Pictorial Essay

Potential role of ^{18}F-2-fluoro-2-deoxy-glucose positron emission tomography/computed tomography imaging in patients presenting with generalized lymphadenopathy

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ABSTRACT

Generalized lymphadenopathy is a common and often vexing clinical problem caused by various inflammatory, infective and malignant diseases. We aimed to review briefly and highlight the potential role of ^{18}F-2-fluoro-2-deoxy-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) in such patients. ^{18}F-FDG PET/CT can play an important role in the management of generalized lymphadenopathy. It can help in making an etiological diagnosis; can detect extranodal sites of involvement and employed for monitoring response to therapy.

Keywords: ^{18}F-2-fluoro-2-deoxy-glucose positron emission tomography/computed tomography, generalized lymphadenopathy, lymphoma, sarcoidosis, tuberculosis

INTRODUCTION

Positron emission tomography (PET) using ^{18}F-2-fluoro-2-deoxy-glucose (^{18}F-FDG) has gradually evolved in its application through the years since its conception, especially with the added dimension of anatomic correlation brought about with the fusion of computed tomography (CT) with PET. Furthermore, the list of indications for ^{18}F-FDG PET/CT imaging has expanded from oncology to now include even a multitude of nononcological diagnoses. In this aspect, ^{18}F-FDG PET/CT can play an important role in the diagnosis and management of clinical entities like generalized lymphadenopathy that are routinely encountered in clinical practice.

Generalized lymphadenopathy is defined as an enlargement of more than two non-contiguous lymph node groups and can be caused by a wide range of conditions ranging from benign self-limited diseases to the most aggressive malignancies. The list of etiologies for generalized lymphadenopathy itself can be quite elaborate and exhaustive. However, in this review, we have attempted to discuss the most common as well as a few interesting and noteworthy causes of generalized lymphadenopathy and the role of ^{18}F-FDG PET/CT in the diagnosis and management of each of these pathological conditions. An attempt has also been made to highlight the pattern of lymphadenopathy and other imaging features on ^{18}F-FDG PET/CT that can be pointer to the cause of lymphadenopathy.

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Rosai Dorfman disease

This condition was initially described as giant cell sinus reticulosis by John Smith in 1947, and later renamed by Rosai and Dorfman as sinus histiocytosis with massive lymphadenopathy.[1] Although no specific etiological agent has been demonstrated, the morphological features suggest a greatly exaggerated reactive process. The clinical presentation is, usually, that of a young adult presenting with massive, painless cervical lymphadenopathy. Extranodal involvement has been observed in 25-43% of patients[2] especially the upper respiratory tract, salivary glands, orbit, testis and skin. The natural history is that of gradual, spontaneous resolution, although surgery has been used for relief from compressive symptoms.[3] Although the clinical presentation is often typical as described above, atypical presentations are not uncommon. Cases have been described in the literature about utility of ^{18}F-FDG PET/CT in many atypical patients with

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isolated intracranial,[4] pure cutaneous,[5] bone involvement[6] and the likes. Rosai Dorfman disease (RDD) can present as massive generalized lymphadenopathy and can mimic lymphoma on ^{18}F-FDG PET/CT. Usually in RDD the involved lymph nodes reveal intense central ^{18}F-FDG uptake with reduced uptake in the periphery [Figure 1]. This can provide a diagnostic clue as lymphoma shows homogenous intense uptake and tuberculosis (TB) shows central necrosis.[2] Being a sensitive and whole-body imaging technique, ^{18}F-FDG PET/CT has the potential to be used for assessment of disease burden, prognostication, treatment planning, and response assessment in RDD.[7]

Castleman's disease

One of the causes of nonneoplastic lymphadenopathy, this condition has been known historically by many names such as "giant lymph node hyperplasia," "angiomatous lymphoid hyperplasia," "angiofollicular mediastinal lymph node hyperplasia," etc., Although the original case was described by Castleman and Towne as a mediastinal mass resembling a thymoma, lymph node groups in the neck, axilla, mesentery, and pelvis have been known to be involved in this disease.[8] Also, involvement of other sites such as the pancreas, adrenal and the retroperitoneum has also been reported.[8] Two morphological types are identified, namely unicentric and multicentric; the unicentric variant can be often treated with surgery, whereas the multicentric disease requires a multi-modality approach including chemotherapy, steroids, antiviral therapy and antiproliferative regimens as only surgery cannot be used for curative purpose. The pathogenesis, although unknown, points toward a faulty immune regulation resulting in excessive B-cell and plasma cell proliferation. The association of this disease with human immunodeficiency virus (HIV) and Kaposi sarcoma herpes virus have been well-documented, typically for the multicentric variant.[8]

