Pictorial Essay

Fluoro-deoxy-glucose positron emission tomography/computed tomography in lymphoma: A pictorial essay

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ABSTRACT

F-18 fluoro-deoxy-glucose (FDG) positron emission tomography/computed tomography (PET/CT) has emerged as a powerful imaging modality in the field of oncology. F-18 FDG PET/CT is now an established tool in the management of lymphoma. This has been shown to be useful in staging, detection of bone marrow involvement (BMI), early response assessment and end of therapy response assessment in lymphoma. Interpretation of F-18 FDG PET/CT in lymphoma is carried out by various qualitative response assessment criteria. London criteria are used for interpretation of interim PET/CT and International Harmonization Project (IHP) criteria are used to interpret PET/CT done after the end of chemotherapy. Quantitative analysis is also found to be useful in assessment of response early after two cycles of chemotherapy in patients with diffuse large B cell lymphoma (DLBCL). This pictorial essay provides few images describing the FDG avidity of lymphoma, patterns of bone marrow uptake and their relevance in predicting BMI, role of staging PET/CT, quantitative analysis in response assessment, example images of response according to London criteria and IHP criteria. Few pitfalls in imaging of lymphoma with PET/CT are also discussed in the images legend.

Keywords: F-18 fluoro-deoxy-glucose, lymphoma, positron emission tomography/computed tomography

INTRODUCTION

F-18 fluoro-deoxy-glucose (FDG) positron emission tomography/computed tomography (PET/CT) is now an established tool in the management of patients with lymphoma, especially for staging, detection of bone marrow involvement (BMI), early response assessment and end of therapy response assessment. We, in this pictorial depict few images highlighting the role of FDG PET in the management of lymphoma with respect to patterns of FDG avidity and response evaluation according to different criteria. Few pitfalls in imaging of lymphoma with PET/CT also have been discussed.

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MATERIALS AND METHODS

The positron emission tomography/computed tomography (PET/CT) scans were acquired 60 min after intravenous injection of 370-444 MBq of fluoro-deoxy-glucose (FDG) via an already secured peripheral venous catheter. Images from the base of the skull to the mid-thigh were acquired in three dimensional modes at 2 min per bed position in the supine position with their arms raised over the head, using a PET/CT scanner (Discovery STE 16, GE Healthcare, Milwaukee, USA) having16 slice light speed CT component. It was ensured that all the patients had fasted for at least 6 h before the radiotracer injection. Fasting blood glucose level of less than 150 mg/dl was a standard requirement for imaging in all patients. Non contrast-enhanced CT images (120 kVp) were acquired in helical mode with slice thickness of 5 mm. The acquired data was reconstructed using standard ordered subset expectation maximization algorithm. The CT, PET and co-registered PET/CT images were reviewed in transaxial, coronal and sagittal planes along with maximum-intensity projection whole-body coronal images. All images [Figures 1-15] were reviewed jointly by two nuclear medicine physicians. These images highlight the role of

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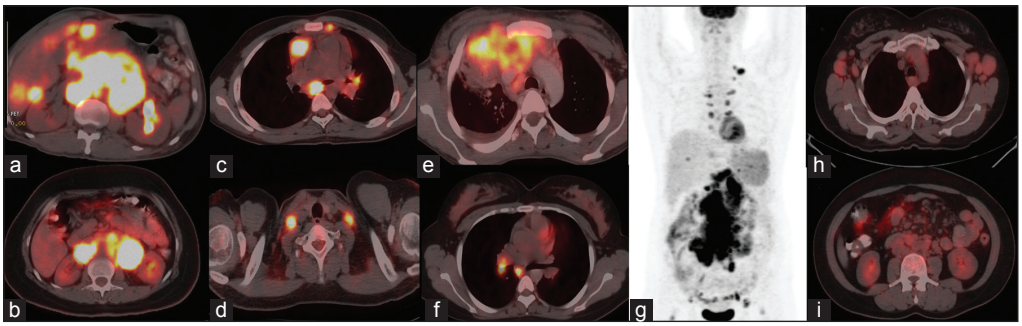

Figure 1: Transaxial F-18 fluoro-deoxy-glucose (FDG) positron emission tomography/computed tomography (PET/CT) images of two patients (a and b) with diffuse large B cell lymphoma (DLBCL) showing intense F-18 FDG uptake with maximum standardized uptake value (SUV_{max}) of 20.3 and 21.6 respectively. Transaxial F-18 FDG PET/CT images of a patient with Hodgkins lymphoma (c and d) showing intensely F-18 FDG avid lymph nodes in the mediastinum and neck (SUV_{max} = 14.2). The images discusses about F-18 FDG avidity of lymphomas. In general high grade lymphomas are known to be F-18 FDG avid with higher SUV_{max} and low grade lymphomas are known to be less F-18 FDG avid with lesser SUV_{max} values.[1] According to International Harmonization Project recommendations HL, DLBCL, Follicular lymphoma, Mantle cell lymphoma are considered to be routinely F-18 FDG avid.[2] anaplastic large cell lymphoma (ALCL) is also considered as 100% F-18 FDG avid according to recent literature[3] and images (e and f) are consistent with this, showing intense F-18 FDG uptake in lymph nodal mass in the mediastinum and mediastinal lymph nodes in two patients with ALCL. Follicular lymphoma, which is a low grade lymphoma is also known to be routinely F-18 FDG avid[4] and the maximum intensity projection image of a patient with Follicular lymphoma (g) shows intensely F-18 FDG avid lymph nodal mass in the abdomen (SUV_{max} = 21.2). on the contrary low grade lymphomas like small lymphocytic lymphoma (SLL) show very low F-18 FDG avidity as can be noted in transaxial images of the thorax and abdomen (h and i) of a patient with SLL involving b/l axillary and multiple retroperitoneal lymph nodes (SUV_{max} = 3.4). Due to variable FDG uptake in low-grade lymphomas, staging PET/CT is required to demonstrate the FDG uptake for response assessment at a later stage

