Beyond Lymphoma And Tuberculosis: Role of imaging By 18F-FDG PET/CT In Pyrexia Of Unknown Origin.

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Learning objectives

1. Understand the definition, various causes of pyrexia of unknown origin [PUO].

2. Introduce briefly the technique of 18F-FDG PET/CT, common pitfalls and mimics in the context of PUO.

3. Understand the role of 18F-FDG PET/CT in PUO and its usefulness in scanning the entire body, allowing detection of metabolically active lesions by integrating anatomical details with functional alterations.
Background

PUO is a common but sometimes challenging clinical condition. FDG PET/CT have the synergy of anatomical and metabolic information of the pathology concerned and thus can replace other imaging techniques in the evaluation of PUO. It reveals functional alterations that precede the morphological changes. Whole body scanning, identification of unusual causes, localization of the precise site for biopsy, recognition of coexisting pathologies are its unique advantages. Various pathologies present as PUO without their typical clinical and imaging features. Earlier, tuberculosis and lymphoma were the most common diagnosis when all possible investigations for PUO would not help in diagnosis. Though infectious conditions dominate the underlying cause, neoplastic and inflammatory pathologies are next in the line. $^{18}$F-FDG is attractive in patients with PUO as the causes most often responsible for the condition are usually FDG avid. This exhibit describes the various possible underlying causes of PUO and highlights the importance of $^{18}$F-FDG PET in the diagnostic work-up of PUO. Suggestion of using 18F-FDG PET/CT as an initial non invasive diagnostic modality in evaluation of patients with PUO is not far from reality in future.
Findings and procedure details

Pyrexia of unknown origin (PUO) is defined as a temperature higher than 38.3°C on several occasions lasting longer than 3 weeks with a diagnosis that remains uncertain after at least three days of in-patient appropriate investigation or two weeks of outpatient investigation [1,2]. This poses a diagnostic challenge and can be due to a spectrum of pathologies including infection, inflammatory diseases, neoplastic conditions and miscellaneous pathologies. About 9% - 30% of patients in different studies even go undiagnosed, representing ‘true’ PUO [1]. Series of non invasive investigations follow a thorough history taking and clinical examinations. Imaging studies including chest radiographs, abdominopelvic ultrasound, chest/abdomen/pelvis CT/MRI will be done as appropriate. Also PET/CT and lower limb doppler may be indicated when clinically relevant. Final diagnoses are determined in a number of ways including natural history, biopsy, surgery, postmortem examinations.

Earlier, tuberculosis and lymphoma were the most common diagnosis when all possible investigations for PUO would be negative. Here, we discuss various causes of PUO and imaging findings under:

1. **Infectious**: FDG accumulates at the sites of infection like: renal abscess, focal nephritis, cholecystitis, pericarditis, infected transplant kidney, Tuberculosis including a case of unusual isolated splenic tuberculosis, infection in orthopedic prosthesis.

2. **Inflammatory**: Arteritis, subacute thyroiditis, inflammatory bowel disease, autoimmune and granulomatous diseases like sarcoidosis.

3. **Uncommon conditions**: like Castleman’s disease, Rosai Dorfman disease, Kikuchi-Fujimoto disease.


5. **PUO in HIV infected patients**.

**Technical considerations in FDG PET/CT:**

In 1931, Dr.Otto Warburg described that the tumor tissue metabolizes glucose anerobically under aerobic conditions. He showed that cancer cells used glucose anerobically to produce lactic acid in non hypoxic tissues, rather than using the more
efficient tricarboxylic acid cycle [TCA] of oxidative phosphorylation to drive ATP synthesis in the mitochondria. This effect is called 'Warburg effect' [Figure 1].

