Original article

Persistence of Granuloma or granulomatous Inflammation after Six Months of CAT-1 Anti Tuberculosis Therapy in Tubercular Lymphadenitis Patients

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Abstract

Background: Tuberculous Lymphadenitis is the most common form of extra-pulmonary tuberculosis. Paradoxical enlargement and new lymph nodes appearance are observed after completion of anti-tuberculous therapy. **Objective**: The objective of the study was to assess whether granuloma can persist in persisted or paradoxically enlarged lymph node after anti-TB treatment in tubercular lymphadenitis patient**.** ***Method***: An observational cross sectional study was conducted in the Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University from March 2014 to February 2016 among patients of TB-lymphadenitis who had persistent or enlargement of previous or developed new lymph node after anti-TB therapy. History was taken; previous records were analyzed to ascertain the diagnostic basis of tuberculosis. History and physical examination were done for present status. Cytological or histopathological analysis was done at Department of Pathology, BSMMU. ***Result:*** Most of the patients were in the 21-30 years age group (Mean 25.53±7.93). Majority of them were female. Most of the respondents were student. More than half of the patients came from lower socioeconomic status. About 89% had typical symptoms of tuberculosis like fever, weight loss and loss of appetite during initial diagnosis and about one third had typical symptom of TB like fever weight loss and loss of appetite and one third had no symptoms after treatment. Majority mode of diagnostic tool was FNAC in both initial and after treatment. Majority (88.9 %) cases granuloma persisted after treatment. ***Conclusion***: In spite of anti TB treatment with good compliance granuloma or granulomatous inflammation persisted in majority patients of persisted lymph nodes.

Keywords: Tubercular Lymphadenitis; persistent lymph node; post anti-TB treatment

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Introduction

Tuberculosis is considered a vigorous threat to public health all over the world but disproportionately afflicts low-income nations.[1] Nearly one-third of the global population is infected with mycobacterium tuberculosis and tuberculosis ranks as the second leading cause of death from an infectious disease worldwide.[2] Bangladesh is the sixth highest TB-

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burden country in the world.[3] TB-lymphadenitis is the most common comprises 68% of all extra-pulmonary tuberculosis patients.[4] Lymph nodes are usually involved in the early stages of the pulmonary disease or as secondary TB by hematogenous spread[5]. However, tuberculous lymphadenitis may arise without a detectable preceding pulmonary involvement. Tuberculous lymphadenitis affects mainly the cervical lymph node group and is an important cause of lymphadenopathy worldwide[6] Tuberculosis case finding and treating effectively is always challenging especially in low resource settings. In Bangladesh tuberculosis is a health problem since long. Tuberculous lymphadenitis usually presents as a gradually increasing painless swelling of one or more lymph nodes of weeks to months duration. Patients with extensive disease may have systemic symptoms i.e. fever, weight loss, fatigue and night sweats. Anti-TB therapy is often prescribed after confirmation by granuloma or granulomatous inflammation with or without caseation necrosis on FNAC or histopathology. Paradoxical reaction during anti-tuberculosis treatment is a well-known phenomenon since 1955, defined as the clinical or radiological worsening of pre-existing tuberculous lesions or development of new lesions in a patient who initially improves with anti-tuberculosis therapy in the absence of disease relapse.[7] It occurs in about 11-15% of patients with tuberculosis. Though, they found commonly among HIV-positive patients and frequently in those with extra-pulmonary and disseminated tuberculosis. Tuberculous lym phadenitis is usually pauci-bacillary condition that response slowly on treatment. According to WHO global report 2016, the overall prevalence of multi-drug resistant tuberculosis in Bangladesh is very low (<1.6%), so the chance of treatment failure or development of resistant strains in gland-TB is unlikely if compliance is assured properly. TB-lymphadenitis may also develop by atypical mycobacterium / MAC which is unresponsive to conventional anti-TB therapy and it is uncommon in our country.[8] As per National Tuberculosis Control Programme guideline, existing anti-tuberculous regimen is adequate for treatment of tuberculous lymphadenitis patients. In our country tuberculous lymphadenitis patients are diagnosed on the basis of clinical features of tuberculosis and presence of granuloma or granulomatous inflammation with or without caseation in FNAC or biopsy and sometimes with positive MT test. After starting anti-TB drugs in some cases during or at the end of treatment the existing lymph node persists or starts to enlarge or even new lymph node appears in the same or another site. So the physicians dealing with the patients considered as delayed responder or non-responder, patients either advised to extend the present anti-TB regimen or change to another regimen and thus these groups of patients receive extended or repeated courses of anti-TB regimen. So this study was done to evaluate status of lymph node, granuloma or granulomatous inflammation in enlarged lymph nodes in TB-lymphadenitis patient after completion anti-TB therapy to guide the clinicians to treat this group of patients more effectively in future.

