Original Article

Magnetic resonance imaging in response assessment of mediastinal tuberculous lymphadenopathy: Going beyond size

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ABSTRACT

Background: Assessment of response to antitubercular treatment (ATT) in mediastinal tuberculous lymph nodes (LNs) is challenging. Gold standard techniques such as biopsy and culture involve invasive procedures. Radiographic persistence of mediastinal LNs even after completion of ATT poses a treatment dilemma. In this study, we evaluated the changes in signal intensity (SI) and apparent diffusion coefficient (ADC) values of mediastinal LNs on magnetic resonance imaging (MRI), for response assessment to ATT. **Materials and Methods:** After institute ethics approval, a retrospective analysis of MRI images of 22 patients with 55 mediastinal tuberculous LNs was done. Clinically responsive patients of mediastinal tuberculous LNs who underwent chest MRI prior to ATT, or within 1 month of starting ATT, and second MRI performed at least after 2 months of start of the treatment were included. LN size, T1 and T2 signal characteristics (homogenously/heterogeneously and hyperintense or hypointense), T2 and T1 SI ratio, ADC values, and contrast enhancement characteristics were compared. Paired *t*-test and McNemar test were performed at a significance level of α =0.05. **Results:** Size of LN reduced, but 45 LNs measured >8 mm in second MRI. There was statistically significant decrease in the T2 and T1 SI ratios in second MRI, P = 0.026 and 0.008, respectively. No statistically significant difference was found in ADC values, P = 0.31. **Conclusions:** Decrease in T2 and T1 SI ratios of mediastinal tuberculous LNs can be used as a noninvasive imaging parameter to suggest response to ATT. However, ADC value is not a useful indicator of treatment response.

KEY WORDS: Chest TB, drug resistance, lymph nodes, mediastinal, magnetic resonance imaging, tuberculous

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INTRODUCTION

Tuberculous lymphadenitis is one of the most common manifestations of extrapulmonary tuberculosis (EPTB). Commonly involved sites include cervical, mediastinal, axillary, mesenteric, hepatic portal, perihepatic, and inguinal lymph nodes (LNs) in order of prevalence.[1] Right paratracheal and subcarinal LNs are the most frequently involved sites in mediastinum. Assessment of treatment response to antitubercular treatment (ATT) involves clinical, laboratory, and radiological evaluation. Clinical assessment includes overall performance

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status, weight gain during treatment, and resolution of systemic and organ-based symptoms.[2] Commonly used laboratory tests include monitoring of blood level of acute phase reactants (C-reactive protein and erythrocyte sedimentation rate). Radiological assessment includes follow-up chest X-ray (CXR), contrast-enhanced computed tomography (CECT), ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT), and magnetic resonance imaging (MRI). CXR is often used, but it has poor specificity. Stability on CXR over 4–6 months interval is taken as an indicator of radiographically stable disease and disease inactivity.[3] On CECT, reduction in size, change in enhancement pattern from peripheral to homogenous, appearance of perinodal fat, and calcifications suggest response to treatment.[4] ^{18}F-FDG PET CT provides a combination of metabolic and anatomic information of LNs and has been used to monitor disease activity as early as 1 month.[5] However, repeated use of both CT and PET-CT is associated with hazards of radiation exposure.

Recent advances in MRI have led to rapid and improved quality of acquisition of MRI images. Being radiation free, repeated use of MRI is not associated with hazards of radiation exposure. Sequences such as T1, T2, diffusion-weighted imaging (DWI), and postcontrast have been proposed for optimal evaluation of mediastinal LNs.[6] Imaging features of tuberculous lymphadenitis have been described in literature, depending on the presence and the degree of granuloma formation, caseation or liquefaction necrosis, fibrosis, and calcifications. However, interval changes in the magnetic resonance (MR) signal intensity (SI) of mediastinal LNs following ATT have not been described in the literature. Persistence of LNs during treatment course poses diagnostic dilemma of inactive disease versus drug resistance. This has significant clinical importance in terms of treatment modification and duration.

In this study, we evaluated the changes in SI and apparent diffusion coefficient (ADC) values of tubercular mediastinal LNs on MRI, performed during the course of treatment as a tool for response assessment. In addition, we also evaluated interval changes in LN size, diffusion restriction, and contrast enhancement characteristics.

