FDG PET/CT in Evaluation of Pyrexia of Unknown Origin

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Abstract: Pyrexia of unknown origin (PUO) is defined as fever above 38.5°C lasting for 3 weeks, of which at least 1 week has been spent in thorough investigation without a conclusive cause. Tuberculosis remains an important cause of PUO, particularly with the rising incidence of human immunodeficiency virus infection. It may strike virtually any organ in the body and can even mimic metastases especially in a known treated case of carcinoma. Bacterial infections, human immunodeficiency virus, hidden malignancy, sarcoidosis, and autoimmune disorders are some other important causes of PUO. Initial investigations include examination of blood, urine, stool, blood biochemistry, culture, etc. Typical radiologic investigations include chest radiography, computed tomography, and magnetic resonance imaging. Presented here is an atlas of cases where these investigations had been inconclusive but fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography demonstrated the site of pathology and directed histologic diagnosis.

Key Words: pyrexia of unknown origin, FDG PET/CT, tuberculosis, thyroiditis, lymphoma, sarcoidosis, autoimmune disorder

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MATERIALS AND METHODS

Presented here are cases of pyrexia of unknown origin (PUO) in the past 3 years, which had evidence of involvement of various organ systems on fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT). Their subsequent evaluation based on the clues provided by FDG PET/CT had resulted in arriving at the diagnoses.

Whole-body FDG PET/CT was performed on 6-hour fasting state in all these patients. Blood sugar was controlled below 170 mg/dL in patients with diabetes. A dose of 6 to 15 millicurie (222–555 MBq) was used depending on the body weight. An uptake time of 60 minutes was allowed followed by whole-body acquisition (222–555 MBq) was used depending on the body weight. An uptake time of 60 minutes was allowed followed by whole-body acquisition using Biograph Duo—Lutetium oxyorthosilicate (LSO)-based Siemens Medical PET/CT system. Images were reconstructed and displayed in standard short axis, vertical long axis, and horizontal long axis views.

The suspected sites of abnormal FDG localization were histologically evaluated to reach a diagnosis. Help was also taken from circumstantial evidence such as tumor/disease marker and clinical profile.

CASES AND DISCUSSION

Discussed here is an atlas of 7 cases of PUO related to 5 causes with reference to Indian subcontinent.

Tuberculosis

Tuberculosis (TB) is estimated to infect between 20% and 40% of the world population.1 The disease has become more aggressive with rising incidence of immunodeficiency disorder. It is most commonly transmitted by airborne droplets and subsequently spreads either by lymphatic or hematogenous routes. In immuno-competant individuals, the infection is curtailed by T-cell–mediated immunity. About 10% of such individuals with latent infection develop active disease in their lifetime. Up to 50% of human immunodeficiency virus infected individuals develop active TB within 2 years of exposure.2

Case 1 (Fig. 1) illustrates absence of any striking findings on other imaging modalities such as sonography and CT. However, there was FDG-avid involvement of the basal right pleura, mediastinal as well as retroperitoneal lymph nodes. The case highlights the fact that FDG PET/CT is more sensitive than conventional imaging in diagnosing pulmonary as well as extrapulmonary TB.

Extrapulmonary TB may involve the lymph nodes, skeleton, abdominal viscera, genitourinary system, and the nervous system. Histopathology usually shows giant cell granulomas with caseating necrosis. Paucity of bacilli is the usual diagnostic problem with extrapulmonary TB.3

Skeletal TB usually affects the elderly; however, it may be seen in all ages. Almost any bone may be affected. It represents about 35% of all the cases of extrapulmonary TB. Skeletal TB most frequently involves the spine (50%), followed by hip and knee involvement (30%). Less common sites are pubis, wrist, and tarsal bones (20%).2 It can cause paravertebral abscesses (Potts spine), aseptic polyarticular inflammatory arthritis (Poncet disease), monoarticular tuberculosis arthritis, and osteomyelitis.4 Multifocal skeletal involvement in TB is rare and constitutes about 5% of all skeletal TB.5

Case 2 (Fig. 2) had the pyrexia lasting 2 months. Physical examination and CT were unremarkable. A whole-body FDG PET/CT demonstrated multiple metabolically active skeletal foci. Histology from the sternum showed caseating granulomas thus confirming the diagnosis of skeletal TB. Whenever the disease strikes multiple skeletal sites, it mimics metastases especially in a previously treated case of malignancy.

Case 3 (Fig. 3) demonstrates a similar puzzling situation. The patient had a history of surgery for renal cell carcinoma, and later developed skeletal symptoms and fever. FDG PET/CT demonstrated multiple sites of involvement including the lung, spleen, and bones. In an established case of malignancy, multiple lesions would favor metastases. However, histology confirmed the diagnosis of multifocal tubercular involvement.

