

## REVIEW

# Extranodal manifestations of lymphoma on [<sup>18</sup>F]FDG-PET/CT: a pictorial essay

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### Abstract

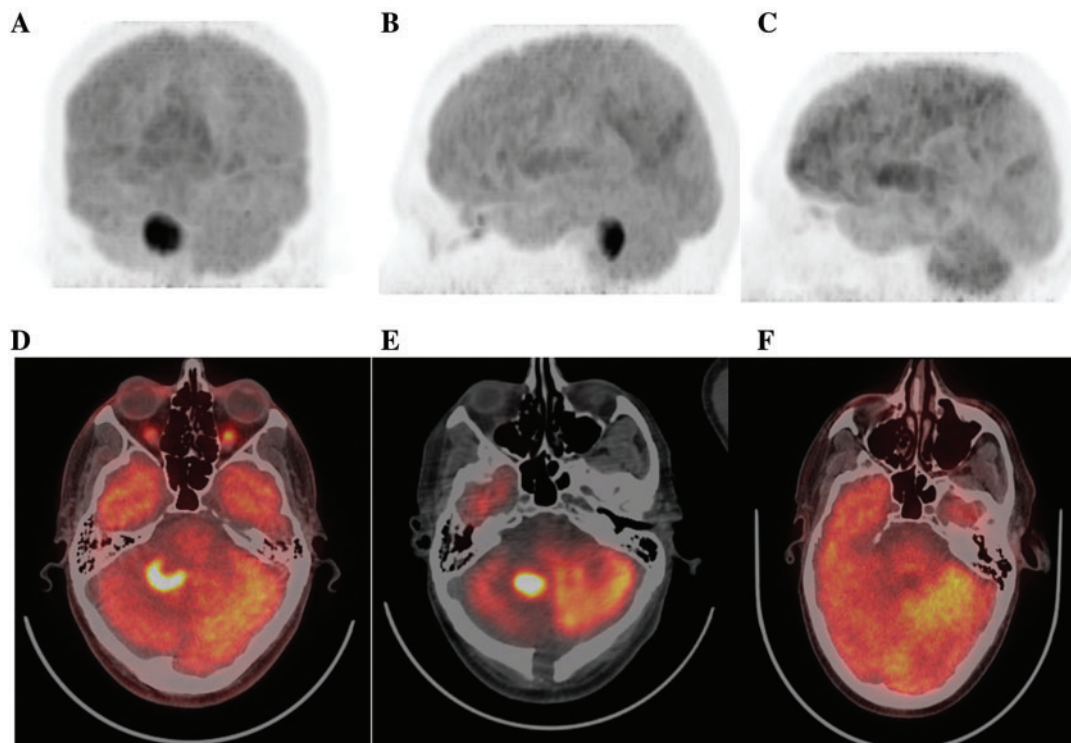
Lymphoma is the seventh most common type of malignancy in both sexes. It is a neoplastic proliferation of lymphoid cells at various stages of differentiation and affects lymph nodes with infiltration into the bone marrow, spleen and thymus. However, extra nodal involvement is frequently seen in many cases. With the development of dedicated positron emission tomography (PET) scanners with fused computed tomographic (CT) systems in the same gantry, [<sup>18</sup>F]fluorodeoxyglucose (FDG)-PET/CT has become a major tool in the evaluation of lymphomas and it is inimitable in certain situations such as assessment of response to therapy. Extranodal lymphoma can present with diverse manifestations and sometimes mimics other organ-related pathologies. Knowledge of the protean manifestations of extranodal lymphoma is required to accurately detect the disease and differentiate it from the various physiologic and benign causes of FDG uptake in various organs. We present a case series of extranodal involvement of histologically proven cases of lymphomas detected on FDG-PET/CT at our institute to demonstrate the challenges in interpretation of extranodal lymphoma.

**Keywords:** *Lymphoma; extranodal, [<sup>18</sup>F]FDG; PET/CT.*

### Introduction

Lymphoma is a neoplastic proliferation of lymphoid cells at various stages of differentiation and affects lymph nodes, with infiltration into the bone marrow, spleen and thymus, which form the primary lymphatic organs. Lymphoma is the seventh most common malignancy in both sexes together<sup>[1]</sup>. Extranodal involvement can be seen with lymphoma in approximately 25–40% of cases and almost any organ can be involved<sup>[2,3]</sup>. Extranodal involvement is less common with Hodgkin disease (HD) with direct extension into adjacent organs in 15% and hematogenous spread in 5–10%<sup>[4]</sup>. Extranodal lymphoma, by definition, involves sites other than lymph nodes, spleen, thymus and the pharyngeal lymphatic ring. Involvement of the spleen in HD is considered as nodal disease but in the case of non-Hodgkin lymphoma