MATERIALS AND METHODS

This was a retrospective study and approval was obtained from the institute ethics committee. MRI scans of patients with mediastinal lymphadenopathy diagnosed as tuberculous etiology who underwent chest MRI prior to ATT, or within 1 month of starting ATT, and had a second MRI performed at least after 2 months after start of the ATT with clinical response to therapy were analyzed. Twenty-two such patient's MRI scans were found on picture archiving communication system during January 2015–December 2019 time period. Diagnosis of tuberculosis was based on microbiological and/or cytological or histopathological findings.

Magnetic resonance imaging protocol

MRI was performed on a 1.5 Tesla MR scanner using a body coil, following the departmental standard protocol. The scan was performed from the lung apices to the domes of diaphragm. The following sequences were used - balanced SSFP in axial and coronal plane, T2-weighted SSFSE fat sat in axial and coronal plane, T1 in-phase and opposed phase in axial plane, T2-weighted SSFSE non- fat sat in axial plane, DWI(single-shot spin echo planar technique at b value of 0, 400, and 800 s/mm2, and post gadolinium T1FS at 30s, 1 min in axial/coronal planes, and delayed at 3 min.

Image analysis

MR images were evaluated by two chest radiologists (PN and ASB) in consensus. The following MRI features of LNs were compared between first and second MRI scans:

- LN size: It was measured in short-axis dimension on T2W
- T2 signal characteristic of LNs was categorized as one of the following patterns based on SI relative to the paraspinal muscle:
  a. Homogenously hyperintense
  b. Heterogeneously hyperintense
  c. Homogenously hypointense
  d. Heterogeneously hypointense [Figure 1a-d].
- T1 signal characteristic of LNs was categorized as one of the following patterns based on SI relative to the paraspinal muscle:
  a. Heterogeneously hypointense
  b. Homogenously hypointense
  c. Heterogeneously hyperintense
  d. Homogenously hyperintense [Figure 1e and f].
- T2 SI ratio: T2 SI of LN/T2 SI of multifidus muscle. The region of interest (ROI) included at least 2/3rd of the LN area
- T1 SI ratio: T1 SI of LN/T1 SI of multifidus muscle. The ROI included at least 2/3rd of the LN area
- Diffusion restriction in LN was recorded as present or absent
- ADC value of LNs was recorded using ROI placed on at least 2/3rd of the LN area
- Contrast enhancement pattern of LN was recorded as absent/peripheral rim/solid patterns [Figure 1g and h].

Statistical analysis

Continuous variables were compared using paired *t*-test; and categorical variables were compared using McNemar test. All the statistical tests were performed at a significance level of $\alpha = 0.05$. Analysis was conducted using StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

RESULTS

MRI of 22 patients with tuberculous mediastinal lymphadenopathy was evaluated. The mean age of the