Castleman's disease (CD) is a benign lymphoproliferative disease, which, usually, shows hypermetabolism on ^{18}F-FDG PET/CT [Figure 2]. Multicentric form of CD can present with multiple lymph nodes with ^{18}F-FDG avidity on whole body PET/CT and can mimic lymphoma.[9] The confirmative diagnosis is made by pathologic examination. Currently, multicentricity of the disease is the most significant prognostic factor in CD.[10] Patients with unicentric CD, which is more common, can be cured with a good prognosis,[11] whereas multicentric CD is more aggressive and demonstrates poorer clinical course with potential for malignant transformation.[11] ^{18}F-FDG uptake has been found to have a significant correlation with multicentricity and presence of clinical manifestations.[12] For the diagnosis of CD lesions, ^{18}F-FDG PET/CT is more sensitive than contrast-enhanced CT,[13] as lymph nodes without significant enlargement may be missed on CT. ^{18}F-FDG uptake on PET/CT can be a surrogate imaging marker for severity or prognosis of CD. ^{18}F-FDG PET/CT has a useful role in the management of HIV-associated CD in selecting appropriate sites for biopsy and in staging and monitoring disease.[13]

Sarcoidosis

Sarcoidosis is multisystem granulomatous disease characterized by the formation of non caseating granuloma in the affected tissues.[14] Yet to have a definitively proven causative agent, the disease is characterized by various patterns of presentation. The disease primarily affects the pulmonary and lymphatic systems and hence a patient of sarcoidosis presenting with generalized lymphadenopathy is not uncommon. Extra-pulmonary manifestations can be seen in up to 50% of patients,[15] with many presenting with mediastinal/intra-thoracic lymphadenopathy. Though hilar/mediastinal lymph nodes are mainly involved, involvement of other groups of lymph nodes (such as the abdominal, pelvic and inguinal lymph nodes) as well as spleen is not uncommon, especially after antineoplastic therapy for any concurrent cancers.

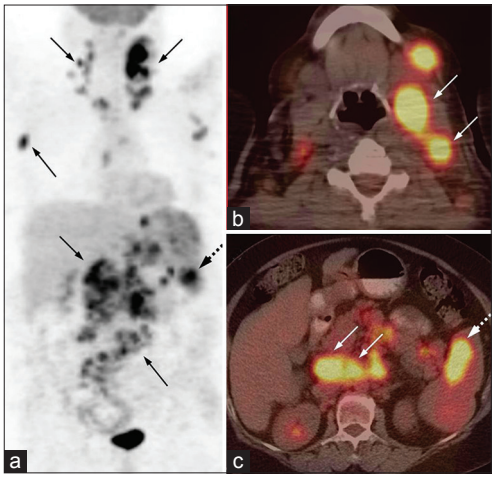

Figure 1: (a-c) A 58-year-old female with histologically confirmed Rosai Dorfman disease. Maximum intensity projection positron emission tomography (PET) image (a) and trans-axial PET/computed tomography images of neck (b), and abdomen (c), revealed multiple enlarged ^{18}F-2-fluoro-2-deoxy-glucose avid bilateral cervical, axillary, retroperitoneal and mesenteric lymph nodes (arrows) along with splenic lesion (broken arrow)

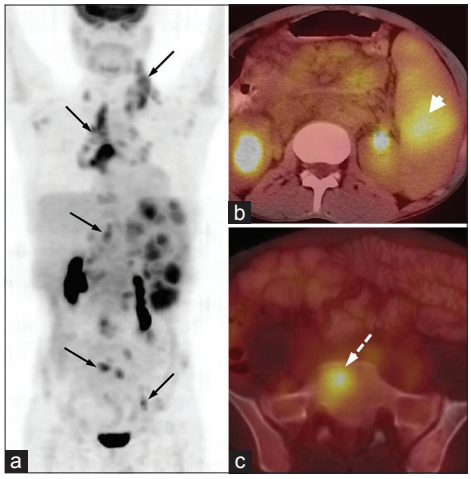

Figure 2: (a-c) An 18-year-old male with Castleman's disease. Maximum intensity projection positron emission tomography (PET) image (a) revealed multiple enlarged ^{18}F-2-fluoro-2-deoxy-glucose avid cervical, axillary, mediastinal, retroperitoneal and inguinal lymph nodes (arrows). Transaxial PET/computed tomography images demonstrating splenic (b, arrowhead) and bone marrow (c, broken arrow) involvement

