# The Value of Ultrasonography in The Diagnosis and Evaluation of Early Therapeutic Response of Cervical Tuberculous Lymphadenitis

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## ABSTRACT

**Background:** Tuberculosis is a worldwide infectious disease in spite of advancement in health care system. Tuberculous lymphadenitis is the most prevalent form of extra pulmonary tuberculosis with predilection of cervical lymph nodes.

**Objectives**: To evaluate the reliability of grey scale ultrasonography together with color Doppler in the diagnosis of cervical tuberculous lymph adenitis and evaluation of early therapeutic response.

**Subjects and methods:**From July 2015 to May 2016 in Al-Karama teaching hospital /Kut city- Wasit-Iraq, 25 patients (14 males and 11 females) with ages range from (6-50) years. Ultrasonography examination was done for all patients and grey scale criteria (distribution, size, shape, echogenicity, echogenic hilum, intranodal necrosis and ancillary features) and vascular distribution were recorded to help in tuberculous lymphadenitis diagnosis. Excisional biopsy was done to confirm the diagnosis histopathologically. After chemotherapy the Patients were followed up after 46 days of treatment, again the grey scale criteria were recorded and compared with the 1st reading.

**Results:** Ultrasonography could identify 88% of the patients (22/25) as having cervical tuberculous lymphadenitis while histopathology proved that only 80% of patients really have the disease. This mean that ultrasonography had good sensitivity (100%), specificity (60%) and accuracy (90%) with no false negative and 8% false positive.In following up the patients, grey scale ultrasonography criteria showed a significant difference for the same patients before and after 46 days of treatment.

**Conclusions:** Ultrasonography was found to play a paramount role in detection, localization and delineation of cervical tuberculous lymph nodes hence grey scale and color Doppler are reliable in diagnosis of the disease and the evaluation of therapeutic response of the patients.

**Keywords**: diagnosis, lymph node, neck, sonography, tuberculosis.. **(J Bagh Coll Dentistry 2017; 29(1):76-82).**

## INTRODUCTION

Tuberculosis is a worldwide infectious disease and constitute second killer infectious disease after HIV despite advanced modalities for diagnosis and treatment. [(1)]

Many organs can be affected by extra pulmonary tuberculosis but lymph nodes are the commonest site and the most affected nodes are the cervical lymph nodes.[(2)]

Inmost instances the tubercular bacilli gains entrance through the tonsil of the corresponding side of the lymphadenopathy. Both bovine and human tuberculosis may be responsible. . [(3)]

Granuloma formation and caseation necrosis are important histopathological features to diagnosetuberculosis. [(4)]

The difficulty of examining cervical lymph nodes clinically is due to their multiple number and different location. Here ultrasonography appears to be better than clinical examination in sensitivity for detection of cervical lymph nodes (96.8%) (73.3) respectively.

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In cases of lymph nodes smaller than 0.5 cm the sensitivity of ultrasonography is superior than that of CT and MRI. Due to these facts and the availability of high frequency probes, ultrasonographybecome important in maxillofacial diagnosis. [(5)]

Grey scale sonographic merits took into account for analysis of cervical lymphadenopathy were as follows:(i)size of the lymph node: depend on the assessment of the short diameter;(ii)shape of the lymph node: depends on the ratio of short axis to long axis (S/L);(iii)nodal borders: classified as sharp or smooth;(iv)internal echogenicity: classified as hypo- or hyperechoic;(v)echogenic hilum;(vi)nodal necrosis were assessed and recorded whether present or absent [(5)] . In1970scolor Doppler ultrasonography has been used in the assessment of lymph node enlargement. It can evaluate the vascular pattern and displacement of vascularity. [(6)]

Follow up of treatment emphasize for eradication systemic disease and its local discomfort.[(7)]

For the purpose of monitoring of the disease and evaluation of the treatment, Ultrasonography is a beneficial imaging modality in the estimation of cervical lymph nodes because of itshigh-resolution. [(8)].The current study was done to

analyzethe effectivenessof Sonography in the diagnosis of cervical tuberculous lymphadenitis.

## SUBJECTS AND METHOD

This study was carried out from July 2015 to May 2016 on(25) patients, (11) females and (14) males, their ages range from(6-50) years with a mean age of (31.04) years, these patients had suspected cervical tuberculous lymphadenitis (CTLA)

All patients participated in this study were well informed about it, asked to co-operate, and get their approval before including them.

