Baseline PET-CT evaluation of Bone Marrow-Liver-Spleen Type of Diffuse Large B-Cell Lymphoma: A Rare Aggressive Extranodal Lymphoma

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ABSTRACT

Bone marrow-liver-spleen (BLS) type lymphoma is a rare subgroup of diffuse large B-cell lymphoma, characterized by bone marrow involvement without lymph nodes. Symptoms include fever, anemia, and hemophagocytic lymphohistiocytosis. Early diagnosis and treatment are crucial for proper management and prevention. We report a case of a 59-year-old male with diffuse large B-cell lymphoma (DLBCL) involving bone marrow. He was diagnosed with a bone marrow-liver-spleen (BLS) subtype of lymphoma with the help of F-18 FDG PET-CT. BLS is an unusual subgroup of extra-nodal DLBCL. Very few cases have been reported to date. The disease showed unique clinico-pathological features of involvement of bone marrow with or without liver and/or spleen, but no lymph node or other extra-nodal sites are involved, hence the name BLS.

Keywords: Bone marrow-liver-spleen (BLS) subtype of diffuse large B-cell lymphoma (DLBCL), extra nodal lymphoma, hemophagocytic lymphohistiocytosis (HLH), 18F-FDG PET

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INTRODUCTION

Bone marrow-liver-spleen (BLS) type lymphoma is a rare subgroup of diffuse large B-cell lymphoma (DLBCL) (1). The disease shows unique clinico-pathological features of involvement of bone marrow with or without liver and/or spleen, but no lymph node or other extra-nodal sites are involved hence named BLS. Patients usually present with fever, anemia, and features of hemophagocytic lymphohistiocytosis (HLH). These symptoms and unusual pattern of involvement by BLS-type DLBCL may mimic infection and potentially lead to delayed diagnosis and treatment. Moreover, BLS-type DLBCL is a very aggressive disease with early mortality (2).Adequate knowledge about this rare condition is essential for prompt diagnosis which is crucial for proper management.

CASE REPORT

A 59-year-old male was referred to Institute of Nuclear Medicine and Allied Sciences (INMAS), Dhaka for a baseline PET-CT scan. He presented to physician primarily with high fever and weakness for which he was treated with antibiotics but did not respond. His complete blood count (CBC)revealed pancytopenia (RBC-2.7 m/mm3, platelet –17,000/mm3, WBC-2500/mm3) withHb% count 6.2 gm/dl leading to 2 units of blood transfusion. He had elevated serum ferritin (250 ng/ml), LDH (730U/L) and SGPT (56 U/L).

Table-1: Laboratory reports showing increased LDH, ESR, SGPT, urea, pancytopenia and normal other findings

Name of investigation	Value	Unit	Normal value	Name of investigation	Value	Unit	Normal value
LDH	**730**	U/L	80-285	RBS	5.0	mmol/l	3.9-6.9
Hb%	6.2	gm/dl	13-18	Serum ferritin	250	Ng/ml	<200
ESR	**138**	Mm/1sthr	<10	Urea	**52**	mg/dl	<45
RBC count	**2.75**	m/cumm	4.5-5.5	Creatinine	0.9	mg/dl	<1.3
WBC count	**2500**	/cumm	4000-11000	SGPT	**72**	IU/L	<42
Platelent count	17,000	/mm^3	1.5-4.5 ml	Ca	10	mg/dl	8.5-11

Bone marrow cytomorphologic study revealed lymphoproliferative disorder suggestive of acute lymphoblastic leukemia and bone marrow biopsy suggested hematolymphoid malignancy. Repeat bone marrow study showed atypical mononuclear cells. No distinct atypical cell population was detected by flow cytometry by leukemia panel.

Table-2: Histopathological investigations of 59-year-old male patient with suspected DLBCL

Investigations	Findings
Bone marrow examination and trephine biopsy	Plenty atypical mononuclear cells.
Bone marrow biopsy	Hematolymphoid malignancy
Flowcytometry (leukemic panel)	Negative for leukemia
Immunophenotypic Chronic lymphoproliferative disorder	T-cell-64% polyclonal and matured with altered CD4/CD8 ratio B-cells-11% polyclonal NK cells-25% (normal<4.5%)
BCR-AB gene arrangement	Negative

Patient was advised immunohistochemistry of bone marrow, which showed PAX5, CD 43 positive and CD 20 negative diffuse large B cell lymphoma. BCR-ABL gene was negative. Ultrasonography of whole abdomen revealed huge hepatosplenomegaly with few simple hepatic cysts. Serum bilirubin (0.7 mg/dl) and creatinine (0.9 mg/dl) levels were normal.

