

# Extensive Extranodal Involvement in a case of Non-Hodgkin's Lymphoma with sparing of lymph nodes and lymphatic organs

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## ABSTRACT

Non-Hodgkin lymphoma (NHL) is a group of malignant lymphoproliferative disorders arising predominantly in the lymph nodes with various clinical and histological characteristics. At least 25% of NHL originates from tissues other than lymph nodes and sometimes even from sites that do not contain lymphoid tissue. These are referred to as primary extranodal lymphomas (pENLs). pENL is a universal diagnostic challenge to the clinicians and pathologists due to their varied clinical presentations, morphological mimicry, and molecular alterations. The GIT is the most common site of pENL followed by nasopharynx/oropharynx, testis, uterus/ovary, thyroid, and central nervous system. Long bones (tibia), maxillary sinus, skin, and paraspinal soft tissues are the other rare anatomic sites of pENL. We reported a case of a 60-year-old female presented with pain and mass in the pelvis region. <sup>18</sup>F-Fluorodeoxyglucose (<sup>18</sup>F-FDG) positron emission tomography (PET) and fused PET/CT was done, which revealed extensive extranodal involvement of the lung, bilateral kidneys, uterus, ovaries, bones, and muscles with no involvement of lymph nodes or lymphomatous organs. Extensive extranodal involvement with sparing of lymphomatous organ has not been reported earlier.

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## Introduction

Lymphoma is composed of indolent as well as aggressive human malignancies that arise from cells of the immune system at different stages of differentiation. They can manifest in a wide range of morphologic, immunologic, and clinical findings. Malignancies of lymphoid cells may present as leukemia (i.e., primary involvement of bone marrow and blood), or as lymphoma (i.e., solid tumors of the immune system) (1). Both Non-Hodgkin lymphoma and Hodgkin lymphoma may arise from or involve almost any organ of the human body. The term extranodal lymphoma has been used to describe this unique form of lymphoid malignancy, in which there is neoplastic proliferation at sites other than the expected native lymph nodes or lymphoid tissues.

A more practical operational definition is that a lymphoma should be considered extranodal when it presents with the main bulk of disease at an extranodal site, usually directing the focus of treatment towards that site. Traditionally,

lymphomas arising in primary lymphoid organs, such as the spleen and thymus, have been considered together with nodal lymphomas. However, modern lymphoma subclassification employing molecular genetics has identified new entities, such as splenic marginal zone lymphoma and thymic large B-cell lymphoma, which are unique to their organs of origin and biologically dissimilar to nodal lymphomas. Therefore, it is appropriate from a pathogenetic and clinical view point to regard these organs as properly extranodal. In contrast to its predecessors, the Kiel and Lukes-Collins classifications, which placed lymphomas into broad groups according to clinical behavior, the current World Health Organisation (WHO) classification focuses on defining individual lymphomas as distinctive clinicopathological entities based on the integration of all available clinical, pathological and genotypic data. Although extranodal lymphomas are not rare, the frequency of involvement of any particular site is not high