Exclusion criteria were: 1. Any patients have primary malignancy in the head and neck region 2.Any patient has single involved LN were excluded from the study because of follow up negation. 3.The patients that do not cooperate and come back for follow up.

The 1st assessment depended on history and physical examination and further assessment need laboratory and radiological examination, ultrasonography was done using (7.5 MHz) linear array transducer

The examination was done when the patients in supine position with hyperextended neck . The scanning was done followingHajek et al classification (1986) of the cervical lymph nodesstarted from region 1 in transvers plane then asking the patient to turn the head to the opposite side, starting with region 2 and ending with region 8, following the sequence of (submandibular→ parotid→ upper cervical →middle cervical→ lower cervical →supraclavicular →posterior). [9]

Grey scale evaluates the nodal distribution, shape, size, internal architecture and ancillary features. Doppler sonography provide information about the vasculature of the lymph nodes.

The key US features of CTLA include hypoechogenecity, roundness, unsharp border, destructed hilum , nodal matting, adjacent soft tissue changes, strong internal echoesand displaced hilar vascularity[10]. Although these sonographis features are typical for CTLA, none are pathognomonic so three or more criteria should be taken into account to tell that the patient has CTLA.[10,11]

After recording these sonographic parameters probable diagnosis was gain and when combined with clinical diagnosis we can reach to primary diagnosis. To confirm this diagnosis the patients were referred to general surgery clinic and prepared for FNAC and lymph node excisional biopsy which is submitted for histopathological examination and a final diagnosis was reached.

The patients were diagnosed to have CTLA would have anti tuberculosis medication for 6 months. Evaluation of early therapeutic responseby Ultrasonography was started46 days after the 1st dose of treatment. In this visit grey scale ultrasonography was taken and the previous parameters were recorded and compared with the previous visit readings so the treatment can be evaluated.

Statistical analysis was done using SPSS version 19 computer software (Statistical Package for Social Science).Then the sonographic diagnosis statistically analyzedon the basis of the final lymph node diagnoses to calculate sensitivity, specificity, positive predictive value PPV, negative predictive value NPV and accuracy of sonography in the diagnosis of CTLA.

To evaluate efficacy of ultrasonography in assessing anti tuberculous treatmentafter short term(46 days) Chi square and p-value was calculated for each sonographic feature. P value less than the 0.05 level of significance was considered statistically significant.

## RESULTS

All the 25 patients (14 males, 11 females); their age range (6-50) years ; had cervical swelling but with different durations. All of them had fever , pain, loss of appetite and generalized weakness, however, 22 subjects represent 88% showed firm neck swelling on clinical examination and 3 with fluctuant swelling. Unilateral swelling present in 8 patients (32%) while bilateral swelling was in 17 patients represent 68%. Fifteen patients represent 60% come with swelling duration of three months or less while the other 10 subjects come with swelling of more than 3 months duration.

Out of the 25 patients with cervical LAP in the current study, only 20 patients (80%) provedto have CTLA by histopathological examination.

Age distribution of the 20 patients was higher in the 40s oflife with mean age (30.15) (SD=±15.57). Eleven of them were males representing 55% and the other 9 subjects were females representing 45% with male to female ratio of (1.2:1). (fig.1)

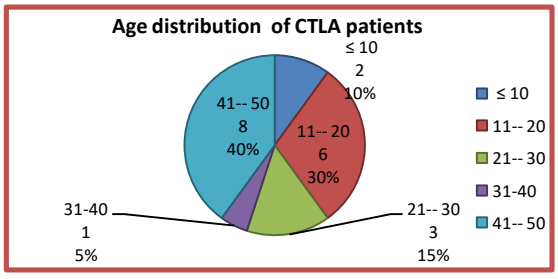


**Figure 1: Pie chart showing the age distribution of patients with CTLA**

All the 25 subjects examined by ultrasoundand according to sonographiccriteriaonly 3 subjects were negative i.e. they don't have CTLA and 88% of the patients hadthe disease. (Table .1)

**Table 1: Number of CTLA patients diagnosed by US**

| Ultrasound | N | % |
|---|---|---|
| Negative | 3 | 12 |
| Positive | 22 | 88 |
| Total | 25 | 100 |

All the patients showed an enlargement of the involved LN both in short and longaxis. The enlarged LN can be detected and measuredby US to reveal that the average long axis was 25.7mm (maximum47mm and minimum 13.4) and the average short axis was 14.4mm ( max 24.4mm and min 6.5mm), but the size alone cannot give accurate diagnosis (not specific feature).

