PET/CT OF EXTRANODAL INVOLVEMENT IN LYMPHOMA

Parra CM, Tomich GR, Quaranta A, Staffieri RL, Villavicencio RL.

Abstract

Lymphomas are involved in a group of heterogeneous histology tumors derived from Immune System Cells. The term extranodal lymphoma is used to describe neoplastic proliferation in different sites from lymph nodes or lymphatic tissue. Lymphoma’s prevalence is rising and extranodal manifestations are diagnosed frequently in every day practice. The 18 FDG PET/CT has been proven to be superior to computed tomography (CT) alone in staging, restaging and monitoring therapy response in patients with lymphoma. This article reviews the utility of PET/CT in the evaluation of extranodal manifestation in Hodgkin (HL) and Non Hodgkin Lymphoma (NHL).

Key Words: Extranodal lymphoma, PET/CT.

Introduction

Lymphomas comprise a histologically heterogeneous group of tumors originating from the immune system. The main characteristic of this disease is the increase in size and the overgrowth of lymph nodes or secondary lymphoid tissue. Although infrequent, the HL and NHL can originate in or compromise almost any organ. The term “extranodal lymphoma” is used to describe the overgrowth of neoplasm in different parts of the lymph nodes or lymphoid tissue (1).

The increasing incidence of the HL and NHL has been characterized by a marked growth of the extranodal lymphoma form. The presence of extranodal involvement has prognostic indicators. When there is a secondary extranodal extension (excluding the spleen) the disease is considered to be in stage III or IV. However, in patients with primary extranodal involvement, the disease can be considered to be still in stage I or II (1).

The Positron Emission Tomography (PET) is more precise when identify extranodal involvement compared to Computed Tomography (CT). The PET/CT fusion image has an additional value in the evaluation of the extranodal disease since it differentiates the disease from areas of physiological uptake, especially in abdomen and pelvis, and from adjacent...
affected nodes (2). The current indications of PET/CT in patients with lymphoma are shown in Table 1.

The intensity of the 18 Fluorodeoxyglucose (18FDG) uptake in the lymphoma is determined by a several factors, including histological types (HL vs. NHL), degree (indolent vs. aggressive tumor), fraction of tumor viable cells, overgrowth of tumor cells, local perfusion, and hypoxia. Since it is a multifactor process there is an important heterogeneity in the lesions uptake of identical histological type (3). Table 2 shows the avidity of 18FDG in the different types of HL and NHL.

Extranodal lymphoma

Head and neck lymphoma

It is the second most frequent neoplasm in head and neck and the second most frequent location of the NHL (20%). The Waldeyer's tonsillar ring is the most common extranodal location of the head and neck lymphoma (50%) and the most frequent location in 30% of patients with extranodal NHL (4). The diffuse large B-cell lymphoma is the most frequent in head and neck. The nasopharynx is affected in 40% of patients with head and neck lymphoma. The nasopharynx lymphoma tends to spread to the airway and the tonsils whereas the nasopharynx carcinoma or sarcoma spreads to the skull base (Fig. 1A) (5).

Primary NHL of the salivary glands is not common and it is most frequent in the parotid gland. The secondary involvement is most frequent in diffuse large B-cell or follicular NHL (4).

Primary thyroid lymphoma is rare (2% of the extranodal lymphomas). 70% are diffuse large B-cell lymphomas and 25% are MALT lymphomas. It is more frequent in women aged 70-80 and 80% are associated with Hashimoto’s thyroiditis (4). The thyroid lymphoma can appear with diffuse or focal uptake, but both are unspecific and are associated with other conditions such as papillary thyroid carcinoma and thyroiditis (1).

Laryngeal lymphoma is less frequent and usually a MALT lymphoma; it is present in a similar age group as the laryngeal carcinoma (average: 60 years old) (Fig. 1B). (4).

The evaluation of orbital lesions with PET/CT is limited because of their small size and of the similar background physiological activity of the extraocular muscles and brain (1).