18F-Labeled FDG is a structural analog of 2-deoxyglucose with a half-life of 110 min. The mechanisms of transport [3] that are responsible for the uptake of glucose and 18F-FDG into the cells include [1] passive diffusion, which is of minor importance for human tissues, [2] active transport by a Na+ dependent glucose transporter (GLUT), which is of importance in kidney epithelial cells and in the intestinal tract [3] the most important pathway for 18F-FDG to enter the cell body of almost all human cells, is mediated by the facultative GLUT-1 through GLUT-13. Once 18F-FDG has entered the cell, it is subsequently phosphorylated to 2-deoxyglucose-6-phosphate by the hexokinase enzyme. This further does not get into glycolytic pathway unlike glucose-6-phosphate, thus getting trapped in the tissues and tumor cells with low glucose-6-phosphatase enzyme [which is necessary for dephosphorylation]. 18F-FDG is preferably taken up in tissues with high glucose consumption. Imaging is started as early as 30-60 min after injection. High FDG is accumulated in brain in cortex and basal ganglia. Cardiac uptake is seen, which can hamper diagnosis of endocarditis or myocardial sarcoidosis. A fatallowed, carbohydrate restricted diet starting the day before F18-FDG administration can suppress myocardial F18-FDG uptake satisfactorily [3]. Smooth muscle peristalsis may result in bowel wall uptake. Urinary accumulation of the FDG can result in difficulty in interpretation of pelvis. Bone marrow uptake is variable [4, 5]. Uptake of FDG in bone marrow may be high especially in patients with fever where there is an interleukin-dependent up-regulation of glucose transporters. This uptake might cause a false impression of bone marrow involvement and often requires a correlative biopsy for verification. Patchy bone marrow uptake is, however, more suggestive of pathologic involvement [6]. Thymic uptake, especially in children, can also be observed. FDG uptake by brown adipose tissue (BAT) in humans is more pronounced during fasting and in cold climatic conditions. Patient preparation rooms with a comfortable warm temperature can help in this regard [3]. Starting steroids before FDG PET should be avoided as normalization of FDG uptake in the inflammatory lesions has been demonstrated, which would hamper the diagnostic value of the procedure. Also, as avid FDG uptake occurs in muscle tissues, limiting physical activity before injection can minimize striated muscle uptake of FDG. In diabetics, peripheral insulin resistance may cause decreased uptake at the site of inflammation. In malignancies, sensitivity may be lowered by high glucose levels (>180 mg/dL or >10 mmol/L) at the time of the study but not by diabetes itself. However in infection and inflammation, impact on false negative rate was not significant [3].

18F-FDG accumulates in malignant tissues but also at the sites of infection/inflammation and in autoimmune and granulomatous diseases by the over expression of distinct facultative glucose transporter (GLUT) isotypes (mainly GLUT-1 and GLUT-3) and by an overproduction of glycolytic enzymes in cancer cells and inflammatory cells [4].
FDG uptake is present in all activated leukocytes (granulocytes, monocytes as well as lymphocytes) enabling imaging of acute and chronic inflammatory processes [3].

Imaging by F18 FDG- PET/CT is helpful in many ways [4,5]

1. Early detection by accumulation of radiotracers, even before they are morphologically evident[Figure 2].

2. It is a whole body scan, hence allows detection of both the location and the number of foci, also at sites that are clinically not suspected.

3. A great diagnostic tool in autoimmune and noninfectious inflammatory diseases when other imaging modalities fail to detect the pathology.

4. High negative predictive value of this technique in the assessment of PUO: A negative scan on FDG PET/CT [after excluding non-focal systemic diseases] helps to allow-wait and watch strategy, temporarily halting the need for further investigations [3].

**Infectious conditions:**

18F-FDG PET has about 90% sensitivity in diagnosing abdominal and pelvic abscesses, active tuberculosis, atypical pneumonias, renal abscess, focal nephritis[ Figure 3,4] bacterial colitis, diverticulitis, and infected vascular grafts [4]. Early infectious processes are picked up on FDG PET/CT when other diagnostic procedures are normal. Tuberculosis is the most common infectious disease that causes PUO in developing countries [6] [Figure 5,6a,6b].

Infective endocarditis is one of the known sources of infection that can cause PUO. Clinical and laboratory data, along with the echocardiographic identification of valvular vegetations are usually sufficient. However, vegetations identified on echocardiography may not be infected. Also, small vegetations in patients with prosthetic heart valves may be obscured by the intense echoes produced by the prosthesis and may be difficult to detect on echocardiography. In spite of the normal myocardial FDG uptake, FDG PET accurately helps identify sites of infective endocarditis in majority of the patients [7].

**Pericarditis:** Inflammatory process that can result from localized or systemic diseases, including infection, connective tissue disorders, and uremia show mild FDG uptake. Pericardial thickening, pericardial enhancement, minimal to mild FDG uptake, and pericardial fluid are imaging features [Figure 7] on FDG PET/CT[8].
**Soft tissue infections:** can be easily identified on PET. In musculoskeletal system FDG PET/CT can demonstrate new sites of infection and can subsequently guide surgical management [9]. Asymptomatic chronic osteomyelitis, especially of the central skeleton can present as PUO. Accuracy is about 97% for peripheral skeleton and 93% for axial skeleton [4] [Figure 8a,8b,8c].