(NHL) the spleen is regarded as an extranodal site<sup>[4]</sup>. Distinct radiologic features are seen when such extranodal involvement is noted. Differentiation between disseminated lymph nodal disease involving an extranodal site and primary extranodal disease is challenging. Primary extranodal disease usually presents at an early stage; up to 74% in stage II<sup>[3]</sup>. Therefore disease with involvement of an extranodal organ along with draining lymph nodes only or disease in which the predominant site is extranodal are grouped in this category. [<sup>18</sup>F]Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) has a pivotal role in evaluating patients with lymphoma and is commonly used. The utility of PET/CT has been well illustrated in a review by Peas et al.<sup>[5]</sup>. In this article, we present our experience with extranodal manifestations of lymphoma and the challenges in interpreting on PET/CT.



**Figure 1** A 43-year-old man with a history of seizures. PET scan showed a hypermetabolic lesion in the cerebellum (A,D) which after craniotomy (B,E) and biopsy turned out to be primary CNS lymphoma involving the cerebellar region of diffuse large B cell subtype. Chemotherapy with methotrexate showed good response (C,F). PET scan in this case helped rule out demyelination, which was one of the differentials at the presentation, by showing the lesion to be intensely hypermetabolic.

## Central nervous system

Central nervous system (CNS) lymphomas constitute approximately 6.6–15.4% of CNS neoplasms. CNS lymphomas are usually primary lesions of the brain in up to 93% of cases<sup>[6]</sup>. The incidence of CNS lymphoma is higher in immunocompromised individuals. CNS lymphomas are usually of B cell type. On CT scan, the lesions are hyperdense and enhance. However, magnetic resonance imaging (MRI) is considered the imaging modality of choice in evaluation of CNS lymphoma. FDG-PET/CT is now well established in the initial evaluation of lymphomas. However, the presence of physiologic uptake in the cerebral cortex may hinder the evaluation of CNS lymphomas. However, in patients with acquired immune deficiency syndrome (AIDS), FDG-PET/CT may be useful in differentiating between toxoplasmosis and lymphoma, which form the major differentials of an enhancing brain lesion<sup>[7]</sup>. Lymphomas demonstrate intense FDG uptake (Fig. 1) unlike toxoplasmosis.

## Head and neck

### *Orbit*

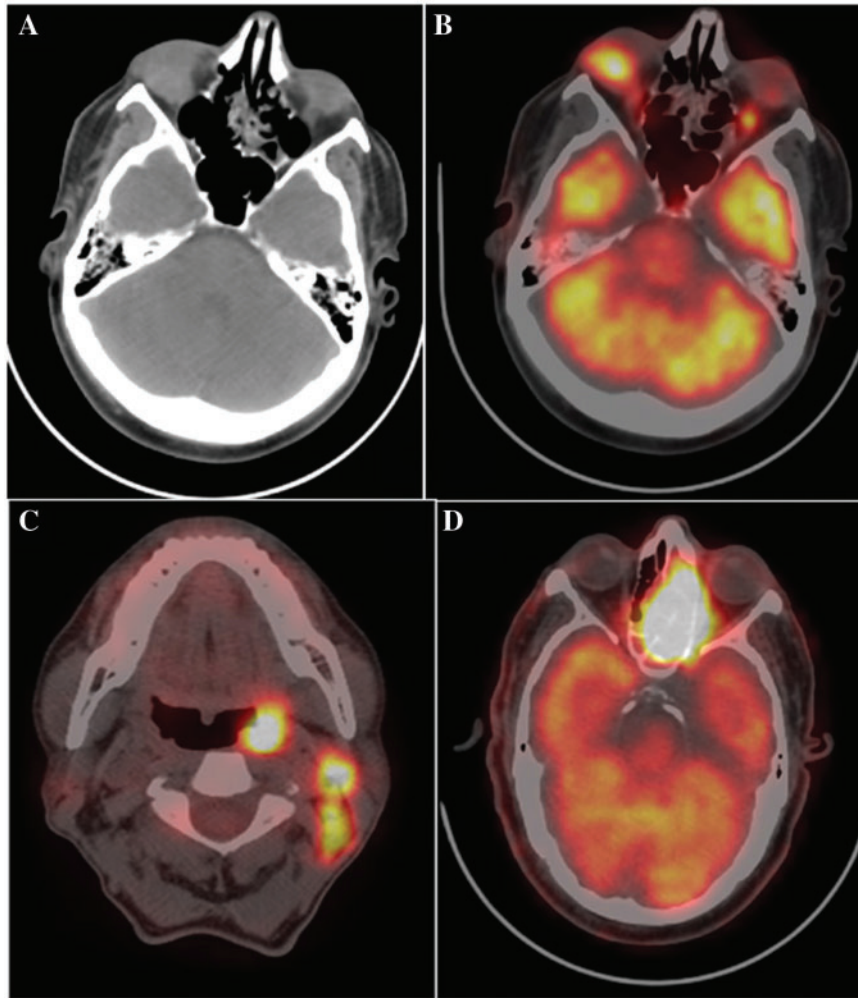
Orbital lymphomas constitute approximately 8% of extranodal disease<sup>[2]</sup> with predominant involvement seen in