Subacute Painless Lymphocytic Thyroiditis

Subacute painless lymphocytic thyroiditis is characterized by generally indolent course. Thyrotoxicosis is transient and resolves spontaneously. Sporadic subacute lymphocytic thyroiditis as well as postpartum thyroiditis have been described in this category. It has been observed to be common among individuals migrating from iodine-deficient areas to iodine-sufficient zones. It is most likely autoimmune and is not preceded with viral illness. It can be differentiated from chronic lymphocytic thyroiditis by its self-limiting course and lower extent of lymphocyte infiltration. The phase of thyrotoxicosis may last for 2 to 4 months followed by hypothyroidism in some cases.6,7 Subacute thyroiditis presenting as PUO has been reported.8

Case 4 (Fig. 4) is that of a middle-aged woman who had fever of 4 weeks duration, the cause of which could not be identified with conventional investigations. Subsequent FDG
PET/CT scan revealed hypermetabolic thyroid gland showing diffuse thyroid inflammation. Tc-99m-pertechnetate thyroid scan and antithyroid antibodies were compatible with the diagnosis of subacute thyroiditis.

Sarcoidosis

Sarcoidosis is a granulomatous disorder of unknown etiology that most frequently involves the lungs but can strike almost any organ. Fever is a common symptom associated with malaise. Involvement of lungs leads to dyspnea, skin affection presents as erythema nodosum, and affection of salivary glands and other mucin-secreting glands leads to Sicca syndrome. Asymptomatic patients may sometimes be detected as having incidental mediastinal or cervical lymphadenopathy. Laboratory tests usually reveal leucopenia, elevated erythrocyte sedimentation rate, hypercalcemia (5%), and hypercalciuria (20%). Angiotensin-converting enzyme level is elevated in 40% to 80% of patients with active disease. Tissue diagnosis is usually made with demonstration of non-caseating granulomas in the involved organs.11

The most common radiologic finding in sarcoidosis is intrathoracic lymphadenopathy seen in about 85% of cases.12 Abdominal lymphadenopathy is seen in about 30% of cases.13 Case 5 (Fig. 5) demonstrates multifocal skeletal and hepatic lesions in sarcoidosis. Skeletal lesions in sarcoidosis can mimic malignancy.14,15 Our case had skeletal symptoms and multifocal bone involvement causing initial suspicion of metastases or multifocal skeletal TB.

An association between sarcoidosis and lymphoma has been described.16,17 It has also been observed that the incidence of lymphoproliferative disorder is 5.5 times higher in sarcoidosis as compared with other patients in the same age group.18 Sarcoidosis has been reported to coexist with Sjogren syndrome.19–21 Although sarcoidosis per se may explain the dryness of mucosa in the presented case, lip biopsy had suggested the features of Sjogren syndrome raising a possibility of coexistence of the 2 entities.

Lymphoma

Lymphoma remains one major cause of PUO. In cases with clinically obvious lymphadenopathy, obtaining biopsy from an accessible site can settle the diagnosis. However, in the absence of
FIGURE 3. A 55-year-old man presented with fever, weight loss, and backache over several weeks. Twenty years ago, he underwent right nephrectomy for renal cell carcinoma. Plain radiograph and bone scan revealed pattern suggestive of degenerative changes in the lumbar vertebrae (B $\rightarrow$). MRI revealed abnormal signals in lower lumbar vertebrae (C [white arrowhead]). In view of past history of malignancy and a nonspecific appearance on bone scan, he was referred for a whole-body FDG PET/CT scan to look for evidence of metastasis. The test revealed multiple organ involvement as follows: the lungs (D $\gg$), the spleen (F $\nearrow$), and the bones at lumbar region (G $\rightarrow$). A diagnosis of metastases from internist tumor was suspected. However, histology revealed tuberculosis.

FIGURE 4. A 48-year-old woman with fever and evening rise in temperature of 4-week duration had a visible goiter and no other positive finding on clinical examination. Blood Widal test was negative for enteric fever. Sonography of abdomen and chest radiograph was normal. Sonography of neck revealed enlarged left lobe of thyroid gland as well as isthmus with a complex lesion. There was a small lymphadenopathy on right side of the neck. Antinuclear antibody was negative. T3 and T4 levels were marginally raised. Whole-body FDG PET/CT revealed metabolically active well defined hypodense lesion in the left lobe of thyroid, and isthmus measuring 18 $\times$ 14 mm with SUV of 14.09. (A, B $\nearrow$) No obvious cysts or calcification was noted within it. Mild diffuse increased FDG uptake was also seen within the right lobe of thyroid. There were FDG-avid tiny, left, level III and bilateral level IV cervical lymph nodes with SUV maximum of 3.47. There was no other focus of abnormal FDG uptake noticed elsewhere. On the basis of these findings, a diagnosis of subacute thyroiditis was proposed. Thyroid scan performed on another day using 5 millicuries (185 MBq) of Tc-99m pertechnetate revealed diminished inhomogeneous tracer uptake by both the lobes of thyroid gland compatible with the diagnosis of thyroiditis (C). Subsequently, antiperoxidase and antithyroglobulin antibody tests were positive.
clinically palpable lymphadenopathy, FDG PET/CT is of immense value in documenting a normal-sized hypermetabolic lymph node that could be the only source of demonstrable disease activity, which would otherwise be dismissed as normal on conventional CT.\textsuperscript{22,23}

