Original Article

Potential Clinical Utility of FDG-PET in Non-malignant Pulmonary Disorders: A Pilot Study

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Abstract

Background. Fluorodeoxyglucose (FDG) positron emission tomography (PET) is emerging as an important non-invasive investigation in benign pulmonary conditions too. The aim of this study was to investigate its utility in the diagnosis and monitoring of various benign pulmonary diseases.

Methods. In this prospective observational hospital-based study 50 consecutive patients (26 males) with benign lung diseases underwent computed tomography of chest followed by FDG-PET at baseline and after treatment where appropriate. The findings of FDG scan are reported in the context of clinical, histopathological, physiological and radiological findings.

Results. All patients showed increased FDG uptake in the lung corresponding to CT findings. Of the 9 patients with sarcoidosis stage 1 (n=1), stage 2 (n=3) and stage 3 (n=5), additional uptake in the myocardium and thyroid was noted in two patients which resulted in a change in the modality of treatment. Repeat FDG scan post-treatment showed decreased uptake in all patients which was consistent with clinico-radiologic, microbiological or spirometry findings. Increased uptake was seen in one patient with pulmonary tuberculosis (TB) and in one patient with TB mediastinal lymphadenopathy at the end of intensive phase discordant with clinical and microbiological response. Of nine cases of idiopathic interstitial pneumonias (IIPs), additional intense FDG uptake was found in two cases which corresponded to the areas of honeycombing.

Conclusions. FDG-PET scan can be used as an important adjunct non-invasive investigation in diagnosing and monitoring of various benign lung conditions. It also helps in assessing whole body disease burden which may change therapeutic decisions. **[Indian J Chest Dis Allied Sci 2016;58:165-172]**

Key words: Pulmonary tuberculosis, Tuberculous mediastinal lymphadenopathy, Interstitial lung disease, Sarcoidosis, Non-specific interstitial pneumonitis (NSIP), Idiopathic pulmonary fibrosis (IPF), Silicosis, Diffuse panbronchiolitis, Tropical pulmonary eosinophilia (TPE).

Introduction

Fluorodeoxyglucose (FDG) positron emission tomography (PET) is emerging as an important non-invasive investigation in the last decade, especially in malignant cases in disease staging, planning appropriate therapy, monitoring response to treatment, detecting recurrence, and predicting prognosis.[1] With advances in nuclear medicine its role in assessing infection and inflammation is now well-described, particularly in granulomatous diseases.[2] Infectious diseases, like mycobacterial, fungal, bacterial infection, sarcoidosis, radiation pneumonitis and post-operative surgical conditions, occupational diseases, pleuropulmonary complications have shown intense uptake on FDG-PET.[3] It is now being considered as more relevant investigation for the diagnosis of several infectious and inflammatory diseases, particularly for therapy monitoring, in assessing whole body disease burden and disease prognostication.[4,5]

Material and Methods

A prospective, observational, hospital-based study was conducted in our tertiary care hospital. Ethics committee approval was obtained for conducting the study. The study group consisted of 50 consecutive patients (26 males) with benign pulmonary diseases, who attended our out-patient department. FDG-PET was performed at baseline and was repeated for treatment monitoring in appropriate cases.

The test was explained to the patient and due precautions like adequate hydration, good control of

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diabetes, discontinuation of breast feeding were taken prior to the procedure. Full rings detector Bismuth Germanate Orthosilicate (BGO) PET scanner (GE Advance PET Scanner, General Electric, USA) was used. Image analysis was done using (i) qualitative analysis, i.e., PET images were visually analysed by looking for local differences of FDG uptake in the regions imaged; (ii) quantitative standard uptake value (SUV) measurement. Since the patients had computed tomography (CT) scan/high resolution computed tomography (HRCT) undertaken as a routine standard management protocol just prior to FDG-PET. PET-CT (with a diagnostic CT) was not considered in order to reduce the radiation burden. All PET studies were interpreted in conjunction with the CT findings available. The findings of FDG-PET are reported in the context of clinical, histopathological and radiological findings. FDG-PET was repeated for monitoring treatment response when necessary.