cases of NHL but extremely rare in HD. Marginal zone lymphomas constitute the majority of the histological variants; diffuse large B cell is the second most common type (Fig. 2A,B). They are invariably FDG avid ranging from moderate to high uptake<sup>[8,9]</sup>. The conjunctiva and the lacrimal glands are the possible sites of origin. Orbital lymphomas rarely erode the underlying bone.

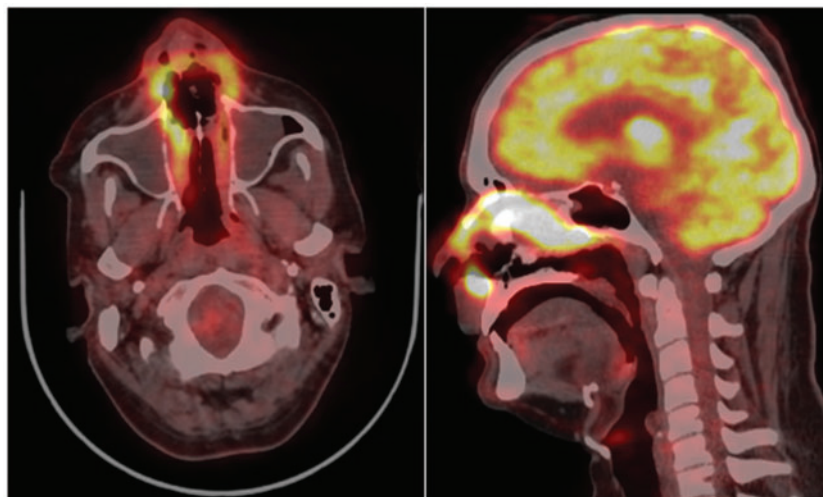
### *Nose and paranasal sinuses*

Involvement of the Waldeyer ring is sometimes classified as extranodal disease and its status is still controversial. However, B cell lymphomas affect the Waldeyer ring commonly and they are usually intensely FDG avid (Fig. 2C,D). Co-existing involvement of the gastrointestinal (GI) tract is also commonly seen when Waldeyer ring involvement is noted. The major hurdle is differentiation between reactive uptake in these lymphatic tissues and lymphomatous involvement. Mild symmetrical uptake usually suggests reactive changes; intense and asymmetrical uptake with enlargement of the organs and corresponding changes in the anatomic imaging favor lymphomatous involvement.

A particular variant of lymphomas involving the nose and paranasal sinuses is the NK/T cell variant (Fig. 3). This is also termed lethal midline granulomatosis. It is a