A whole body FDG PET CT scan was acquired from vertex to mid-thigh in Philips 128 slice ingenuity TF PET CT, one hour after intravenous injection of 5.74mCi (212.38 MBq)

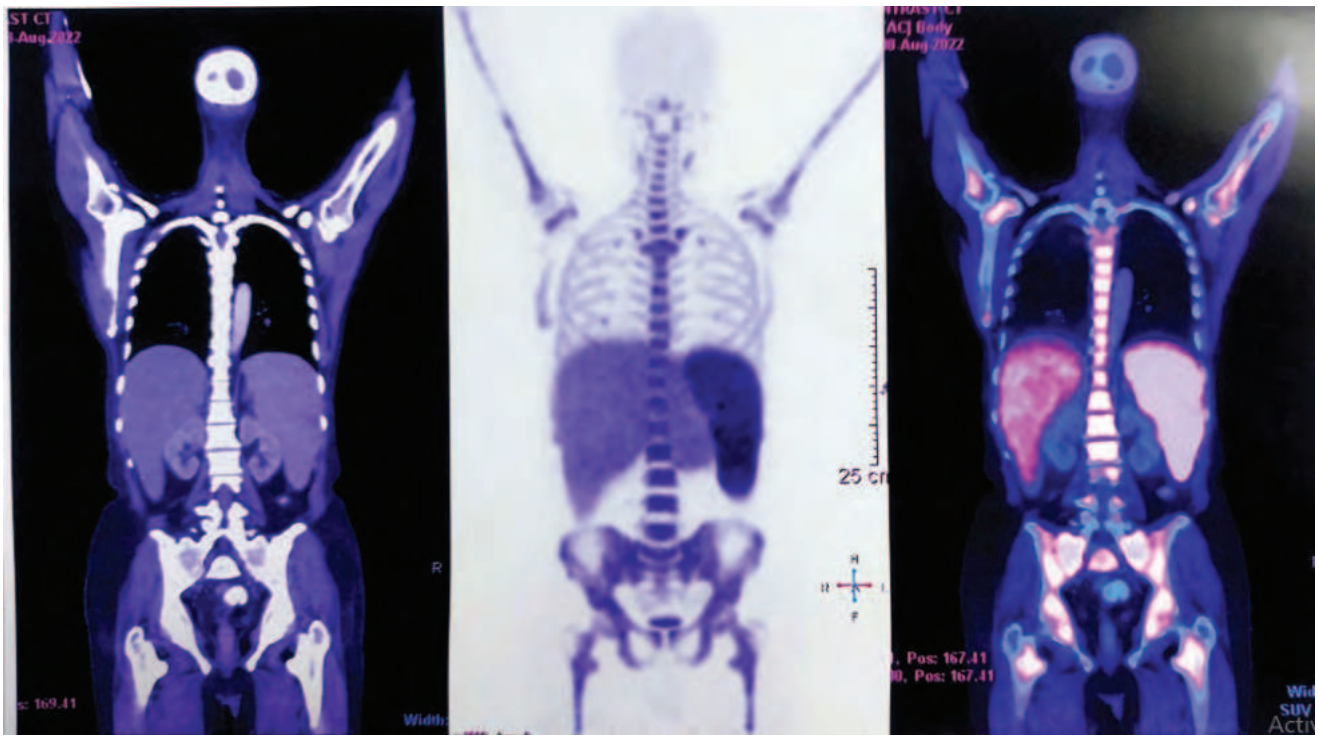

Figure 1: CT, PET and PET-CT image of 59-Yr old male with Bone Liver Spleen subtype of Diffuse Large B Cell Lymphoma showing hepatosplenomegaly with diffusely increased FDG uptake in liver spleen and bone marrow of axial and appendicular skeleton. No significant lymphadenopathy was noted.

of ^{18}F-FDG. Diagnostic CT scan with 2 mm slices was also obtained of the whole body without contrast. Images were reconstructed using List mode TF HD algorithm and slices were reformatted into transaxial, coronal and sagittal views. Semi-quantitative estimation of FDG uptake was performed by calculating SUVmax value, corrected for dose administered and body weight (g/ml).

Diffusely increased FDG uptake in bone marrow (SUV max: 7.5), liver (SUV max: 5.01) and spleen (SUV max: 9.29) was found. Few subcentimetric non FDG avid bilateral cervical, axillary and inguinal lymph nodes with preserved hilar fat and no appreciable FDG uptake was also noted and was likely to be reactive nodes (Figure 1). There was no other suspicious lesion or appreciable abnormal FDG uptake elsewhere in the body surveyed. Our overall impression was bone marrow liver spleen (BLS) type of DLBCL. Further clinicopathological correlation was advised.

Oncologists planned a chemotherapy schedule for the patient. Unfortunately, the patient expired after 2 months of the PET-CT scan while undergoing treatment.