Central nervous system lymphoma (cnsL)

They represent 1 to 4% of the malignant brain tumors. The primary central nervous system lymphoma is supratentorial in the 87% of cases. The typical locations include brain hemispheres, periventricular white and gray matter and corpus callosum. The intense physiological activity of the FDG in the brain mantle makes difficult to detect the involvement of the intracranial lymphoma (sensibility: 87%). (6) The Magnetic Resonance Imaging (MRI) is very useful in the primary diagnosis and in the post-treatment monitoring of patients with primary brain and cord lymphoma (1).

The spinal lymphoma is located, in a decreasing order of frequency, in bones, in extradural/epidural, in intradural extramedullary or in intradural intramedullary areas (Fig. 2) (6).

The neurolymphomatosis is a rare form of NHL and it is characterized by infiltration of cranial and peripheral nerves, plexus and roots. The PET shows a hypermetabolic activity in the nerves and it is useful for diagnosis (6).

Thoracic lymphoma

The intrathoracic involvement is more common in HL than in NHL. The lung parenchyma pathology in HL is a direct consequence of mediastinal lymph node disease (1). The appearance of the lung lymphoma is variable (Fig. 3). The primary lung lymphoma is rare and it is a NHL associated with bronchial lymphoid tissue. It appears as one or several nodules or consolidations with low uptake of FDG. The high-grade pulmonary lymphoma is present in transplanted patients or suffering from Acquired Immunodeficiency Syndrome (AIDS); they are B-cell NHL and they appear as multiple nodules with high uptake of FDG (7). When the PET/CT is performed for staging, the pulmonary lesions can be interpreted as lymphomatous involvement,
granulomatous diseases or as a secondary location. In the post-treatment PET/CT, the increase in the pulmonary uptake can occur due to benign concomitant conditions (1).

The thoracic wall involvement occurs in the 6% of the HL and it is usually a consequence of a direct extension from the anterior mediastinal lymph nodes. Isolated masses in the thoracic wall are rare and they are associated with NHL (7).

The pleural involvement can be present in HL and NHL as a manifestation of the systemic disease (7). PET/CT is useful to identify and locate focal points of the disease, with good anatomic correlation (1).

Cardiac lymphoma
Metastatic involvement of the heart and pericardium is rare. The myocardial pathology must be differentiated from the physiological uptake; hence the importance of the simultaneous examination with CT.

Thymus lymphoma
In HL, thymus involvement does not alter the staging since it is considered a nodal organ. The increase in size of the thymus is common in patients with HL, usually due to thymus hyperplasia during or after chemotherapy; it has moderate avidity of FDG. It can often simulate the recurrence of the disease (1).

Breast lymphoma
The primary extranodal NHL in breasts represents 0.5% of the malignant breast tumors. The primary unilateral breast lymphoma clinically appears as breast carcinoma. Secondary involvement of breast with NHL is more common. The lymphomatous involvement is associated with an increase in the diffuse and bilateral uptake of FDG or in a breast mass. PET/CT is useful when there is suspicion of lymphomatous involvement in women with very dense breast since it cannot be observed in mammography and CT.

Bone lymphoma
Primary bone lymphoma is rare: 3-5% of malignant bone tumors, 1% of all lymphomas and 5% of extranodal NHL (8). The primary lymphoma is originated from the appendicular skeleton, while the secondary lymphoma usually affects the axial skeleton (skull, column, ribs and pelvis) (Fig. 4). Secondary bone involvement is present in 10 to 25% of patients with HL (8). PET/CT has proved to be more sensitive and specific than the bone scintigraphy to determine bone involvement with lymphoma (1).

Muscle lymphoma
Primary lymphoma of skeletal muscle is very rare (0.3% with HL and 1.5% with NHL). The most common locations are thighs, chest and arms (8). Most cases of metastatic involvement of the muscle are a consequence of secondary involvement (Fig. 5). Its imaging aspect varies (8). PET/CT is useful in the identification of muscle involvement (1).