^{18}F-2-fluoro-2-deoxy-glucose-positron emission tomography/computed tomography can play a significant role in the diagnosis and management of sarcoidosis. It can improve the accuracy for diagnosis of extra-pulmonary involvement, specify the respective contributions of active and fibrotic components of lesions, guide the selection of the biopsy site, provide prognostic information and guide therapeutic management,[15] The lymph nodal involvement in sarcoidosis on ^{18}F-FDG PET/CT is invariably symmetrical. Predominant involvement of mediastinal lymph nodes with high ^{18}F-FDG avidity (typically called the "lambda sign") can provide a diagnostic clue [Figure 3]. Furthermore, a study by Aide *et al*.[16] suggested that in cases of their coincidence, an early ^{18}F-FDG PET/CT can be helpful in differentiating sarcoidosis from cancer recurrences through a trial of systemic corticosteroids to which patients of sarcoidosis respond well.

Tuberculosis

Tagged with the infamy of being one of the most prevalent infectious diseases in the world, TB can have a broad array of clinical presentations. Granulomatous lymphadenopathy caused by TB is one of the leading causes of generalized lymphadenopathy in adults. While the primary site of infection in TB is the lungs, in up to 15% of cases an extrapulmonary site may produce the first symptoms; and lymph nodes constitute the most common extrapulmonary presentation in TB. The peak incidence age is between 20 and 40 years,[17] with majority of affected patients presenting with cervical lymph nodes and a fair proportion of them harboring the disease at >1 lymph nodal site.[18] Transient flares of lymphadenitis tend to occur in patients during initiation of antitubercular therapy and in HIV affected patients who are started on antiretroviral therapy,[17] which has to be kept in mind in case such patients undergo ^{18}F-FDG PET/CT. Also, the concurrent presence of TB lymphadenitis in the setting of any malignancy[19] might lead to faulty staging of the malignancy and can have a significant impact on further management of the patient. When compared with CT, ^{18}F-FDG PET/CT imaging has been found to be significantly more efficient for the identification of sites of involvement, especially extra pulmonary TB.[20] On ^{18}F-FDG PET/CT, associated changes in lungs, areas of calcification and lesions with central necrosis may provide some diagnostic clues favoring tuberculous etiology in patients presenting with generalized lymphadenopathy [Figure 4]. However, histopathology remains the gold standard. ^{18}F-FDG PET/CT can demonstrate lesion extent, serve as a guide for biopsy with aspiration for culture, assist surgery planning and contribute to follow-up. ^{18}F-FDG PET/CT imaging can also help in the evaluation of therapeutic response in TB patients.[21] Early response evaluation in TB, especially in the setting of suspected multi-drug resistant TB is a strong indication where PET scores over culture with PET as early as 3-4 weeks after start of treatment being able to demonstrate response to no response.

Actinomycosis

Actinomycosis is caused most commonly by the anaerobic bacterium *Actinomyces israelii*. It can affect any organ in the body as a chronic suppurative infection, but cervico-facial, abdomino-pelvic, and the thoracic are the three most common types in the order of incidence.[22] However, unlike the case with other chronic infections, the immunocompromised status of the patient does not seem to increase its infection rate.[23] The abdomino-pelvic and thoracic types have a tendency to cause abdominal and mediastinal lymphadenopathy, respectively, with involvement of lymph node groups on the other side of the diaphragm as the disease progresses [Figure 5]. The thoracic disease, which initially colonizes the lung parenchyma or the airways, is notorious for its tendency to spread to chest wall with involvement of ribs and