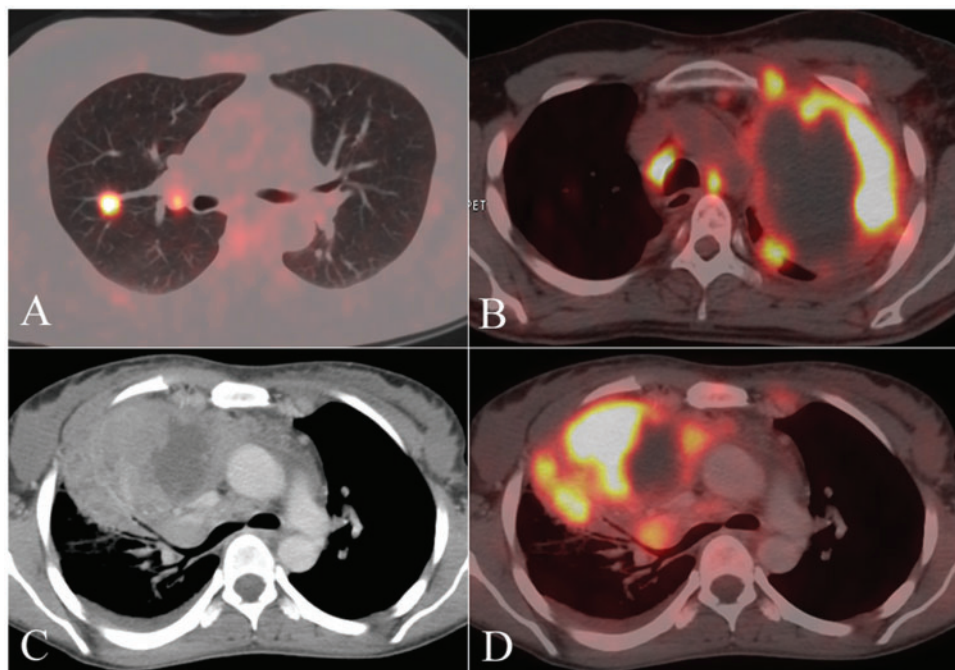


**Figure 2** (A) CT of a 46-year-old man showing a homogeneous soft tissue lesion in the right orbit. (B) Intense FDG uptake is seen in the orbital lesion, which was proven to be diffuse large B cell lymphoma. (C) Tonsillar lymphoma in a 53-year-old man of T cell subtype. (D) Lymphoma of T cell subtype involving the ethmoid sinus on the left side in a 62-year-old male patient. All these lesions were found on PET/CT scans that were referred for staging purposes.



**Figure 3** Intense FDG uptake in a destructive soft tissue lesion involving the nasal septum in a case of NK/T cell lymphoma, also called midline lethal granuloma/ulcerating midline granuloma, in a 38-year-old man, which was found on a staging PET/CT scan. The patient had presented with foul smelling nasal discharge, which led to the diagnosis of lymphoma.





**Figure 4** Various manifestations of lymphoma involving the lungs. (A) Nodular presentation of diffuse large B cell lymphoma in a 39-year-old man. (B) Hodgkin disease presenting as a mass lesion in a 24-year-old man. (C,D) NHL presenting as a mass-like consolidation in the right lung with intense uptake along with pleural effusion on the right side in a 28-year-old woman.

locally aggressive variant of lymphoma involving the nasal cavity, septum, paranasal sinuses and hard palate with erosion of the underlying bone unlike the B cell types. These lesions are also intensely FDG avid.

## Chest

### *Pulmonary lymphoma*

Pulmonary involvement can be discussed with respect to the findings at presentation and that of interim or post-therapy changes. Initial presentation can be either due to primary involvement of the lungs or secondary changes. Secondary changes are more common. These can be due to mediastinal nodes compressing the bronchi and resulting in atelectatic changes or secondary consolidation or collapse secondary to effusion.

Pulmonary lymphoma is more common with HD than with NHL<sup>[10]</sup>. Lung involvement is usually associated with mediastinal nodal disease in HD; NHL can present with lung disease alone. Parenchymal involvement in HD is seen in up to 11.6% of cases<sup>[11]</sup>. The most common histologic variant of primary pulmonary lymphoma is mucosa-associated lymphoid tumour (MALT) arising from the bronchus<sup>[12]</sup>. MALT lymphoma as described above has variable FDG uptake. Morphologically, lymphoma can present with a whole spectrum of changes ranging from nodules, mass lesions with or without cavity, endobronchial mass, ground glass opacities,

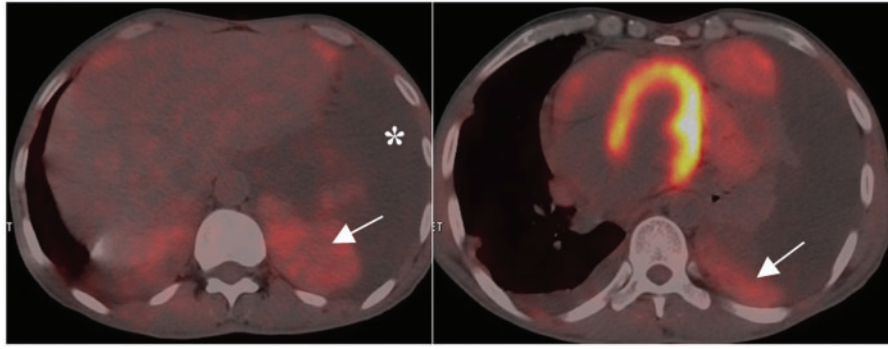
reticular interstitial pattern with involvement of interstitial lymphatics or consolidation with an air bronchogram (Fig. 4).

