Int J Clin Exp Med 2018;11(8):8741-8745
www.ijcem.com /ISSN:1940-5901/IJCEM0070242

*Case Report*

# A case of primary bone marrow, liver, and spleen lymphoma with hemophagocytic lymphohistiocytosis and a slightly increased uptake of 18F-fluodeoxyglucose

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Received December 3, 2017; Accepted May 14, 2018; Epub August 15, 2018; Published August 30, 2018

**Abstract:** Diffuse large B cell lymphoma (DLBCL) presenting initially in bone marrow, liver, and spleen (BLS-type) without lymphadenopathy has been recently recognized. It progresses rapidly, aggressively, usually accompanied by hemophagocytic lymphohistiocytosis (HLH) with a 2-year survival rate of 18%. 18F-fluodeoxyglucose (18F-FDG)-positron emission tomography/computed tomography (PET/CT) imaging, serving as representative molecular imaging, is of utmost value in initial evaluation of lymphoma staging. A slightly increased uptake of 18F-FDG detected by PET/CT may still be a reminder of lymphoma. Herein, we present a case of DLBCL BLS-type with HLH as a preceding symptom and a slightly increased uptake of 18F-FDG as detected by PET/CT.

**Keywords:** BLS-type lymphoma, HLH, PET/CT

## Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for about 31%-40% of all cases of lymphoma [1, 2]. Recently a new subtype of DLBCL presenting initially in bone marrow, liver, and spleen (BLS-type) without lymphadenopathy has been recognized. It progresses rapidly and aggressively, with a 2-year survival rate of 18% [1]. In patients with hemophagocytic lymphohistiocytosis (HLH), non-Hodgkin B-cell lymphomas are rarer compared to T-cell lymphomas [3]. 18F-fluodeoxyglucose (18F-FDG)-positron emission tomography/computed tomography (PET/CT) imaging, serving as the representative molecular imaging, is of utmost value in initial evaluation of lymphoma staging [4]. A slightly increased uptake of 18F-FDG detected by PET/CT may also be a reminder of lymphoma. Herein, we presented a case of DLBCL BLS-type with HLH as a preceding symptom and a slight increase uptake of 18F-FDG as detected by PET/CT.

A 66-year-old man was admitted into our hospital (Hangzhou Red Cross Hospital, Hangzhou, China) on June 14, 2017 due to a 7-week of fever. His physical examination was negative for lymphadenopathy but a notably palpable spleen. Laboratory results showed bicytopenia (leukocytes 4.5 × $10^9$/L, Neutrophils 2.9 × $10^9$/L, hemoglobin 114 g/L, and platelets 58 × $10^9$/L) and increased levels of ferritin: 621.5 μg/L (21.8-274 μg/L), soluble CD25: 3,941 U/mL (223-710 U/mL), lactate dehydrogenase: 1,794 IU/L (60-245 IU/L). Chest and abdominal CT showed mild hepatosplenomegaly.

Following one week of anti-infection treatment with Tazocin (4.5 g, ivgtt, q8h), no clinical symptoms seemed to be improved. For bicytopenia, a bone marrow (BM) aspiration was performed to find the cause. Hemophagocytichistiocytes were observed in the bone marrow smears (**Figure 1**). Karyotyping revealed normality: 46, XY. Flow cytometry (FCM) analysis showed no neoplastic cells. polymerase chain reaction (PCR) assays were negative for Epstein-Barr virus and human tiny B19 virus-DNA. Considering the examination results including hemophagocytichistiocytes in BM aspirate and hepatosplenomegaly, as well as other symptoms such as fever, increased levels of ferritin, and