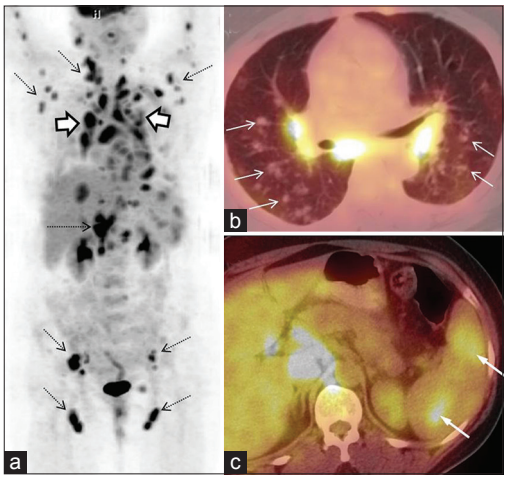

Figure 3: (a-c) A 31-year-old female with sarcoidosis, for baseline evaluation. Maximum intensity projection positron emission tomography (PET) image (a) revealed multiple enlarged ^{18}F-2-fluoro-2-deoxy-glucose (^{18}F-FDG) avid cervical, axillary, mediastinal, portal, retroperitoneal and inguinal lymph nodes (broken arrows). Note is made of the "lambda sign" due to typical symmetrical ^{18}F-FDG avid mediastinal lymph nodes involvement (a, bold arrows) transaxial PET/computed tomography images demonstrating lung (b, arrows) and splenic (c, arrows) involvement

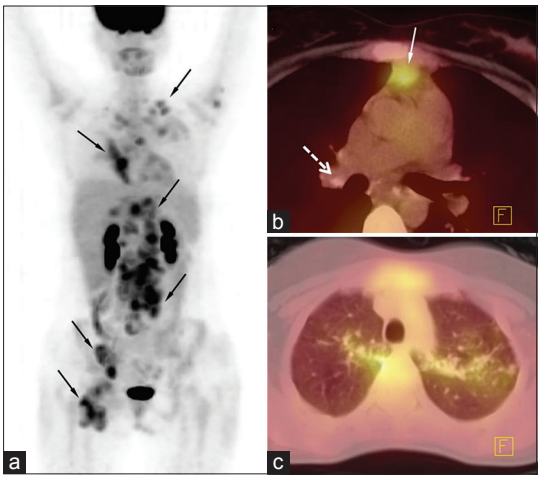

Figure 4: (a-c) A 21-year-old female, known case of tuberculosis. Maximum intensity projection positron emission tomography (PET) image (a) revealed multiple enlarged ^{18}F-2-fluoro-2-deoxy-glucose (^{18}F-FDG) avid cervical, axillary, mediastinal, mesenteric, retroperitoneal and inguinal lymph nodes (arrows) transaxial PET/computed tomography (CT) images of thorax (b) ^{18}F-FDG avid nodal (arrow) involvement. Note the calcification in mediastinal nodes (broken arrow). Transaxial PET/CT image of the lungs (c) ^{18}F-FDG avid pulmonary involvement

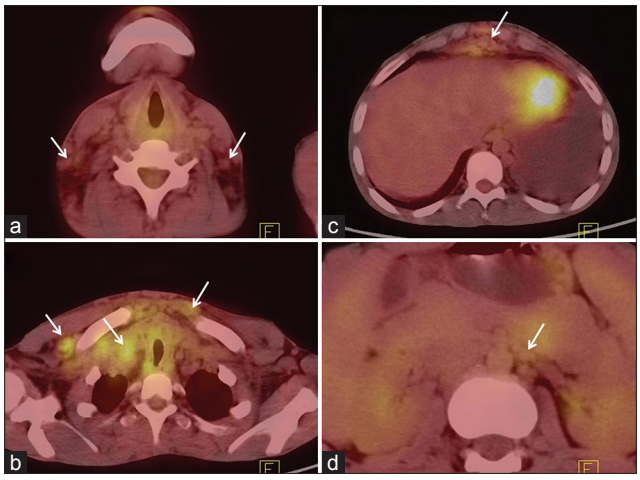

Figure 5: (a-d) A 27-year-old male who presented with generalized lymphadenopathy. Transaxial positron emission tomography/computed tomography images (a-d) revealed mildly ^{18}F-2-fluoro-2-deoxy-glucose avid bilateral cervical, axillary, mediastinal and abdominal lymph nodes (arrows). Biopsy from the lymph node was positive for actinomycosis

vertebrae,[24] owing to the organism's ability to produce proteolytic enzymes. The abdomino-pelvic disease may simulate the natural history of lymphoma[25] or a malignant process, masquerading as an intra-abdominal mass with constitutional symptoms and a prolonged course. A few cases of ^{18}F-FDG PET/CT appearance of actinomycosis have been documented.[26]