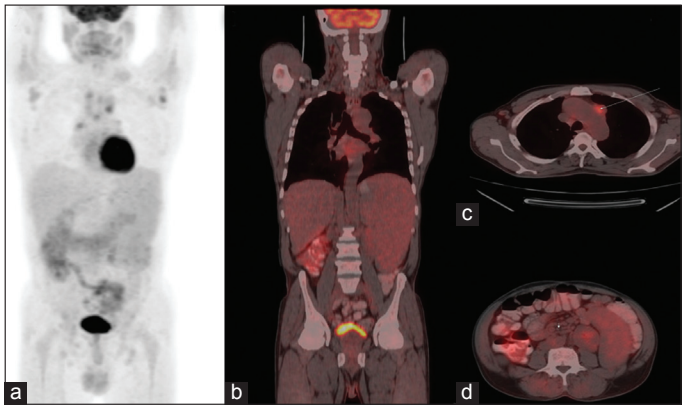

Figure 2: Maximum intensity projection image (a) shows faint F-18 fluoro-deoxy-glucose (FDG) uptake in mediastinal, b/l axillary lymph nodes and mild diffuse uptake in enlarged spleen Coronal images showing mild F-18 FDG uptake in enlarged spleen. Transaxial images showing mild F-18 FDG uptake in mediastinal lymph node (hottest lesion with maximum standardized uptake value [SUV_{max}-4.3]) and retroperitoneal lymph nodes (SUV_{max}-2.3). This image shows a rare case of diffuse large B cell lymphoma (DLBCL) with very low F-18 FDG uptake. Though DLBCL is considered routinely F-18 FDG avid about 3% of the cases with DLBCL can be lowly F-18 FDG avid.[3] This image also highlights the need of baseline scan to demonstrate F-18 FDG avidity of the involved lymph nodes for better assessment of response after chemotherapy

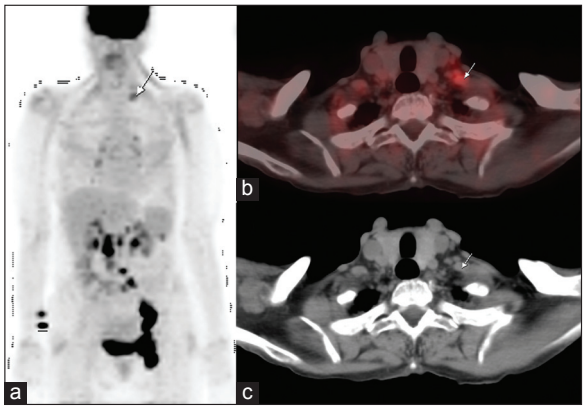

Figure 3: Maximum intensity projection image of a patient with diffuse large B cell lymphoma showing intensely F-18 fluoro-deoxy-glucose (FDG) avid disease below the diaphragm. F-18 FDG positron emission tomography/computed tomography (PET/CT) in addition identified metabolically active disease in subcentimetric left supraclavicular lymph nodes (which could have been missed by CT criteria of 1 cm for involved lymph nodes) and upstages the disease to stage III from stage II. This image highlights the incremental value of F-18 FDG PET/CT in staging patients with lymphoma over CT alone. PET/CT has been shown to be very useful in staging of lymphoma in comparison with anatomic imaging and frequently upstages the disease.[5] Upstaging of disease can have therapeutic and prognostic implications as according to international prognostic index[6] stage III/IV disease is associated with poor prognosis when compared to stage I and II disease