Results

The study included pulmonary diseases, such as pulmonary tuberculosis (TB) (n=16), sarcoidosis (n=9), TB mediastinal lymphadenopathy, idiopathic pulmonary fibrosis (IPF) (n=5 each), non-specific interstitial pneumonitis (NSIP) (n=4), hydatid disease (n=3), connective tissue disease (CTD) related interstitial lung disease (ILD), silicosis, tropical pulmonary eosinophilia (TPE) (n=2 each), diffuse panbronchiolitis, pulmonary alveolar microlithiasis (PAM) (n=1 each). FDG-PET findings (Figures 1A and 1B) in all cases of pulmonary TB at baseline and end of intensive phase of anti-TB treatment (ATT) corresponded to clinical and microbiological examination for *Mycobacterium tuberculosis* (smear and/or culture) except in two cases. One patient had discordant increased uptake at end of intensive phase of ATT inspite of clinical improvement and microbiological culture conversion whereas another patient with unfavourable response (Figure 2) was proven to have multidrug-resistant TB on sputum culture and drug-suscetibility testing. All five patients with TB mediastinal lymphadenopathy proven on fine needle aspiration cytology (FNAC) or fine needle aspiration biopsy (FNAB) sample positivity for *Mycobacterium tuberculosis* (smear and/or culture) showed significant uptake at baseline (Figure 3A) with concordant response in four patients at the end of intensive phase of ATT (Figure 3B). However, one patient showed a discordant increased uptake at the end of intensive phase of ATT inspite of clinical improvement and microbiological conversion. The nine patients of sarcoidosis consisting of one, three, five patients of stage 1 (n=1), stage 2 (n=3), stage 3 (n=5) disease, respectively, showed increased FDG uptake corresponding to diseased areas on the CT. Additional uptake was noted in two

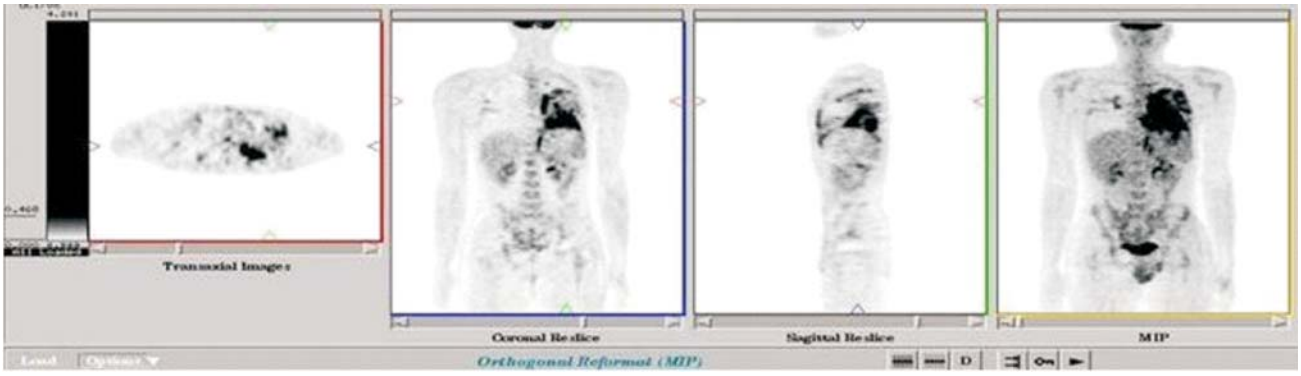

Figure 1A. Baseline FDG-PET showing significant uptake in the lungs bilaterally in case of pulmonary tuberculosis.

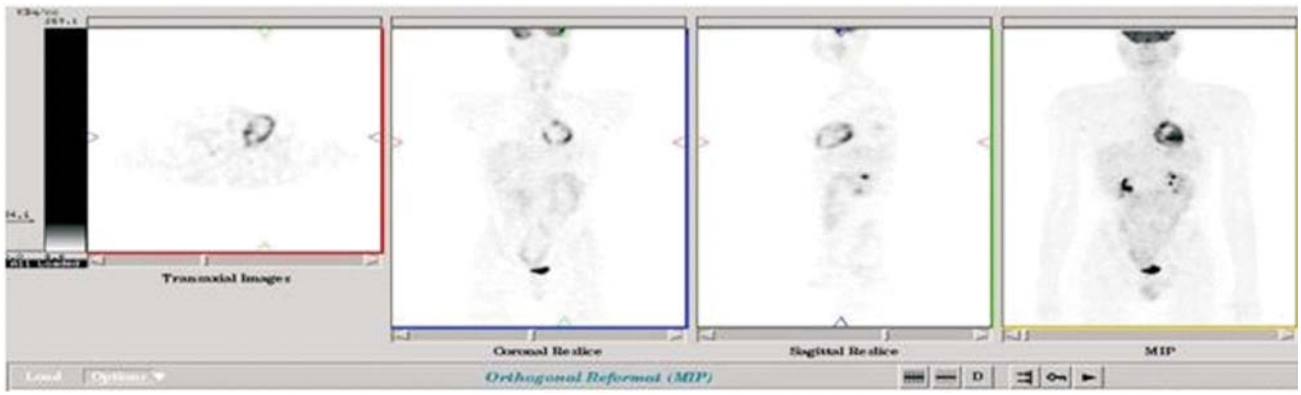

Figure 1B. FDG-PET showing no uptake at the completion of anti-tuberculosis therapy.