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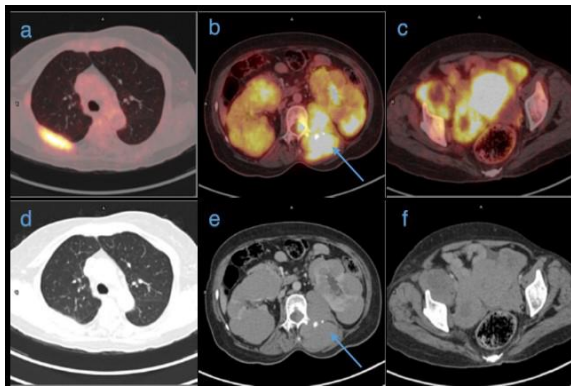
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enough for a single institution to answer the major question about their natural history and proper therapy. Attempting to overcome these difficulties, in the late 1990s, the International Extranodal Lymphoma Study Group (IELSG) was created to provide an adequate network to study the extranodal lymphomas. This international collaboration has originated a number of retrospective and prospective trials aimed to clarify the management issues distinct to extranodal presentations (<http://www.ielsg.org>). Distribution among the nonlymphoid tissues is uneven, with a greater predilection for some organs than for others, and includes the gastrointestinal tract, central nervous system (CNS), lung, bone, and skin (2). PET/CT has become integral to the management of patients with  $^{18}\text{F}$ -FDG avid lymphomas, including staging, prognosis, response assessment and treatment planning (3).  $^{18}\text{F}$ -FDG PET/CT is a more effective technique than contrast-enhanced computed tomography (CECT) for the evaluation of extranodal involvement in Hodgkin and non-Hodgkin lymphoma patients. PET/CT has a significant advantage for the diagnosis of diffusely infiltrating organs without mass lesions or contrast enhancement compared to CECT (4). Qualitative, Semi quantitative (Deauville criteria) and quantitative criteria ( $\text{SUV}_{\text{max}}$ ,  $\text{SUV}_{\text{peak}}$ ,  $\text{SUV}_{\text{mean}}$  and Metabolic tumor volume (MTV) on FDG PET/CT can be used for prognosis of lymphoma. Fluoro-deoxyglucose positron emission tomography (FDG-PET/CT) at baseline, after 2 cycles of chemotherapy (interim PET/CT), and at end of treatment can be used for prediction of remission and survival, as suggested by CALGB 50303 clinical trial (5). Many cases of extranodal involvement of NHL have been reported along with the involvement of lymphatic organs. We report a rare case of extensive extranodal NHL involving bilateral kidneys, lung, uterus adnexa bones, and muscles with no involvement of lymph nodes, spleen, or liver.

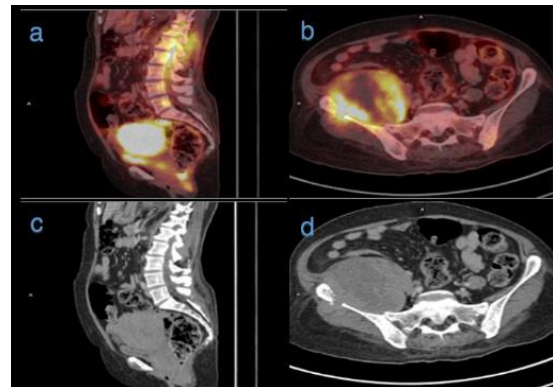
### Case Report

A 60-year-old female presented with the complaint of pain on the right side of the pelvis for two months; the pain was progressively increasing in severity. She also complains of swelling in the gluteal region, which is progressively increasing in size. Clinical examination revealed a tender mass on the right side of the pelvis. She also complains of significant weight loss in last 1 month and episodes of