Interpreting pulmonary changes in a post-therapy setting can be tricky at times. The development of new nodules that are not seen in the baseline study is considered to be lymphoma if the size is greater than 1.5 cm and FDG avidity is more than the mediastinal background. They are considered negative for lymphoma regardless of size or metabolic activity if complete response is seen in the rest of the sites<sup>[13,14]</sup>.

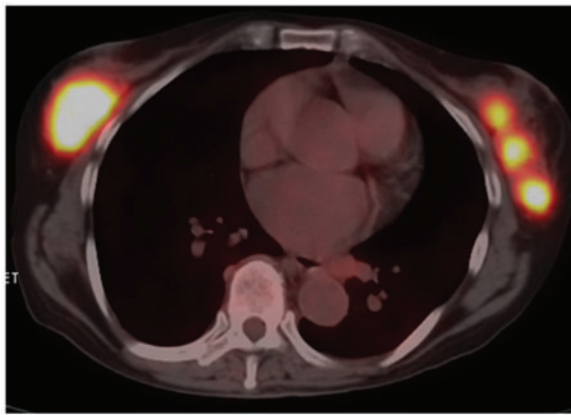
The co-existence of tuberculosis may pose a problem in staging of disease in countries where incidence of tuberculosis is high. Standardized uptake values show a wide range and can sometimes be as high as in malignant lesions<sup>[15]</sup> and imaging alone might not be able to differentiate the cause. However, in a patient who has not been treated with chemotherapy, the presence of calcification within the nodes and sometimes the pattern of uptake can usually give an indication as to the possibility of co-existent infective pathology.

### *Pleural and pericardial lymphoma*

Pleural effusion can be present even without direct involvement of lymphoma and might be as a result of venous obstruction. However, the presence of pleural nodules (Fig. 5) or plaques is highly suggestive of pleural involvement with lymphoma. Pericardial effusion, unlike pleural



**Figure 5** T cell NHL in a 35-year-old man presenting as multiple large mass-like deposits (arrows) along the pleura associated with large pleural effusion (\*) on the left side.



**Figure 6** A 68-year-old woman with bilateral breast lumps, which on PET/CT showed intense FDG avidity. The lesions were histologically proven to be diffuse large B cell lymphoma.

effusion, is presumed to represent lymphomatous invasion<sup>[16]</sup>.

### Breast

Breast lymphomas constitute 0.1–0.5% of all breast neoplasms<sup>[17]</sup>. Involvement is by mostly NHL, we did not come across any reports of HD involving the breast. Lymphomas are difficult to identify on both mammography and CT especially in a patient with dense breasts. Intense FDG avidity in the breast tissue in a patient with lymphoma should raise suspicion although FDG uptake alone cannot be used to differentiate other types of breast tumors (Fig. 6).

## Abdominopelvic lymphoma

### Stomach

The stomach is the most common site of GI lymphoma. Primary NHL is more common than HD in the stomach

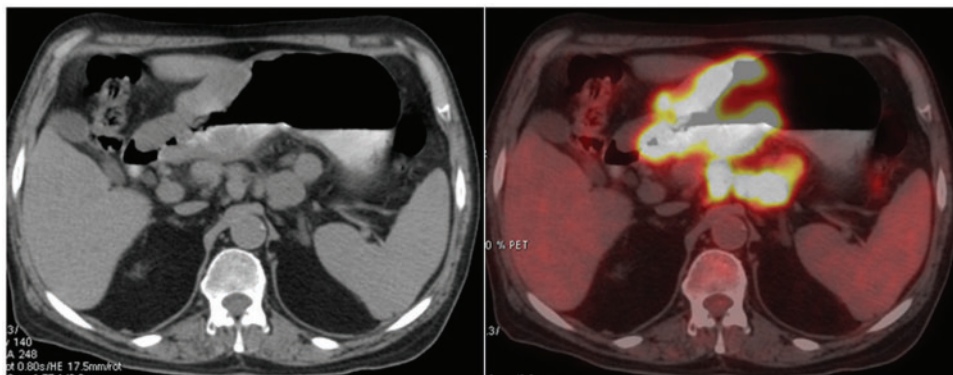
and MALT lymphoma is the most common variety. HD represents approximately 9% of all gastric neoplasms<sup>[18]</sup>. It is associated with *Helicobacter pylori* infection and is invariably FDG avid. Physiologic uptake and gastritis should be differentiated from lymphomatous involvement. Although gastric lymphoma has no site predilection, FDG uptake is usually more than that of the adjacent liver (Fig. 7).