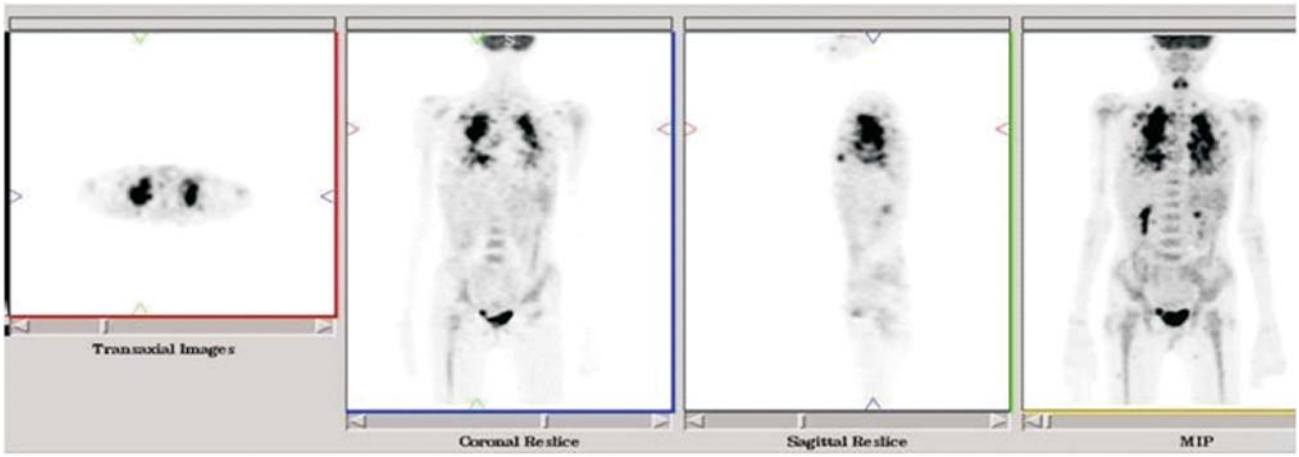

Figure 2. Unfavourable response on FDG-PET at the completion of intensive phase of antituberculous therapy was proved to be multidrug-resistant tuberculosis.

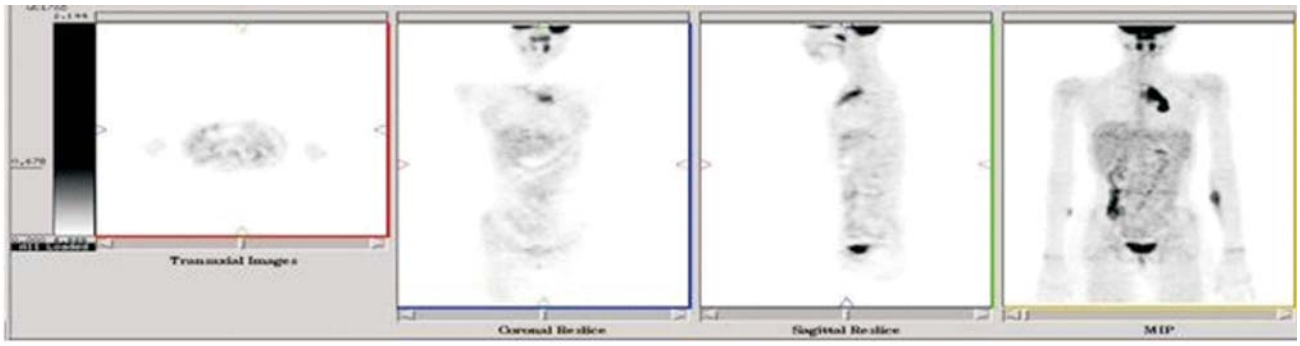

Figure 3A. Significant FDG uptake in mediastinal lymph node TB.