Skin lymphoma
Skin lymphoma can be primary (without extracutaneous involvement at diagnosis) or secondary (8). Primary skin lymphoma is the second most frequent extranodal location with NHL, while skin involvement is rare in patients with HL (8). 25% of cutaneous lymphomas show extracutaneous involvement at diagnosis. PET/CT is useful in staging and post-treatment monitoring (Fig. 6) (1).

Bone marrow lymphoma
Bone marrow condition is present at diagnosis in 50-80% of patients with low-grade NHL, in 25-40% of high-grade NHL and in 5-14% of patients with HL. Biopsy is considered the best procedure to identify bone marrow involvement. PET/CT has proved to be highly sensitive for early detection of bone marrow disease: in patients without previous treatment a higher uptake than the hepatic indicates condition (8).

Two patterns are described (8):
1- Diffuse disease: it can be confused with activation due to chemotherapy.
2- Focal involvement: mono or polyostotic, out from the place of the biopsy.

PET/CT is considered a complement and not a
substitute of the biopsy in the evaluation of bone marrow disease (1).

**Splenic and hepatic lymphoma**

The spleen is an extranodal region in NHL and it is involved in 20% of the patients (Fig. 7). In HL it is considered a nodal organ and it is affected in 30 to 40% of the cases at diagnosis. Primary splenic lymphoma is rare and generally associated with NHL.

Imaging findings in splenic lymphoma (9):
1. Marked splenomegaly without mass
2. Increased uptake solitary mass
3. Multifocal nodules
4. Diffuse infiltration

The presence of splenomegaly is not a diagnostic judgment that can indicate metastatic involvement (the spleen can have a normal size with tumor infiltrations or it can have an increased size without neoplastic involvement.) PET/CT has a high accuracy to detect primary hepatosplenic condition in initial staging, but in post-treatment monitoring, the evaluation of spleen secondary involvement can be limited due to splenic activation (useful pattern to differentiate the secondary involvement from activation post-treatment: splenic uptake greater than liver and bone marrow.)

The primary hepatic lymphoma is very rare; secondary hepatic involvement is more common (Fig. 8). There are different patterns (9):
1. Hepatomegaly (diffuse hepatic infiltration)
2. Multiple focal lesions (Differential diagnosis with metastasis: in PET/CT, areas with homogeneous increases of uptake accompanied by splenomegaly; hepatic metastasis of solid tumors is a large heterogeneous mass without splenic involvement.)
3. Milial-type lesions, more common in HL.

**Pancreatic lymphoma**

Pancreatic involvement is extremely rare in HL and almost all cases are secondary NHL to direct extension from adjacent nodes.

Two forms of the pancreatic involvement can be distinguished (9):
1. Well circumscribed focal mass, not associated with dilatation of the duct of Wirsung and without atrophy of the remnant pancreatic parenchyma (Fig. 8)
2. Diffuse increase in size of the pancreas with irregularities in the peripancreatic fat.

In PET/CT a diffuse or focal increase of the uptake in the peripancreatic tissue is often detected.

**Peritoneum lymphoma**

Peritoneal lymphomatosis is a rare clinic condition associated with high-degree NHL of the GIT. In PET/CT, peritoneal lymphomatosis dropsy has a high density and moderate uptake of FDG.

**Renal lymphoma**

The renal lymphoma is present in systemic forms of the disease since the kidney does not have lymphatic tissue and is more common in aggressive forms of NHL (9).

In PET/CT, renal involvement appears as an area with increased uptake with or without lesions corresponding to CT (Fig. 9) (1).

**Adrenal glands lymphoma**

The primary lymphoma of the suprarenal glands is very rare. More than 25% of patients with NHL develop a secondary involvement of adrenal glands. In 50% of patients, there is a bilateral involvement and it is characterized by a diffuse increase in size (Fig. 10) (9). In patient with adrenal lymphoma, the PET showed an uptake increase even when the rest of the examinations threw a negative result (1).

