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Multiple Benign Metabolically Active Lesions on F-18 FDG PET/CT can Mimic Malignant Lesions

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Oncology, F18-fluoro2-deoxy-D-glucose, Malignant tissue, Infection, Inflammation, granuloma.

Introduction
Nowadays positron emission tomography/computed tomography (PET/CT) with F18-fluoro2-deoxy-D-glucose (FDG) has established role in oncology, and consider as a standard care in many malignancies. FDG PET/CT has already gained widespread acceptance in the initial staging of cancer, detection of recurrent cancer, restaging and monitoring response to therapy.

FDG is an analog of glucose and is used as an indicator of glycolysis. Malignant tissue and cells in contrast to normal cell often showed increased rate of glycolysis for rapid proliferation, due to increased number of glucose transporter protein and increased intracellular hexokinase and phosphokinase levels [1,2]. FDG uptake is semiquantitatively measured in the form of the most widely used parameter maximum standardized uptake value (SUVmax). SUVmax reflects the highest pixel in a volume of interest (VOI) [3].

It was shown that incorporation of FDG PET/CT in the management of oncological patients, in different disease stages leads to significant changes in patient management in up to 20-40% of patients [4]. However, FDG is not cancer-specific as increased FDG uptake can be seen in many benign diseases or non-malignant conditions, as inflammation and infection [5,7].

Not every FDG-positive lesion means cancer. At the site of infection and inflammation there is enhanced FDG uptake due to increased tissue perfusion [8] and enhanced FDG uptake by the activated inflammatory cell through release of multitude cytokines, up regulation of GLUT-1 and 3 and increase in hexokinase activity [9].

As a result of the previous mentioned mechanism, variety of non-malignant benign lesions have increased FDG radiotracer including infection, inflammation, autoimmune processes and sarcoidosis may result in false positive results in FDG PET/CT in cancer patients. If such false positive results are not early and accurately identified misdiagnosis can lead to inadequate or unneeded therapies.

In this study we retrospectively reviewed FDG PET/CT scans with multiple metabolically active lesions from Sep. 2010 to Nov. 2018 which proved by histopathological examination to be non-malignant benign, to clarify the incidences and varieties of benign multiple metabolically active lesions that can mimic malignant lesions, resulting in false positive results in FDG PET/CT scans.

Material and Methods
We reviewed the FDG PET/CT scans in our hospital from September 2010 to November 2018 looking for patients with suspicious multiple metabolically active lesions with unknown diagnosis. Then we included only patients with later on histopathology confirmed benign histology of these multiple lesions seen in PET/CT scan. Descriptive statistical analysis was performed. We analyzed the PET/CT scans for those patients with pathology confirmed benign lesions regarding patient's presentation, scan indication, involvement of lymph node only or with other organ involvement, which organs are involved, the main organ involved, differential diagnosis based on PET/CT scan, possible follow-up imaging studies and final diagnosis based on histopathology.

Results
We found 95 FDG PET/CT scans in our hospital data base from September 2010 to November 2018 for patients with multiple suspicious metabolically active lesions with unknown diagnosis.

Twenty six patients (27%) of them showed histopathology confirmed benign histology of these multiple lesions. Patient's age ranged from 12 to 85 years (mean 48±21.5 years), 13 female and 13 male.

Nine patients presented with generalized lymphadenopathy, 6 with fever of unknown origin (FUO), 4 with cough an chest pain with lung lesions in CT, 3 with weight loss and generalized weakness, one with chronic abdominal pain and vomiting with abdominal lymphadenopathy in CT, one with treated brain tumor and CT showed multiple lung and gastric masses, one with breast cancer and CT showed supra and infra diaphragmatic lymphadenopathy and finely one patient with bilateral lower limbs pain and bone scan showed multiple bony lesions. Indication of the PET/CT scans was to rule out malignancy in 20 patients and to localize the cause of fever in 6 patients.