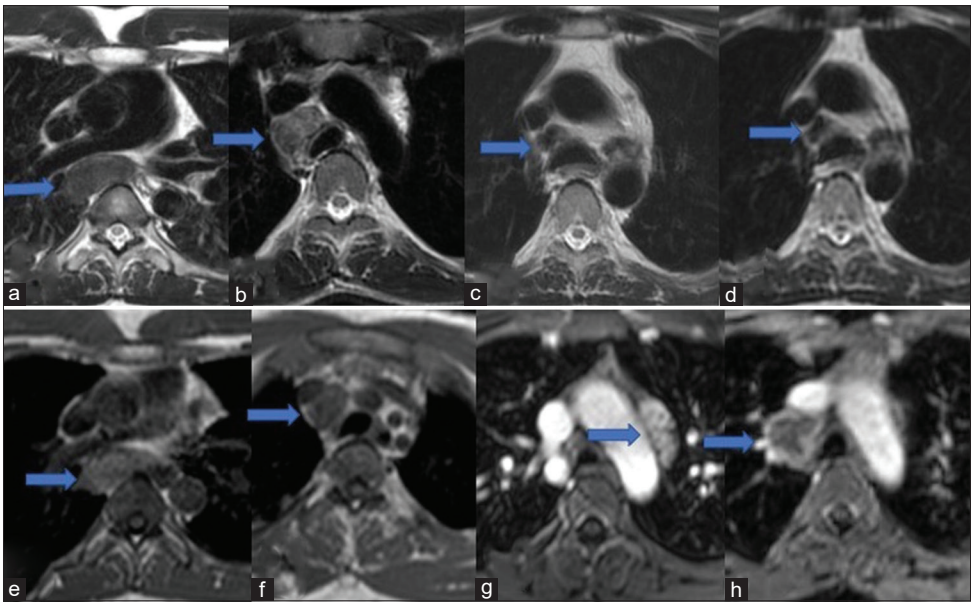

Figure 1: T2, T1 signal intensity and contrast enhancement patterns of lymph nodes. (a-d): T2W images depicting (a) T2 homogenously hyperintense, (b) heterogeneously hyperintense, (c) heterogeneously hypointense and (d) homogenously hypointense lymph nodes (arrows); (e and f): T1 W images showing (e) heterogeneously hyperintense and (f) hypointense lymph nodes (arrows); (g and h): Postcontrast images depicting (g) solid and (h) peripheral rim pattern of enhancement (arrows)

patients was 29 years (range 13–65 years) and included 10 females and 12 males. The mean duration between two MRI scan was 3.5 months, with maximum and minimum interval being 11 and 2 months, respectively. The total number of LNs in the first MRI scans (measuring >8 mm in size) was 61 and in follow-up MRI scans was 55. On follow-up MRI, the number of LNs measuring <5 mm was 1 (2%), 5–8 mm was 9 (16.2%), and >8 mm was 45 (81.8%). Six LNs were completely resolved in the follow-up imaging. Fifty-five LNs were evaluated for T1, T2 characteristics. Forty-nine LNs were evaluated for the contrast enhancement patterns as intravenous contrast could not be administered in three patients due to deranged renal function. Those LNs measuring >8 mm in size (n = 45) were analyzed for DWI and ADC to avoid errors due to small ROI for ADC values [Figure 2].

Comparison between size of the lymph nodes

The mean size of the LNs in the first MRI scan was 15.68 mm ± 4.79 mm, whereas in the second MRI scan, it was 11.63 mm ± 5.04 mm [Table 1]. Overall, there was a decrease in the size of LNs on follow-up MRI, and it was statistically significant (P = 0.001) [Figure 3 a and b]. However, still 45 LNs (>80%) were measuring >8 mm in size in second MRI [Figure 4 a and b].

Comparison between T2 and T1 signal intensity ratio

There was decrease in the mean T2 SI ratio of the LNs: 2.27 ± 0.611 and 2.03 ± 0.734 in first and second MRI, respectively [Figure 3c and d; 4c and d; 5c and d]. Similarly, the mean T1 SI ratio of the LNs was 1.058 ± 0.283 and 0.91 ± 0.28 in the first and second MRI, respectively [Figure 3e and f; 4e and f]. This decrease in the T2 and T1 SI ratios of the LNs was statistically significant [Table 1].

Table 1: Comparison between lymph node size, signal intensity ratio and apparent diffusion coefficient vales

	Mean±SD		*P*
	First MRI	Second MRI	
Size (mm)	15.68±4.79	11.63±5.04	0.001
T2 SI ratio	2.279±0.611	2.032±0.734	0.0262
T1 SI ratio	1.058±0.283	0.910±0.277	0.008
ADC values	1.29±0.40	1.233±0.400	0.316

MRI: Magnetic resonance imaging, ADC: Apparent diffusion coefficient, SD: Standard deviation

Comparison between qualitative assessment T2 and T1 signal intensity

In first MRI, 46 (83.6%) of the LNs showed heterogeneously hyperintense SI on T2W images and 9 (16.4%) of the LNs showed T2 homogenously hyperintense SI. On the other hand, on follow-up MRI, 41 (74.5%) LNs showed heterogeneously hyperintense SI. Seven (12.8%) of LNs showed T2 hypointense SI [Figure 3a and b; 5a and b]. Similarly, majority of the LNs showed T1 heterogeneously hypointense SI, with increase in the number of LNs having T1 heterogeneously hypointense SI in the second MRI. This change in the pattern of the T2 and T1 signal characteristics was, however, not statistically significant [Table 2].