Histoplasmosis

Histoplasmosis, a systemic mycosis, is caused by the fungus *Histoplasma capsulatum*. The clinical spectrum of the disease ranges from an asymptomatic infection, an acute or chronic pulmonary infection, mediastinal fibrosis or disseminated histoplasmosis.[27] A chronic infection caused by the organism often results in a diagnostic dilemma due to the resemblance with other chronic diseases. The clinical and imaging features of chronic pulmonary histoplasmosis resemble reactivation of pulmonary TB (with hilar or mediastinal lymphadenopathy and diffuse reticulonodular infiltrates/cavitation in the lungs).[28] On the other hand, chronic disseminated histoplasmosis is, usually, seen affecting the immunocompromised patients and can involve multiple organs and systems. In immunocompromised state, patients with opportunistic fungal infection can present with generalized lymphadenopathy. Mediastinal lymphadenopathy can lead to troublesome compression of structures such as esophagus, superior vena cava and the airways;[28] however, the pulmonary parenchyma is, usually, unaffected in the disseminated form of the disease. Rarely histoplasmosis can present with oropharyngeal involvement in immunocompromised patients with disseminated disease in the form of generalized lymphadenopathy.[29] On PET/CT, lesions of the histoplasmosis are, usually, ^{18}F-FDG avid. Since, ^{18}F-FDG is a highly sensitive but not specific radiotracer for infection imaging, histoplasmosis is likely to be a cause for a false-positive examination, reducing the specificity of ^{18}F-FDG PET/CT for the detection and staging of lung carcinoma.[30]

Hodgkin's lymphoma

Hodgkin's lymphoma is one of the malignancies on which an immense amount of research has been and is still being done owing to its curability. In fact, the current literature suggests that with appropriate treatment, 65–90% of the patients can be rendered disease-free, depending on the clinical type and the stage.[31] Associated with a bimodal age distribution, the disease, usually, presents with a painless superficial lymphadenopathy with a contiguous spread by lymphatic network. Untreated cases lead to extranodal and visceral involvement, including bone marrow, spleen and liver along with generalized lymphadenopathy [Figure 6a and b]. ^{18}F-FDG PET/CT has a central role in the management of Hodgkin lymphoma. It has been shown to have a higher sensitivity compared with conventional imaging in staging and assessment of treatment response.[32] Although bone marrow involvement is uncommon, its identification on PET/CT has important clinical implications by identifying a site for marrow biopsy as well as accurate staging. A recent study by Ömür *et al*.[33] has shown that in cases with nodal and extranodal involvement, there was a high positive correlation ($r = 0.67$) between the SUVmax values of the highest ^{18}F-FDG accumulating lymph nodes and the involvement of extranodal sites.

High grade B-cell non-Hodgkin's lymphoma

High-grade non-Hodgkin's lymphomas (NHL) follow a more aggressive course and carry a poorer prognosis. Although there are 50 distinct subtypes of NHL, as per the Revised European-American Lymphoma classification, the following subtypes are labeled as high grade: Mantle cell lymphoma, follicular center lymphoma, grade III, diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma.[34] The affected lymph node groups in these subtypes, usually, tend to be intensely ^{18}F-FDG-avid on PET/CT and tend to have earlier involvement of extranodal sites such as the spleen and bone marrow.[35] In a patient presenting with generalized lymphadenopathy, intensely ^{18}F-FDG avid lymph nodes along with involvement of bone marrow and/or spleen on PET/CT may provide a clue to high grade lymphomatous etiology [Figure 6c and d]. Necrosis or calcification in the lymph nodes is almost never seen on baseline PET/CT but can be seen post chemotherapy. A recent study by Khan *et al*.[36] showed that ^{18}F-FDG PET/CT has a sensitivity of 94% in identifying bone marrow involvement in patients affected with DLBCL, when compared to 40% with bone marrow biopsy and thus, may be used as an effective diagnostic tool in identifying bone marrow involvement in aggressive lymphoma. Like in any lymphoma, PET/CT has a two-prong function in management of these aggressive lymphomas; while an interim PET/CT can be helpful in assessment and identification of early treatment response, an end-of-treatment PET/CT can be used to assess remission.[37] However, the literature is still inconclusive as to whether interim PET/CT should be included in standard therapy guidelines in the management of this group of disorders.[38]

