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PICTORIAL REVIEW

FDG-PET/CT in abdominal post-transplant lymphoproliferative disease

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ABSTRACT

Post-transplant lymphoproliferative disease (PTLD) is a major cause of morbidity and mortality following both solid organ and haematopoietic stem cell transplantation. PTLD has a broad range of manifestations with extranodal involvement more common in the abdomen than nodal involvement. Fludeoxyglucose positron emission tomography/CT (FDG-PET/CT) is sensitive and specific to detect PTLD and can upstage or detect occult PTLD compared with conventional CT imaging. As functional imaging, FDG-PET/CT also has a role in monitoring treatment response. In this pictorial essay, we will discuss the role of FDG-PET/CT in the diagnosis and staging of abdominal PTLD and describe the advantages of functional imaging in assessing response to therapy.

INTRODUCTION

Post-transplant lymphoproliferative disease (PTLD) comprises a wide spectrum of lymphoproliferative conditions following solid organ or haematopoietic stem cell transplantation (HSCT) and may occur in up to 10% of adults post transplant. PTLD represents a major cause of morbidity and mortality, with up to 40–70% mortality rates reported in patients with solid organ transplants and 90% in patients post HSCT.¹ Risk factors for the development of PTLD include high level of immunosuppression, Epstein–Barr virus infection, human leukocyte antigen mismatching and T-cell depletion. The median onset of disease is approximately 6 months in solid organ transplant patients and 2–3 months in HSCT recipients, although it has been reported as soon as 1 week and as late as 10 years after transplant.¹ The World Health Organization classification of PTLD includes three main categories: (1) hyperplastic, early lesions; (2) polymorphic; and (3) monomorphic lesions (such as diffuse large B-cell lymphoma/Burkitt lymphoma).² Early lesions and polymorphic PTLD often respond to withdrawal of immunosuppression, but the prognosis of monomorphic and EBV-negative disease is much more variable, and patients with advanced disease at presentation may benefit from antibody-based therapy, often in combination with chemotherapy.¹

CLINICAL PRESENTATION

The clinical presentation of PTLD can be non-specific. However, PTLD should be suspected in patients who

develop lymphadenopathy or other mass lesions, fever, weight loss, transplant dysfunction or other unexplained symptoms.^{1,3} PTLD has a broad range of manifestations with extranodal involvement more common in the abdomen than nodal involvement. In the abdomen, extranodal PTLD is seen as organ involvement, such as hepatic portal masses and bowel wall thickening.³ The anatomic distribution of PTLD is influenced by the allograft itself, preferentially in the anatomic region of the transplanted organ or within the allograft. The abdominal cavity is the body compartment most frequently involved by PTLD, and seen in 50–75% of patients with PTLD following renal, liver or heart transplantation. PTLD localizes preferentially in the anatomic region of the transplanted organ or in the allograft itself.⁴

ROLE OF FDG-PET IN THE DIFFERENTIAL DIAGNOSIS AND STAGING OF PTLD

Medical imaging has a central role in the diagnosis, staging and treatment monitoring of PTLD.^{3–7} PET has emerged as an important diagnostic tool in the management of lymphoma with its superior sensitivity to anatomical imaging, particularly for extranodal disease.⁷ Upstaging occurs more frequently than downstaging and may alter patient management. A recent consensus document from the International Conference on Malignant Lymphomas Imaging Working Group in Lugano, Switzerland, has defined the indications for PET for staging of FDG-avid lymphomas and for patient follow-up.⁸