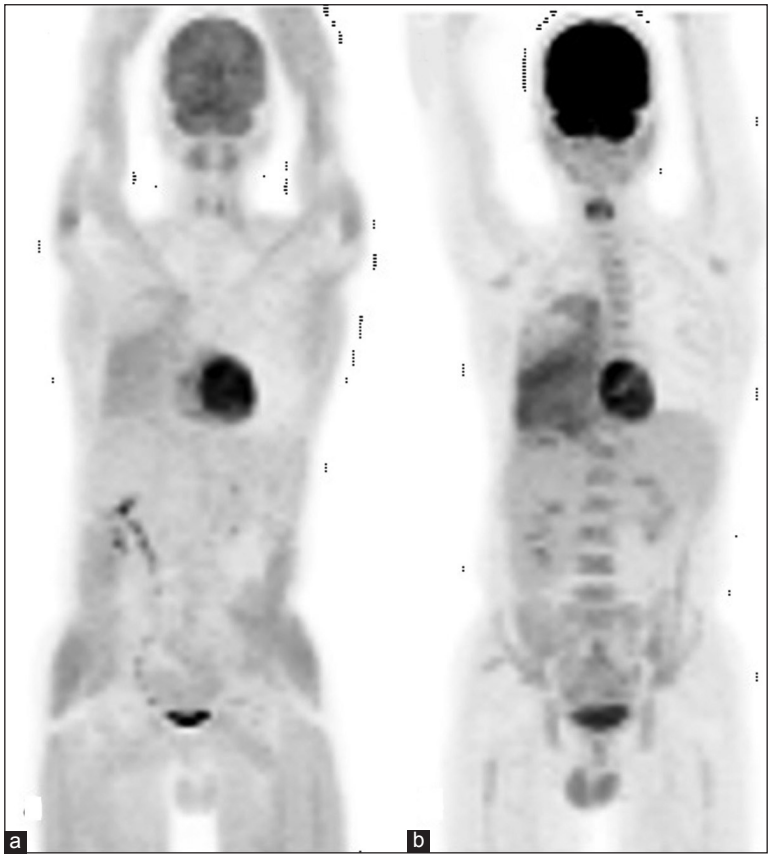

Figure 4: Positron emission tomography (PET) scan of a patient with diffuse large B cell lymphoma involving right lung done 3 h after intake of food. Maximum intensity projection image (a) diffusely increased uptake in muscles and faint uptake noted in the right lung (maximum standardized uptake value [SUV_{max} = 3.1]). However repeat study after adequate preparation and 6 h of fasting shows (b) increased F-18 fluoro-deoxy-glucose (FDG) uptake in the right lung lesion (SUV_{max} = 12). Learning point in this image is that inadequate fasting increases insulin mediated muscle uptake with a decrease in tumoral uptake of F-18 FDG that might lead to false negative interpretations and inadequate baseline study to evaluate response at a later date. This image highlights the importance of adequate fasting prior to F-18 FDG PET/computed tomography scan

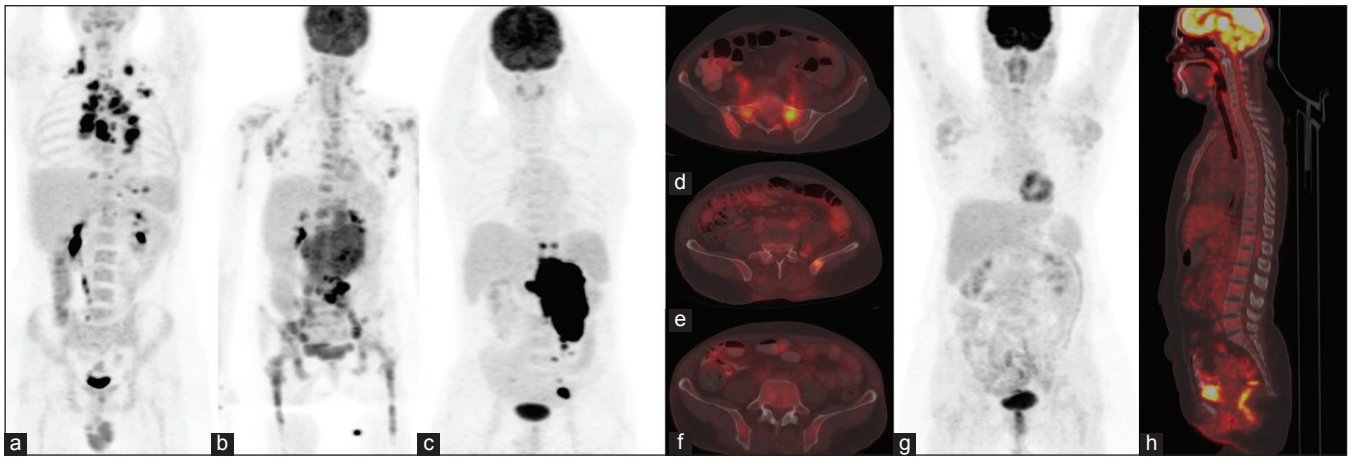

Figure 5: Maximum intensity projection (MIP) image (a) of a patient with Hodgkin's lymphoma (HL) shows homogenously diffuse fluoro-deoxy-glucose (FDG) uptake in the marrow of the entire skeleton. This image represents the patterns of bone marrow F-18 FDG uptake and their relevance in predicting bone marrow involvement (BMI). Diffuse FDG uptake in a patient with HL occurs due to cytokine induced reactive bone marrow uptake and does not usually reflect BMI:[7] accordingly bilateral iliac crest biopsies were negative in this patient. On the contrary focal and heterogeneously diffuse F-18 FDG uptake in marrow is highly predictive of BMI.[8] MIP image of a patient with diffuse large B cell lymphoma (DLBCL) (b) shows heterogenous F-18 FDG uptake in the entire marrow and also increased F-18 FDG uptake in right iliac crest, (d) the iliac crest biopsy was positive for BMI in this patient. MIP image (c) of another patient with DLBCL shows focal FDG uptake in left iliac bone. However iliac crest biopsy was negative for BMI as FDG uptake (e) was a bit distant from usual iliac crest biopsy site and was not sampled. However, the same focal FDG uptake (f) resolved after four cycles of chemotherapy confirming BMI. A positron emission tomography (PET) directed biopsy at the time of staging would have probably revealed BMI in this case. On the contrary FDG PET/CT has low sensitivity in detecting BMI in patients with low grade lymphoma as illustrated in these images (g and h). MIP image (g) and sagittal section images (h) of patient with small lymphocytic lymphoma does not show any significant FDG uptake in entire skeleton. However iliac crest biopsy revealed BMI in this patient