The lymph node is the most common organ involved as seen in 94 scans out of 95 and in 25 patients out of 26 patients. Lymph nodes were the only sites of involvement in 9 patients. One patient with Erdhiem Chester disease (ECD) showed no lymph node involvement. Both Infra and supra-diaphragmatic lymph nodes involvement were seen in 16 patients. Eight patients had only supra diaphragmatic lymph nodes involvement and 1 patients had only infra-diaphragmatic lymph nodes involvements. Lung involvement was seen in 12 scans, bone and spleen noted in 4 scans each, kidneys, bone marrow, ovaries, peritoneum and mesentery and liver were seen in 3 scans each, muscles, skin, pleura and myocardium in 2 scans each, while brain, pituitary, orbit, parotid and salivary glands, nose and nasal sinuses, bowel and pericardium in 1 scan each (Table 1).

Organ Involved	Number of Scans	Percentage
Lymph nodes	94	98.9%
Lung	12	12.6%
Bone	4	4.2%
Spleen	4	4.2%
kidney	3	3.15%
Bone marrow	3	3.15%
Ovaries	3	3.15%
Peritoneum and mesentery	3	3.15%
Liver	3	3.15%
Muscles	2	2.1%
Skin	2	2.1%
Pleura	2	2.1%
Myocardium	2	2.1%
Brain	1	1.1%
Pituitary	1	1.1%
Orbit	1	1.1%
Parotid and salivary glands	1	1.1%
Nose and nasal sinuses	1	1.1%
bowel	1	1.1%
Pericardium	1	1.1%

Table 1: Organ involvement in 95 FDG PET/CT scans.

The lymph nodes were the main organ involved in 19 patients, the lung in 4 patients, bone in 2 patients and brain in one patient.

Table 2 demonstrates the final diagnosis based on biopsy and histopathological examination of the 26 patients. The most prevalent diagnosis was TB in 9 patients followed by sarcoidosis in 5 patients and granulomatous disease in 4 patients, collectively representing 69.2% of studied patients.

Final diagnosis	Number	Percentage
Tuberculosis	9	34.6%
Sarcoidosis	5	19.2%
Granulomatous disease	4	15.4%
Dermatopathic lymphadenitis	2	7.7%
Non-granulomatous infection	1	3.8%
Granulomatosis with polyangiitis	1	3.8%
Erdhiem Chester disease,	1	3.8%
Kikuuchi disease	1	3.8%
Cytomegalovirus lymphadenitis	1	3.8%
Anthracosis of lungs	1	3.8%
Total number	26	

Table 2: Final diagnosis based no biopsy and histopathological examination of 26 patients.

Patients with granulomatosis with polyangiitis (GPA) and ECD showed widespread metabolically active lesions with multiple organ involvement.

One patient with known breast cancer with supra and infra diaphragmatic lymphadenopathy proved by histopathological examination to be granulomatous disease with no evidences of malignancy and other patient with brain tumor and multiple lung and gastric mass also proved to be granulomatous disease.

In all patients FDG PET/CT could not differentiated between malignant and benign lesions based on degree of metabolic activity however; PET/CT suggested the site of biopsy in all the 26 patients.

The following are 2 illustrated cases from our patient population:

Case 1

A 12-year-old girl with generalized lymphadenopathy, suspicious of lymphoma or infection. PET/CT images (Figure 1) revealed extensive widespread hypermetabolic bilateral cervical, bilateral axillary, mediastinal and hilar, paraortic, pelvis and bilateral inguinal lymphadenopathy.

Excisional left inguinal lymph node biopsy revealed CMV lymphadenitis while adenoids excisional biopsy revealed Follicular lymphoid hyperplasia.

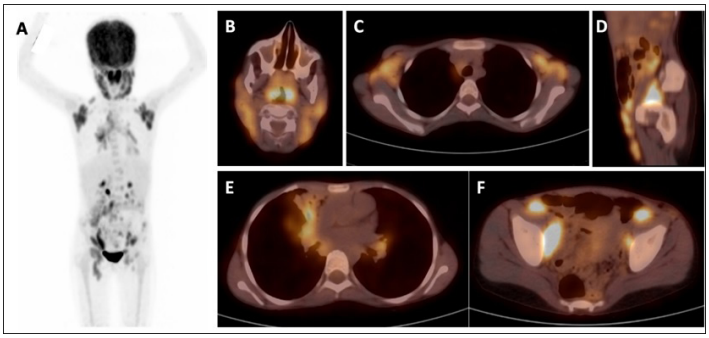

Figure 1: F-18 FDG PET/CT images showing widespread enlarged hypermetabolic regional lymph nodes allover the body in the anterior projection MIP image (A). More accurate localization is noted in the fused PET/CT images showing bilateral cervical (B), bilateral axillary (C), mediastinal and hilar (E), abdomino-pelvic and bilateral inguinal (D, F) lymphadenopathy.