### Small intestine

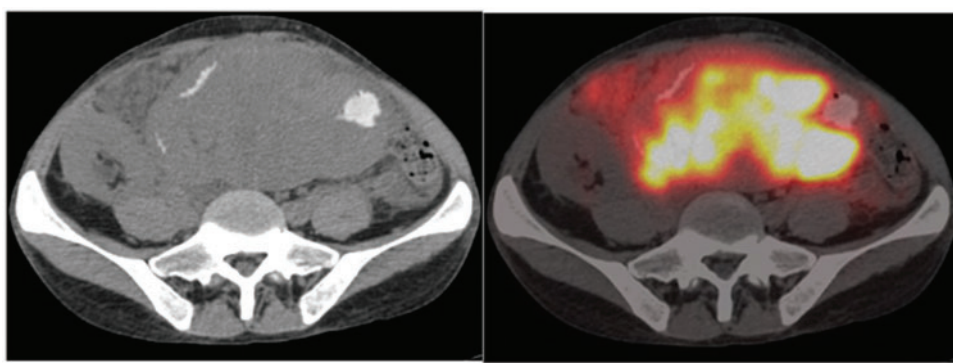
The small intestine is the second most common site of GI lymphoma. A heterogeneous group of lymphomas affect the small bowel including MALT, Mantle cell lymphoma, Burkitt lymphoma, enteropathy-associated lymphoma and B cell variants.

Mantle cell lymphoma presents as multiple polypoid<sup>[19]</sup> in the elderly commonly involving the terminal ileum and the jejunum. Burkitt lymphoma is an aggressive variant with endemic forms occurring more commonly in African children commonly involving the ileocaecal region. Post-transplant lymphoproliferative disorder is a variant of B cell lymphoma that is seen in recipients of allogeneic transplant. It is a high-grade B cell tumor that can involve the small bowel. Enteropathy-associated lymphomas are primarily T cell variants and tend to be FDG avid. B cell lymphomas also commonly affect the distal small bowel and are strongly FDG avid.

Lymphoma most commonly presents in an infiltrative pattern, causing wall thickening nodularity, luminal narrowing or aneurysmal dilatation<sup>[20]</sup>. Lymphomatous involvement results in lesser desmoplastic reaction compared with carcinoma and therefore intestinal obstruction is uncommon (Fig. 8). HD involvement of the small bowel is less common and is usually a result of disseminated disease. Colonic involvement of lymphoma has features similar to small bowel disease with wall thickening without obstruction.



**Figure 7** NHL showing intense FDG uptake in the anteropyloric region of the stomach along with perigastric lymph nodes in a 70-year-old man. Gastric lymphomas are usually associated with *H. pylori* gastritis.



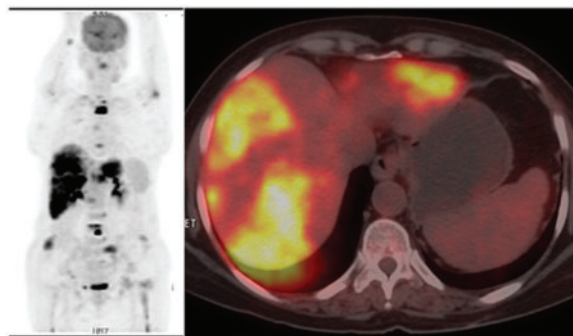
**Figure 8** A 30-year-old male renal transplant patient (which is visible in the right iliac region). Intense FDG uptake is seen along the grossly thickened wall of a large segment of small bowel. This was confirmed to be plasmablastic variant of B cell lymphoma.

### Liver

Primary lymphoma of the liver is extremely rare and mostly NHL type (Fig. 9). At the time of presentation, the liver is involved in up to 15% of patients with NHL and in up to 10% of patients with HD<sup>[21]</sup>. Secondary involvement is more common and presents as either hepatomegaly or nodular lesions. Nodular lesions present with more FDG uptake than the surrounding parenchyma.

