
CASE REPORT

Positron-emission Tomography/Computed Tomography Staging and Evaluation of Post-transplant Lymphoproliferative Disorder after Paediatric Liver Transplant: a Case Report

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INTRODUCTION

Since the first description of post-transplant lymphoproliferative disorder (PTLD) in 1969,¹ there have been considerable improvements in its diagnosis and treatment. However, PTLD still represents a major threat to solid organ transplant recipients, accounting for significant post-transplant morbidity and mortality. Its pathophysiology is only partially understood. Epstein-Barr virus (EBV) infection before transplant and exogenous immunosuppressive drugs after transplant are considered unquestioned aetiological elements of PTLD.² The clinical spectrum ranges from benign lymphoid hyperplasia to aggressive lymphoma. The 2008 World Health Organization classification groups PTLD into early lesions, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma-type PTLD.³ The incidence of PTLD depends on the type of organ transplanted, the recipient's viral status prior to transplantation, and the intensity of immunosuppression. In paediatric orthotopic liver transplantation, the incidence ranges from 2% to 27%.⁴ The clinical

presentation is diverse and may mimic infection or allograft rejection.

¹⁸Fluorine-fluorodeoxyglucose (¹⁸F-FDG) positron-emission tomography/computed tomography (¹⁸F-FDG PET/CT) has a proven role in the management of lymphoma. This case report highlights the utility of FDG PET/CT in staging and treatment response evaluation of paediatric PTLD after liver transplantation.

CASE REPORT

In August 2012, a 5-year-old boy, who had undergone living donor liver transplantation at age 3 months for biliary atresia, was admitted with a history of abdominal distension for 2 weeks. Physical examination showed gross abdominal distension with mild generalised tenderness. Abdominal radiography was unremarkable. Laboratory results showed normal liver function, urate, and lactate dehydrogenase levels. He was suspected to have PTLD. ¹⁸F-FDG PET/CT demonstrated extensive hypermetabolic lesions involving the peritoneum,

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Submitted: 22 Jul 2018; Accepted: 22 Oct 2018.

Contributors: All authors contributed to the concept of study. EYLK and KKFF were responsible for acquisition of data and wrote the article. All authors analysed the data and had critical revision for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of Interest: All authors have disclosed no conflicts of interest.

Funding/Support: This case report received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics Approval: Informed consent was obtained from the patient's parents.

