Brief Report

Positron-emission-tomography in tubercular lymphadenopathy: A study on its role in evaluating post-treatment response

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SUMMARY   Lymph node tuberculosis is one of the most common forms of extrapulmonary tuberculosis worldwide. The study aimed to evaluate the role of positron emission tomography-computed tomography (PET-CT) in determining post-treatment response in lymph node tuberculosis. A PET-CT was done in all treatment naïve tubercular lymphadenitis adults at baseline and after six months of therapy. The post-treatment clinical response was compared with the metabolic response on PET-CT. Of the 25 patients with tubercular lymphadenitis, 9/25 patients showed a complete metabolic response (CMR) at six months, while 16 patients had a partial metabolic response (PMR). All patients with CMR had a good clinical response. However, discordance between clinical and PET findings was noticed in those with PMR. The role of PET-CT in evaluating post-treatment response in patients with tubercular lymphadenitis needs further evaluation with a larger sample size.

Keywords   FDG PET-CT, lymph-node, tuberculosis

1. Introduction

Tuberculosis has affected humanity since ages and continues to be a significant global public health epidemic even today (*1*). Extrapulmonary tuberculosis (EPTB) forms a substantial proportion of the total number of cases (*2-4*). Lymph node tuberculosis (LNTB) has been reported as the most frequent form of EPTB, with an incidence of 30.8 per 100,000 population (*3*). The management of lymph node tuberculosis is a challenging ordeal as many patients continue to have persistent swelling despite the prescribed duration of treatment. Often, the endpoint of therapy is difficult to determine objectively (*4*). The present guidelines of LNTB have been mainly extrapolated from experience with pulmonary tuberculosis. The duration of treatment in tubercular lymphadenitis is usually guided by a clinical response alone. There is a need for a more accurate objective tool for evaluating response to therapy in patients with LNTB. This study aimed to determine the role of positron emission tomography-computed tomography (PET-CT) in assessing the treatment responses in patients with LNTB.

2. Materials and Methods

This is a prospective study in which treatment naïve adults (> 14 years of age) diagnosed as LNTB were enrolled in the study after taking written informed consent. Patients with significant comorbidities (malignancy, immunosuppression) were excluded from the study. Pregnant and lactating females were also excluded. An approval from the Institute Ethics Committee was obtained before the study was initiated (IECPG/384/29.06.2016). Clinical findings and baseline laboratory investigations were noted for all patients. A PET-CT scan (pre-therapy) was done at the baseline before the initiation of treatment. The treatment for lymph node tuberculosis was guided by the national guidelines for lymph node tuberculosis (*2*). A repeat PET-CT (post-therapy) was done after six months for all the recruited patients. Before the post-therapy scan was done, they were classified to have "complete clinical response (CCR)" or "partial clinical response (PCR)" based on the resolution of clinical symptomatology by a team of expert clinicians not involved in the treatment process. After the post-therapy scan was done, both the images were analyzed and reported by two nuclear medicine physicians blinded to the clinical response. Anatomical regions and the total number of sites of abnormal tracer accumulation were noted. Based on the pre-therapy scan and post-therapy scan parameters, the patients were classified to have "complete metabolic response (CMR)" and "partial metabolic response

(PMR)". The treatment was stopped in those patients with CCR. The decision to continue or stop treatment in patients with PCR was taken by the treating clinician not involved in the study.

Lymph nodes with the most intense FDG-uptake were carefully identified on both the scans. The maximum standardized uptake value (SUV-max) of tracer in the nodes was assessed using a circular region of interest. A receiver operating characteristic (ROC) curve analysis was performed to find the sensitivity and specificity of delta SUV-max (% change between the SUV-max pre-scan and post-scan) in predicting clinical response. The differences in the percentage change in SUV-max were assessed using an unpaired non-parametric Wilcoxon test. A p-value of less than 0.05 was considered significant.

3. Results and Discussion

Of the 62 patients who were screened, 37 patients were recruited for the study. After a baseline scan, 12 patients did not return for the repeat scan. A total of 25 patients were included in the final analysis. All patients were diagnosed based on the clinical and radiological features. Concurrent histopathological and microbiological evidence was present in 80% ($n = 20$) and 40% ($n = 10$) of the patients respectively. The study group consisted of 13 males and 12 females with a median age of 29.7 years (range 14-75 years). A total of 80% ($n = 20$) of the patients had mediastinal lymphadenopathy, while cervical and abdominal lymphadenopathy was seen in 76% ($n = 19$) and 40% ($n = 10$), respectively. Multiple lymph node sites were involved in 76% ($n = 19$) of the patients. In nine patients, PET demonstrated additional involvement sites, including liver, spleen, ileocecal region, pleura, pericardium, and dorsal spine. The clinical, radiological, pathological and microbiological features are summarized in Table 1.