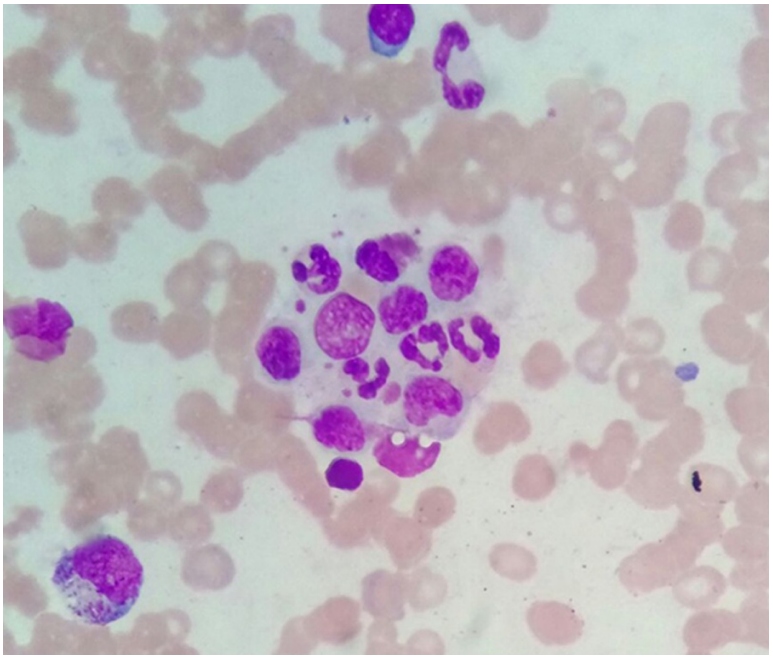

**Figure 1.** Bone marrow smear revealed hemophagocytosis. A histiocyte engulfed neutrophils and lymphocytes (HE stain, original magnification × 1000 with oil immersion).

**Table 1.** Clinical and Laboratory Findings of the Patient Obtained During Research on the Diagnosis of DLBCL associated HLH

| Criterion | On Admission | Reference Values |
|---|---|---|
| Fever | Yes | - |
| Splenomegaly | Yes | - |
| Hemoglobin | 10.8 g/dl | < 9 g/dl |
| Platelets | 58.000/mm$^3$ | < 100.000/mm$^3$ |
| Neutrophils | 2900/mm$^3$ | < 1000/mm$^3$ |
| Triglyceride | 104 (30-168) mg/dl | ≥ 265 mg/dl |
| Fibrinogen | 379 mg/dl | ≤ 150 mg/dl |
| Hemophagocytosis | Yes | - |
| NK-cell activity | - | Decreased or absent |
| Ferritin | 621.5 ug/L | ≥ 500 mg/L |
| Soluble CD25 | 3,941 U/mL | ≥ 2,400 U/mL |

Reference values according to hemophagocytic lymphohistiocytosis guidelines.

increased levels of CD25, suspicion of secondary HLH was based on the HLH guidelines [5] (**Table 1**). Since the possibility of secondary HLH caused by infection is low, malignancy of blood system, particularly the splenic T cell lymphoma associated with HLH was considered. Subsequently, whole-body PET/CT imaging with 18F-FDG, a glucose analog, was performed to try to find the primary lesion site. As detected, a slight increase of standard uptake value (SUV) of 18F-FDG in the reticuloendothelial system (Full liver shape with SUV maximum to 2.8; increased spleen shape accounting for 7 rib units with SUV up to 2.7; and bone and BM cavity with SUV maximum to 3.7) (**Figure 2**). Later, another BM aspiration test was performed, along with liver and spleen biopsy. As shown by BM aspiration, near to 1% abnormal cells were found in the BM smear, indicating the possibility of lymphoma. The immune globulin heavy chain (IGH) mutation was positive and T cell receptor (TCR) was negative, but the BM cells investigated by FCM remained negative. Spleen biopsy demonstrated a scattered large nucleus and abnormal lymphocytes in the small splenic tissue. Related immunohistochemical results showed: CD21(±), CD20(+), CD79a(+), MUM1(+), BCL-2(+), BCL-6(-), CD10(-), Ki-67(+), C-Myc(-), CD3(-), CD5(-), CD30(-), CD38(-), CD138(-), TIA-1(-), CD56(-), CD4(-), CD8(-), Granzyme-B(-), Perforin(-), CD68(-), CD31(-), CD34(-), Kappa(-), Lambda(-), EBER(-) (**Figure 3**). Combined with clinical manifestations, DLBCL (non germinal center B cell like) was suspected. Additionally, lymphocytic infiltration was seen in the hepatic portal area and stoma (the number of such cells is too little to diagnose) as detected by liver biopsy. Moreover, the forward scatter/side scatter (FSC/SSC) abnormalities of cloned B lymphoma cells were detected through FCM. Given all these examination results along with the clinical manifestations of the patients, ultimately, the patient was diagnosed with DLBCL and HLH was considered as a preceding symptom.

Based on these data, systemic chemotherapy with rituximab + low-dose CHOPE (R-miniCHOPE) was determined as an appropriate treatment for the patient in the first cycle period.