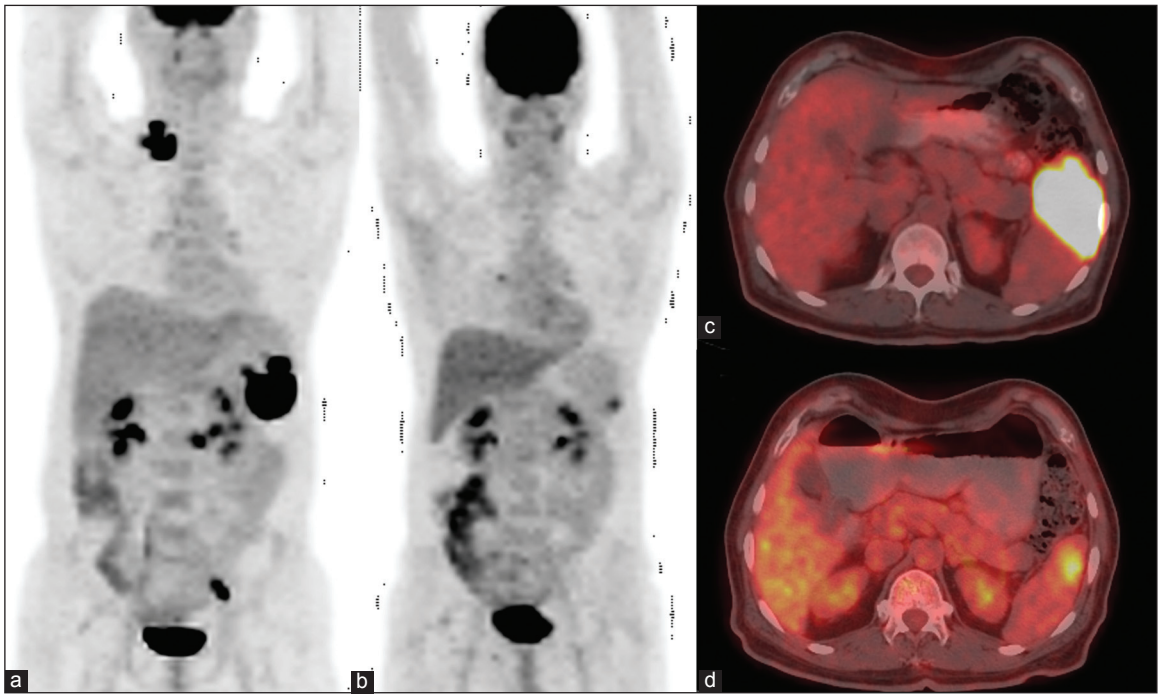

Figure 6: Maximum intensity projection images of pre and post therapy scans (a and b) of a patient with diffuse large B cell lymphoma (DLBCL) showing the focus of persistent fluoro-deoxy-glucose (FDG) uptake in spleen suggestive of positive positron emission tomography/computed tomography (PET/CT) indicating poor prognosis. However maximum standardized uptake value (SUV_{max}) decreased from 24.0 to 3.1 with a decrease of 82% (higher than the threshold of 66%) suggesting good response to treatment. the patient achieved a complete response (CR) after standard six cycle chemotherapy and was disease free on follow-up of 2 years. This image highlights the role of quantitative analysis in interpreting interim FDG PET/CT studies. It is well known that positive interim FDG PET/CT is highly predictive of inadequate response to chemotherapy with a higher chance for relapse and non-achievement of CR. However, visual analysis is inadequate to predict prognosis if PET/CT is done after two cycles of chemotherapy in patients with DLBCL. Less than 66% reduction in SUV_{max} from staging to interim PET/CT after two cycles has been suggested as a better poor prognostic indicator than positive scan by visual analysis[9]