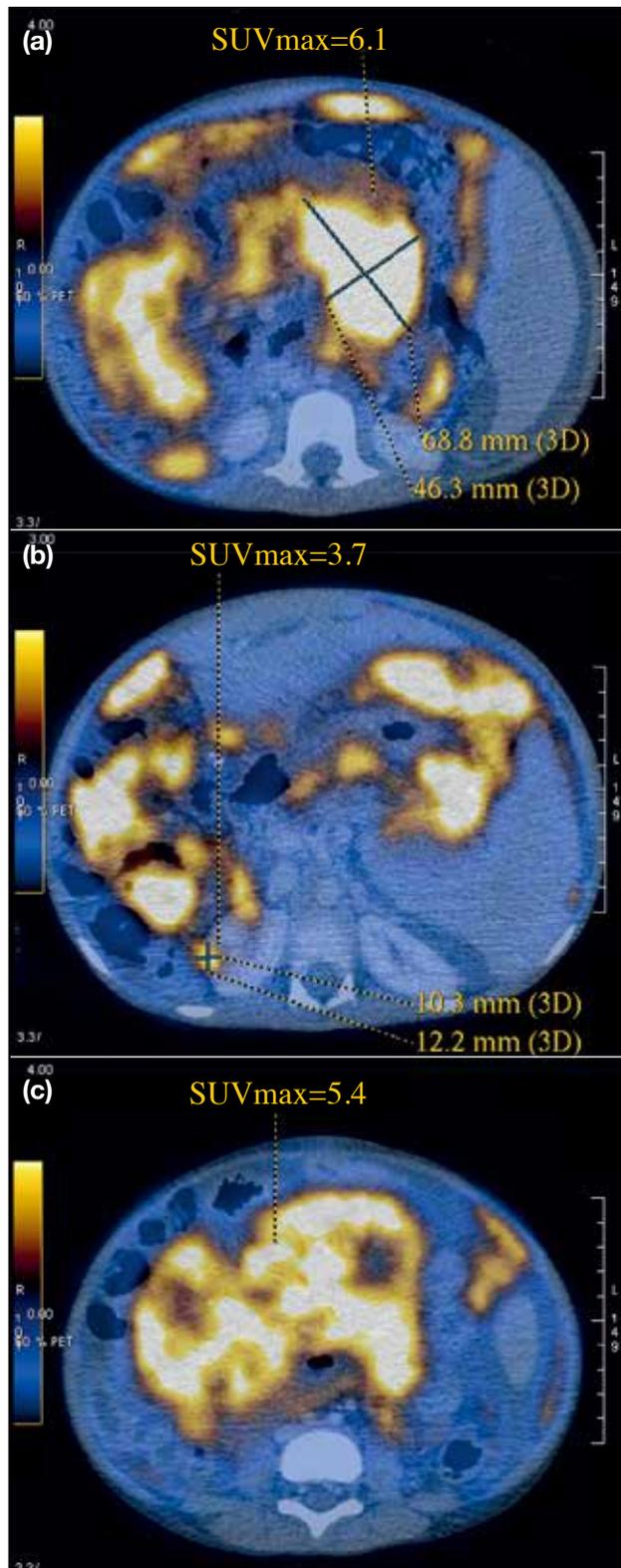


Figure 1. Selected axial fusion images of initial positron emission tomography-computed tomography demonstrating extensive hypermetabolic lesions involving (a) mesentery, (b) kidney, and (c) small bowel.

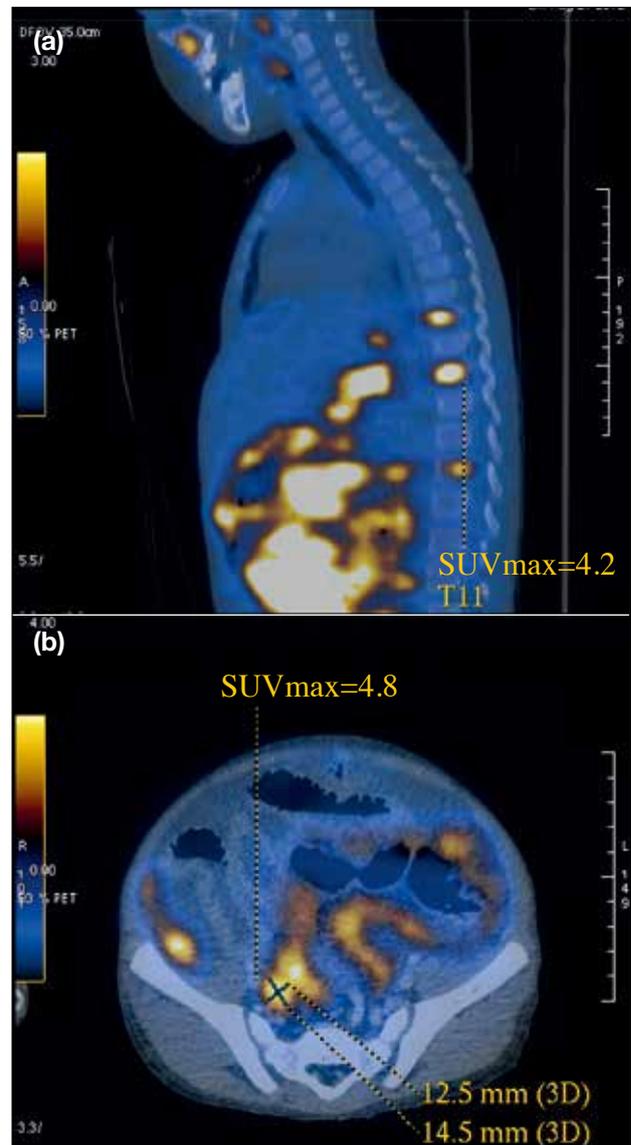


Figure 2. Initial positron emission tomography-computed tomography showing (a) multifocal hypermetabolic bone lesions indicating marrow involvement; (b) no hypermetabolic lesion in the iliac crests.