The visual analysis of FDG/PET-CT showed a CMR in 9/25, all of whom showed a CCR (Table 2). Figure 1 shows CMR in one of the recruited patients. A PMR

Table 1. Clinical, laboratory and radiological features of the study population

	Variable	N (%)
A	Clinical Features	
1	Fever	20 (80)
2	Cough	19 (76)
3	Weight loss	15 (60)
4	Neck swelling	12 (48)
5	Abdominal pain	9 (36)
6	Chest pain	6 (24)
7	Back pain	5 (20)
B	Radiological manifestations (PET/CT)	
1	Cervical	19 (76)
2	Mediastinal	20 (80)
3	Abdominal	10 (40)
4	Pelvic	5 (20)
5	Extra-nodal	8 (40)
6	Necrotic lymphnodes	22 (88)
C	Cytopathological Diagnosis of TB	
1	Necrotizing granuloma	20 (80)
D	Microbiological Diagnosis	
1	AFB positive	3 (12)
2	CB-NAAT (Gene-Xpert) positive	9 (36)
3	MGIT Culture positive	3 (12)

Table 2. Patient characteristics, PET/CT findings and imaging and clinical outcome in 25 patients

Study No	Sex	Age	Station	Mode of diagnosis	Metabolic response	Clinical Response
1	F	74	Cervical, Abdominal	Microbiological	Partial	Complete
2	F	24	Cervical, Mediastinal, Extra-nodal	Histology	Partial	Complete
3	F	20	Cervical, Mediastinal, Extranodal	Microbiological	Complete	Complete
4	F	36	Mediastinal	Microbiological	Partial	Complete
5	M	23	Mediastinal	Microbiological	Complete	Complete
6	M	37	Mediastinal, Pelvic	Histology	Complete	Complete
7	F	32	Cervical	Microbiological	Partial	Partial
8	F	18	Pelvic, Extranodal	Radiological	Partial	Complete
9	F	23	Cervical, Mediastinal	Histology	Partial	Complete
10	M	70	Cervical, Mediastinal	Radiological	Partial	Partial
11	M	28	Mediastinal	Histology	Complete	Complete
12	M	19	Cervical, Mediastinal	Microbiological	Complete	Complete
13	F	30	Cervical, Abdominal	Histology	Complete	Complete
14	F	20	Mediastinal	Radiology	Partial	Partial
15	M	19	Cervical, Mediastinal, Abdominal, Pelvic, extra-nodal	Microbiological	Complete	Complete
16	M	30	Cervical	Histology	Complete	Complete
17	F	15	Cervical, Mediastinal, Abdominal, Pelvic	Histology	Partial	Partial
18	F	14	Cervical, Mediastinal, Abdominal, Extra-nodal	Histology	Partial	Complete
19	M	28	Cervical, Mediastinal, Abdominal, Pelvic	Histology	Partial	Partial
20	M	47	Cervical, Mediastinal, Extra-nodal	Histology	Complete	Complete
21	M	22	Cervical, Mediastinal, Abdominal, Extra-nodal	Microbiological	Partial	Partial
22	F	28	Cervical, Mediastinal, Abdominal, Extra-nodal	Histology	Partial	Partial
23	M	35	Cervical, Mediastinal, Abdominal, Pelvic, Extranodal	Microbiological	Partial	Complete
24	M	18	Cervical, Mediastinal	Histology	Partial	Complete
25	M	32	Cervical, Mediastinal, Abdominal	Microbiological	Partial	Complete
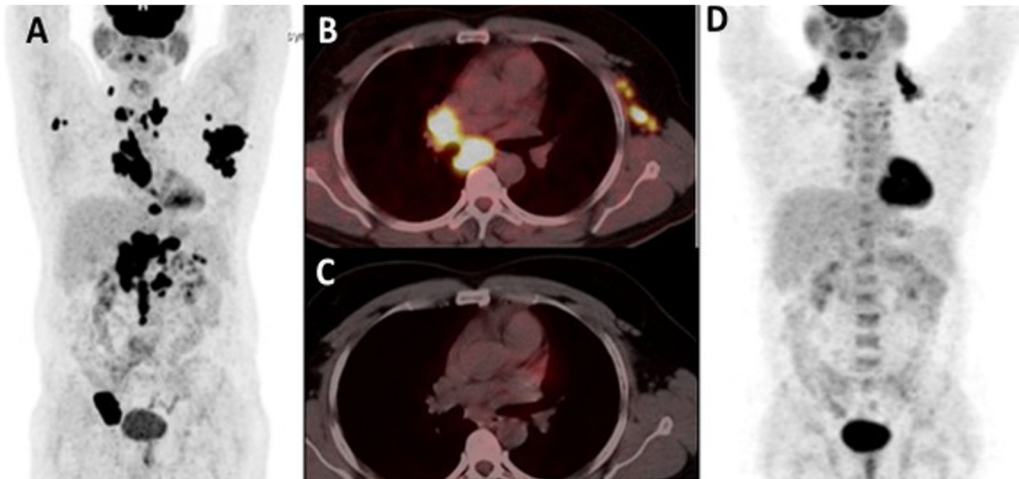
Figure 1. Before ATT showing multiple lesions of intense FDG uptake in cervical, axillary, mediastinal, abdominal and inguinal lymph nodes (A and B). After 6 month of ATT all pathological foci showed complete metabolic response (C and D).