**Infection of an orthopedic prosthesis** (mainly of the hip or the knee) can cause fever for extended period in some patients. Though sensitivity is high, differentiation between abrasion-induced inflammation and bacterial inflammation is not always possible by 18F-FDG PET. Thus a negative PET in a case of PUO in suspected prosthesis infection eliminates the need for further investigations or revision surgery. However, a positive result does not differentiate inflammation and infection. Also, aseptic loosening and infection of a prosthetic joint are both accompanied by an inflammatory response, hence are difficult to differentiate [3,7]. Overall sensitivity and specificity of F18-FDG PET for diagnosing prosthetic joint infection were 82% and 87%, respectively [3]. Also FDG uptake can be increased in inflammatory arthritis, in acute fractures, and in normally healing bone up to 4 months after surgery. These factors are to be excluded before deciding the cause of increased FDG uptake [7].

FDG PET has not shown significant role in the diagnosis of meningitis as cause of fever due to physiological uptake in that region [5].

**Noninfectious Inflammatory Diseases:**

Autoimmune and connective tissue diseases, vasculitis syndromes, granulomatous disorders (sarcoidosis, Crohn's disease), subacute thyroiditis and "miscellaneous" diseases, constitute about 15%-30% of all causes of PUO [4].

**Vasculitis** is defined as blood vessel inflammation with leukocytic infiltration in the vessel wall and reactive damage to mural structures and surrounding tissues [4]. Takayasu's arteritis predominantly affects female patients between the ages of 10 and 40 years. The disease occurs worldwide but is most prevalent in Asian populations [8]. Large-vessel vasculitis, especially giant cell arteritis (GCA) is mainly seen in older patients, older than 50 years, and the highest rates are reported in Scandinavian and North American countries [8]. PET may be the first study to help identify vasculitis in patients who are referred for whole-body imaging for constitutional symptoms and fever of unknown origin, before anatomic changes are identifiable at CT or MR imaging. Circumferential region of increased metabolic activity in the vessel walls is considered diagnostic of active disease on FDG/PET [8]. Wall thickening, wall enhancement, and alternating focal areas of luminal narrowing and dilatation are seen on CT and MR imaging [8]. A homogeneous smooth linear and long segmental uptake in the thoracic aorta and its main branches
[Figure 9], with higher intensity compared to the liver, is considered to be a characteristic pattern of giant cell arteritis (GCA)[3]. Takayasu's arteritis may have similar clinical presentation. A positive hypoechogenic halo on duplex sonography correlates well with FDG PET in larger arteries, but not in arteries less than 4mm [4,5], since the spatial resolution of F18-FDG PET is of 4-6 mm. Thus it is less useful in medium and small vessel inflammation[3]. FDG PET is useful in these conditions, only when there is large vessel involvement or in case of damage to the adjacent tissues.

Another added value of FDG/PET is that it helps in assessment of extent of disease in the whole body. Thus whole-body 18F-FDG/ PET can be used as the investigation of choice if vasculitis of the large arteries is suspected, because the chance of a positive finding may be higher with PET than with MRI [4,5]. Disease activity and monitoring response to therapy is another area where FDG PET appears to be reliable noninvasive investigation. Thus FDG PET is very useful in detection of early Takayasu's arteritis and demonstrating extratemporal disease in atypical giant cell arteritis. Early diagnosis leads to early treatment which would help prevent life threatening complications of these conditions [4,5].

Vasculitis of medium and small vessels like Churg-Strauss syndrome, Wegener's disease, and polyarteritis nodosa are less studied and FDG PET would help in detection only when larger vessels are involved[4,5].

**Sarcoidosis**, a multisystem granulomatous disease of unknown etiology, is another cause of PUO[Figure 10]. Elevated FDG uptake in mediastinal and hilar nodes, without other radiological findings may be seen on FDG PET/CT. Visualization of the so-called "Lambda sign" (#) is a helpful clue [6]. Assessment of disease is important to determine the type of treatment. The degree of FDG uptake correlates well with disease activity and FDG/PET could be used for monitoring response to treatment, which is an additional advantage of FDG PET/CT[7]. However FDG/ PET cannot distinguish sarcoidosis from other causes of lymphadenopathy with uptake in the same locations [4].

**Crohn’s disease**: 18F-FDG/ PET had a sensitivity of 85.4% and a specificity of nearly 90% in detecting foci of uptake in atypical Crohn's disease [4].