Case 2

A 41-year-old male presented with fever, shortness of breath, bilateral parotid swelling and cough with increased erythrocyte sedimentation rate and elevated C-reactive protein.

On CT there was a large left upper lobe enhancing pulmonary mass with high FDG uptake on PET/CT with SUVmax of 7.7 (Figure 2). FDG PET/CT and CT head and neck, chest, abdomen, and pelvis revealed high metabolic uptake in nasal region with mucosal hypertrophy, high uptake in the enlarged parotids, pericardial effusion, focal hypermetabolic hypodense bilateral renal cortical lesions and hypermetabolic enlarged prostate (Figure 3).

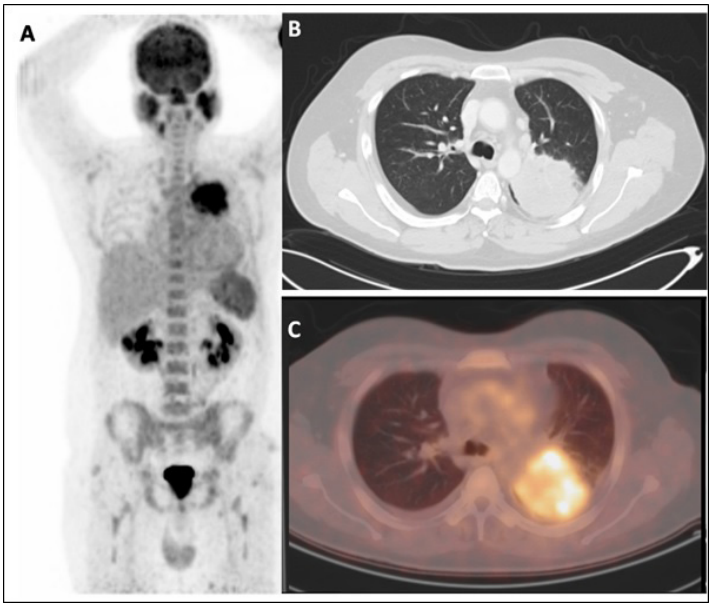

Figure 2: CT (B) showing large left upper lobe enhancing pulmonary mass with high FDG uptake on PET/CT (A, C) [25].

Biopsy of the lung mass showed granulomatous noncaseating inflammation with no evidence of malignancy. Lab findings demonstrated high antineutrophil cytoplasmic antibody (ANCA) titer with elevated c-ANCA and anti-PR3 titers (119 units) while negative myeloperoxidase antibodies. According to the above clinical, radiological, laboratory and histopathological findings, diagnosis of GPA was proposed [25].

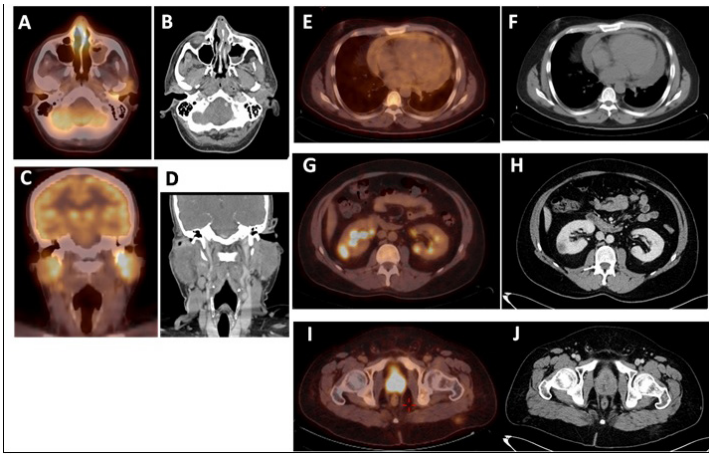

Figure 3: F-18 FDG PET/CT and CT head and neck, chest, abdomen, and pelvis revealed high metabolic uptake in nasal region (A) with mucosal hypertrophy on computed tomography (B), high uptake in enlarged parotids (C and D), pericardial effusion (E and F), focal hypermetabolic bilateral hypodense renal cortical lesions (G and H), and hypermetabolic enlarged prostate (I and J) [25].