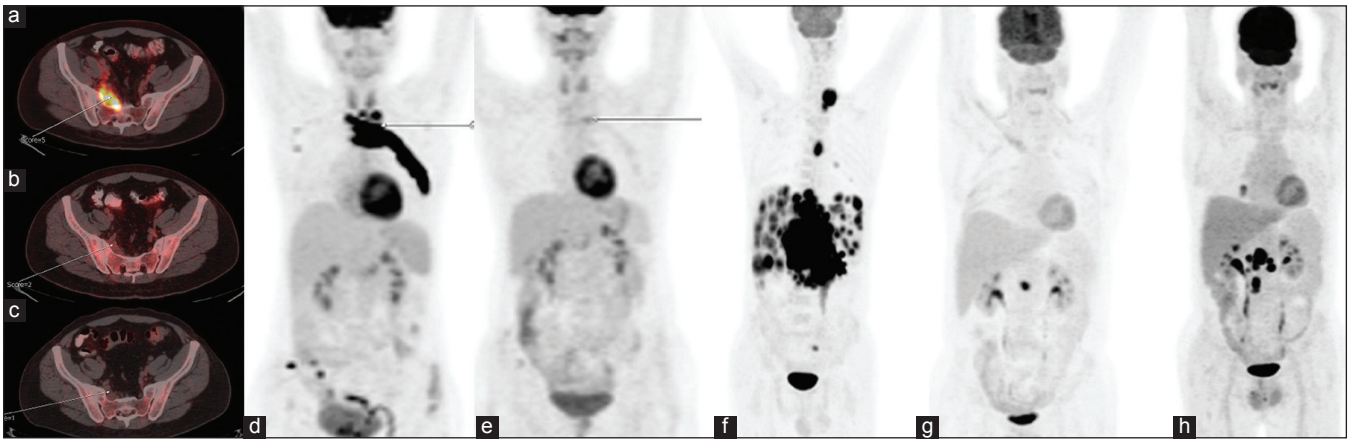

Figure 7: Transaxial image, (a) of a patient with diffuse large B cell lymphoma (DLBCL) shows intensely fluoro-deoxy-glucose (FDG) avid (maximum standardized uptake value [SUV_{max} = 16.2]) presacral lymph nodal mass, which is significantly higher than liver uptake (London criteria score of 5), (b) Transaxial images of FDG positron emission tomography/computed tomography (PET/CT) of the same patient after two cycles of chemotherapy shows mild FDG uptake in the lymph nodal mass (SUV_{max} of 2.1), which is slightly higher than mediastinal uptake and less than liver (London criteria score of 2). Transaxial PET/CT images (c) of the same patient after four cycles of chemotherapy show FDG uptake equal to background tissues (London criteria score of 1). Maximum intensity projection (MIP) image (d) of a patient with DLBCL involving D4, D5 vertebrae and left 4th rib in staging PET/CT. MIP image, (e) of the same patient showing mild FDG uptake above background but equal to liver (London criteria score of 3) in the previously involved site. MIP image of staging PET/CT (f) of a patient with DLBCL showing intensely F-18 FDG avid disease in liver, spleen and abdominal, mediastinal and cervical lymph nodes. MIP image (g) of the same patient after four cycles of chemotherapy shows moderate FDG avidity above the liver in a retroperitoneal lymph node (London criteria score of 4) and the patient presented with progressive disease (H) after 3 months of chemotherapy. London criteria have been proposed for interpretation of interim FDG PET/CT to achieve inter-center reproducibilities.[10] According to London criteria FDG uptake of tumor is scored according to relative uptake to surrounding background, mediastinum and liver with scores ranging from 1 to 5. Early studies indicate that scores of 4 and 5 in interim PET/CT studies are associated with progression and non-achievement of complete response in patients with high-grade non-Hodgkin's Lymphoma and Hodgkin's Lymphoma respectively.[11,12] This image illustrates various scores for interpretation of interim F-18 FDG PET/CT according to London criteria

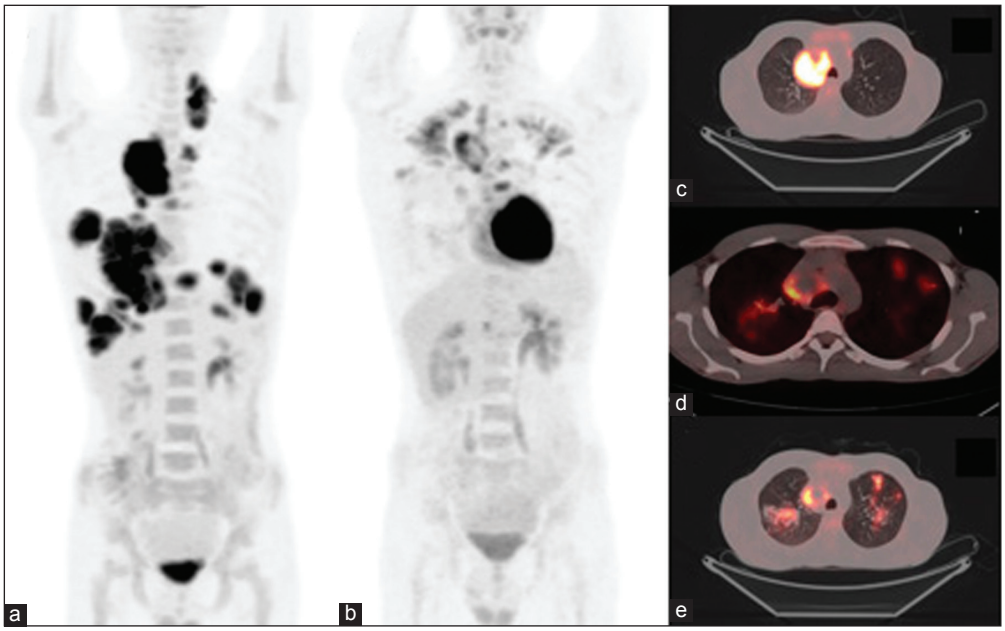

Figure 8: A 22-year-old male patient with newly diagnosed Hodgkin's lymphoma diagnosed from left supraclavicular lymph nodal biopsy underwent staging positron emission tomography/computed tomography (PET/CT) study. PET/CT scan revealed intensely fluoro-deoxy-glucose (FDG) avid multiple left supra and infra clavicular and right paratracheal mass, left lower paratracheal, subcarinal lymphnodes along with lymphomatous involvement of lower lobe of the right lung and also few FDG avid focal lesions in spleen (a) Diffuse homogenous marrow uptake of FDG was seen consistent with cytokine induced bone marrow hyperplasia. Subsequently he underwent bilateral iliac crest bone marrow biopsies that did not reveal marrow involvement. No calcification or necrosis was noted in any of the lymph nodes or spleen was noticed. Patient was not known to have any past history of tuberculosis. After four cycles of adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy, he developed a cough with expectoration and fever with evening rise of temperature for 20 days, which was not revealed with conventional antibiotic therapy. Follow-up PET/CT revealed disappearance of metabolically active disease in left supra and infra clavicular lymph nodes and lower lobe of the right lung. However, intensely FDG avid paratracheal mass showing central necrosis was seen along with few subcarinal lymph nodes and a focus in spleen (b). New infiltrates with mild FDG uptake were noted in bilateral lung fields suggestive of infectious pathology. On the basis of patient's symptomatology and necrotic mediastinal lymph nodes along with bilateral lung infiltrates (c-e) tubercular pathology was suspected. Subsequently patient underwent guided biopsy of the necrotic mediastinal lymph node, which revealed caseation necrosis and granuloma formation and cultures revealed Mycobacterium Tuberculosis. Subsequently patient was started on anti-tuberculosis treatment with relief of symptoms and clinical improvement. Learning points in this case are that in a tuberculous endemic country like India, TB can always co-exist with lymphoma and should be suspected when the symptomatology along with necrotic mediastinal lymph nodes and lung filtrates are seen on interim PET/CT scan