**Subacute thyroiditis**: is a quite common noninfectious, inflammatory cause of PUO[4]. Inflammation of the thyroid tissue is accompanied by decreased glandular iodine content (decreased attenuation on CT). This finding on CT along with diffusely increased FDG avidity[Figure 11] supports a diagnosis of thyroid inflammation [6].

**Kikuchi-Fujimoto disease (KFD)**: is histiocytic necrotizing lymphadenitis, a rare and benign condition described in young women, characterized by cervical lymphadenopathy
and fever and is often mistaken for more serious conditions[10]. An immune response of the T cells and histiocytes to an inciting agent is said to be behind pathogenesis. Fever is the most prominent symptom, with lymphadenopathy [axillary, mediastinal, iliac, intraparotid, retrocrural, peripancreatic and celiac nodes], most common being cervical[Figure 12]. Other causes of generalized lymphadenopathy including tuberculosis (TB), lymphoma, HIV-AIDS, toxoplasmosis, secondary syphilis, Lymphogranuloma venereum and Kawasaki disease are to be considered in the differential diagnosis[11]. CT shows diffuse enhancing lymph nodes. Many cases have been wrongly diagnosed as tuberculosis or lymphoma. Thus definitive diagnosis is by biopsy. PET/CT would help in locating site of accessible, active node for biopsy. Though this disease is self limiting and managed supportively, it needs follow up as these patients can develop autoimmune diseases like systemic lupus erythematosus [10].

**Rosai-Dorfman Disease** [Multicentric sinus histiocytosis], [Sinus histiocytosis with massive lymphadenopathy] is a rare, benign granulomatous disease that typically presents with massive cervical lymphadenopathy[ Figure 13]. In 43%, the disease can be extranodal and it usually includes skin, soft tissues, respiratory system, genitourinary system, bones, central nervous system (CNS), orbit, thyroid and breast. CNS and renal involvement is uncommon. Fever, leukocytosis, increased erythrocyte sedimentation rate and hypergammaglobulinemia can be the initial presentation. The final diagnosis is by histologic examination, which typically shows intrasinus histiocytic proliferation with cells showing lymphocytophagocytosis. Rosai-Dorfman disease should be considered in the differential diagnosis of granulomatous infection, pseudogranulomatous lesion and malignancy[12].

**Castleman disease:**

Castleman disease is also known as angiofollicular lymph node hyperplasia or giant lymph node hyperplasia. Castleman disease is one of the causes of non neoplastic lymphadenopathy. It commonly involves lymphatic tissues. Extra lymphatic sites of involvement include the lungs, larynx, parotid glands, pancreas, meninges, and muscles. Plasma cell and hyaline types are described, the former most commonly presenting in the form of multicentric disease. Hyaline vascular disease is more common and is unicentric in 90% of the cases and usually manifests as an asymptomatic mass lesion with a benign course. Plasma cell castleman disease is commonly associated with fever, night sweats, and malaise; hematologic and immunologic abnormalities such as anemia, thrombocytopenia, hyperglobulinemia and splenomegaly.

Hyaline vascular disease commonly presents as solitary enlarged lymph node or localized nodal masses that demonstrate homogeneous intense enhancement on contrast scans. Hyaline vascular disease has a considerable predilection for involvement of the thorax, where it typically manifests as an avidly enhancing mediastinal nodal mass.
Plasma cell disease typically demonstrates less avid enhancement after contrast material administration compared with hyaline vascular type, thus making the differentiation from reactive or neoplastic nodal involvement more difficult. Calcification is uncommon. Intralesional fibrosis and necrosis may lead to a heterogeneous appearance, especially in lesions larger than 5 cm. Plasma cell disease occurs more frequently as multicentric disease, with diffuse lymphadenopathy that involves multiple anatomic regions, including bilateral hilar and mediastinal lymphadenopathy and diffuse thoracic, abdominal, pelvic, or cervical lymphadenopathy. There is a tendency for increased abdominal and pelvic involvement compared with hyaline vascular disease.

In patients with known primary malignancy, F18 FDG PET/CT will help differentiating metastatic node from benign activity as in castleman disease. Notable difference between the glycolytic activity of the involved nodes and the primary tumor should be suggestive of the possibility of nonmetastatic nodal disease, including Castleman disease.

The systemic forms of the disease especially are associated with an increased risk for neoplasms like Kaposi sarcoma and follicular dendritic cell tumors, non-Hodgkin lymphoma, Hodgkin disease and plasmacytoma.

Deep vein thrombosis as the cause of PUO is reported in 2% to 6% of patients.