Comparison between diffusion restriction and apparent diffusion coefficient value

In the initial MRI, all except one LN showed diffusion restriction [Figure 5e and f]. In the second MRI, 6 (13.3%) of the LNs showed facilitated diffusion. This change on visual assessment was statistically significant with P = 0.025. However, changes in ADC value were not statistically significant [Figure 3g and h; 4g and h; Table 1].

Comparison between the enhancement patterns of lymph nodes

Forty-nine LNs were evaluated for enhancement characteristics as mentioned [Table 3]. In 7 LNs, enhancement pattern had changed from peripheral rim to solid. The change in the pattern of enhancement in follow-up MRI scan was statistically significant. One LN showed solid to peripheral rim enhancement pattern [Figure 5g and h].

DISCUSSION

Assessment of response to ATT in EPTB, especially in mediastinal tuberculosis, is challenging. Biopsy and culture of the diseased LNs are gold standard for assessing disease activity and drug resistance in tuberculous lymphadenopathy.[7,8] It involves invasive procedures such as endobronchial ultrasound guidance for LN sampling, unlike pulmonary tuberculosis where it is usually assessed with sputum-based assays such as 2 months sputum culture conversion and GeneXpert.[9] Based on response assessment, treatment regime and duration are tailored.

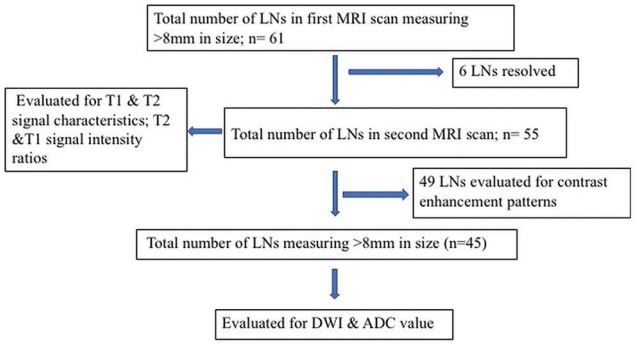

Figure 2: Flowchart of lymph nodes in the study

Immunological response in *Mycobacterial tuberculosis* infection is delayed-type hypersensitivity reaction. It leads to macrophage activation, granuloma formation, and necrotic material in the center forming caseous necrosis. Pathologically, active tubercular lymphadenitis can be categorized into into stages depending on the duration of disease.[10] Stage 1: There is lymphoid hyperplasia with granuloma formation, which may or may not be associated with minimal necrosis; Stage 2: Caseating necrosis occurs; Stage 3 - There is capsular disruption; and Stage 4: Following capsular disruption, caseous material extrudes into the surrounding soft tissue resulting in a confluent abscess cavity. On imaging, granulation tissue appears T2 and T1 hypointense and shows enhancement on postcontrast images. Whereas, caseous necrosis appears T2 hyperintense and T1 hypointense and does not show any enhancement on contrast images. Capsular disruption appears as perinodal T2 hyperintensity. During course of ATT, LNs may change to prior stage/may disappear/undergo reactive lymphoid hyperplasia/may result in residual fibrotic mass and may contain calcifications.[11,12] Similarly, MRI appearance of the LNs change during the course of ATT. This radiological and pathological correlation can be applied in assessing the treatment response on MRI.

In this study, we performed quantitative and qualitative assessment of signal characteristics on MRI. There