small bowel, kidneys, lymph nodes, and bone marrow (Figures 1 and 2). The maximum standardised uptake value (SUVmax) of these lesions ranged from 2.5 to 6.4, with the most hypermetabolic lesion located in the porta hepatis. The largest lesion (SUVmax 6.1) was found in the central mesentery. Laparotomy was performed, showing extensive omental lymphadenopathy and about 1 L of clear peritoneal fluid. Biopsy was obtained from a large para-splenic mesenteric lymph node (corresponding to the largest central mesenteric lesion detected on PET/CT) for tissue diagnosis. Bone marrow aspiration and

cerebrospinal fluid cytology were negative for abnormal lymphocytes. The histology was confirmed to be EBV-associated monomorphic PTLD of Burkitt lymphoma origin, stage IV. Treatment with four doses of rituximab and six cycles of cyclophosphamide, vincristine, and prednisolone (COP) was instituted. The abdominal distension improved. ^{18}F -FDG PET/CT at 4 months after the end of treatment showed complete resolution of the previously noted lesions; however, there was interval development of multiple new hypermetabolic lesions around the conus medullaris, and in the gastric fundus, left lung, and mesenteric nodes with SUVmax ranging from 3.3 to 14.0 (Figure 3). A lumbar puncture was performed, and cytological analysis of cerebrospinal fluid showed the presence of B lymphocytes. The patient was treated as a relapse with intense chemotherapy using the protocol for high-grade B cell lymphoma with central nervous system involvement. The end-of-treatment scan showed complete resolution of all lesions, indicating a complete metabolic response; he has remained disease-free for 3 years.

DISCUSSION

The use of ^{18}F -FDG PET/CT for the evaluation of Hodgkin and non-Hodgkin lymphoma has increased dramatically in recent years.⁵ The utility of ^{18}F -FDG PET/CT has extended to adult PTLD with overall sensitivity and specificity of up to 89%.⁶ A 2012 study on paediatric PTLD suggested ^{18}F -FDG PET/CT's utility for staging and assessment of therapy response.⁷ Hybrid ^{18}F -FDG PET/CT combines functional and anatomical information, which is superior to functional PET alone, particularly in identifying extranodal disease such as in the bowel and mesentery as in our case, as well as in solid organs; 80% of PTLD sites are known to be extranodal and the gastrointestinal tract is the most common site, found in 17% of patients.⁸ There is preferential involvement of the allograft itself or the region surrounding the allograft. Liver-based PTLD is observed in 22% of liver transplant recipients. Manifestations of hepatic PTLD on conventional imaging can be highly variable and non-specific, ranging from solitary or multiple discrete low-attenuation hypovascular parenchymal lesions, an ill-defined infiltration or encasement of the porta hepatis.⁹ Whilst hepatic lesions were not observed in our patient, a discrete hypermetabolic right renal lesion was detected on the initial staging scan. Routine unilateral bone marrow biopsy may result in false negativity in some cases due to focal bone marrow involvement in lymphoma.¹⁰ The overall sensitivity of detecting bone marrow involvement by ^{18}F -FDG PET/CT is 92%,