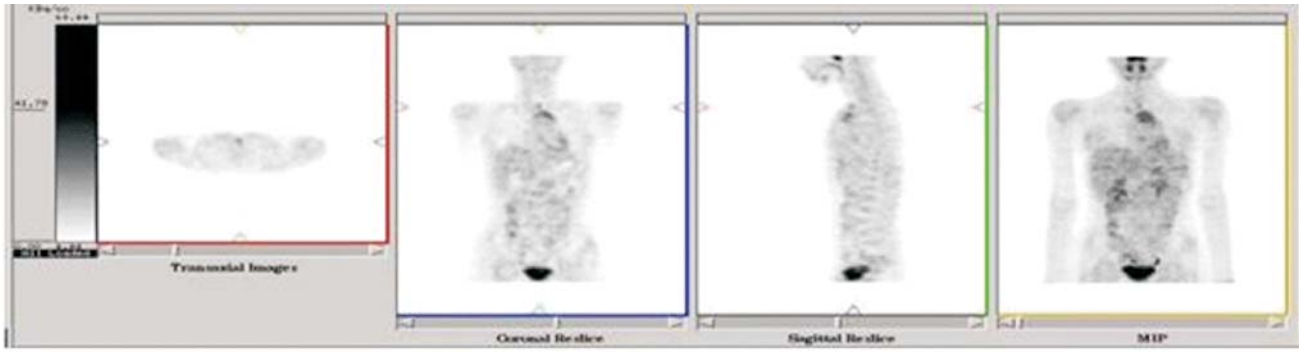

Figure 3B. Gradual reduction in FDG uptake in mediastinal nodes at two months of anti-tuberculosis treatment.

patients; one with bilateral epitrochlear area with intense foci of multiple FDG uptake in myocardium and another with thyroid and cardiac uptake. Repeat FDG-PET after treatment suggested improvement in all patients which was consistent with clinico-radiologic and spirometry findings (Figures 4A and 4B). Sixteen patients were diagnosed to have ILDs: idiopathic interstitial pneumonias (IIPs) (n=9) that included idiopathic pulmonary fibrosis (n=5) and non-specific interstitial pneumonitis (n=4); CTD related ILDs, tropical pulmonary eosinophilia (TPE), silicosis (n=2 each); and one patient with pulmonary alveolar microlithiasis (PAM). IIPs and CTD related ILDs had bilateral low-grade FDG uptake (Figure 5) with additional uptake in two IPF cases corresponding to honeycombed areas on CT (Figure 6). The patient with PAM showed sandstorm appearance on HRCT but did not show any significant FDG uptake. Cases with TPE showed low-grade diffuse FDG uptake in bilateral lung parenchyma. Two cases with silicosis diagnosed on clinico-radiological basis in flour mill workers with significant exposure to silica during the process of chiselling using a grinder made up of Agra stone (which has silica as a constituent) had high uptake on FDG-PET which corresponded to the CT opacities.

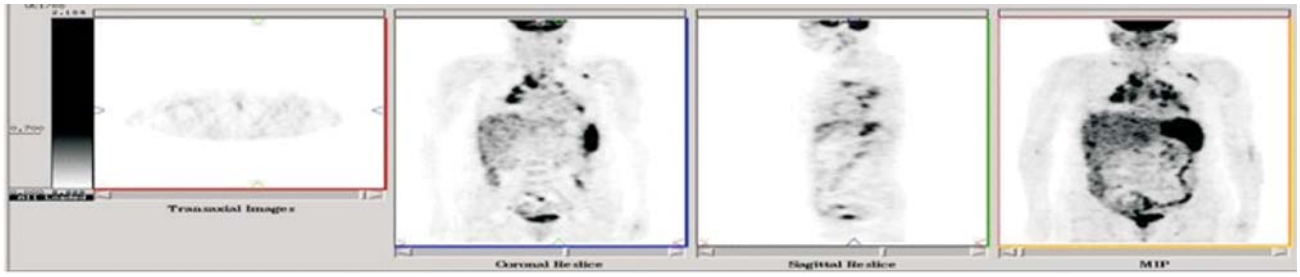

Figure 4A. FDG-PET demonstrating disease involvement in the liver, spleen and mediastinal lymphnodes in sarcoidosis.