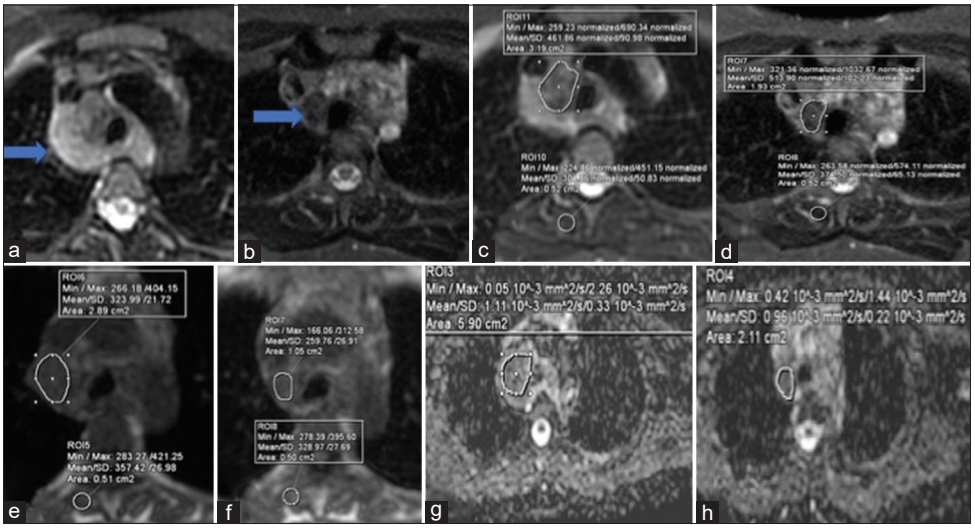

Figure 3: Twenty-two years/female with tuberculous mediastinal lymphadenopathy; magnetic resonance imaging images showing measurements of T2, T1 signal intensity ratios. Interval between first magnetic resonance imaging (a, c, e, and g) and second magnetic resonance imaging (b, d, f, and h) was 2 months. (a and b) show T2 characteristics of lymph node heterogeneously hyperintense in (a) and heterogeneously hypointense in (b); lymph node was reduced in size and became hypointense compared to first magnetic resonance imaging. (c and d) show T2 signal intensity ratio which was decreased in second magnetic resonance (ratio 1.5 in first magnetic resonance imaging and 1.37 in second magnetic resonance imaging). (e and f) show T1 signal intensity ratio which was decreased in second magnetic resonance imaging (ratio 0.9 in first magnetic resonance imaging and 0.78 in second magnetic resonance imaging). (g and h) show apparent diffusion coefficient values which was decreased in second magnetic resonance imaging(apparent diffusion coefficient value in first magnetic resonance imaging $1.1 \times 10 - {}^{3}$ mm^2/s and in second magnetic resonance imaging $0.96 \times 10 - {}^{3}$ mm^2/s)

Table 2: Magnetic resonance imaging signal characteristic of lymph nodes

	T2 signal characteristics		T1 signal characteristics	
	First MRI	Second MRI	First MRI	Second MRI
Homogenously hyperintense (%)	9 (16.4)	7 (12.7)	0	0
Heterogeneously hyperintense (%)	46 (83.6)	41 (74.5)	9 (16.4)	3 (5.5)
Homogenously hypointense (%)	0	3 (5.4)	0	0
Heterogeneously hypointense (%)	0	4 (7.4)	46 (83.6)	52 (94.5)

P value of T2 signal characteristic -0.062; *P* value of T1 signal characteristic -0.057. MRI: Magnetic resonance imaging

Table 3: Contrast enhancement patterns

	First MRI	Second MRI
Peripheral (%)	37 (75.5)	31 (63.3)
Solid (%)	12 (24.5)	17 (34.7)
Absent (%)	0	1 (2)

P-0.033. MRI: Magnetic resonance imaging

was overall significant decrease in the size of the LNs in the follow-up MRI, as compared with first MRI scan ($P = 0.001$). We found that there was a significant decrease in the T2 and T1 SI ratio of LNs in the second MRI with $P = 0.0262$ and 0.008, respectively. Although no change in the size of LNs was noted in four patients 9/55(16.3%); T2 and T1 SI ratios were significantly decreased in these LNS. This can possibly be due to fibrosis or granulation tissue, which occurs in the LNs following ATT. Fibrous and granulation tissues show T2 hypointense SI.[13,14] Therefore, decrease in the SI ratios of LNs on second MRI can be an indicator of response to ATT. No previous study has evaluated quantitative SI changes of tuberculous LNs during the treatment.