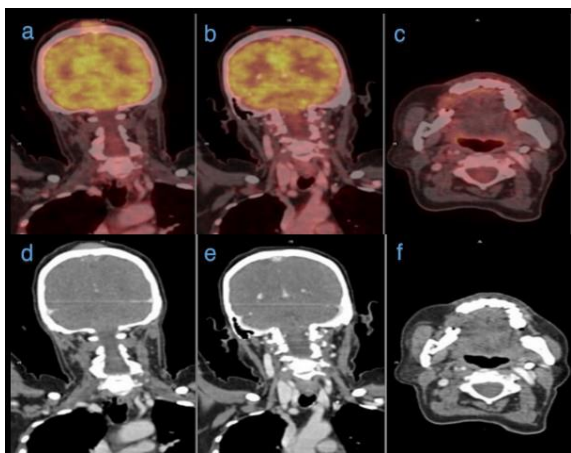
recurrent fever. Haematological parameters were, Haemoglobin (Hb) =7.6 gm/dl, RBC count=2.9 millio/cmm, Differential Leucocyte Count suggestive of lymphopaenia (N91L7M2). Peripheral smear (PS) suggestive of predominantly normocytic normochromic picture. Bone Marrow Biopsy (BM) suggestive of infiltration by Lymphoma/leukemia cells. ESR was found to be 22 mm/hour. Kidney function test parameters were within normal range [Serum Creatinine (S. Cr) =0.9 mg/dl, Serum Uric acid= 3.7 mg/dl, Serum Calcium (S. cal) =8.2 mg/dl, Serum potassium=5.1 mmol/l, Serum Sodium=135 mmol/l]. Eastern Cooperative Oncology Group Performance status (ECOG-PS) Score was 2. The abdominal, respiratory, and cardiovascular examination was unremarkable. CECT scan of the abdomen and pelvis revealed a large mass in the right iliac bone with bulky uterus and adnexa. Kidneys were mildly enlarged with normal renal function. Guided biopsy of the pelvis mass was done, and it revealed B Cell Non-Hodgkin's Lymphoma. Serum lactate dehydrogenase levels were elevated (895 IU/L). The patient was referred for  $^{18}\text{F}$ -FDG PET/CT. PET/CT showed abnormally increased tracer uptake in bilaterally enlarged kidneys with multiple SOLs, consolidation in the upper lobe of right lung, bulky uterus, bilateral adnexal masses, lytic bone lesions with soft tissue component and diffusely enlarged left psoas muscles (Figure 1, 2). However, no active lymphadenopathy was noted. Spleen, liver, thymus, tonsils, and nasopharynx were unremarkable (Figure 3, 4). The patient was given three cycles of R-CHOP chemotherapy regimen [Rituximab, Cyclophosphamide, Hydroxydaunorubicin (Doxorubicin) Oncovin (Vincristine), and prednisone]. She tolerated the chemotherapy regime well, and no significant untoward side effects were noted. Interim  $^{18}\text{F}$ -FDG PET/CT was done to assess treatment response. It showed a significant decrease in number, size, and FDG avidity of all lesions. Overall scan finding was suggestive of partial treatment response (Figure 5 and 6). Standardized uptake value ( $\text{SUV}_{\text{max}}$ ) and sizes of various lesions at baseline and follow up scan are given in Table 1. Post chemotherapy haematological parameters improved (Hb=9.7 mg/dl, RBC=4.2 million/cmm, ESR=20 mm/hr). ECOG-PS score also improved with score of 1. Kidney fuction parameters were within normal range (S.Cr=0.8 mg/dl, S. Uric acid=3.9 mg/dl, S. Potassium=4.1 mmol/l, S. Sodium=138 mmol/l and S. Cal=8.6 mg/dl).



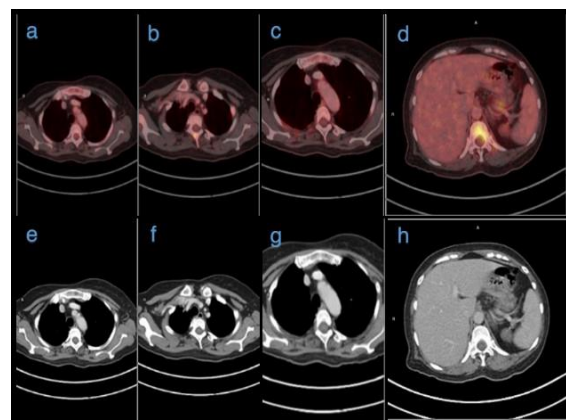
**Figure 1.** Trans axial section Fused PET/CT and CT image of lung, Kidney and Pelvis in Baseline scan



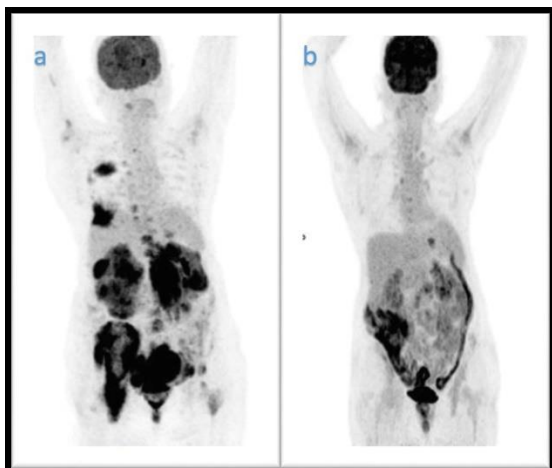
**Figure 2.** Fused PET/CT and CT image in sagittal section reveals increased tracer uptake in enlarged uterus (a, c) and FDG avid expansile lytic lesion involving Right iliac bone with soft tissue component (b, d)