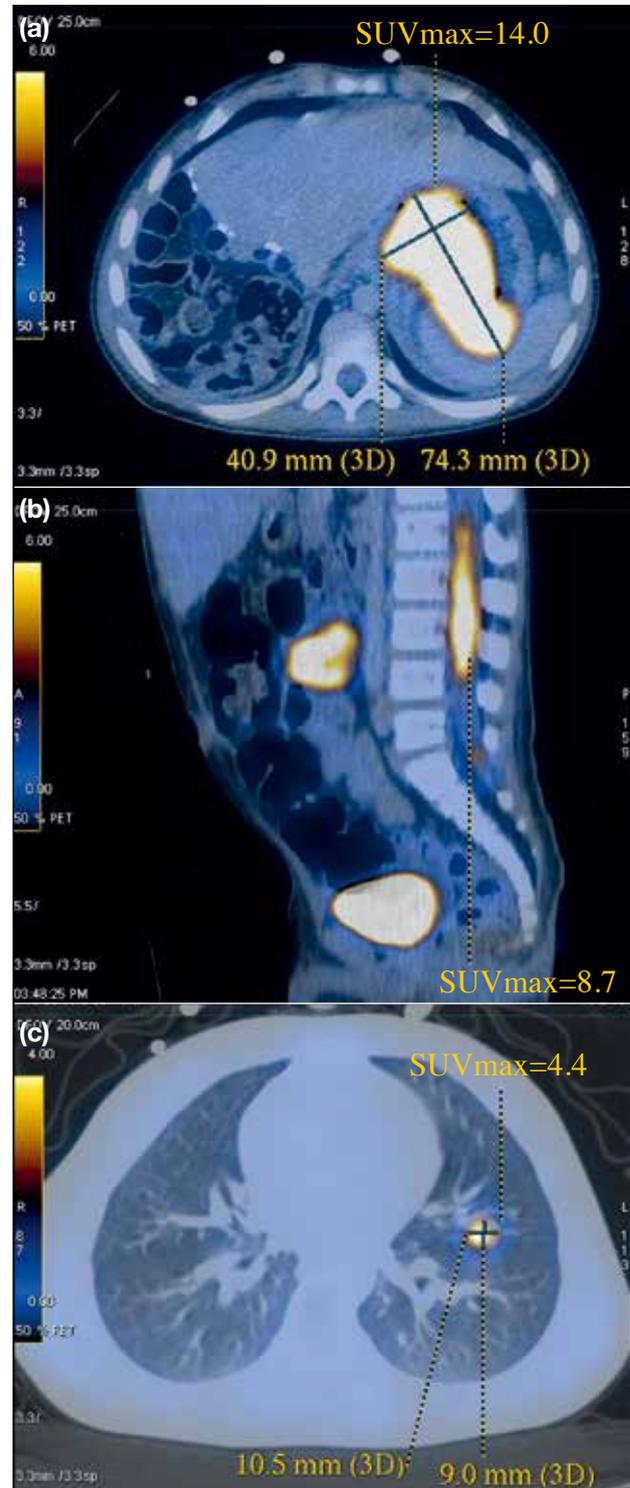


Figure 3. End-of-treatment positron emission tomography-computed tomography showing new hypermetabolic lesions in (a) stomach, (b) conus medullaris and (c) lung. Patient was diagnosed to have recurrent disease with central nervous system involvement.

compared to 54% by bone marrow aspiration.¹¹ Thus, ^{18}F -FDG PET/CT may result in disease up-staging by detection of bone marrow involvement, which is an

independent risk factor for poor survival in paediatric PTLD.¹² As illustrated in our patient, the disease would have been understaged if bone marrow involvement had been determined by marrow aspiration alone (Figure 2). Another potential advantage of ¹⁸F-FDG PET/CT is its ability to characterise metabolic phenotype; metabolic activity of the lesions has been found to correlate with the morphological characteristics of PTLD in that monomorphic lesions will have higher metabolic activity than polymorphic lesions due to differences in cell proliferation, and this may have clinical implications and carry prognostic significance.¹³ Monomorphic lesions usually resemble high-grade lymphoma, which will require aggressive chemotherapy and cannot be treated solely by reduction of immunosuppression.¹⁴ In our patient, rituximab and COP had resulted in complete response in the initial lesions but it did not prevent the relapse. The use of intense chemotherapy as the initial treatment may have altered the clinical course. In guiding biopsy, the lesion with highest FDG uptake can be targeted because PTLD is known to have histopathological variability.⁸ In addition, the ¹⁸F-FDG PET/CT performed 4 months after the end of the rituximab and COP regimen identified new hypermetabolic lesions around the conus medullaris, suggesting early relapse. This led to a lumbar puncture and cytological analysis of cerebrospinal fluid that showed the presence of B lymphocytes, avoiding the need for a second open biopsy of the intra-abdominal lesions. Finally, the initial FDG PET-CT scan can serve as baseline for evaluating therapeutic response.