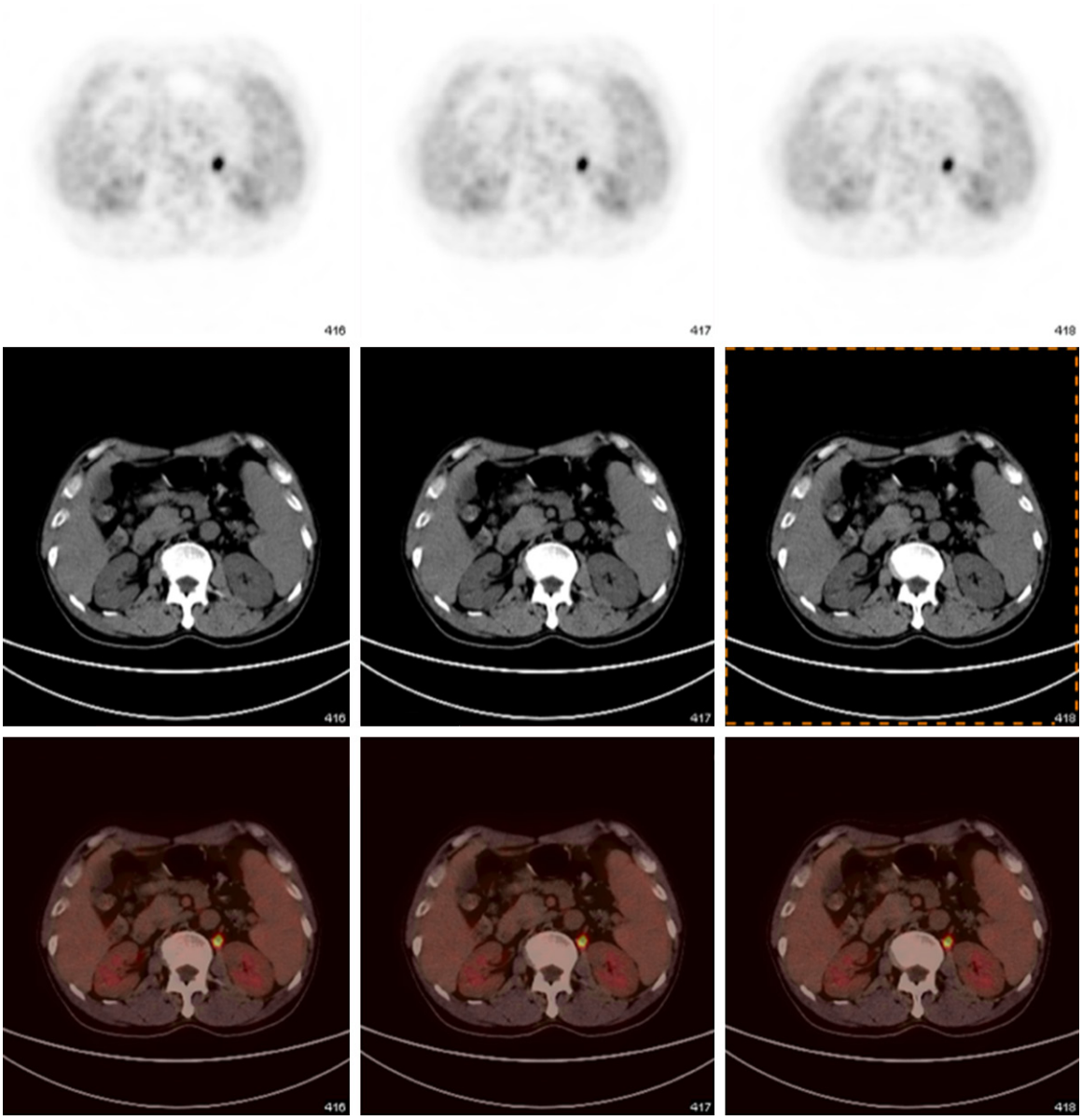


**Figure 2.** PET/CT full liver shape with SUV maximum to 2.8; increased spleen shape accounting for 7 rib units with SUV up to 2.7; and bone and BM cavity with SUV maximum to 3.7.

As expected, his body temperature dropped to normal level immediately. Nevertheless, it started to rise to 38.9 centigrade prior to the initiation of the second treatment cycle, which might due to the low therapeutic power of R-miniCHOPE. Later, R-miniCHOPE was replaced with R-dose-adjusted (DA)-EPOCH during the next four treatment cycles. For almost 4 months post-treatment, the patient has had a good quality of life.

This case shows several note worthy findings. First, for NHL with extranodal involvement, the sensitivity of PET/CT was almost two-fold better than that of enhanced CT (88% *vs*. 50%), while the specificities were similar (100% *vs*. 90%) [6]. The final diagnosis of all cases was based on comprehensive analysis of laboratory, imaging results, and biopsy. Scans were considered positive if the specific SUV of a suspicious lesion was more than 2.5 [7]. BM biopsies were reviewed along with diagnostic specimens. In this case, SUV maximum in liver was 2.8 and SUV maximum in spleen was 2.7, which is hard to distinguish malignancy from infection. We attempted to puncture the liver and spleen and definite diagnosis was eventually achieved.

