Hodgkin lymphoma (NHL) (9). Lymphoma arising directly from bone marrow is not rare (2). Although arising from bone marrow, LBL, marginal zone lymphoma and Burkett lymphoma are not classified as PBML (2-4). Other types of lymphoma rarely originate from the bone marrow, including DLBCL and follicular lymphoma (10). If DLBCL or follicular lymphoma initially arises from bone marrow, it is termed PBML (10). In accordance with the World Health Organization's classification of lymphoid neoplasms and

criteria (11), PBML is rare. The most common histological subtype of PBML is DLBCL, which accounts for 1.16% of lymphoma and 2.65% of all DLBCL (7). Patients with BML typically present with diffuse bone marrow involvement and leukemia syndrome, increased WBC and immature cells, at the initial diagnosis. To the best of our knowledge, there was no case report of a patient with BML presenting with an isolated mass in the bone marrow cavity.

The patient in the present case report presented with pain in the right distal humerus, a repeated fever of unknown origin, splenomegaly and pancytopenia. Following the completion of examinations, the patient was diagnosed with HLH. Secondary HLH was initially considered due to the age of the patient. Clinicians attempted to identify the cause of secondary HLH and lymphoma was included in consideration. Following overall examination and biopsy, the patient was diagnosed with LBL. LBL which arises from extra-nodal and extramedullary tissue is not rare; for instance, B cell LBL typically involves the skin, liver and bone (12,13). Initially, a number of patients exhibit normal CBC and BMA results at an early stage. However, patients typically develop diffuse bone marrow infiltration and acute lymphocytic leukemia (ALL) transformation in a short time (14). Other patients with onset of bone marrow LBL, directly present with diffuse bone marrow involvement and ALL transformation (14). The present case is unique due to the onset of an isolated mass in the bone marrow cavity. Local pain in right distal humerus was the only complaint at the early stage and 2 months after the initial presentation, the patient experienced HLH manifestation. Subsequently, 6 months after the initial presentation, the patient exhibited diffuse bone marrow involvement without ALL transformation (6). The bone marrow karyotype of the

patient was normal. The patient exhibited BML, which did not originate from extramedullary tissue or diffuse bone marrow, but originated from an isolated mass in the bone marrow cavity of the right distal humerus. In addition, pathology revealed B cell LBL with negative Philadelphia chromosome. According to a search by the authors, BML as an isolated mass in bone marrow cavity was not reported in PubMed.

The present case was difficult to diagnose due to the onset of an isolated mass in the bone marrow cavity. At an early stage, CT did not reveal abnormal findings in the right distal humerus, and BMA and BMB results were identified as normal. PET examination served a critical role in identifying the abnormal region early and enabled treatment to begin, despite the CT revealing no abnormality. Although BMA and BMB results revealed the presence of lymphoma cells at a later stage, the number of lymphoma cells was limited for validation of the pathological type. Surgical removal and pathology of the primary abnormality were important for diagnosis and determining the pathological type. Therefore, PET examination may be used to identify an abnormal region and provide a target for surgery and pathology, which may help validate a pathological diagnosis.

Despite the onset of an isolated mass in the bone marrow cavity, the patient developed bone marrow infiltration at a later stage. Additionally, bone marrow involvement is an important characteristic in patients with BML (15). BMA and BMB are important methods to diagnose this type of disease. The morphology of marrow lymphoma cells, observed in the patient, was typical of the disease, with incisura and folding in the round, oval, irregular or rare double nuclei. The coarse granular chromatin was deep purple and the nuclear membrane was thick, determined using Wright-Giemsa staining. There were nucleoli in a limited number of cells, and the lymphoma cells were rich in cytoplasm. Furthermore, there was cytoplasmic extension. IHC of BMA and BMB are required for diagnosis of lymphoma (16). In the present case, IHC of BMB enabled a definitive diagnosis to be made. IHC was able to mark the signal molecules on the lymphoma cells, and the signal molecules may provide information about the characteristics of tumor cells. For example, as a ligand of immunoglobulin on the cell membrane, CD5 mediates the adhesion between cells (17). Therefore, CD5<sup>+</sup> may indicate increased adhesion and invasion of lymphoma cells. For a number of cases with a limited number of lymphoma cells involving bone marrow, FCM may assist with diagnosis (18,19). However, there may be different results between BMA/BMB and FCM (20,21).

Patients with NHL, in particular those with BML, may present with HLH. Previous studies have identified that ~43% (21/49) patients with PBML exhibited HLH (22,23). Patients with HLH exhibit NK cells with decreased activity, rendering NK cells unable to eliminate excessive activated T cells, which release a number of cytokines, including interferon- $\gamma$  and interleukin-10. Excessive cytokines may activate an increased number of macrophages, which serve an important function in cytophagy, leading to HLH (24,25). Therefore, patients with HLH manifest with decreased activity of NK cells and an increased level of CD25, indicating the excessive activation of T cells. To the best of our knowledge, the underlying molecular mechanism of HLH remains unknown and requires additional investigation (26,27). Although the present patient

did not exhibit PBML, the patient presented with symptom of HLH including fever, pancytopenia, splenomegaly, a decreased activity of NK cells, an increased level of soluble CD25 and phagocytes engulfing hemocytes in BMA. The manifestation of splenomegaly at the early stage was due to HLH, not lymphoma infiltration, as the PET examination revealed no increased uptake in the spleen. Previous studies have demonstrated that patients with B cell lymphoma and HLH exhibit a poor prognosis, with a median survival time between 8 and 11 months (28,29). In the present report, the patient had a poor prognosis. Although treated with a standard ALL strategy, the patient rapidly relapsed and succumbed following a transient complete remission.

BML with the onset of an isolated mass in bone marrow cavity is extremely rare (14). At the early stage, the patient presented only with HLH and no local bone damage or diffuse bone marrow involvement, which made the present case difficult to diagnose. PET examination enabled a region of focus to be identified early and guided biopsy, which was necessary to validate the diagnosis. In spite of treatment with ALL combined chemotherapy, the present patient relapsed, developed ALL and succumbed. Therefore, the identification of an appropriate treatment strategy is required.

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