was seen in 16/25 patients, nine of these patients showed a CCR and their treatment was stopped. The remaining seven patients with PMR and PCR were continued on therapy for a variable range of duration. All patients were followed up until the end of the study period. None of the patients with CCR (including 9 with CMR and 9 with PMR) relapsed until the end of the follow-up period. The mean duration of follow-up after completion of treatment was 127 +/- 57 days.

SUV max of lymph nodes for both the scans was computed. The percentage change in standardized uptake value (ΔSUV-max) was analyzed between baseline PET and the scan after six months of treatment. The changes in the SUV-max values were statistically significant in cervical and mediastinal lymph node stations with a p-value of 0.043 and 0.006, respectively. However, abdominal lymph nodes did not show a statistically significant change. A receiver operating characteristic (ROC) curve analysis was done to analyze the diagnostic utility of the per cent change in SUV-max as a marker of clinical response to treatment in patients with cervical/ mediastinal lymph nodes. A change in 77% or more in the SUV-max of cervical lymph nodes had a sensitivity and specificity of 75% (95%CI: 42.8-94.5%) and 100% (95%CI: 47.8-100%) respectively in predicting clinical response. A change in 52% or more in the SUV-max of mediastinal lymph nodes had a sensitivity and specificity of 75% (95%CI: 47.6-92.7%) and 100% (95%CI: 54.1-100%) respectively in predicting clinical response.

FDG PET-CT is increasingly being used for diagnosis and guiding therapeutic decisions in patients with infectious diseases. The available literature on FDG/PET-CT for assessing results and treatment response in patients with pulmonary TB is limited and suggests a good correlation between the two of them (5). However, there is a paucity of literature evaluating FDG/PET-CT's role in EPTB in particular. PET-CT has been hypothesized to predict the need for treatment intensification or prolonged therapeutic strategies or change in the treatment regimen (6). Experimental animal models have shown that FDG PET-CT activity seems to be in direct correlation to the bactericidal activity of anti-tuberculosis treatment (7,8).

It is pertinent to note that FDG uptake is based on the glycolytic activity in the neutrophils, lymphocytes and macrophages and represents inflammation (9,10). Therefore, the absence of uptake suggests a decrease in inflammation, suggesting that the patient has responded to treatment. This is the reason why in patients with no metabolic uptake in the post-therapy scans had all responded clinically. It is evident from our results that the persisting activity may not suggest active disease. In such cases, clinical assessment should be given more importance in deciding the course of action (11-18). Similar to a previously published study, our study showed that change in SUV-max could be used as a surrogate for predicting clinical response as well (15). We found that percentage decrease of 77% for cervical lymph nodes and 52% decrease for mediastinal lymph nodes had excellent specificity and considerable sensitivity. However, there is a need for a larger sample size to validate the cut-offs that we derived.

In conclusion, although PET may be useful as an adjunct to clinical response in guiding duration of therapy in some cases of tubercular lymphadenitis, its routine use as a stand-alone guide for treatment response needs to be ascertained with further studies with larger sample size.

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