Methodology

This study was conducted in the Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University. It was observational cross sectional study which was conducted from March 2014 to February 2016. TB-lymphadenitis patient who had symptoms and signs of TB and confirmed by finding of granuloma or granulomatous inflammation in FNAC or biopsy with or without caseation necrosis, completed 6 months of CAT-1 anti-TB treatment but lymph remained persistently enlarged or new lymph node appeared at the same or another site was selected. Convenient sampling was used. The study was conducted on approximately available subjects within that period as per inclusion criteria and that was 72. Patients with TB lymphadenitis diagnosed on the basis of findings of granuloma or granulomatous inflammation with or without caseation necrosis on FNAC or biopsy, with symptom and sign of tuberculosis and completed CAT-1 anti TB treatment at least for six months and lymph node remained persistently enlarged or new lymph node appeared at the same or another site were included in the study. Inadequate aspiration or sample in FNAC or biopsy and no documentation of cytology or histopathology report of diagnosis were excluded. After taking permission of technical committee of Department of Internal Medicine, I took approval from the Institutional Review Board (IRB), and permission from respective department like Department of Pathology and Department of Otolaryngology and Head-neck Surgery and then the study was started. All available patients attending outpatient and inpatient department of Bangabandhu Sheikh Mujib Medical University with TB lymphadenitis who had persistently enlarged or newly appeared lymph node at the same or another site after six months of CAT-1 anti TB treatment

were selected. After written consent, diagnostic basis of tuberculous lymphadenitis ascertained by history of sign, symptoms of tuberculosis compliance of anti-TB drugs and follow up during the period of treatment. Previous records were analyzed to see the cytology or histopathology reports of diagnosis whether diagnosis was made by presence of granuloma or granulomatous inflammation. Those patients who had granuloma or granulomatous inflammation during diagnosis, completed CAT-1 anti TB were enrolled for the study. After enrolling history was taken to evaluate new symptoms of tuberculosis and physical examination was done for present status of lymph nodes. Then patients were sent for fine needle aspiration (FNA) in Department of Pathology, BSMMU, biopsy in Department of Otolaryngology and Head-neck Surgery. Sample was sent for cytology or histopathology. To analyze the data Statistical Package for Social Science (SPSS) version 21.0 was used. After entry, range and consistency were checked. Statistical analysis was done by using descriptive statistics. Continuous variables were presented as mean values ± standard deviation (SD), and categorical variables were presented as percentages. Data were presented by table and graphs.

Ethical clearance: This study was approved by ethics committee of BSMMU. Memo no: BSMMU/2015/13039; Date: 02/11/2015

Results

Seventy-two diagnosed cases of tubercular lymphadenitis attending the Internal Medicine Department of BSMMU, were enrolled as per inclusion criteria. Age ranges of the patients were from 13-48 years. Mean age was 25.53±7.93 years. Table I shows most of the patients were in the 21-30 years age group. Majority of them were female. Most of the respondents were student. More than half of the patients came from lower socioeconomic status. Table II shows about 89% had typical symptoms of tuberculosis like fever, weight loss and loss of appetite and some presented only with fever. Table III & VII reveal that majority mode of diagnostic tool was FNAC in both initial and after treatment. Table IV & V indicate most of the patients had granulomatous inflammation or granuloma without caseation in cytology report during TB diagnosis. Table VI shows that about one third had typical symptom of TB like fever weight loss and loss of appetite and one third had no symptoms. Table VIII & IX show most of the patients had granuloma or granulomatous inflammation without caseation after anti-TB treatment. Table X shows most granuloma persisted in persisted lymph nodes after treatment.

Table I: Socio-demographic characteristics of patients (n=72)

Variables	Number	Percentage
Age (in years)		
≤20	28	38.9
21-30	34	47.2
31-40	6	8.3
≥41	4	5.6
Mean±SD	25.53±7.93	
Sex		
Male	18	25.0
Female	54	75.0
Education		
No schooling/illiterate	10	13.9
Primary	26	36.1
Secondary	20	27.8
Higher-secondary	16	22.2
Occupation		
Housewife	18	25.0
Service holder	14	19.4
Business	4	5.6
Student	28	38.9
Others	8	11.1
Socioeconomic status		
Lower	38	52.8
Middle	22	30.6
Higher	12	16.7

Table II: Frequency of constitutional symptoms during initial diagnosis (n=72)

Variables	Number	Percentage
Fever, weight loss & loss of appetite	64	88.9
Weight loss & loss of appetite	2	2.8
Fever	6	8.3

Table III: frequency of diagnostic tests before anti TB treatment (n=72)

Variables	Number	Percentage
FNAC	66	91.7
Biopsy	6	8.3
Total	72	100

Table IV: Frequency of Cytological findings of lymph nodes during initial diagnosis (n=66)