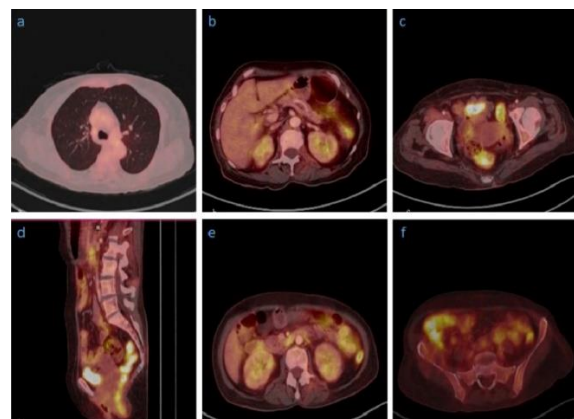
**Figure 3.** Fused PET/CT and CT image from cervical region in sagittal and trans axial view Images revealed Physiological tracer uptake in brain with no significant lymph nodes in cervical region. (a, b, c, d, e, f)



**Figure 4.** Trans-axial section Fused PET/CT and CT images from axillary region (a, e, b, f) and mediastinal region (c, g) revealed no involvement of lymph node; Trans-axial view fused PET/CT and CT images also revealed no involvement of liver and spleen(d, h)



**Figure 5.** Maximum intensity projection image of Baseline and Interim FDG PET/CT  
A-Baseline PET/CT scan shows multifocal increased <sup>18</sup>F-FDG uptake in the Lung, Kidney, Uterus, Ovaries, Bones, and Muscles. B- Interim PET/CT scan shows a significant reduction in FDG avidity in lesions compared to Baseline PET/CT



**Figure 6.** Interim PET-CT images show focally no abnormal <sup>18</sup>F-FDG uptake in the lung (a). Bilaterally enlarged kidneys with focal areas of FDG uptake (b) bulky uterus (c), bulky adnexa (d) left psoas muscle with no abnormality (e), and destructive lytic lesion in the right iliac bone without FDG avidity (f). These findings are suggestive of partial treatment response

**Table 1.** Size and SUV<sub>max</sub> of various lesion in baseline and interim PET/CT

Organ of involvement	Baseline SUV <sub>max</sub>	Baseline size (cm)	Interim SUV <sub>max</sub>	Interim size (cm)
Lung	11	4.4×1.8	Not seen	-
Kidney	10	12×8×11	Not seen	-
Uterus	17.3	8×6	2.5	3.8×3.6
Adnexae	10	6×5.5	2.0	2.8×2.2
Iliac bone	11.2	9.3×9.8	3	5.5×3.3
Muscle mass	9.2	8.5×6.3	Not seen	-

## Discussion

Primary extranodal NHL (pENHL) is common and usually involves stomach followed by head and neck region. Its prognosis depends upon the grade, stage, and site of involvement. Compared to nodal NHL, the pENHL are more frequently localized, belonged more often to aggressive histologies, and had more often distal extra nodal relapses. The etiology of extranodal lymphomas appears to be multifactorial and includes immune suppression, infections, both viral and bacterial, and exposure to pesticides and other environmental agents. Nevertheless, despite the considerable progress made in the understanding of MALT lymphoma and its relationship to bacterial infections, the precise cause of most lymphoid neoplasms remains unknown. The histological spectrum of extranodal lymphomas somehow differs from that of nodal lymphomas. Nearly half of the extranodal cases are of diffuse large cell histology. Aggressive subtypes, mainly diffuse large B-cell lymphomas (DLBCLs) are predominant in NHL of the central nervous system (CNS), testis, bone, and liver while in the gastrointestinal tract a broad spectrum of histological disease entities can be seen, comprising DLBCL, MALT lymphoma (including the immunoproliferative small intestinal disease), Burkitt's lymphoma, enteropathy-associated T-cell lymphoma, mantle cell lymphoma, and follicular lymphoma. Although extranodal lymphomas are not rare, the frequency of involvement of any particular site is not high enough for a single institution to answer the significant question about their natural history and proper therapy. Complete remission rates (CR), disease-free status, and overall survival were significantly better for pENHL (6). Extranodal NHL may involve almost any organ in the body such as gastrointestinal tract, bone, brain, genitourinary organs, etc (2). <sup>18</sup>F-FDG - PET/ CT is more effective than CECT in evaluating extra nodal lymphomatous infiltration. It is mostly attributed to the detection of FDG avid, normal-sized lymph nodes, and of extranodal sites that were previously missed at CT (most commonly

the liver, spleen, cortical bone, bone marrow, and skin) (7).