**Gastrointestinal tract (git) lymphoma**

The GIT is the most common location of the extranodal NHL (20%). The primary form (better prognosis) represents the 0.9% of GIT tumors, being more frequent than the secondary involvement. The organs involves are: stomach (50%), small intestine (33%), large intestine (10% to 16%) and esophagus (1%) (10).

Esophagus primary involvement with NHL is extremely rare. Most cases are secondary and are originated by extension from cervical and mediastinal lymph nodes. In PET/CT esophagus lymphoma appears due to circumferential thickening with a diffuse increase of the 18 FDG uptakes (Fig. 11) (10).

The gastric lymphoma corresponds to approximately the 3-5% of malignant stomach tumors. The primary gastric lymphoma is 10 times more frequent in NHL and the most common histologi-
cal subtypes are low-degree MALT lymphomas associated with Helicobacter Pylori (50% to 70%) and large B-cell diffuse lymphomas. Secondary involvement is more common (10). In PET/CT the uptake pattern in the gastric lymphoma varies and it is generally diffuse (1).

Small intestine condition in HL and NHL is usually the result of the disease extension from affected mesenteric lymph nodes. From the GIT organs, the second most frequent affected organ in NHL is the small intestine; the distal ileum is the most common location (Fig. 12) (10). In PET/CT it appears as a multiple area with increase uptake arranged in a curved pattern (1).

Secondary colonic involvement is present in 35% of patients with lymphoma (10). The PET shows a diffuse, nodular or focal pattern of increased uptake.

**Reproductive organs lymphoma**

Of the female reproductive organs, the ovaries are most frequently affected by NHL, followed by the uterus. In PET/CT multiple areas with increased uptake are visualized (9).

Primary testicular lymphoma represents the 5% of the total of testicular tumors and 2% of the NHL. In patients over 60, it is the most frequent testicular tumor (9). In PET/CT an area with increased asymmetric uptake is generally identified in the affected testicle (1).
Secondary bone involvement in patient with HL. A: Axial CT scan with bone window not showing density or bone structure alterations. B: PET/CT fusion image showing focal increased uptake in sacral bone.

Secondary muscle involvement in patient with diffuse large B-cell NHL. A) Axial CT scan showing the muscles the left arm posterior region without mass nor apparent density alterations. B) PET/CT fusion image showing hyperactivity in muscles of the left arm posterior region. The imaging aspect of muscle involvement in the lymphoma varies: focal or diffuse increase in size, infiltrate lesions or mass. A unique asymmetric area or multiple areas with increased uptake in muscle PET/CT seem to show lymphomatous involvement, even when the muscle has physiologically variable 18 FDG uptake.

Secondary skin involvement in 67-year-old patient with a diffuse large B-cell lymphoma diagnosis. A) Axial CT scan showing solid nodular image with skin and subcutaneous cell tissue involvement. B-C) PET/CT fusion images showing hypermetabolism of that image. In the cutaneous lymphoma, the imaging findings are not specific (increase in soft tissues thickness, infiltrate or mass) and PET/CT provides adequate anatomic and metabolic information which is useful in its staging and post-treatment monitoring.
Fig. 7: Splenic involvement in 66-year-old patient with NHL in initial staging exam. A) CT coronal reconstruction showing a normal sized spleen and homogeneous parenchyma with right axillary adenopathy. B) PET/CT fusion images showing diffuse increases uptake in spleen, greater than liver and bone marrow uptake.

Fig. 8: Tail of pancreas involvement in patient with NHL. A) Axial CT scan showing discrete mass effect and loss of normal acinar cells of the pancreatic tail. B) Axial PET/CT fusion image showing focal hypermetabolism in the pancreatic tail. The main differential diagnosis would be a pancreatic carcinoma.