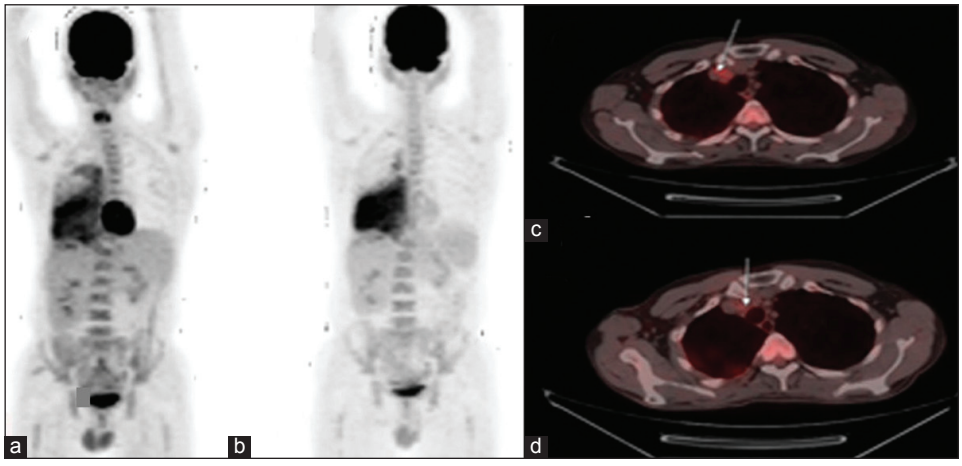

Figure 9: A patient with known diffuse large B cell lymphoma of lung on staging positron emission tomography/computed tomography (PET/CT) (a) was treated with two cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) chemotherapy and subjected to PET/CT for interim response assessment. Maximum intensity projection image (b) shows a reduction of fluoro-deoxy-glucose (FDG) uptake from 12.0 to 7.0 and reduction in extent suggesting partial response (PR). However, new FDG avid lymph nodes are noted in the anterior mediastinum (c) but not seen in staging study (d). According to any interpretation criteria new lesion suggestive of lymphomatous involvement should be considered as progressive disease and the patient should be labeled as a progressor. However in this patient the initial chemotherapy was started after a 2 months delay of staging PET/CT that might have led to increase in volume of disease prior to chemotherapy. So the study was interpreted as PR. Later the patient completed six cycles of chemotherapy and achieved PR at the end of therapy and did not progress over a follow-up period of 2 years. This image highlights the role of careful history taking and clinical correlation with respect to chemotherapy timing to avoid false positive interpretations during reading of interim PET/CT studies

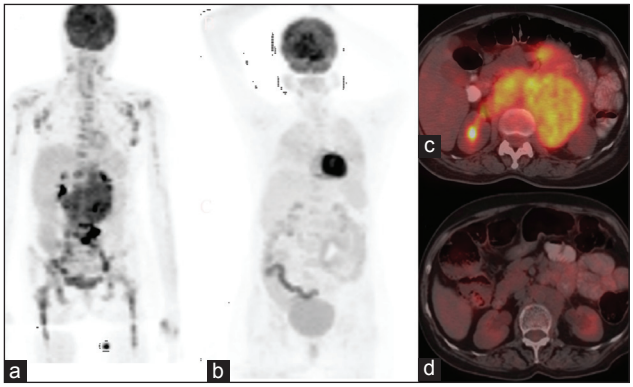

Figure 10: Maximum intensity projection (MIP) image (a) of a patient with diffuse large B cell lymphoma at staging positron emission tomography/computed tomography shows extensive marrow involvement, bilateral axillary lymph nodal and retroperitoneal lymph nodal involvement. MIP image (b) of the same patient after six cycles of chemotherapy showing no abnormal fluoro-deoxy-glucose (FDG) up-take anywhere in the body. Transaxial images of pre-therapy and post therapy scans respectively (c and d) show residual mass of size of 4.4 cm × 2.2 cm in the retro-peritoneum. However no increased FDG uptake is noted in the mass (equal to background) and according to International Harmonization Project criteria persistent mass of any size with negative FDG uptake should be categorized as complete response. Accordingly this patient was classified as complete responder and was disease free on follow-up of 2 years

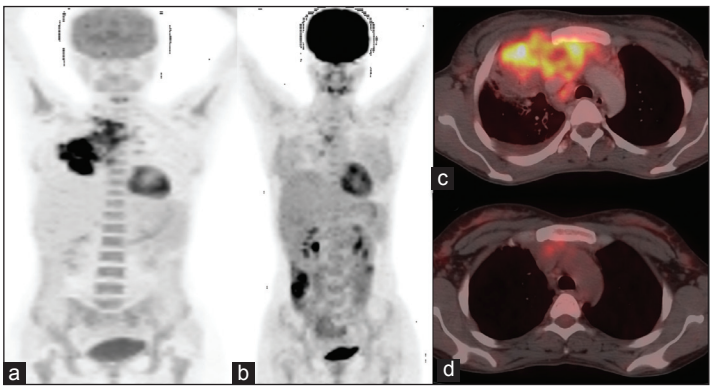

Figure 11: Maximum intensity projection image (a) of a patient with anaplastic large cell lymphoma shows intensely fluoro-deoxy-glucose (FDG) avid disease in the mediastinum in staging positron emission tomography/computed tomography (PET/CT). PET/CT done after eight cycles of chemotherapy show (b) mildly FDG avid disease in mediastinum. Transaxial images of pre and post therapy scans (c and d respectively) show mild FDG uptake in the mass that is above mediastinal blood pool activity. Also the sum product diameter of the mass has decreased by more than 50%. According to International Harmonization Project criteria decrease of 50% or more of lymph nodes involved along with persistent FDG uptake above mediastinal blood pool is classified as a partial response. Accordingly the patient was classified as partial responder and patient presented with progressive disease 4 months after the post therapy scan and was put on salvage chemotherapy