Renal involvement in patients with lymphoma is relatively common, particularly in the setting of disseminated disease, and it can result from direct invasion or hematogenous spread (8). Renal lymphoma may be unilateral or bilateral. It may present as a solitary mass or as multiple renal masses, and it may develop as infiltrative renal disease or as a direct invasion from contiguous retroperitoneal adenopathy (9). PET/CT feature of high metabolic activity is handy for differentiating RCCs from renal involvement in patients with lymphoma with solid renal masses (10). In our case, both kidneys are enlarged in size with multiple large areas of soft tissue mass lesion showing mild enhancement and intense FDG avidity. Inspire of extensive involvement renal functions were unremarkable .

Primary NHL of the lung is very rare, accounting for only 0.4% of all malignant lymphomas. Primary pulmonary NHL is most commonly represented by marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma) (11). Their development depends on MALT of the bronchus that is thought to be acquired as a result of chronic antigenic stimulation such as smoking, autoimmune disease or infection. They usually pursue indolent courses, remaining localized to the lung for long periods before dissemination (11). The CT appearance may include a direct extension from nodal disease, ill-defined central nodules, or rounded-segmental consolidation with air bronchogram. In NHL, lung involvement can occur without enlarged mediastinal nodes, which makes the differentiation from radiation pneumonitis, drug-related pneumonitis, and pulmonary infection on CT difficult (12). The correlation of radiologic findings with clinical, biochemical, and microbiological findings is often required for correct diagnosis. This patient had FDG avid pleural based consolidation in the right lung, which disappeared in the interim PET CT .

Primary lymphomas arising from the female genital organs are rare. Lymphomas in these

organs are generally secondary lymphomas, rather than nodal or extranodal NHL, and most commonly involve the adnexa, followed by the uterine body and cervix. DLBCL (45% of cases), and Burkitt's lymphoma (19%), constitute the major histologic subtypes (13). Primary uterine non-Hodgkin's lymphomas are extremely rare, accounting for <1% of all extranodal non-Hodgkin's lymphomas (14). Several benign and malignant conditions such as physiological endometrial uptake, adenomyosis, endometrial hyperplasia, leiomyoma, cervical cancer, endometrial cancer, uterine sarcoma, and uterine metastasis may be responsible of tracer uptake (15). In this patient, the uterus was grossly enlarged in size with increased radiotracer uptake.

The involvement of the ovaries accounts for only 0.14% of all ENL, and only 1.5% of ovarian neoplasms are lymphomas. Primary Ovarian Non-Hodgkin's Lymphoma (PONHL) is very rare because the ovary lacks lymphatic tissue. It has been suggested that the PONHL arises from lymphocytes in the ovaries, surrounding blood vessels and the corpus luteum (16). Non-Hodgkin's lymphoma has been associated with HIV infection. In countries where HIV is highly endemic, clinicians should also consider the diagnosis of PONHL in women who present with adnexal mass in the background of an HIV infection (17).

Secondary involvement of the ovaries is found in around 25% of autopsies of lymphoma patients. Ovarian lymphomas present as well-defined hypodense lesions showing mild contrast enhancement on CT. Our patient presented with significant enlarged both ovaries and diffuse tracer uptake. Interim PET CT revealed normal size ovary with no significant uptake.

Lymphomatous involvement of muscles has been reported to occur in only 1.4% of cases, with 0.3% occurring in Hodgkin lymphoma and 1.1% in NHL. It occurs as a part of disseminated lymphoma. On MRI, it usually presents with muscle enlargement with the orientation of the tumor along muscle fascicles and traversing vessels within. They exhibit characteristic T1, T2, and contrast enhancement patterns (18, 19). Our patient had diffuse enlargement of left psoas muscle with mild contrast enhancement and diffuse increased tracer uptake.

Secondary skeletal involvement occurs in both HD and NHL, affecting mostly the axial skeleton. There is a diaphyseal predilection, usually solitary, within the long bones, with the pelvis and vertebral column being the next most common sites. The imaging features of osseous lymphoma at conventional radiography, CT, and MR imaging are nonspecific, usually reflecting an aggressive

pattern of bone destruction. FDG PET is more specific and sensitive than conventional bone scintigraphy in identifying osseous involvement by malignant lymphoma (20). Our patient presented with the destructive lytic lesion in the right iliac bone with a significant soft tissue component. Lytic lesions were also noted in the occipital bone.

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