The validity of each grey scale sonographic criteria (shape, echogenicity, borders, hilum, matting, intra-nodal necrosis, peri-nodal edema and posterior enhancement) in diagnosis of CTLA is expressed in terms of sensitivity, specificity, PPV, NPV and accuracy indices. Comparison of these indices was done to report that echogenicity had higher sensitivity, destructed hilum had higher specificity PPV and NPV and posterior enhancement had higher accuracy. (Table 2)

**Table 2: Comparison of the indices for each grey scale sonographic criteria**

| Grey scale characteristics | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|
| Shape | 60% | 40% | 80% | 20% | 56% |
| Echogenicity | 100% | 0% | 80% | 0% | 80% |
| Border | 65% | 80% | 92% | 36.36% | 68% |
| Hilum | 60% | 100% | 100% | 62.5% | 68% |
| Matting | 65% | 80% | 92.85% | 36.36% | 68% |
| Intranodal necrosis | 65% | 60% | 86.67% | 30% | 64% |
| Perinodal edema | 70% | 60% | 87.5% | 33.3% | 68% |
| Posterior enhancement | 85% | 80% | 94% | 57% | 84% |

Incolor Doppler sonography all the patients showed hilar vascularityhowever they were displaced in 50% ofsubjects, except two patients where one of them hadavascular LN and the other hadmixed (hilar and peripheral) vascularity.

**Figure 2: A 6 years old patient has enlarged lymph nodes of right posterior triangle**

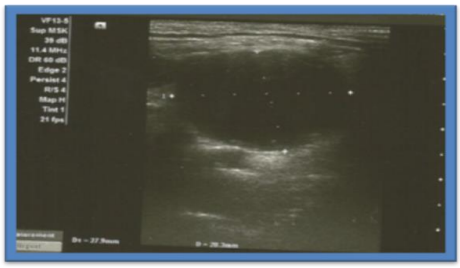

**Figure 3: Ultrasonography of right submandibular lymph node that is enlarged and round (S/L ratio=0.57) with lost hilum and posterior enhancement**

**Overall validity of ultrasonography compared with histopathology:**

When patients had three or more positive ultrasonographic criteria he/she was considered TB+ . As a result 22 subjects were positive in US while 20 patients really have the disease i.e. only 2 subjects were false positive representing 8%.and there is no false negative.(table 3).

However ultrasonography had moderate specificity 60% it had high sensitivity, PPV, NPV

and accuracy 100%, 90.9%, 100% and 92% respectively.

**Table 3: Positive and negative sonographic results in tuberculous and non-tuberculous patients**

| US | TB+ | TB- | Total |
|---|---|---|---|
| Test + | 20 | 2 | 22 |
| Test - | 0 | 3 | 3 |
| Total | 20 | 5 | 25 |

Sensitivity=100%,Specificity = 60%,PPV = 90.9%,NPV= 100%,Accuracy = 92%,False positive = 8%andFalse negative = 0

Histopathological results

Histopathology has the highest sensitivity and may produce a more rapid and favorable symptomatic response and has been recommended in cases involving multiple nodes[7].Twenty five (25) subjects underwent histopathological examination of their enlarged cervical LNout of them 20 subjects were consistent with TB lymphadenitisrepresenting 80% while the remaining: three of them were consistent with reactionary LA (due to viral infection) (12%)and the other 2 (8%) consistent with pyogenic LA.Histologic features: there are two specific pathologic criteria for identifying tuberculous lymphadenitis, caseation and granuloma formation. Caseation has been found to be more specific and sensitive. Granuloma with caseationnecrosis had higher rate of positivity 47% compared to non- caseating necrosis.[12] Caseation necrosis recorded in 95% of the patientsin this study and the only patients that did not show caseation necrosis had positive ZN stain for acid fast bacilli (AFB).