Fig. 9: Secondary renal involvement in patient with NHL. A) Mass effect of great size, solid, hypodense with left renal cortex and medulla involvement. B) Axial PET/CT fusion image showing a marked metabolic activity of that mass. Renal lymphoma can appear with different patterns: diffuse renal infiltrate, multiple renal mass, solitary renal mass (in this case) or perirenal infiltrates. Differential diagnosis include renal cells carcinoma, transitional cells carcinoma and kidney infection.
Fig. 10: Large cell NHL with secondary involvement of both suprarenal glands. A) PET/CT fusion images showing an increase in size associated with and enhanced uptake of the tracer in both suprarenal glands.

Fig. 11: Esophagus involvement in patient with lymphoma. A) Axial CT scan showing parietal asymmetric thickening of the esophagus wall in the esophagogastric union. B) Axial PET/CT fusion view showing increased uptake of tracer in this area of focal thickening of the wall. The most important differential diagnosis is the esophagus carcinoma and it can only be excluded performing biopsy.

Fig. 12: Lymphomatous involvement of the thin loops of Henle in 26-year-old patient with NHL. A) Axial CT scan showing diffuse parietal thickening of distal thin loops. B) Axial PET/CT fusion view showing marked increased uptake of 18FDG in those loops.
The prevalence of lymphoma is increasing so a larger number of extranodal forms are identified daily in clinical practice. The PET/CT has been established as the best technique for the staging and monitoring of patients with extranodal involvement in HL and in most NHL. The possible presence of extranodal involvement must be taken into account in every stage of the disease since it can change the prognosis and treatment. The diagnosis should always be confirmed through biopsy.

**Current indicators of PET/CT in patients with lymphoma**

- Pre-treatment staging of patients with lymphomas showing avidity of 18 FDG and they are potentially curable.
- It is not recommended routine pre-treatment in patients considered incurable or in histological types which do not show avidity or have an indolent behavior regarding the 18 FDG.
- PET/CT treatment only in clinical trials. (3)

**Tab. 1**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B-cell NHL</em></td>
<td></td>
</tr>
<tr>
<td>Large B-cells diffuse lymphoma</td>
<td>Increased</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>Increased</td>
</tr>
<tr>
<td>Large and anaplastic cell lymphoma</td>
<td>Increased</td>
</tr>
<tr>
<td>Follicular lymphoma (Grade 3)</td>
<td>Moderate/Increased</td>
</tr>
<tr>
<td>Follicular lymphoma (Grade 1 and 2)</td>
<td>Low to Moderate</td>
</tr>
<tr>
<td>Mantle cells lymphoma</td>
<td>Low to Moderate</td>
</tr>
<tr>
<td>Marginal zone lymphoma (including MALT)</td>
<td>None or Increased</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>None or low</td>
</tr>
<tr>
<td><em>HL</em></td>
<td></td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>Increased</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>Moderate/Increased</td>
</tr>
<tr>
<td>Lymphocyte depletion</td>
<td>Moderate/Increased</td>
</tr>
<tr>
<td>Lymphocyte predominance</td>
<td>Low</td>
</tr>
<tr>
<td><em>T-cell lymphomas</em></td>
<td></td>
</tr>
<tr>
<td>T-cell extranodular lymphoma/Natural killer</td>
<td>Increased</td>
</tr>
<tr>
<td>T-cell peripheral lymphoma</td>
<td>Increased</td>
</tr>
<tr>
<td>Adult T cell leukemia-lymphoma</td>
<td>Moderate</td>
</tr>
<tr>
<td>T-cell cutaneous lymphoma</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fungoid Mycosis</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Tab. 2**

**Conclusion**

The prevalence of the lymphoma is increasing so a larger number of extranodal forms are identified daily in clinical practice. The PET/CT has been established as the best technique for the staging and monitoring of patients with extranodal involvement in HL and in most NHL. The possible presence of extranodal involvement must be taken into account in every stage of the disease since it can change the prognosis and treatment. The diagnosis should always be confirmed through biopsy.
Bibliography