The MRI appearances of tuberculous LNs include T2 homogenously hyperintense LNs with homogenous contrast enhancement, T2 hyperintense with thin rim of T2 hypointense SI, and peripheral rim contrast enhancement, or T2 heterogenous hyperintense with minimal or no enhancement.[13] On qualitative assessment of the T2 and T1 SI characteristics of LNs, seven (12.8%) and eight (14.5%) of LNs became hypointense on follow-up MRI, respectively, but was not statistically significant ($P = 0.062$ and 0.057). All LNs pretreatment showed T2 hyperintense SI. This is in concordance with previous study by Becker *et al*., in which majority of the abdominal tubercular LNs were T2 hyperintense.[15] 46/55 (83.6%) LNs were heterogeneously hyperintense on T2-weighted images with presence of hypointense foci in the periphery as well as center. Peripheral hypointense SI can be attributed to granulation tissue; and in the center to paramagnetic substance such as free radicals. In one patient, T1 hypointense SI of two LNs changed to T1 hyperintensity on follow-up. T2 signal characteristic of this LN changed from heterogeneously hyperintense in the first MRI to heterogeneously hypointense on follow-up. This may be due to paramagnetic substances produced during phagocytosis lead to T2 and T1 relaxation time shortening, hence T1 hyperintense and T2 hypointense SI.[16] Following response to ATT, LN tissue is composed of fibrous and granulation tissue which appears T2/T1 hypointense. These results support that T2 and T1 hypointensity of LNs in the follow-up MRI suggest response to ATT.

Previously, multiple studies have evaluated the diagnostic accuracy of DWI in differentiating benign from malignant mediastinal LNs and had defined ADC cutoff value for this differentiation.[17,18] In this study, the mean ADC values of LNs in the first and second MRI were 1.29 ± 0.40 and 1.23 ± 0.4, respectively. This ADC value for benign LNs is similar to previous studies by Abou Youssef *et al*. and Vandecaveye *et al*.[17,19] There was decrease in the ADC value of the LNs in the follow-up MRI. However, it was not statistically significant ($P = 0.316$). Varying degree of diffusion of water protons in the extracellular and intracellular compartment contributes to the SI of DWI and ADC value. It has been described that low ADC value in the reactive LNs is due to inflammatory cells and stromal fibrosis, altering the diffusion of water proton in extracellular compartment.[20] All except one LN showed diffusion restriction in the pretreatment MRI, in contrast to the second MRI where six LNs did not diffusion restriction. Absence of diffusion restriction in the LNs during disease is course likely to suggest disease response. However, its converse is not correct. In our study, diffusion restricting LNs also showed decrease in T2 and T1 SI ratio. Therefore, interpretation of DWI and ADC value should be done in combination with T1 and T2 MRI sequences.

Peripheral rim pattern of the enhancement was the predominant pattern seen in both the MRI scans. In a study by Moon *et al*., peripheral rim enhancement and low central attenuation suggested active disease.[4] In one of the review articles, rim and heterogenous pattern of LN enhancement is likely to suggest active disease.[6] In our study, enhancement of LNs persisted during the disease course. 7/49 (14.3%) LNs showed change in the enhancement pattern from peripheral to solid. All the patients in this study had clinical response and imaging was done during the treatment course, not at the end of treatment. Hence, the presence of persistent contrast enhancement within these LNs may still be seen. Granulation tissue along with hypervascularity in the LNs could be possible reason for postcontrast enhancement.[14] We could not evaluate the enhancement pattern of LNs in patients who completed treatment compared with those still on treatment due to limited number of LNs in the former group.

Our preliminary study showed that decrease in the T2 and T1 SI ratios of mediastinal tuberculous LNs, which is assessed quantitatively, is a reliable indicator of response