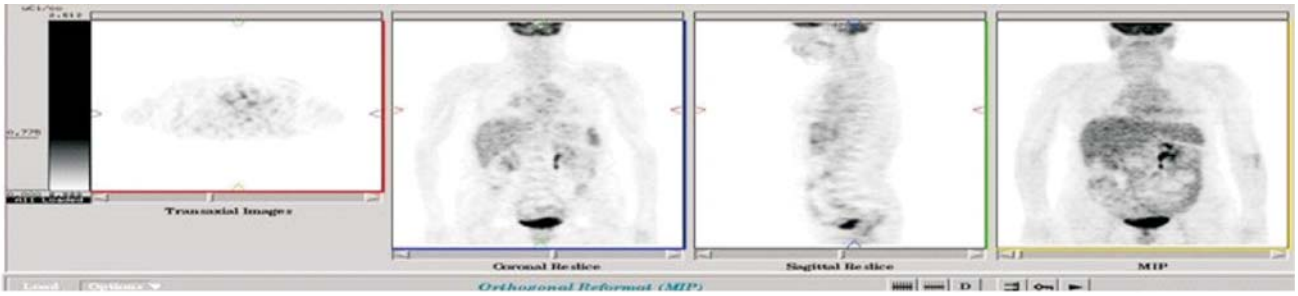

Figure 4B. Excellent response with steroid therapy at one month in sarcoidosis.

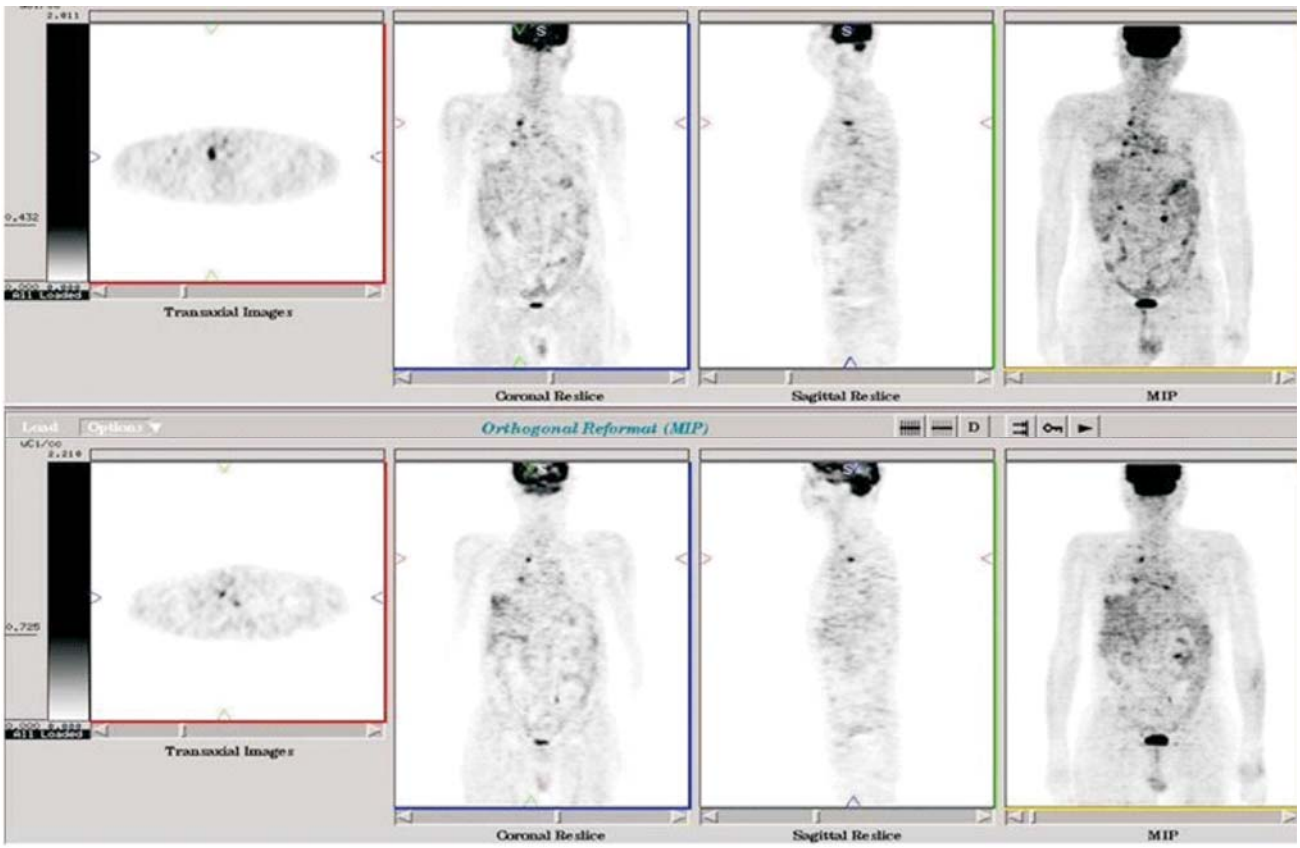

Figure 5. Diffuse low-grade FDG uptake in both the lungs in a case of connective tissue disease related interstitial lung disease.

