Positron emission tomography findings in patients with lymphoma-associated haemophagocytic syndrome

Yiu C R, Kao Y H, Phipps C, Tan D

ABSTRACT

Lymphomas that manifest initially with haemophagocytic syndrome (HPS) often pose a diagnostic challenge, as the majority of cases have no significant lymphadenopathy for early histological diagnosis. There is paucity of data on specific features of fluorine-18-fluorodeoxyglucose (FDG)-positron emission tomography with integrated computed tomography (PET/CT) in patients with lymphoma-associated HPS (LHPS). We describe three cases of LHPS and their characteristic PET imaging features. All three patients had pyrexia and pancytopenia. Their PET/CT images showed extensive and diffuse FDG uptakes in the bone marrow of the axial skeleton, with little involvement in the lymph nodes. They also faced a common initial diagnostic difficulty; the lack of nodal involvement on clinical examination or CT contributed to the delay in the diagnosis of lymphoma. The PET/CT images, however, revealed extensive and distinctive FDG uptakes in the axial skeletal marrow compartment, thus leading to a greater appreciation of the full extent of the disease.

Keywords: haemophagocytic syndrome, lymphoma, positron emission tomography

Singapore Med J 2011;52(7):e156-e159

INTRODUCTION

Haemophagocytic syndrome (HPS) is an uncommon haematological disorder that is characterised by systemic proliferation of histiocytes. The typical clinical manifestations of HPS include fever, cytopenia, liver dysfunction and often, hepatosplenomegaly.[1,2] In addition to haematological malignancies, especially lymphomas, reactive HPS has also been reported to be associated with infective (viral, bacterial or fungal) and autoimmune causes.[2] Lymphomas manifesting initially with HPS often pose a diagnostic challenge, as most of these cases may not demonstrate significant lymphadenopathy or tumour masses for early histological diagnosis.[3,4] Information on the specific features of fluorine-18-fluorodeoxyglucose (FDG)-positron emission tomography with integrated computed tomography (PET/CT) in patients with lymphoma-associated HPS (LHPS) is lacking, as only a few cases have been reported in the literature.[5,6] We describe three consecutive cases of LHPS that presented at our institution, their characteristic FDG-PET/CT features and how it facilitated our diagnostic approach to this rare entity.

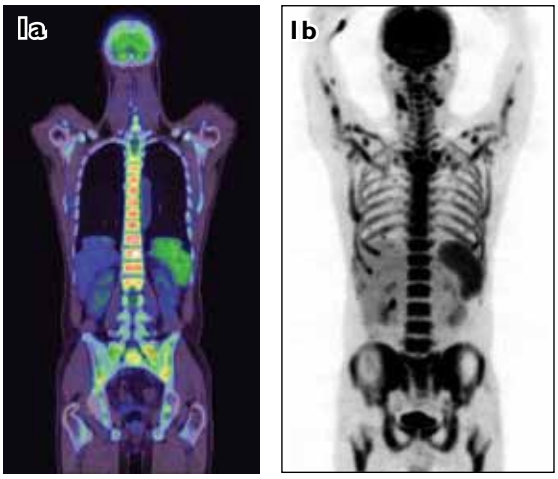

Fig. 1 (a) PET/CT and (b) maximum intensity projection (MIP) images show diffuse lymphomatous involvement of the bone marrow in Case 1.

CASE REPORTS

Case 1

A 47-year-old Chinese man presented with pyrexia of unknown origin. Clinical examination and CT were unremarkable for lymphadenopathy or hepatosplenomegaly. The patient subsequently developed progressive pancytopenia, with the nadir of the full blood count (FBC) showing haemoglobin 9.7 g/dL, total white cell count 0.7 × 10^9/L and platelet count 28 × 10^9/L. His liver enzymes were elevated. Microbiological investigations did not reveal any infective cause, and autoimmune screens were all negative. Bone marrow

Department of Haematology, Singapore General Hospital, Outram Road, Singapore 169608

Yiu CR, MBBS, MMed, MRCP
Associate Consultant

Phipps C, MBBS, MRCP
Registrar

Tan D, MBBS, MMed, MRCP
Consultant

Department of Nuclear Medicine and PET

Kao YH, MBBS, MRCP
Registrar

Correspondence to:
Dr Richard Cheung Yiu
Tel: (65) 6321 4855
Fax: (65) 6225 0210
Email: ryiu@yahoo.com

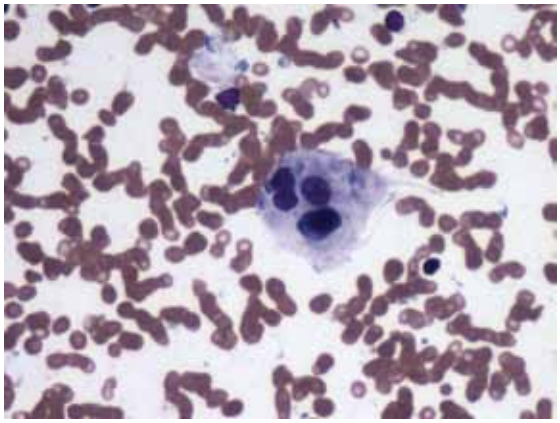

Fig. 2 Photomicrograph of the bone marrow aspirate in Case 2 shows haemophagocytosis (Maygranwald Giemsa, × 100).