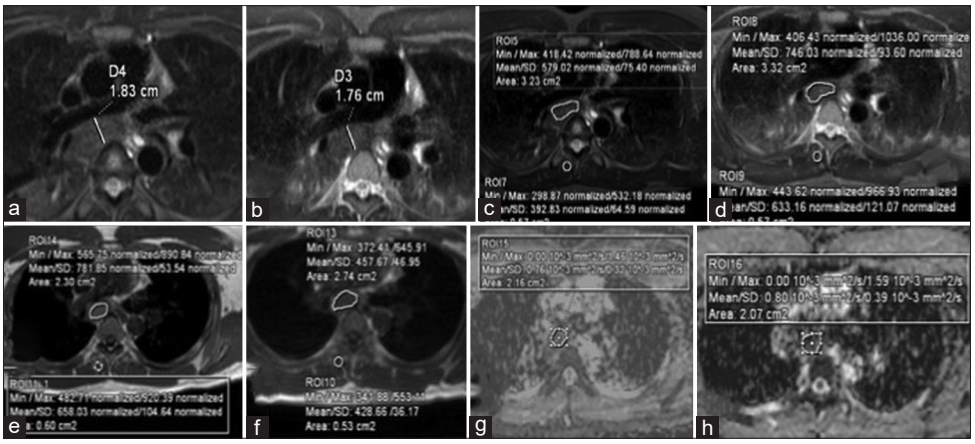

Figure 4: A case of tuberculous mediastinal lymphadenopathy in a 24-year-old female. Interval between first magnetic resonance imaging (a, c, e, and g) and second magnetic resonance imaging (b, d, f and h) was 6 months. On follow-up, lymph node was still of significant size (a and b) and showed low apparent diffusion coefficient values (g and h). However, there was decrease in the T2 and T1 signal intensity ratios (c-f)

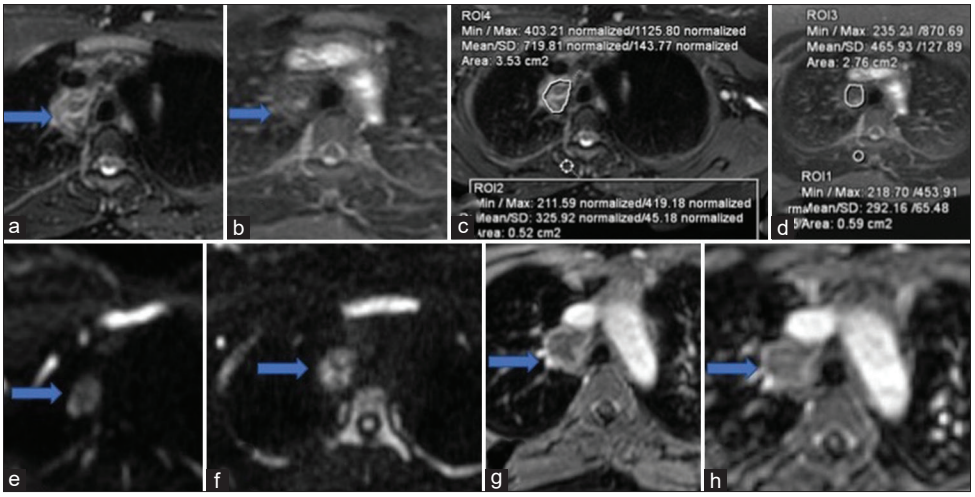

Figure 5: A case of tuberculous mediastinal lymphadenopathy in a 28-year-old female. Interval between first magnetic resonance imaging (a, c, e, and g) and second magnetic resonance imaging (b, d, f, and h) was 6 months. Right paratracheal lymph node was hypointense and T2 signal intensity ratio was decreased in follow-up magnetic resonance imaging (a, b, c, and d). However, diffusion restriction and thin rim of peripheral enhancement was still present in the follow-up magnetic resonance imaging (e, f, g, and h)

to ATT. Diffusion restriction and enhancement of the LNs may persist during disease course and should not always be considered as nonresponse or drug resistance.

There are certain limitations in our study. It was a retrospective study and interval between the first and second MRI was variable. All patients included in our study were clinical responders and hence drug sensitive. Hence, we did not evaluate MR characteristic of drug resistant tuberculous LNs. Sample size of the study is small. Therefore, there is a need for a prospective study with larger sample size, performing MRI at regular fixed interval and evaluating MRI signal characteristics for its implication in the clinical practice.

CONCLUSIONS

This preliminary study has shown that decrease in T2 and T1 SI ratios of the mediastinal tuberculous LNs can be a noninvasive imaging parameter, suggesting response to ATT. However, DWI and ADC values are not useful for evaluating the treatment response. Furthermore, contrast administration may not be necessary in all the follow-up imaging, as a noncontrast scan is in itself a useful parameter.

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Conflicts of interest
There are no conflicts of interest.

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