Some limitations of ¹⁸F-FDG PET/CT in the initial assessment of paediatric PTLD are noteworthy. ¹⁸F-FDG PET/CT is less sensitive for the assessment of brain involvement due to high background physiological uptake. Cytological analysis of cerebrospinal fluid or magnetic resonance imaging would be necessary to exclude central nervous system involvement. In the context of solid organ involvement, ¹⁸F-FDG PET/CT may not reliably differentiate between PTLD, infection, inflammation, or other immunosuppression-associated malignancies such as Kaposi sarcoma. The value of SUVmax was shown to overlap among these hypermetabolic entities.¹⁵ The monitoring of viral load (detection of EBV in PTLD and human herpesvirus 8 in Kaposi sarcoma) and biopsy would aid in addressing the correct diagnosis.¹⁶ The known low diagnostic accuracy of ¹⁸F-FDG PET/CT in low-grade lymphoma is another limitation¹⁷; therefore, making a definitive diagnosis of low-grade PTLD based on ¹⁸F-FDG uptake may be difficult and histological diagnosis is required. However,

as a substantial 30% of paediatric PTLD cases are large cell lymphoma, which is highly ¹⁸F-FDG-avid,^{14,17} makes ¹⁸F-FDG PET/CT a useful modality for evaluating children suspected to have PTLD and beneficial in initial staging.

The target of PTLD treatment is to induce disease regression with minimal morbidity and preservation of graft function. The two basic principles of current standard PTLD treatments are reconstitution of anti-EBV/anti-tumour immune responses, and antineoplastic immunochemotherapy if necessary.² Challenges remain in tailoring the treatment protocol for the individual, as this depends also on factors such as differences in solid organ allografts, risk of rejection, associated comorbidity, and tumour burden at presentation. Stable remission is observed in 60% to 80% of patients, but treatment-related morbidity and mortality are not uncommon. Assessment of therapeutic response with ¹⁸F-FDG PET/CT will be important for individualised treatment so as to achieve a favourable outcome; eg, duration of immunosuppression reduction and addition of aggressive chemotherapy that is dependent on the response will dictate the risk of allograft rejection and long-term complications from drug toxicity.

Similar to its value in other lymphomas, ¹⁸F-FDG PET/CT has been demonstrated to be useful in evaluating therapeutic response of PTLD, and a negative scan at the end of treatment has a high negative predictive value.¹³ This is particularly valuable in solid organ PTLD where the need to biopsy non-hypermetabolic residual masses may be obviated. Our patient's PET/CT scan was performed 4 months after the end of treatment and hence, he was diagnosed with early relapse. These lesions corresponded to recurrent PTLD of an aggressive cell type (large B cell) that shared similar high metabolic activity as the original lesion (Burkitt's). The result of our post-treatment ¹⁸F-FDG PET/CT demonstrated that the initial therapy was inadequate, and institution of a more aggressive treatment protocol was necessary to achieve response and stable remission.

In conclusion, ¹⁸F-FDG PET/CT is a useful modality in evaluating paediatric PTLD. It provides additional information on areas of involvement and is beneficial in staging with the exception of excluding brain involvement. It has a high negative predictive value in assessing therapeutic response using the initial ¹⁸F-FDG PET/CT scan as a baseline, especially for aggressive subtypes. This case report also illustrates the role of

¹⁸F-FDG PET/CT in determining the adequacy of treatment and detection of relapse, thus optimising the therapeutic protocol for the individual. Large-scale prospective studies are warranted to evaluate ¹⁸F-FDG PET/CT for PTLD at initial staging or at mid-treatment for prognostication and early assessment of treatment.