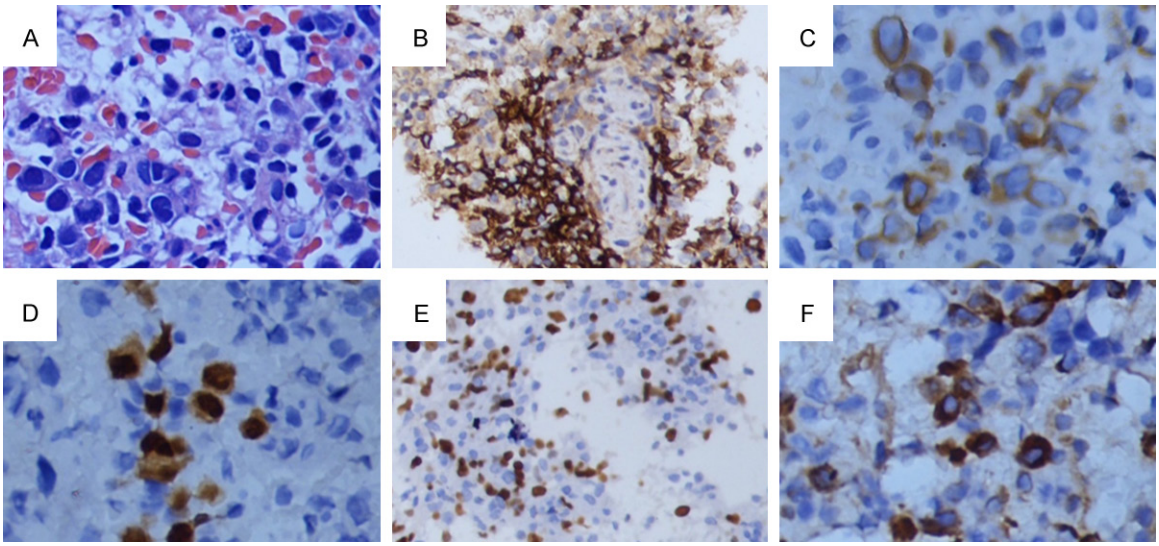


**Figure 3.** Spleen: hematoxylin and eosin stain (A), CD20+ (B), CD79a+ (C), MUM1+ (D), Ki67+ (E), BCL-2+ (F) (original magnification × 400).

Second, DLBCL presenting initially in bone marrow, liver and spleen, associated frequently with hemophagocytic syndrome appears to be representative of an unusual, aggressive entity that eludes prompt diagnosis due to the nonspecific features of the clinical symptoms and the absence of lymph lesions [1]. The presence of HLH in BLS-type LBCL is intriguing without associated EBV infection. The cytogenetic abnormalities in DLBCL are typically heterogeneous, so are BLS-type LBCL cases. Taking care of patients presenting with fever and unexplained cytopenias, BM biopsy was recommend to obtain the first diagnostic tissue specimen [8]. Compared to conventional DLBCL, the overall survival of this variant lymphoma was significantly worse with a 2-year survival rate of 18% and also worse than stage IV conventional DLBCL. Machaczka et al. noted that the prevalence of malignancy-associated HLH was 0.9% in adults with hematologic cancers but could be as high as 20% in those with specific, rare types of B-cell lymphomas without peripheral adenopathies [9].

Third, the first principle for the treatment of secondary HLH is removal of the cause of primary disease, so screening of etiology is of great importance. The core of the treatment is to suppress or eliminate excessive proliferation of activated lymphocytes, to control cytokine storm, and to control multisystem damage. There is no standard treatment for adults with HLH, but usually referring to HLH-2004 scheme or HLH-1994 scheme for children [10]. The difference between the HLH-2004 and the HLH-1994 scheme is that the former advances CSA and adds intrathecal injection [5, 11]. Individualized therapy is essential for HLH, not simply referring to HLH-2004 or HLH-1994.

The high SUV of PET/CT is of significant value in lymphoma diagnosis, but a slightly higher SUV value cannot completely exclude lymphoma, and the final diagnosis of lymphoma still requires biopsy. The treatment of lymphoma associated HLH needs to be individualized and not rigidly adhere to the HLH-2004 or HLH-1994 protocol.

## Disclosure of conflict of interest

None.

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