Figure 1. A 47-year-old female, 7 years post renal and pancreas transplant presented with flu-like symptoms. Abdominal ultrasound (not shown) demonstrated multiple liver masses. Liver MR was subsequently performed. (a) Liver MR, performed without intravenous contrast owing to renal failure, showed a non-cirrhotic liver with multiple focal liver lesions, mildly T_2 hyperintense (left image), with diffusion restriction; high signal intensity on axial high b -value diffusion-weighted imaging (middle image) and low signal intensity on apparent diffusion coefficient map (right image). Given the acute clinical presentation, multifocal abscesses were favoured over malignancy. (b) Axial (top) and coronal (bottom) images from positron emission tomography/CT (PET/CT) (CT, left; fused, middle; PET, right) show multiple fludeoxyglucose (FDG)-avid liver lesions with intense FDG uptake (SUV_{MAX} 16.0). Uptake within lesions is uniform and not target-like, suggestive of tumour rather than abscesses. (c) On the maximum intensity projection PET image, two additional foci of abnormal metabolic activity were also seen in soft-tissue nodules adjacent to the transplant pancreas/duodenal stump (arrows). Liver biopsy confirmed post-transplant lymphoproliferative disease, diffuse-large B-cell lymphoma.

Figure 2. A 67-year-old male, 2 years after cadaveric liver transplant for non-alcoholic steatohepatitis cirrhosis and hepatocellular carcinoma developed liver lesions. Biopsy diagnosed Epstein-Barr virus-positive diffuse large B-cell lymphoma. (a) Axial CT images from study performed after seven cycles of chemotherapy showed a residual liver mass (right image, dotted arrow) measuring 3.5 cm in diameter, compared with 4.4-cm diameter at baseline (left image, arrow), indicating only a modest morphological response to therapy. (b) Axial positron emission tomography/CT (PET/CT) images (CT, left; fused, middle; PET, right) after completion of therapy demonstrate no residual abnormal fludeoxyglucose uptake in the residual mass seen on CT, indicating complete metabolic response. On serial surveillance studies, the lesion continued to regress without further intervention, and the patient remained in clinical remission.

Early detection of PTLD is clinically important as it may be associated with improved patient outcome. Surveillance for PTLD by monthly polymerase chain reaction for circulating

EBV DNA has been suggested, particularly in patients at high risk.¹ When imaging is performed, a high index of suspicion is needed as clinical and imaging features may be non-specific

Figure 3. A 68-year-old male 3 years after liver transplant for non-alcoholic steatohepatitis cirrhosis and hepatocellular carcinoma. (a) Axial CT images show asymmetric nodular gastric thickening (left image, arrow) and mesenteric coalescent nodal enlargement (right image, arrow). Biopsy of the gastric thickening diagnosed post-transplant lymphoproliferative disease (diffuse large B-cell lymphoma). (b) Axial CT images after completion of treatment show resolution of gastric thickening but a persistent small pelvic mass (right image, arrow). (c) Axial positron emission tomography/CT (PET/CT) images (CT, left; fused, middle; PET, right) show no abnormal uptake of fludeoxyglucose (FDG) in the stomach (upper row) and no abnormal FDG uptake in residual pelvic mass (bottom row, arrow), suggesting metabolic complete response.

Figure 4. A 52-year-old male several years after cadaveric liver transplant for primary sclerosing cholangitis developed post-transplant lymphoproliferative disease (diffuse large B-cell lymphoma, Epstein-Barr virus negative), involving the small bowel. (a) Baseline axial CT abdomen shows a large mass involving small bowel adjacent to the distal roux-en-y anastomosis (arrow). (b) Follow-up axial CT abdomen after six cycles of chemotherapy shows improvement in the bowel wall thickening (arrow); however, complete resolution could not be confirmed. (c) Subsequent positron emission tomography/CT (PET/CT) (CT, left; fused, middle; PET, right) show residual mild bowel wall thickening, not metabolically active (arrow), indicating metabolic complete response. The patient remains in remission at 3 years after completion of therapy.

and mimic other disease processes. For instance, in liver transplantation, PTLN may manifest as a solitary lesion or multiple hepatic parenchymal masses, periportal soft tissue,

lymphadenopathy or splenomegaly with ultimately biopsy being required for tissue confirmation.⁹ Patterns of hepatic and biliary PTLN that mimic benign entities include small

Figure 5. A 62-year-old male 4 years after living related donor liver transplant for alpha-1 antitrypsin deficiency-induced cirrhosis developed post-transplant lymphoproliferative disease in the liver, adrenal glands, left kidney, small bowel and mesenteric nodes (diffuse large B-cell lymphoma with germinal centre-related phenotype). (a) Representative axial images from baseline CT show liver masses and left lower pole renal mass (arrow). (b) Follow-up CT (not shown) demonstrated marked improvement, with residual lesions in the liver and kidneys but resolution of other sites of disease. Positron emission tomography/CT (PET/CT) performed to restage showed no abnormal metabolic activity to suggest residual disease. The patient remained in clinical remission with no recurrence on imaging 7 months after PET.