REFERENCES

1. Penn I, Hammond W, Bretschneider L, Starzl TE. Malignant lymphomas in transplantation patients. *Transplant Proc.* 1969;1:106-12.
2. Mynarek M, Schober T, Behrends U, Maecker-Kolhoff B. Posttransplant lymphoproliferative disease after pediatric solid organ transplantation. *Clin Dev Immunol.* 2013;2013:814973. [Crossref](#)
3. Swerdlow SH, Campo E, Harris NL, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008.
4. Roque J, Rios G, Humeres R, Volpi C, Herrera JM, Schultz M, et al. Early posttransplant lymphoproliferative disease in pediatric liver transplant recipients. *Transplant Proc.* 2006;38:930-1. [Crossref](#)
5. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwarz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification. *J Clin Oncol.* 2014;32:3059-67. [Crossref](#)
6. Dierickx D, Tousseyn T, Requilé A, Verscuren R, Sagaert X, Morscio J, et al. The accuracy of positron emission tomography in detection of posttransplant lymphoproliferative disorder. *Haematologica.* 2013;98:771-5. [Crossref](#)
7. Shrikanthan S, Kunam V, Flagg A, Pinar Karakas S. FDG PET/CT in pediatric PTLD. *J Nucl Med.* 2012;53 Suppl 1:2196.
8. Collins MH, Montone KT, Leahey AM, Hodinka RL, Salhany KE, Belchis DA, et al. Autopsy pathology of pediatric posttransplant lymphoproliferative disorder. *Pediatrics.* 2001;107:E89. [Crossref](#)
9. Borhani AA, Hosseinzadeh K, Almusa O, Furlan A, Nalesnik M. Imaging of posttransplantation lymphoproliferative disorder after solid organ transplantation. *Radiographics.* 2009;29:981-1000. [Crossref](#)
10. Hao B, Zhao L, Luo NN, Ruan D, Pang YZ, Guo W, et al. Is it sufficient to evaluate bone marrow involvement in newly diagnosed lymphomas using ¹⁸F-FDG PET/CT and/or routine iliac crest biopsy? A new approach of PET/CT-guided targeted bone marrow biopsy. *BMC Cancer.* 2018;18:1192. [Crossref](#)
11. Cheng G, Chen W, Chamroonrat W, Torigian DA, Zhuang H, Alavi A. Biopsy versus FDG PET/CT in the initial evaluation of bone marrow involvement in pediatric lymphoma patients. *Eur J Nucl Med Mol Imaging.* 2011;38:1469-76. [Crossref](#)
12. Maecker B, Jack T, Zimmermann M, Abdul-Khaliq H, Burdelski M, Fuchs A, et al. CNS or bone marrow involvement as risk factors for poor survival in post-transplantation lymphoproliferative disorders in children after solid organ transplantation. *J Clin Oncol.* 2007;25:4902-8. [Crossref](#)
13. Bianchi E, Pascual M, Nicod M, Delaloye AB, Duchosal MA. Clinical usefulness of FDG-PET/CT scan imaging in the management of posttransplant lymphoproliferative disease. *Transplantation.* 2008;85:707-12. [Crossref](#)
14. Hayashi RJ, Kraus MD, Patel AL, Canter C, Cohen AH, Hmiel P, et al. Posttransplant lymphoproliferative disease in children: correlation of histology to clinical behavior. *J Pediatr Hematol Oncol.* 2001;23:14-8. [Crossref](#)
15. Wareham NE, Lundgren JD, Da Cunha-Bang C, Gustafsson F, Iversen M, Johannesen HH, et al. The clinical utility of FDG PET/CT among solid organ transplant recipients suspected of malignancy or infection. *Eur J Nucl Med Mol Imaging.* 2017;44:421-31. [Crossref](#)
16. Dow DE, Cunningham CK, Buchanan AM. A review of human herpesvirus 8, the Kaposi's sarcoma-associated herpesvirus, in the pediatric population. *J Pediatric Infect Dis Soc.* 2014;3:66-76. [Crossref](#)
17. Paes FM, Kalkanis DG, Sideras PA, Serafini AN. FDG PET/CT of extranodal involvement in non-Hodgkin lymphoma and Hodgkin disease. *Radiographics.* 2010;30:269-91. [Crossref](#)