Discussion

FDG is not cancer-specific as increased FDG uptake can be seen in many benign diseases or non-malignant conditions, as inflammation and infection [5,7] resulting in false positive result in PET/CT oncological scan with a reported false positive rate of 13% and false negative rate
of 9% [10].

At the site of infection and inflammation there is enhanced FDG uptake due to increased tissue perfusion [8] and enhanced FDG uptake by the activated inflammatory cell through release of multitude cytokines, up regulation of GLUT-1 and 3 and increase4d in hexokinase activity [9,11] resulting in increased FDG radiotracer by non-malignant benign lesions such as infection, inflammation, autoimmune processes and sarcoidosis which may result in false positive results in FDG PET/CT in cancer patients. If such false positive results are not early and accurately identified misdiagnosis can lead to inadequate therapies.

There is a considerable increase in referrals for patients with fever of unknown origin (FUO), generalized lymph node (LN) enlargement, and mediastinal or abdominal lymphadenopathy for PET/CT generally to rule out an underlying malignant disease and to detect the best site for biopsy.

In this retrospectively study we showed many patients pathologically proven multiple metabolically active benign lesions in FDG PET/CT scans that can mimic malignancy and may result in mismanagement.

We analyzed these cases regarding the diagnosis of this multiple

benign FDG avid lesions, organ and sites involvement in different disease and what is the main organ involvement.

The most common indication of PET/CT scans in our study patients population is generalized lymph adenopathy followed by FUO. It was concluded by Kouijzer et al. that FDG-PET/CT is a helpful technique in diagnosing FUO in both adults and children and should become a routine procedure in the workup of FUO when diagnostic clues are absent [12].

Multiple metabolically active lymph nodes seen in 25 patients out of 26 (96%). There are 9 patients out of 26 (34.6%) in whom multiple metabolically active lymph nodes were the only sites of involvement while on the other hand there is only one patient out of 26 (3.8%) with Erdhiem Chester disease who showed no lymph nodes involvement and had been previously published as a case report [22].

The lymph node is the most common organ involved as seen in 94 scans out of 95 and in 25 patients out of 26 patients and lung is the second most common organ involved as seen in 12 scans out of 95 (12.6%)

We found that tuberculosis is the most common cause of multiple metabolically active benign lesions in FDG PET/CT scan account for 34.6% of all cases which is expected in Saudi Arabia due to high incidence of TB. The most common organ involvement was the lymph nodes however; many other organ and region were noted such as lung, kidney, ovary and brain. This matched with many studies that documented increased FDG uptake in active TB in different anatomical locations, mimicking malignant processes [13-16].

Sarcoidosis was the second commonest cause of multiple metabolically active benign lesions in FGD PET/CT scan in our study account for 19.2% of all cases. Many studies reported that FDG PET/CT has been shown to be a very sensitive study to assess the inflammatory activity in sarcoidosis as well the disease extent and also can assess response to treatment [17-20].

Patients with GPA and ECD showed widespread metabolically active lesions with multiple organ involvement. many studies and case reports had shown that 18F-FDG PET/CT may aid in establishing a diagnosis, assess disease extent, guide biopsies, and assess treatment response in ECD patients [21-24].

Many studies and case reports showed the value of FDG PET/CT in GPA [25-27]. In our study there are 4 cases out of 26 diagnosed as granulomatous inflammatory disease and it was reported that FDG PET/CT can be used in the management of such disease by guiding the site of biopsy, assess extent of the disease and also in monitoring the treatment response [28,29].

Our study showed that multiple metabolically active lesions on FDG PET/CT do not always represent malignancy and every nuclear medicine physician/radiologist should keep in mind the possibility of benign infectious and inflammatory disease and correlation with histopathological examination is a must to avoid misdiagnoses.

Conclusion

Multiple widespread metabolically active lesions with multiorgan involvement on FDG PET/CT scan can be due to a variety of benign diseases that can mimic malignant lesions. Utmost caution should be taken to avoid interpreting such findings as malignant, prior to thorough clinical and histopathological confirmation.

Nuclear Medicine physicians should always take in consideration the possibility of benign metabolically active disease especially in regions with known endemic granulomatous disease.

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