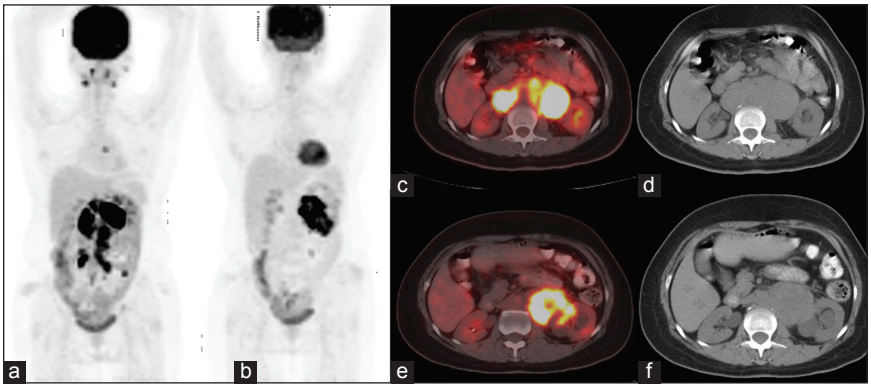

Figure 12: Maximum intensity projection (MIP) image (a) of patient diffuse large B cell lymphoma involving lymph nodes in retroperitoneum. MIP image (b) of the same patient show persistent disease in the abdomen after six cycles of chemotherapy. Also transaxial positron emission tomography/computed tomography (CT) and CT images of pre and post therapy scans respectively (c-f) show persistent fluoro-deoxy-glucose (FDG) uptake in mass which has regressed by less than 50% of sum product diameter (SPD) when compared to baseline scan. Accordingly this patient falls into stable disease category. This image shows stable disease category according to International Harmonization Project (IHP) criteria. According to IHP criteria stable disease is defined as persistently FDG avid disease with less than 50% reduction in SPD of involved lymph nodal masses

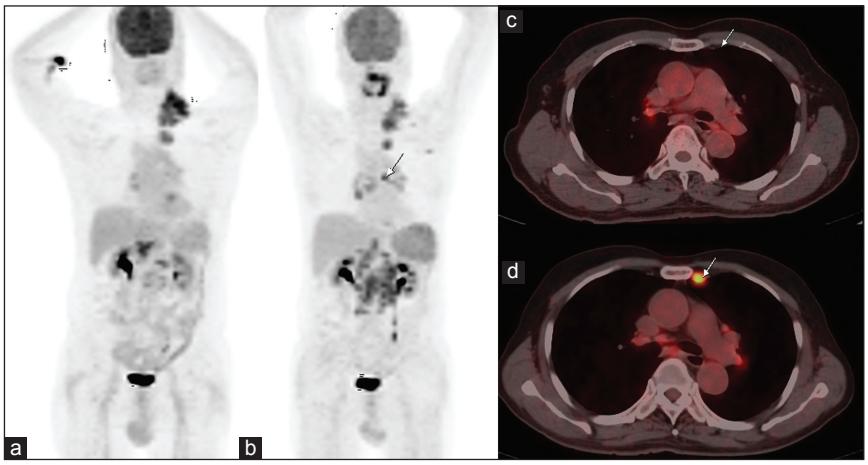

Figure 13: Maximum intensity projection (MIP) image (a) of a patient with diffuse large B cell lymphoma showing intensely fluoro-deoxy-glucose avid disease involving cervical, mediastinal, abdominal lymph nodes and liver. MIP image (b) of the same patient done after six cycles of chemotherapy showing the appearance of new lesions in the abdomen and internal mammary regions (c and d) This image describes progressive disease (PD) according to International Harmonization Project (IHP) criteria. Any new lesion consistent with lymphomatous involvement or increase in sum product diameter of lesions more than 50% is considered as PD. This patient falls into PD category according to IHP criteria