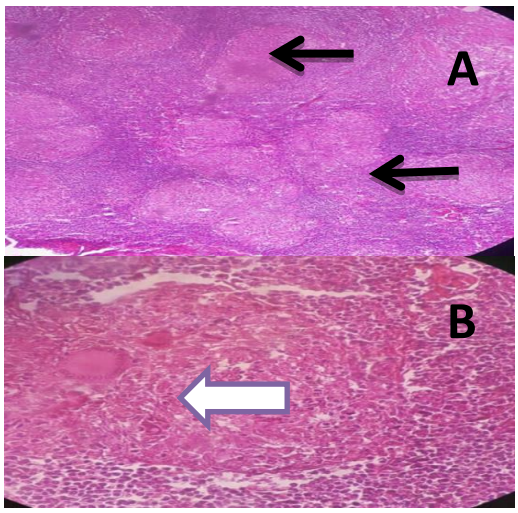


**Figure 4: Histopathology of CTLA of a 45 years old patient, pathological findings A. Multiple epithelial granulomas (*black arrows*). B. Giant Langhan's cell (*white arrow*).**

The patients were diagnosed to have CTLA will be send for the Specialized Respiratory Center of Wasit directorateto be treated by taking anti tuberculosis drugs for six months.

**Evaluation of therapeutic response**:

Evaluation of early therapeutic responseby Ultrasonography was started46 days after the 1st dose of treatment. In this visit grey scale ultrasonography was taken and the previous parameters were recorded and compared with the previous visit readings so the treatment can be evaluated

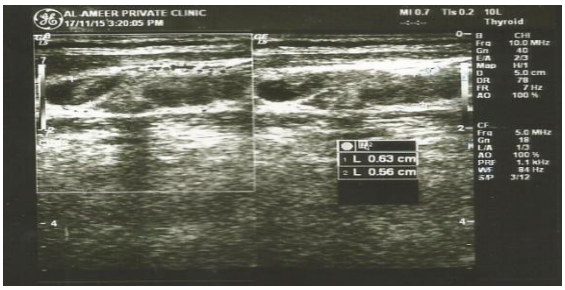


**Figure 5:Grey scale ultrasonography of rightposterior TLA after 45 days of anti TB treatment show decreasing in the size of the lymph nodes and preserving fatty hilum.(1st reading S=12.7mm& 2nd reading S= 5.6mm)**

The mean short axis was (15.34mm) but after treatment it became (10.1mm) and 65% of cases showed LN less than 10mm in short axis. Also the shape changed obviously from round to oval in 7 patients, the destructed hilum returned to appear however they were thin in 10 patients, matted LN which were appeared in 13 patients still present in only 6 patients, ultrasonography of 13 patients showed necrosis while after treatment only 6 patients showed necrosis, posterior enhancement appeared in 17 patients but after treatment it appeared in only 3 patients, finally perinodal soft tissue edema disappear in 12 patients. (Table 4)

**Table 4:Comparisonin grey scale criteria before and after treatment and percent of progression.**

| Criteria | Pretreatment | Percentage | Posttreatment | Percentage | Percent of progression |
|---|---|---|---|---|---|
| **Long axis** | | | | | |
| Max | 47mm | | 32mm | | |
| Min | 13,4mm | | 10.1mm | | |
| Mean | 25.7mm | | 19.8mm | | |
| **Short axis** | | | | | |
| Max | 24.4mm | | 16.7mm | | |
| Min | 6.5mm | | 5.4mm | | |
| Mean | 14.4mm | | 10.1mm | | 65% |
| **Shape** | | | | | |
| Oval | 8 | 40% | 15 | 75% | |
| Round | 12 | 60% | 5 | 25% | 58.3% |
| **Hilum** | | | | | |
| Present | 8 | 40% | 18 | 90% | |
| Absent | 12 | 60% | 2 | 10% | 83.3% |
| **Matting** | | | | | |
| Present | 13 | 65% | 6 | 30% | 53.8% |
| Absent | 7 | 35% | 14 | 70% | |
| **Necrosis** | | | | | |
| Present | 13 | 65% | 6 | 30% | 58.8% |
| Absent | 7 | 35% | 14 | 70% | |
| **Posterior enhancement** | | | | | |
| Present | 17 | 85% | 3 | 15% | 82.3% |
| Absent | 3 | 15% | 17 | 85% | |
| **Soft tissue edema** | | | | | |
| Present | 14 | 70% | 2 | 10% | 85.7% |
| Absent | 6 | 30% | 18 | 90% | |