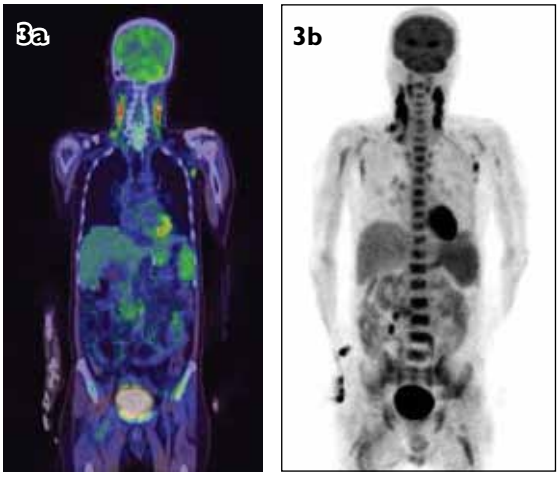

Fig. 3 (a) PET/CT and (b) MIP images show increased FDG uptake in the cervical lymph nodes in Case 2.

aspiration showed prominent haemophagocytosis, and trephine biopsy confirmed the diagnosis of diffuse large B-cell lymphoma (DLBCL). In view of the atypical presentation of DLBCL, features of intravascular lymphoma (Asian variant), including sinusoidal infiltration of tumour cells and reactivity with CD5 stain, were looked for, but the results were negative.[7] FDG-PET/CT demonstrated diffuse and extensive lymphomatous involvement of the bone marrow and spleen, with a maximum standardised uptake value (SUVmax) of 4.6 (Fig. 1). Small, but FDG-avid submandibular, mediastinal and periportal lymph nodes that were not initially appreciated on the CT image were detected on FDG-PET/CT. The patient was treated with six cycles of rituximab, cyclophosphamide, adriamycin doxorubicin, vincristine and prednisolone. Post-treatment FDG-PET/CT and bone marrow biopsy showed complete remission of the disease.

Case 2

A 58-year-old Chinese man with a history of ischaemic heart disease presented with fever for one week. On clinical examination, no palpable lymphadenopathy or hepatosplenomegaly was observed. Initial FBC was completely normal. He subsequently developed progressive pancytopenia that was associated with a rise in serum alkaline phosphatase levels. CT did not demonstrate any significant lymphadenopathy or hepatosplenomegaly. Extensive microbiological investigations did not yield an infective cause. Bone marrow aspiration showed prominent haemophagocytosis (Fig. 2). However, trephine biopsy did not reveal any lymphomatous infiltration. FDG-PET/CT was then performed, which revealed increased FDG uptake in three discrete cervical lymph nodes (SUVmax 12.7) as well as diffuse uptake in the marrow compartment (SUVmax 6.0, Fig. 3). This guided an excision biopsy of his right cervical lymph node, where histology confirmed the diagnosis of anaplastic lymphoma kinase-positive anaplastic large cell lymphoma. The patient was started on a regimen of cyclophosphamide, etoposide, vincristine and prednisolone, as his impaired cardiac function precluded the use of anthracycline. Unfortunately, he succumbed to an infective complication before any meaningful assessment of disease response could be performed.

Case 3

A 65-year-old Chinese man presented with pyrexia of unknown origin that was associated with significant weight loss for two months. Clinically, he had palpable hepatosplenomegaly, but no peripheral lymphadenopathy. Initial FBC showed mild anaemia and leucopenia. He subsequently developed progressive pancytopenia. Serum alkaline phosphatase, aspartate transaminase and bilirubin levels were raised to five times the upper normal limits. Serum ferritin level was markedly elevated at 18,665 mcg/L. Moderate hepatosplenomegaly was evident on the CT image, and no significant lymphadenopathy was detected. Bone marrow aspiration showed prominent haemophagocytosis with few atypical lymphoid cells. Trephine biopsy confirmed the diagnosis of peripheral T-cell lymphoma (unspecified) with diffuse fibrosis. FDG-PET/CT showed diffuse FDG activity in the liver (SUVmax 5.2), spleen (SUVmax 5.1) and marrow (SUVmax 5.7) (Fig. 4). The patient was then treated with chemotherapy, which consisted of two cycles of gemcitabine, dexamethasone and cisplatin, and two cycles of ifosfamide, carboplatin and rtoposide. Post-treatment