Cytology	Number	Percentage
Granulomatous inflammation with caseation necrosis	18	27.3
Granulomatous inflammation without caseation necrosis	48	72.7
Total	66	100

Table V: frequency of histopathological findings of lymph nodes during initial diagnosis (n=6)

Histopathology	Number	Percentage
Granuloma with caseation	2	33.3
Granuloma without caseation	4	66.7
Total	6	100

Table VI: Frequency of new constitutional symptoms after completion of treatment (n=72)

Variables	Number	Percentage
Fever, weight loss & loss of appetite	24	33.3
No symptoms	22	30.6
Fever	10	13.9
loss of appetite	6	8.3
weight loss	4	5.6
fever & loss of appetite	6	8.3

Table VII: frequency of diagnostic tests after anti TB treatment (n=72)

Variables	Number	Percentage
FNAC	56	77.8
Biopsy	16	22.2
Total	72	100

Table VIII: Frequency of Cytological findings of lymph nodes after completion of treatment (n=56)

Cytology	Number	Percentage
Granulomatous inflammation with caseation necrosis	8	14.3
Granulomatous inflammation without caseation necrosis	42	75
No granulomatous inflammation	6	10.7
Total	56	100

Table IX: frequency of histopathological findings of lymph nodes after completion of treatment (n=16)

Histopathology	Number	Percentage
Granuloma with caseation	4	25
Granuloma without caseation	10	62.5
No granuloma	2	12.5
Total	16	100

Table X: frequency of persisted granuloma or granulomatous inflammation after treatment (n=72)

Histopathology	Number	Percentage
Granulomatous inflammation	50	69.4
Granuloma	14	19.5
No granuloma or granulomatous inflammation	8	11.1
Total granuloma or granulomatous inflammation	64	88.9

Discussion

Physicians face problems when lymph nodes start to enlarge after anti-tuberculous therapy. Such situation poses a diagnostic challenge as the apparent clinical deterioration may raise the suspicion of drug-resistant TB, concomitant disorders unrelated to TB or due to paradoxical reaction. We studied the persisted, further enlarged or newly appeared lymph nodes after six months of CAT-1 anti-TB therapy for presence of granuloma or granulomatous inflammation. 72 patients were enrolled for the study. We use history of symptoms and signs of tuberculosis along with cytological or histopathological reports of granulomatous inflammation/granuloma for the diagnostic basis of tuberculous lymphadenitis. This study showed one third had typical constitutional features like combination of fever, weight loss, loss of appetite and one third had no symptoms after completion of anti –TB treatment. In tubercular lymphadenitis systemic symptoms are common. Classically patients present with low grade fever, weight loss and fatigue and somewhat less frequently with night sweats.[9] Patients with the Tubercular lymphadenitis had a longer ($p<0.001$) duration of symptoms before diagnosis but less common ($p<0.02$) local complications at presentation than those with the NTM disease.[10] A study done in Chittagong, Bangladesh showed patients with tubercular lymphadenitis 70% had history of fever, 85% had significant weight loss. Another study from Dhaka, Bangladesh showed patients with tubercular

lymphadenitis, 66.67% had fever, night sweat 50%. Mild paradoxical reaction like recurrence of fever and enlargement of superficial lymph nodes[11], by which we can be explained one of the causes of new symptoms found in this study is paradoxical reaction. The present study showed majority had granuloma or granulomatous inflammation without caseation after treatment. In histopathology Langerhans giant cells, caseating necrosis, granulomatous inflammation and calcification can be seen.[12] In a Bangladeshi study showed caseating granuloma in 85%. This is not similar to present study. Dandapat showed the caseation in 80%.[9] In another study done in tertiary medical college in Dhaka, Bangladesh showed 71.2% had granuloma with caseation necrosis and 28.8% had granuloma without caseation necrosis.[13] Majeed et al. who found 96% cases with caseation and the rest without.[14] Poleski et al showed in biopsy specimen 71% were granuloma with caseation, 17% were granuloma without caseation and 12% had no granuloma, in FNAC specimen 28% granuloma with caseation, 34% had granuloma without caseation 38% had no granuloma.[15]

In this study showed majority granuloma persisted even after six months of CAT-1 anti TB with good compliance. This study shows agreement with study done by Chowdhury MMH et al, and Park K et al, 2013. The studies done by Mohapatra PR et al, and Polesky A et al do not showed agreement with present study.

Conclusion & recommendation

Tubercular lymphadenitis was relatively common in younger age, female gender and low socioeconomic status. Significant percentage of granuloma or granulomatous inflammation found in persistent or newly appeared lymph node even after complete treatment with good compliance and adequate follow up under national TB control programme. This persistent granuloma or granulomatous inflammation can be result of paradoxical reaction of treatment. So patient may not need to extend anti TB drugs. Further study can be done to observe the disease activity of persistent granuloma or granulomatous inflammation.

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