Three patients with hydatid lung disease diagnosed based on immune haemagglutination (IHA) test for echinococcus and clinic-radiological findings revealed significant increased FDG uptake at the periphery of the cyst with central photopenia (Figure 7). In DPB, findings on FDG correlated with CT with decreased uptake post therapy.

Discussion

FDG-PET with use of tracer fluorine-18 (^{18}F) labelled FDG helps to measure metabolic activity in various tissues. Increased FDG activity has been reported in the several inflammatory or infectious processes in the lungs and elsewhere in the body.[3] Inflammatory conditions have increased number of glucose transporters, and thus, enhanced affinity for deoxyglucose. This increased affinity to FDG is due to various cytokines and growth factors;[6] a phenomenon not observed in tumours. Moreover, FDG is known to accumulate in inflammatory cells, such as neutrophils and activated macrophages at the site of inflammation which have enhanced levels of glucose transporters.

Studies have shown utility of FDG-PET in TB evaluation and monitoring of therapeutic response.[7] In pulmonary TB, granulomas typically demonstrate increased FDG uptake, and areas of active TB can be differentiated from old or inactive disease by dual

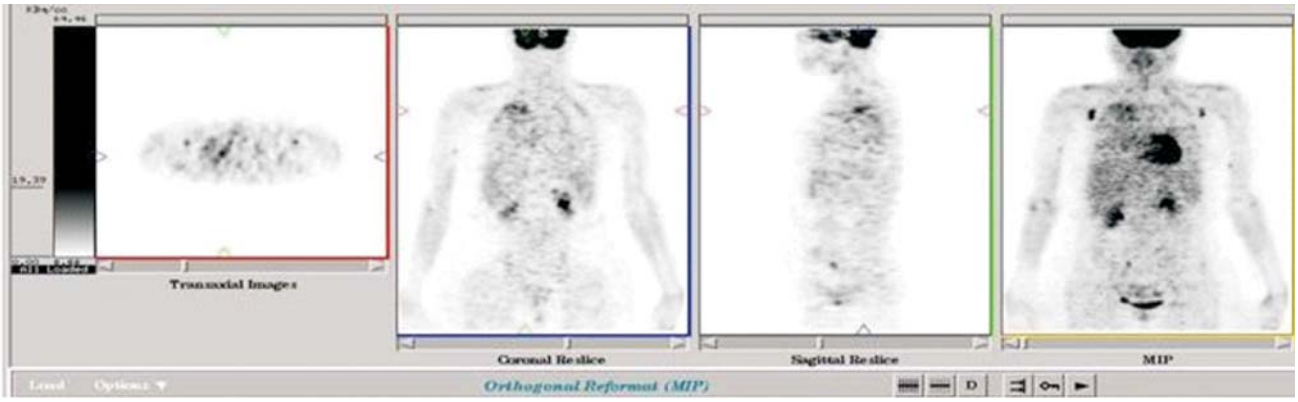

Figure 6. Intense FDG uptake in the right upper lobe (SUVmax 2.55) in interstitial pulmonary fibrosis.