Case 6 (Fig. 6) reveals a similar situation where all typical investigations were unremarkable and FDG PET/CT revealed normal-sized hypermetabolic axillary lymphadenopathy. There was an additional finding of diffuse increased FDG localization in the spleen that raised a suspicion of lymphoma in this patient. FDG PET/CT is a reliable indicator of involvement of spleen in a diagnosed case of lymphoma.\textsuperscript{24} Spleen is involved in 30\% to 40\% of patients with Hodgkin lymphoma and 40\% of patients with non-Hodgkin lymphoma. Splenomegaly alone is not a reliable indicator of disease involvement as 30\% of cases having Hodgkin lymphoma with splenomegaly do not have the organ involvement. Conversely, about one-third cases with normal-sized spleen in lymphoma (both types) will have demonstrable disease at laparotomy.\textsuperscript{25,26}

Lymphoma shows bimodal age predilection with first peak in the second decade and second peak in the fifth decade of life. An old mnemonic of 5 “Ps” has been used to describe the illness, ie, painless lymphadenopathy, pyrexia (Pel-Ebstein fever), pruritis, palpable organomegaly, and paraplegia. Constitutional symptoms such as fever, night sweats, and weight loss are seen in 40\% cases of Hodgkin lymphoma and 20\% cases of non-Hodgkin lymphoma.\textsuperscript{27} Demonstration of Reed-Sternberg cells in the background of inflammatory cells is central to the diagnosis of Hodgkin lymphoma. The disease was first described by Thomas Hodgkin in 1832. The disease has become curable in majority of cases with Hodgkin lymphoma and shows variable course in non-Hodgkin variety ranging from slow indolent to aggressive and rapidly fatal. Imaging plays an important role in precise staging to define the local extent as well as to document distant organ involvement. This is one disease in which correct staging will have direct impact on treatment outcome.\textsuperscript{28,29} The exact tumor burden as well as extranodal disease is best elicited by FDG PET/CT. Most of the lymphomas are hypermetabolic except mucosa-associated lymphoid tumor, small lymphocytic type, and cutaneous lymphomas.\textsuperscript{30,31}

Still Disease
Still disease is characterized by prolonged fever, arthralgia, Still rash, organomegaly, pleuritis, pericarditis, generalized lymphadenopathy, leukocytosis, and raised ferritin.
The diagnosis is usually made after exclusion of infection and malignancy. Still disease accounts for 6% of cases of PUO. Arthritis is seen in 95% of cases. It is usually polyarticular but rarely oligoarticular. Lymphadenopathy is seen in about 63% of cases. Cervical lymph nodes are most commonly involved. Splenomegaly is seen in about 52% of cases and hepatomegaly is seen in about 42%. Raised liver enzymes have been noted in 75% of cases. Focal hepatitis and feathery degeneration have been rarely described. Pleuritis and/or pleural effusion is seen in about one-third of cases.

Pneumonitis, respiratory distress syndrome, and interstitial lung disease have been rarely described. Cardiac involvement may lead to pericarditis and myocarditis. Such findings have been reported on FDG PET/CT scan. Of the various acute phase responses, elevation of serum ferritin seems to be characteristic of adult-onset Still disease (AOSD). Marked hyperferritinemia is pathognomonic of AOSD. Levels of serum ferritin correlate with disease activity and have been used to monitor it.

CONCLUSIONS

PUO is a challenging entity to all the members involved in its management. TB remains the most common cause in developing world. It needs to be considered high on the list of differential diagnoses even in those cases treated previously for malignancy.
Inflammatory conditions such as thyroiditis, rheumatoid-like conditions, and AOSD are some conditions that may go unnoticed unless specifically looked for. Other granulomatous disorder such as sarcoidosis is encountered sometimes. Lymphoma can be diagnosed early in the disease process by using FDG PET/CT. Thus, judicious use of FDG PET/CT is helpful in evaluation of PUO. Understanding various patterns of abnormalities and their possible causes lead to early diagnosis.

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