**Malignancies:**

FDG PET/CT helps in detection of occult neoplasms. Other than lymphomas, colorectal cancer, pancreatic cancer, and soft-tissue sarcomas have also been described as causing PUO and are commonly detected by FDG PET/CT. Malignancies presenting with PUO might represent an early stage of the disease process. Hence early detection may help in initiation of treatment with a curative intent. In a study by Sorensen et al, patients with PUO had higher risk for hematologic malignant diseases; sarcoma; and cancers of the liver, brain, kidney, colon, and pancreas.

In a FDG PET negative scan, limited variety of systemic (non-focal) diseases may still be found through other diagnostic testing, for instance leukemia.

**In HIV infected patients:** FDG PET/CT is has a major role in AIDS patients with central nervous system involvement. Both toxoplasmosis and lymphoma are not infrequent CNS complications of AIDS.

FDG PET/CT plays a major role when CT and MR fail to differentiate the two as CNS lymphoma is highly metabolically active, whereas toxoplasmosis is not. Quantitative assessment has shown that the standardized uptake values of toxoplasmosis are
significantly lower than those of lymphoma, with virtually no overlap between the uptake values of the two conditions, thus asserting the importance of FDG PET[7].

Special imaging considerations have to be kept in mind in FDG PET imaging in these patients[a]Inflammatory foci in the lungs are common in immunosuppressed patients and are a common cause of FDG hyper metabolism[b]Whole-body FDG PET images of HIV-positive patients have shown a clear association between the pattern of lymphoid tissue activation and HIV progression. FDG uptake increases in acute disease, in the head and neck, while at mid stages, hyper metabolism in cervical, axillary, and inguinal lymph nodes is observed. Later stages FDG accumulation is seen in the colon along with mesenteric and ileocecal lymph nodes[15]. Awareness of these patterns are important [c]Also, splenic FDG uptake greater than hepatic FDG uptake is observed in HIV patients. Thus lymph nodes found to be positive by FDG/PET alone may require further study to differentiate malignancy from inflammatory processes, particularly with high viral loads and advanced stage disease [15].

In a study by BecerraNakayoet al[16] on cost effectiveness of FDG PET/CT, €5471 per patient would have been saved if PET/CT had been performed earlier in the work up. They concluded that PET/CT study could not only be cost-effective in the PUO process if used at an early stage, by establishing an early diagnosis, but also would reduce hospitalization days due to diagnostic purposes and the repetition of unnecessary tests.
Images for this section:

**Fig. 1:** Warburg effect

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**Fig. 2**

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Figure 3

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Figure 4: Middle aged man with transplant kidney presenting with PUO: Hypermetabolic focus seen in the upper pole of transplanted kidney suggested possibility of focal nephritis. Patient became symptom free after a course of appropriate antibiotics

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Figure 5: Young adult presenting with PUO. 18F FDG PET/CT showing multiple enlarged FDG avid lymphnodes in the right supraclavicular region and mediastinum (paratracheal, left hilar and subcarinal). Biopsy from the lymphnodes revealed Tuberculosis.

Fig. 5

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Figure 6a: A 54 year old man presenting with history of fever and splenic lesions: PET/CT showed hepatosplenomegaly with focal lesions in liver and spleen some of them demonstrating hypermetabolic activity. Also irregular peripherally enhancing fluid densities seen in perisplenic region with FDG uptake. In addition mildly metabolic hilar and mediastinal lymphnodes were seen. Biopsy of one of the splenic lesions revealed tuberculosis.

Fig. 6

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Figure 7: Middle aged man presenting with PUO, CT image showing moderate pericardial effusion with mild pericardial enhancement. Corresponding PET images and fused PET/CT images show mild FDG uptake in the pericardium- suggestive of pericarditis.

Fig. 7

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Fig. 10

Figure 10: A 63 year old lady presenting with PUO. FDG PET/CT showing hypermetabolic mediastinal lymph nodes seen with increased FDG uptake in the pituitary gland[Arrow] and adrenals[*]. Mediastinal lymph node biopsy revealed sarcoidosis

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Figure 11: A 57 year old lady presented with fever of unknown origin. PET–CT showing enlarged thyroid with diffuse hypermetabolic activity, representing thyroiditis.

**Fig. 11**

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Figure 12

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Fig. 13

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Fig. 14

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Conclusion

The use of F18 FDG PET/CT might reduce the long list of multiple examinations that are needed to arrive at a final diagnosis, hence facilitating quick initiation of treatment. F18 FDG PET/CT has the synergy of anatomical and metabolic information of the pathology concerned and thus can replace other imaging techniques in the evaluation of PUO.
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