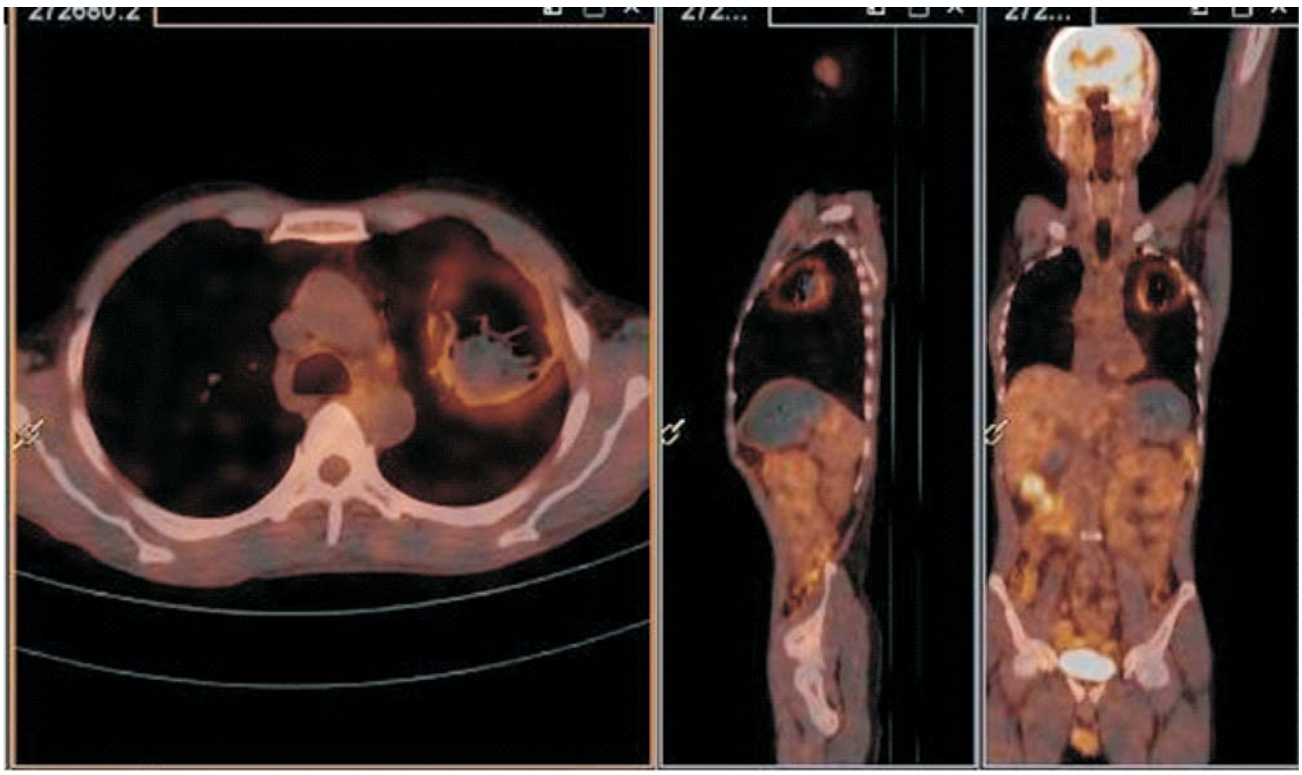

Figure 7. Rim of FDG uptake around a photopenic area in the left mid zone corresponding to hydatid cyst in the lingular segment of the left upper lobe.

time point imaging.[8] Hence, it can be used as a marker for assessing clinical response to therapy.[9] This is attributed to the presence of large number of activated inflammatory cells which have high glycolytic rate and uptake by TB lesions varies according to the grade of inflammatory activity.[10] Studies have shown superiority of FDG-PET over CT in assessing follow-up response after therapy in TB granulomas.[11] However, active fibrotic lesions also have been reported to show increased FDG accumulation and cause false positive PET.[12] In our study, all patients showed increased FDG uptake in the lung parenchyma at the time of diagnosis and intensity of uptake was reduced after intensive phase of ATT. Unfavourable response in one case was proven to be due to MDR-TB. Discordant response in one case could be due to bilateral extensive fibrotic lesions which showed increased uptake at the end of intensive phase. FDG-PET allows an easy evaluation of early therapeutic response in extra-pulmonary TB too. In mediastinal, supraclavicular, and intra-abdominal TB lymphadenitis, a high focal uptake of FDG has been reported, as seen in our patients.[13] It should be complemented with other imaging modalities to confirm results and to minimise false negative findings.[14] One of our patients showed discordant increased uptake at the end of intensive phase of ATT inspite of clinical response and negative microbiological culture. These findings could be due to paradoxical response.[15] Paradoxical increase in FDG uptake is also explained in patients with malignancy while on chemotherapy.[16]

FDG-PET has been shown to be a very sensitive technique for the assessment of inflammatory activity in sarcoidosis by detecting and quantifying the degree of inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body.[17] In patients with proven sarcoidosis, the extent of involvement and quantification of inflammatory activity can be more accurately assessed by FDG-PET than with ^{67}Gallium scintigraphy.[18] In almost two-thirds of the patients with extra-thoracic PET positive lesions, these lesions had not been suspected beforehand. Detection of cardiac sarcoidosis is of the utmost importance with respect to the prognosis, since this is a major cause of serious morbidity and mortality in sarcoidosis. Myocardial inflammatory activity may contribute to fatal arrhythmias and unexplained sudden death. In our study, the extra-thoracic organ involvement was higher than we had suspected before performing FDG-PET. Teirstein *et al*[17] found that PET established the presence of increased extra-cardiac FDG uptake which had not been identified by physical examination, chest radiography or CT as in our two cases. FDG-PET also enables a more accurate clinical assessment of prognostic factors by demonstrating and monitoring organ involvement, like bone involvement, which is associated with a chronic course of the disease.[19] PET is not indicated in the standard work up, but can be of great value to complement more routinely used techniques[20] but is helpful in those persistently symptomatic patients without serological signs of inflammatory activity and in patients with radiologic signs of fibrosis. Moreover, FDG-PET can establish the most appropriate location for a biopsy to obtain histological evidence for the diagnosis. In addition, the assessment of a PET positive lesion can be useful in monitoring the treatment effect.