Low grade B-cell non-Hodgkin's lymphoma

The most common types of NHL that are usually classified as low grade/indolent lymphomas include the B-cell small lymphocytic lymphoma (SLL/CLL), mucosa-associated lymphoid tissue marginal zone lymphoma and the indolent form (Grade I) follicular lymphoma.[39] Enlarged lymph nodes with low ^{18}F-FDG avidity on PET/CT imaging may suggest a low-grade lymphoma [Figure 6e and f]. ^{18}F-FDG PET/CT is sparsely used in the management of these lymphomas through their course in terms of staging, monitoring of therapy and follow-up. Another important role of PET/CT is the identification of infections and second malignancies in this group of lymphomas, particularly SLL.[40] Also, up to 5-10% of patient affected with indolent lymphomas transform to one of the aggressive, high-grade lymphomas and that generally heralds a poor prognosis.[41] ^{18}F-FDG PET/CT can be of great importance in this regard by demonstrating prominent increase in the ^{18}F-FDG uptake in transformed lymphoma.

Many studies have evaluated the role of PET/CT in the diagnosis and management of low-grade lymphomas in multiple possible dimensions. A study by Conte *et al*.[40] done on a large cohort of patients affected with CLL showed that the patients with high ^{18}F-FDG avidity tend to have poorer survival rates than those with low ^{18}F-FDG avid lesions on PET/CT. Also, PET/CT helps in identifying unique sites of extranodal involvement in grade 1 follicular lymphoma.

T-cell non-Hodgkin's lymphoma

T-cell lymphomas contribute to approximately 10-15% of all lymphoid malignancies.[42] T-cell lymphomas are considered as high-grade NHL. A fair proportion of patients present with concurrent nodal and extranodal disease, the commonest extranodal site being bone marrow and spleen. Also, the nodal disease tends to involve nodal groups on either sides of the diaphragm [Figure 7a]. Many of the T-cell lymphoma subtypes have a tendency to present with multiple extranodal site involvement with some subtypes showing up to 100% probability of extranodal disease; so majority of patients have poor risk disease with frequent relapses and unfavorable outcome.[43]

Many studies have evaluated the role of ^{18}F-FDG PET/CT in the management of T-cell lymphomas. In an analysis made by Casulo *et al*.[44] to assess the role of ^{18}F-FDG PET for staging of peripheral T-cell lymphoma, the study group found that