DISCUSSION

DLBCL, the most common type of non-Hodgkin's lymphoma (NHL), is an aggressive tumor usually presenting as enlarging lymph nodes and/or extra-nodal masses (3-5). Secondary bone marrow, liver or spleen involvement may occur, but they are unusual sites to establish the initial diagnosis (5-9). BLS is a rare and aggressive subtype of DLBCL. Only one case series with 11 patients has been reported to date. Patients usually present with fever and anemia of unclear etiology, thrombocytopenia, hemophagocytic lymphohistiocytosis (HLH), and increased LDH without significant lymphadenopathy or other extranodal masses (2, 10). There is no prior history of lymphoma.

HLH is a rare severe hyperinflammatory disease with high mortality. It is caused by uncontrolled proliferation of activated lymphocytes and macrophages, characterized by proliferation of morphologically benign lymphocytes and macrophages resulting in secretion of large amounts of inflammatory cytokines. According to recent protocol (2008) HLH is diagnosed by molecular diagnosis (pathologic mutations of PRF1, UNC13D, or STX11 genes) or fulfillment of five out of the following eight criteria: (1) fever (>100.4°F, >38°C), (2) splenomegaly, (3) cytopenias (affecting at least two of three lineages in the peripheral blood: hemoglobin < 9 g/dL, platelets <100 × 109/L, or Neutrophils < 1 × 109/L), (4) hypertriglyceridemia and/or hypofibrinogenemia (≤150 mg/100 ml), (5) ferritin ≥ 500 ng/ml, (6) hemophagocytosis in the bone marrow, spleen, or lymph nodes, (7) low or absent natural killer cell activity, and (8) soluble CD25 (soluble IL-2 receptor) >2400 U/ml (local reference laboratory) (11, 12). This reported case fulfilled 5 criteria (fever, splenomegaly, cytopenia, hemophagocytosis in bone marrow and slightly high ferritin, though CD25 could not be done).

In a Japanese nationwide survey of HLH patients, lymphoma-associated HLH (LAHS) accounted for approximately one-fifth of the secondary HLH patients and all were above 60 years of age (13). Presence of HLH along with atypical involvement sites may mislead and delay the diagnosis.

On imaging studies small (usually less than 3 cm) lymph nodes may be identified. Bone marrow biopsy usually reveals hemophagocytosis and an interstitial distribution of large lymphoma cells with a mature B-cell phenotype. In another study by gene microarray profiling with bioinformatics analysis, higher expression of the stem cell markers HOXA9 and NANOG, as well as BMP8B, CCR6 and S100A8 were found in BLS-type than conventional DLBCL (14).

PET CT is not a diagnostic tool for BLS type of DLBCL. But it can clearly depict the sites of involvement thus helping in stablishing disease pattern. Specially in BLS type of DLBCL where significant lymphadenopathy is absent and the bone marrow features may be confusing a baseline PET-CT can detect the involved sites which is not possible through conventional anatomical imaging modalities. Studies has shown high sensitivity as well as good specificity of PET-CT in diagnosing bone marrow involvement (15).

In our case, the patient presented with fever and weakness mimicking infection and was treated accordingly. Detection of severe anemia with pancytopenia alarmed his physician and led to bone marrow study which revealed

lymphoproliferative disorder suggesting acute lymphoblastic leukemia. Bone marrow biopsy suggested hematolymphoid malignancy. A repeat bone marrow study showed atypical mononuclear cells which are the precursor of NK cell and macrophage. Flow cytometry was negative for leukemic panel. Moreover, BCR-ABL gene was negative which ruled out leukemia. An immunohistochemistry of bone marrow suggested DLBCL. PET-CT features revealed BLS type of lymphoma. Further genetic analysis could not be done due to unavailability or refusal of the patient. Though several markers were checked by immunohistology, CD25 was not done. Based on previous laboratory finding, patient also full filled the criteria of HLH. So, overall diagnosis may be BLS type of DLBCL with HLH.

Though DLBCL is the commonest type of NHL accounting for about 40% cases, BLS type is rarely found. Such cases have been variably published in the literature (6, 7, 10, 16-22) with different entity (bone marrow only, spleen and bone marrow or spleen, liver and bone marrow) according to involvement site as itis still not currently defined in the WHO classification (1).

The clinical presentation and disease course of BLS type of DLBCL are particularly severe with rapid disease progression and high mortality rate during first few weeks to months after initial symptoms. Overlapping clinical and morphological features can make it challenging to differentiate DLBCL-BLS from more common lymphomas including splenic marginal zone lymphoma or even severe infection if HLH is associated. PET CT is an important tool for confirming disease pattern leading to proper and prompt management of this aggressive disease.

CONCLUSION

BLS-type of DLBCL with associated features of HLH is a rare aggressive disease with controversial entity and high mortality rates during the first few weeks to months. Prompt disease recognition and development of effective therapeutic strategies are needed. PET-CT can play an important role in initial diagnosis.

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