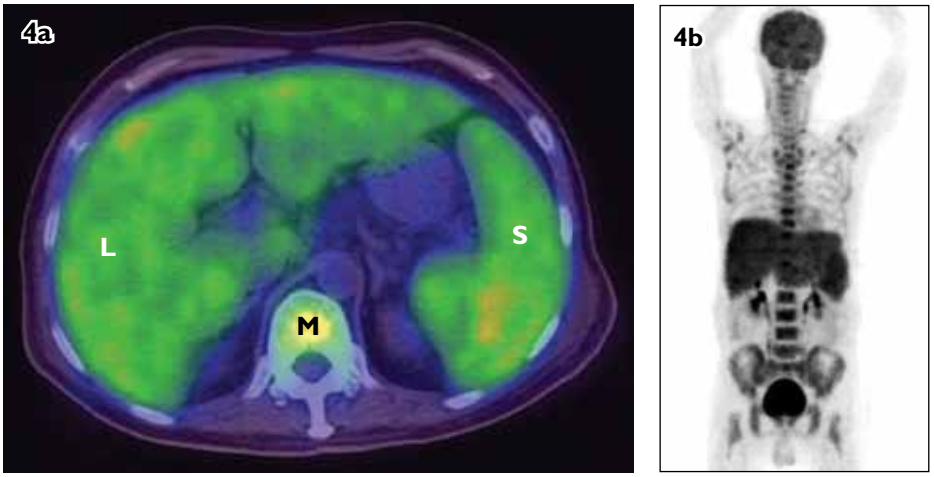

Fig. 4 (a) PET/CT and (b) MIP images show a diffuse increase in FDG activity in the liver [L], spleen [S] and marrow [M] in Case 3.

FDG-PET/CT and bone marrow biopsy showed complete remission of the disease. The patient subsequently proceeded to high-dose therapy with stem cell support.

DISCUSSION

One common problem faced by the treating physicians of our three patients with LHPS was the initial diagnostic difficulty; the lack of tumour masses or nodal involvement on clinical examination or CT resulted in a delay in the diagnosis and institution of definitive treatment. This could have been dangerous, since the haemophagocytic syndrome itself is associated with high fatality if the underlying precipitating causes are not treated accordingly. The FDG-PET/CT images, however, revealed extensive and distinctive FDG uptakes in the axial skeletal marrow compartment and led to a greater appreciation of the full extent of the disease, which could otherwise have been missed on routine CT.

PET/CT has emerged as a powerful imaging tool for assessment of patients with DLBCL and Hodgkin's lymphoma. However, its role in T-cell non-Hodgkin's lymphoma is still being defined. As FDG-PET/CT is highly sensitive in detecting nodal, extranodal and even occult involvement by most histologic subtypes of lymphoma, it may provide complementary information to conventional staging methods, including CT and bone marrow biopsy.[8-10] FDG-PET/CT is currently not recommended as part of the standard lymphoma staging, primarily due to its high cost and the generally small percentage of patients in whom FDG-PET/CT detects additional disease sites that actually modify the clinical stage and alter the management. However, as illustrated by our experience, it is certainly a valuable asset in the diagnostic approach of patients presenting with HPS.[11]

Diffusely increased bone marrow uptake on FDG-PET/CT may also be a result of reactive myeloid hyperplasia due to the use of myeloid growth factors or regenerating marrow after chemotherapy.[12] These possibilities have been ruled out in our patients, as their marrows showed myeloid suppression instead, due to haemophagocytosis. However, whether the FDG activity in the marrow could also be attributed to the presence of activated histiocytes in addition to tumour involvement, remains to be determined.

REFERENCES

1. Tsuda H. Hemophagocytic syndrome (HPS) in children and adults. Int J Hematol 1997; 65:215-26.
2. Kumakura S. Hemophagocytic syndrome. Intern Med 2005; 44:278-80.
3. Allory Y, Challine D, Haioun C, et al. Bone marrow involvement in lymphomas with hemophagocytic syndrome at presentation: a clinicopathologic study of 11 patients in a Western institution. Am J Surg Pathol 2001; 25:865-74.
4. Han AR, Lee HR, Park BB, et al. Lymphoma-associated hemophagocytic syndrome: clinical features and treatment outcome. Ann Hematol 2007; 86:493-8.
5. Suga K, Kawakami Y, Hiyama A, et al. F-18 FDG PET/CT findings in a case of T-cell lymphoma-associated hemophagocytic syndrome with liver involvement. Clin Nucl Med 2010; 35:116-20.
6. Corapcioglu F, Oncel S, Berberoğlu K, et al. False positivity of FDG-PET during hemophagocytic lymphohistiocytosis in a child with Hodgkin lymphoma in remission. J Pediatr Hematol Oncol 2009; 31:74-5.
7. Marase T, Nakamura S, Kawauchi K, et al. An Asian variant of intravascular large B-cell lymphoma: clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haemophagocytic syndrome. Br J Haematol 2000; 111:826-34.
8. Schaefer NG, Hany TF, Taverna C, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging--do we need contrast-enhanced CT? Radiology 2004; 232:823-9.

9. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer 2005; 104:1066-74.
10. Jerusalem G, Beguin Y, Najjar F, et al. Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) for the staging of low-grade non-Hodgkin's lymphoma (NHL). Ann Oncol 2001; 12:825-30.
11. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25:579-86.
12. Carr R, Barrington SF, Madan B, et al. Detection of lymphoma in bone marrow by whole-body positron emission tomography. Blood 1998; 91:3340-6.