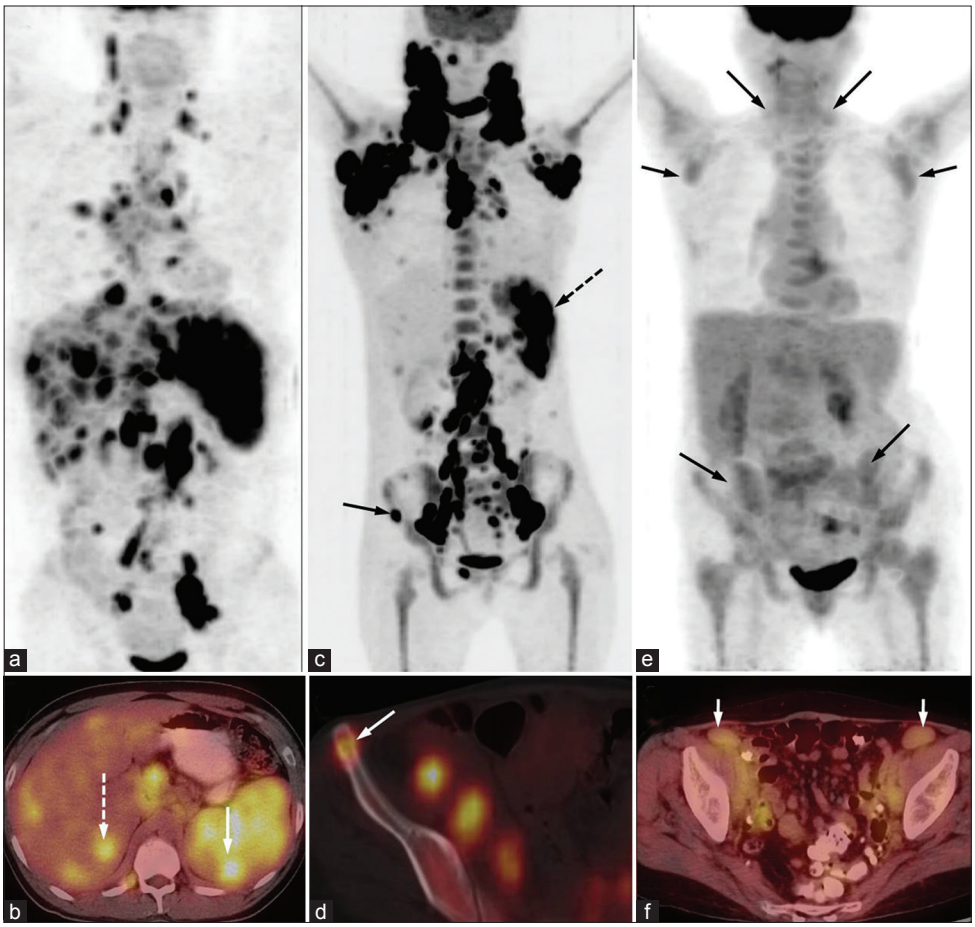

Figure 6: (a-f) A 38-year-old male with Hodgkin lymphoma (a and b), revealing ^{18}F-2-fluoro-2-deoxy-glucose (^{18}F-FDG) avid cervical, mediastinal, abdominal and inguinal lymph nodes, (a) apart from splenic (b, arrow) and liver (b, broken arrow) involvement. 34-year-old female with DLBCL (c and d), revealing ^{18}F-FDG avid enlarged cervical, axillary, mediastinal, abdominal and inguinal lymph nodes, apart from splenic (c, broken arrow) and bone marrow (d, arrow) involvement. 73-year-old female with B-cell SLL (e and f), revealing mildly ^{18}F-FDG-avid generalized lymph node involvement (arrows) with loss of normal architecture (f, arrows)

the ^{18}F-FDG PET/CT can identify additional sites of disease involvement. The study also showed that an interim PET/CT can help in predicting the progression-free survival in this group of patients. Another study by Cheng *et al*.[45] suggested that ^{18}F-FDG PET/CT plays a role in restaging, evaluation of outcome and treatment planning of T-cell lymphomas.

Angioimmunoblastic lymphadenopathy

Initially described in the medical literature as angioimmunoblastic lymphadenopathy, this entity was thought to be a hyperimmune lymphocyte pathology mimicking Hodgkin's lymphoma.[46] This disease has since undergone a change in nomenclature and now has been renamed as angioimmunoblastic T-cell lymphoma owing to an aggressive course and poor mean survival period. Apart from lymphadenopathy, other findings include constitutional symptoms, hepatosplenomegaly and autoimmune phenomena in elderly patients, typically in their sixth or seventh decade of life.[47] The clinicopathological features of this disease qualify it as a subtype of peripheral T-cell lymphomas;[48] however, there is considerable overlap among the various subtypes and hence, the exact classification is still evolving. Irrespective of these factors, this disease carries a poor outcome with a median survival of about 3 years.[48] Not many studies have been done to understand the role of ^{18}F-FDG PET/CT in the management of this disease, perhaps owing to its rarity and its aggressive course with shortened survival. Such patients can present with ^{18}F-FDG avid generalized lymphadenopathy on PET/CT [Figure 7b]. More studies in the future assessing the role of ^{18}F-FDG PET/CT in this entity might offer a better insight in understanding the disease biology and management.