The IIPs are a heterogeneous group of disorders resulting from damage to the lung parenchyma due to varying patterns of inflammation and fibrosis with variable prognosis. Predicting disease progression is less certain in IIPs. HRCT shows changes in lung density but can give no indication of disease activity. Although histopathological diagnosis is related to survival in IIPs, individual clinical courses are highly variable and unpredictable. Furthermore, thoracic surgical procedures are stressful for them and hazardous to repeat, therefore should be avoided, unless absolutely necessary. Other non-invasive, real-time measures of lung inflammation in patients with IIP, which can predict the disease activity, are expected. External imaging using radiolabeled markers of inflammatory processes have great potential for providing a non-invasive and repeatable test for monitoring inflammatory cell behaviour. Recently it has been shown that FDG-PET may be helpful in the evaluation of IIPs. Increased activity on PET may suggest active disease and a decrease uptake correlates with response to therapy.[21] Patients with IPF have shown increased uptake of FDG even in areas of lung with a normal HRCT findings suggesting PET may be more sensitive in the detection of early IPF compared to HRCT. They also imply diffuse hypermetabolic activity to global parenchymal affection in IPF.[21,22] In our study, all the patients showed bilateral low-grade FDG uptake corresponding to HRCT which may be related to underlying diffuse inflammation. Additional intense FDG uptake was found in two cases which were corresponding to areas of honey-combing. While honey-combing suggests burnt out disease; FDG uptake suggests active inflammation amenable to therapy or neo-angiogenesis in the honey-combed areas has been debated on by various authors.[23,24] In TPE; pulmonary inflammation and presence of granulomas on histopathology may be the cause for increased FDG uptake in pulmonary parenchyma. FDG-PET identified metabolically active lesions in 9 of 11 patients in one study.[25] A solid nodule with or without a ground-glass opacity halo showed a higher frequency and level of FDG uptake compared to the pure ground-glass opacity nodule. Presence of FDG

uptake in our patient at baseline study indicates inflammation and presence of disease activity while resolution of uptake on post treatment PET is suggestive of decreased disease activity, and hence response to treatment.

PAM is a rare, chronic lung disease with bilateral intra-alveolar calcium and phosphate deposition throughout the lung parenchyma with predominance to lower- and mid-zone.[26] The disease may progress with chronic alveolar calcification causing interstitial inflammation and fibrosis. Thus, some cases may show a high FDG uptake on FDG-PET scan due to increased rate of glucose utilisation by the inflammatory cells.[27] We studied one patient with this rare disorder where minimal FDG activity in areas of dense calcification was observed suggestive of minimal or no inflammation. In silicosis, FDG-PET can provide additional information to CT regarding the diagnosis of acute silicosis and the rare accelerated silicosis.[28] FDG-PET studies have revealed increased uptake in pneumoconiosis and progressive massive fibrosis.[29] This uptake is perhaps related to the presence of inflammatory cells, such as macrophages, as well as fibroblasts. Inflammatory process associated with pulmonary reaction to crystalline silica result in vasculitis, ischaemic necrosis resulting in increase FDG uptake. In the present study, both patients showed increased FDG uptake that correlate well with CT findings. Studies on hydatid lung disease[30,31] showed peripheral hypermetabolic rim and central photopaenia described as "doughnut sign" on FDG concordant with our results. Usually it is a complicated hydatid cyst, ruptured[32] or infected[33] or both that is detected on FDG-PET or FDG PET-CT. Unruptured hydatid cyst may not show FDG uptake as the membranes are intact and there is no inflammation around the cyst wall.[34]

Conclusions

FDG-PET scan can be used as an adjuvant in diagnosing and monitoring various benign pulmonary conditions. Also it can help in detecting extra-pulmonary involvement and can be used as a guide for biopsy. However, false positive FDG uptake or false negative PET are frequently encountered. Proper interpretation and accurate characterisation of an abnormality can be accomplished by simultaneous clinical, histopathological and microbiological evaluation.

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