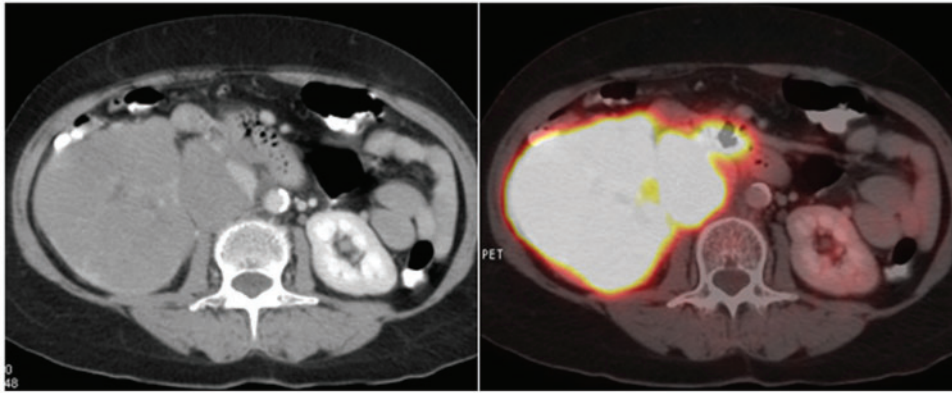
### Kidneys

As in most organs, primary renal lymphoma is rare and is usually an extension of retroperitoneal lymph nodal disease. It can manifest as either renal lesions or disease that is limited to the perinephric fascia. Renal involvement presents as an intensely FDG avid mass that is homogeneous in texture and shows enhancement on CT (Fig. 10). Encasement of vessels and hydronephrosis can also be seen. Unlike primary renal tumors, lymphoma characteristically shows a homogeneous

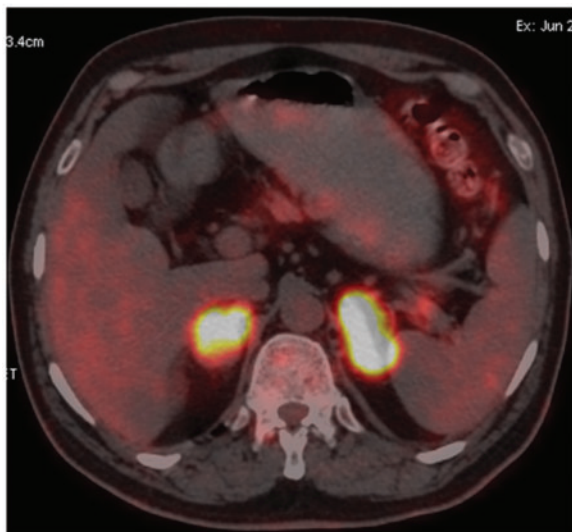


**Figure 9** PET/CT of a 70-year-old woman presenting with pyrexia of unknown origin (PUO) showed intense diffuse uptake in the liver and multiple foci in the bone marrow that was confirmed as NHL of the liver and was CD 20 positive. PET/CT was used for the investigation in this case to evaluate the PUO persisting for 2 months and the patient showed lesions only at extranodal sites, including the bone marrow, apart from the liver.





**Figure 10** A 66-year-old woman presenting with a flank mass on right side, which shows intense FDG uptake within a large homogeneous lesion in the right kidney along with renal hilar nodes on PET/CT. This was proven to be NHL. Primary renal neoplasms usually present as heterogeneously enhancing masses with low to variable uptake on FDG. Therefore in this case, PET/CT prompted the clinicians to undertake fine-needle aspiration cytology, which otherwise is not preferred for suspicion of renal cell carcinoma thereby helping in the diagnosis.

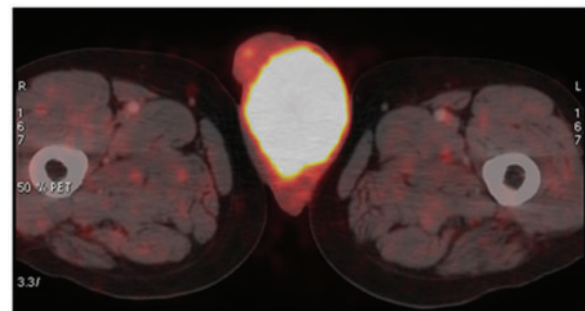


**Figure 11** Lymphoma of T cell type involving both the adrenal glands in 62-year-old man. Bilateral involvement is seen in up to 50% cases in which the adrenals are involved.

attenuation involving the hilum and interstitium. Cyst formation, hemorrhage and necrosis are atypical features<sup>[22]</sup>.

### Adrenal

Adrenal involvement presents with non-specific findings of enlargement and intense FDG uptake (Fig. 11). The adrenal gland is involved in up to 4% of NHL cases<sup>[21]</sup>. Clinically the patients may present with features of Addison disease. Bilateral involvement can be seen in up to 50% of cases.