Metastatic lymphadenopathy

Any malignancy which spreads through lymphatic route can present with generalized lymphadenopathy at an advanced stage; such as carcinoma of breast, lung, digestive tract, melanomas, ovary [Figure 8] and head and neck cancers. Also, lymph nodes are the most common site of metastases encountered in the evaluation of carcinoma of unknown primary.[49] Apart from the changes in their architecture on anatomic imaging, many studies have shown that lymph nodes from metastatic deposit tend to show a higher value of their SUV parameters as against their benign counterparts;[50] however this does not hold true in a significant minority of cases. Although certain cancers can classically present with generalized lymph node enlargement, some cases have been described to arise from such primary sites which are not known to cause isolated widespread nodal dissemination at initial presentation. One such case of prostatic adenocarcinoma has been described by Joshi and Lele[51] where an elderly male presented with lymphadenopathy without any urinary symptoms; the case clinically was mimicking lymphoma. However, the ^{18}F-FDG PET/CT done in this patient helped in identifying the primary, in staging and initiation of appropriate treatment for his actual condition. Also, such situations have been encountered where not the malignancy *per se,* but even

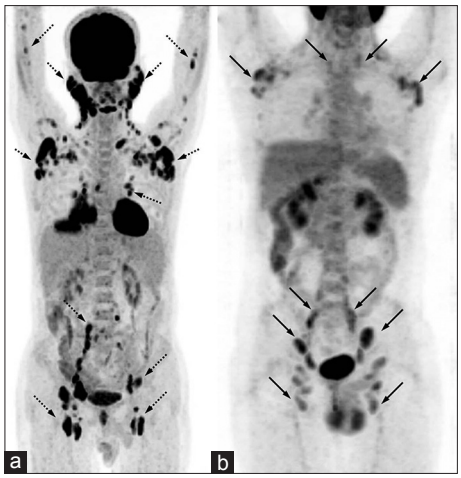

Figure 7: (a and b) A 57-year-old male with CD3+ peripheral T-cell lymphoma. Maximum intensity projection (MIP) positron emission tomography (PET) image (a) revealing ^{18}F-2-fluoro-2-deoxy-glucose (^{18}F-FDG) avid bilateral multiple cervical, axillary, mediastinal, abdomino-pelvic and inguinal lymph nodes (broken arrows), 27-year-old male with angiolymphoblastic T-cell lymphoma. MIP PET image (b) revealing mild to moderately ^{18}F-FDG avid bilateral multiple cervical, axillary, mediastinal, abdomino-pelvic and inguinal lymph nodes (arrows)

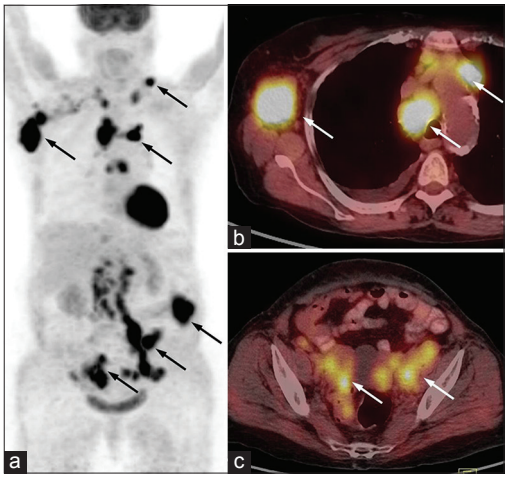

Figure 8: (a-c) A 67-year-old female with biopsy proven ovarian carcinoma. Maximum intensity projection positron emission tomography (PET) image (a) and transaxial PET/computed tomography images (b and c) revealed multiple enlarged ^{18}F-2-fluoro-2-deoxy-glucose avid cervical, axillary, mediastinal, retroperitoneal, mesenteric and pelvic metastatic lymph nodes (arrows)

the treatment modalities employed in its management have caused generalized lymphadenopathy and led to diagnostic ambiguities. One such case has been described by Yune *et al*.[52] where a person with malignant melanoma developed generalized lymphadenopathy after he underwent interferon therapy. Although ^{18}F-FDG PET/CT was not helpful in distinguishing the reactive nodal enlargement, this case brings to fore a pitfall of PET/CT and warns an interpreting physician to be aware of such possibilities.

CONCLUSIONS

Generalized lymphadenopathy is a relatively common clinical problem and can be caused by a wide array of inflammatory,

infective and malignant pathologies. Due to its ability to detect upregulated glucose metabolism, ^{18}F-FDG PET/CT can be used for evaluation of these diseases presenting with generalized lymphadenopathy. It can help in narrowing the differential diagnoses, detect extranodal involvement and be useful for post therapy monitoring in such patients. Familiarity of the nuclear radiologist with the causes and ^{18}F-FDG PET/CT patterns of generalized lymphadenopathy are essential for optimum utilization in this clinical setting.

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