Figure 6. A 58-year-old female with post-transplant lymphoproliferative disease (PTLD) (diffuse large B-cell lymphoma) 7 years after renal transplant. Staging CT abdomen demonstrated small bowel and mesenteric masses. (a) Fludeoxyglucose positron emission tomography/CT (FDG-PET/CT) (coronal fused image, left; PET image, right) performed for a residual mesenteric mass after completion of six cycles of chemotherapy demonstrates complete metabolic response (arrows). (b) PTLD recurred 1 year later with extensive abdominal lymphadenopathy, bowel involvement and a large pelvic mass. Coronal image from restaging CT after salvage chemotherapy shows residual mesenteric mass (dotted arrow) but resolution of lymphadenopathy and bowel lesions. (c) Restaging FDG-PET/CT: coronal image (CT, left; fused, middle, PET, right) shows progressive disease with metabolically active soft tissue surrounding the previously inactive residual mesenteric mass (arrows), extensive metabolically active disease in nodal and extranodal sites including transplant perirenal tissue (marked "R"), pelvic masses and bone marrow deposits (dotted arrow). There was also new metabolically active soft tissue surrounding the previously inactive mesenteric mass, indicating recurrence at that site as well.

discrete or geographic areas of decreased attenuation and diffuse gallbladder wall thickening.³

PET/CT has utility in differential diagnosis of PTLD and can contribute to more accurate evaluation of disease extent and stage (Figure 1). The level of FDG uptake correlates with the grade of tumours, with higher FDG uptake seen in higher grade lesions.⁷ A recently published single-institution series including 150 patients with suspected PTLD has shown that FDG-PET is sensitive (89%) in detecting PTLD.⁵ This study also suggested that PET also has a high specificity (89%) in

differentiating PTLD from benign aetiologies. PET may help direct the most appropriate site for biopsy to confirm the diagnosis.

FDG-PET/CT IN CONFIRMING DISEASE REMISSION OR RECURRENCE

According to the International Conference on Malignant Lymphomas Imaging Workgroup recommendations on imaging in staging and response assessment of all FDG-avid lymphomas, PET/CT is the standard of care for remission assessment (Figure 2). A negative PET at completion of

therapy may obviate the need for percutaneous biopsy to confirm remission, as a negative PET has a high negative-predictive value for residual viable tumour (Figure 3). This is especially important for lesions that are not easily amenable to biopsy (Figure 4). Although the role of PET in routine surveillance in patients with complete morphological response is not established, on occasion, PET/CT performed for the assessment of residual mass may detect residual disease at remote or occult sites that would be difficult or impossible to detect with CT alone. Serial PET/CT has been reported as useful in follow-up after paediatric renal transplantation to diagnose relapsed PTLT.¹⁰ PET/CT may be particularly useful in assessing patients with multiple residual abnormalities, as multiple biopsies are impractical (Figure 5). Caution should be taken when assessing residual metabolic activity at sites which may be prone to

false-positive results, such as inflammation or physiological metabolic activity, as is often seen in the gastrointestinal tract. Histological confirmation is recommended when there is suspicion of residual or recurrent disease prior to salvage therapy (Figure 6).⁸

CONCLUSION

Although data in the literature are relatively scarce and little prospective data exist, it appears that FDG-PET/CT may have a role in the work-up, staging and therapy response assessment of patients with PTLT. Given the prevalence of transplants and high mortality associated with this disease, early diagnosis and more accurate response assessment may prove clinically beneficial. Nonetheless, the true impact of PET on the management and outcome of patients with PTLT should be determined prospectively in future trials.

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