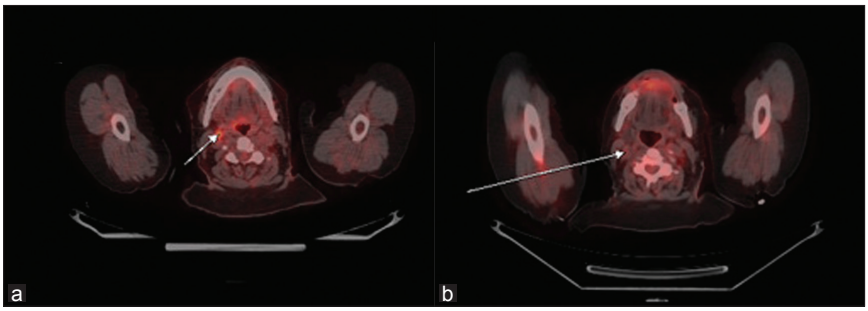

Figure 14: Fluoro-deoxy-glucose positron emission tomography/computed tomography (PET/CT) (a) after 6 months as a part of surveillance in a patient with Hodgkin's lymphoma treated with six cycles of chemotherapy and achieved complete remission showing uptake in the right level II cervical lymph nodes raising suspicion of recurrent disease. Patient underwent FNAC from the involved lymph nodes, which revealed only inflammation and no evidence of tumor. On retrospect, these lymph nodes were not involved in baseline scan (b) This image highlights poor positive predictive value (PPV) of PET/CT in surveillance of patients with lymphoma. According to literature, PPV is only around 21% for PET/CT findings in surveillance of patients with lymphoma.[13] Comparison with previous studies might help in avoiding false positive interpretations. Also false positive interpretations are more likely to occur when the new uptake occurs in supra-diaphragmatic locations than in infra-diaphragmatic locations.[14]

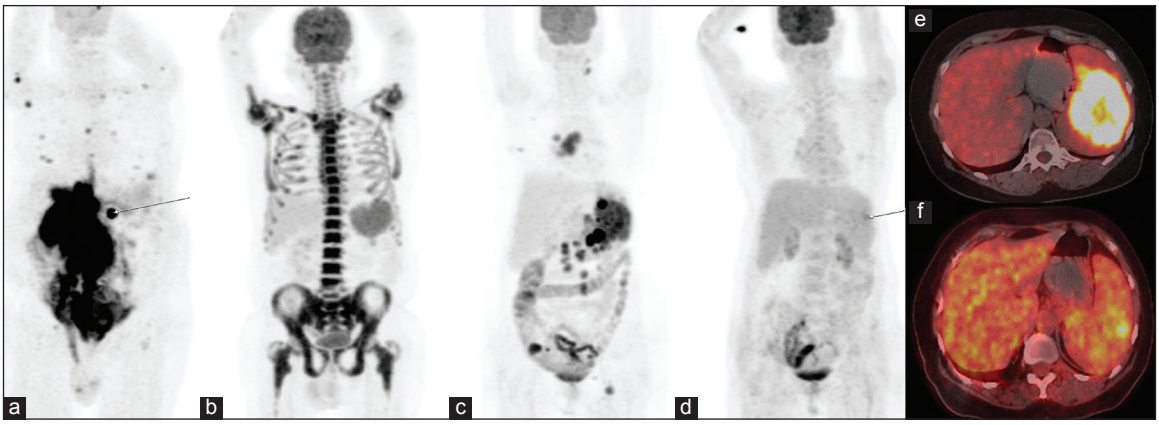

Figure 15: Maximum intensity projection (MIP) image (a) of staging positron emission tomography/computed tomography (PET/CT) of a patient with diffuse large B cell lymphoma (DLBCL) shows abdominal lymph nodal mass and few other lymph nodes in thorax. However there is no splenic involvement. Interim PET/CT (b) done after two cycles after chemotherapy shows intense fluoro-deoxy-glucose (FDG) uptake in entire marrow and spleen along with residual disease in left adrenal gland. PET/CT was done after 2 days after granulocyte colony-stimulating factor (G-CSF) administration and the uptake is noted diffusely in spleen and bone marrow suggestive of reactive bone marrow uptake post G-CSF administration, moreover there was no splenic involvement in staging PET/CT. MIP image, (c) of staging PET/CT of another patient with DLBCL showing heterogeneous FDG uptake in spleen suggesting involvement along with abdominal and thoracic lymph nodal disease. MIP image, (d) of PET/CT scan done after two cycles of chemotherapy show a focal FDG uptake in spleen. Though G-CSF was administered in this patient too, it was administered 11 days prior to interim PET/CT and also the residual uptake was focal and related to previously involved site suggesting true positive residual disease in spleen. This image highlights the false positive uptake in spleen and bone marrow following G-CSF administration in patients with lymphoma. Correlation with duration since G-CSF administration, knowledge about previous involved sites and pattern of uptake aids in accurate differentiation of false positive uptake from disease involvement

Table 1: Indications for FDG PET/CT in patients with lymphoma

Indication	Role of FDG PET/CT
Diagnosis of lymphoma	Not indicated
Staging	Definite role in Hodgkin's' lymphoma, DLBCL and AIDS related B cell lymphoma Useful in selected cases to rule out systemic involvement in localized follicular lymphoma, mantle cell lymphoma, nodal and splenic marginal zone lymphoma, peripheral T-cell lymphoma, mucosa associated lymphoid tumors
Prognostication based on semi-quantitative parameters in initial staging scan	Early studies show that metabolic tumor volume and total lesion glycolysis can be useful prognostic markers in patients with DLBCL
Detection of bone marrow involvement when compared to iliac crest biopsy	Definite complementary role in HL and DLBCL, while its role is limited in patients with low-grade lymphomas
Interim response assessment	May be indicated in patients with HL and DLBCL. However, more studies are required to establish the role conclusively
End of therapy response assessment	Indicated in all FDG avid lymphomas especially in patients with a residual mass on anatomical imaging
Prognostication prior to autologous stem cell transplantation	Potential role, which needs to be elucidated more with further studies
Surveillance	Limited role

FDG: F-18 fluoro-deoxy-glucose, PET: Positron emission tomography, CT: Computed tomography, DLBCL: Diffuse large B cell lymphoma, HL: Hodgkin lymphoma, AIDS: Acquired immunodeficiency syndrome

PET/CT in staging, interim response, response evaluation and interpretation criteria. Various indications of FDG PET/CT are depicted in Table 1.

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