**Figure 12** Intense asymmetric uptake in the grossly enlarged left testis in a 62-year-old man. The patient was diagnosed with B cell NHL on the right side for which he was subjected to orchidectomy followed by chemotherapy. He presented with enlargement of the left side, which was proven to be NHL.

### Genital lymphoma

Testicular lymphoma accounts for up to 5% of testicular masses<sup>[23]</sup> (Fig. 12) and presents as painless swelling. It is usually aggressive with spread into the nervous system. Asymmetrical intense FDG uptake helps differentiate physiologic activity from that of lymphoma.

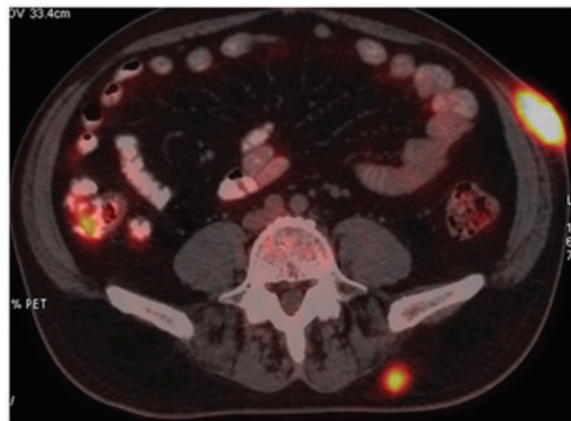
The adnexae are common sites of involvement in females. Rare involvement of the body of the uterus and the cervix (Fig. 13) has been reported<sup>[24]</sup>.

### Cutaneous

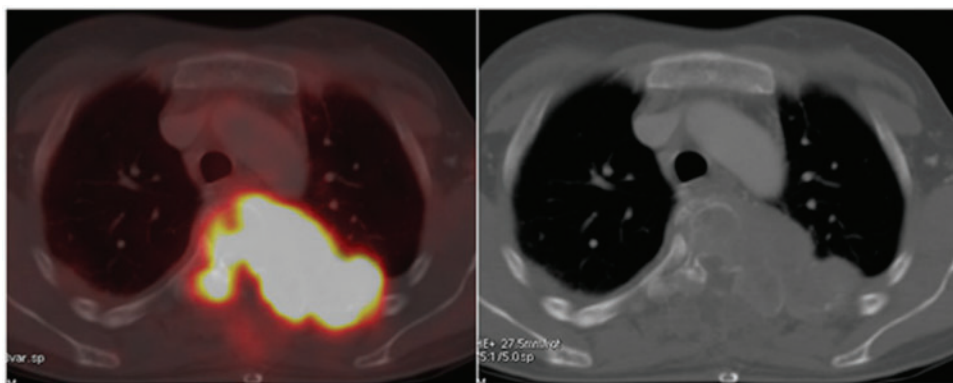
Most cutaneous lymphomas are NHL (Fig. 14) with T cell lymphomas constituting up to 65% of cases<sup>[25]</sup>. Extracutaneous involvement is seen in up to 25% of these cases in the form of nodal or hepatosplenic disease.



**Figure 13** B cell NHL involving the body of the uterus in a 53-year-old woman.



**Figure 14** T cell cutaneous lymphoma showing intense FDG uptake in a skin lesion and subcutaneous nodules in a 62-year-old man.



**Figure 15** Diffuse large cell lymphoma involving the vertebra and adjacent rib causing expansile lytic destruction in a 40-year-old woman.

T cell lymphomas have variable FDG uptake with mycosis fungoides and Sézary syndrome showing low uptake.

bone lymphoma has been recorded at our institute to date.

## Bone

Primary involvement of bone is classified as stage I disease; involvement in a disseminated lymphoma is grouped as stage IV. Most are NHL type<sup>[26]</sup>. Diffuse large B cell lymphoma is the most common type<sup>[27]</sup> and primary Hodgkin lymphoma of the bone is very rare. Presentation can be of the following patterns: permeative lytic destruction (Fig. 15), blastic sclerotic changes, near normal appearance on CT with destructive pattern being the most common type<sup>[28]</sup>. The near-normal variant has drastic findings on skeletal scintigraphy and FDG-PET/CT, which may show intense uptake. Diffuse or focal skeletal uptake on PET/CT may also represent marrow involvement especially when no definite radiographic changes are noted. No case of primary

## Conclusion

FDG-PET/CT has become an invaluable investigation in staging and response assessment of lymphoma. We present a pictorial review of the extranodal manifestations of lymphoma that we have encountered at our institute. Knowledge of these findings will help better stage the disease and help differentiate normal or physiologic uptake of FDG from disease processes.

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