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In ultrasonography, grey scale criteria showed a significant difference for the same patients before and after the treatment. In comparison of short axis of the involved LNs before and after treatment by using t-test = 3.09 andρ-value= 0.00185 i.e. it is significant for ρ<0.05

For the shape $X^2$=5.02 & ρ-value= 0.05,for echogenic hilum $X^2$=10.989 & ρ=0.0009,

For matting $X^2$= 4.912 & ρ= 0.0267,for intranodal necrosis $X^2$= 4.912 & ρ= 0.0267,

For posterior enhancement $X^2$=19.6 & ρ= 0.0001and for adjacent soft tissue edema $X^2$=15 & ρ=0.0001,

All these values are significant ( ρ< 0.05)

## DISCUSSION

Tuberculous lymphadenitiswas a common cause of cervical lymphadenopathy in the young adult below 45 year, in a study held in Nigeria, where the age range of patients were (2-38) years [13].While the peak age of the CTLA in the United statesis the thirties and forties [7]. Both the range and frequency of the patients age in the present study is consistence with these results where the range was (6-50 years) with 40% of cases were in the forties and 30% in the 2nd decade of life.

TLA has more frequency in females with a male to female ratio of (1:1.4) whereas pulmonary TB is more frequent in males [7]. The male to female ratio in this study was 1.2:1 i.e. the disease is more in males which is different from other studies , this is may be due tosocial and sample size differences. If matching between age and gender was done, CTLA appeared to be more frequentin male children and young adult females [11]. In the present study 100% of patients below 20 years were males whereas 69% of the patients above 20 were females.

***Park and Kim(2012)***agreed with ***Fontanilla (2011)***results, in their study 97.5% of patients complaining of swelling and it is tender in 5% of

patients , other signs and symptomslike fever weight loss recorded with low frequency, the swellings were bilateral in 12.5.[7] [11]

In the present study the presentation was early due to typical response of immunological system for the invading organism that inforce most of the patients to seek medical advice , in addition to thatin our study there were no HIV positive patient.

Almostalways chest x-ray is recommended if tuberculosis is suspected to rule out pulmonary involvement. From analysis of multiple studies in endemic and non-endemic areas ***Fontanilla et al(2011)*** declared that Lung involvement recorded in 18-42% of patients with CTLA, patients have HIV show higher percent of pulmonary tuberculosis than non HIV patients. [7]

In the current study chest x-ray show no pulmonary involvement in all patients.

CTLA are more conspicuous than pulmonary tuberculosis but its diagnosis is difficult since it resemble other types of LAP so it has been named as "dangerous masquerader".[10]

Ultrasonographyappearedas a first line diagnosing imaging modality.Grey scaleis used to detect LN and evaluate its characteristic[13]and color Doppler assess the vascularity and its displacement.[14].

From the analysis of all the previously mentionedcriteria we noticed that there is nofeature solely exhibitboth high sensitivity in diagnosis of CTLA. If three or more criteria is taken into account this will increase both sensitivity and specificity and as a result accuracy of US in the diagnosis of CTLA. Therefore we could reachto Sensitivity=100%, Specificity = 60%, PPV = 90.9%,NPV= 100% and Accuracy = 92% in sonographic diagnosis of clinically suspectedCTLA patients which are comparable with ***Park & Kim*** **( 2014)** who had a sensitivity,specificity, PPV, NPV and accuracy of95.0%, 79.5%, 82.6%, 93.9%, and 87.3%, respectively in the group of patients that have (2 or more ) category.. In the present study we had no false negative and only 2 false positive but unfortunately because the sample is not big enough thespecificity is decreased to 60% otherwise our results are accepted and reliable. The false positive cases are ofchronic bilateral pyogenic infection, the long period of this infection (2 months) make their sonographic featuresmimic that of CTLA.

Despite that most of the detected features were typically of CTLA, no feature known to be pathognomonicfor TLA . Even though features of internal structure of LN were of greater value in diagnosis than size and shape of LN. Ancillary features like matting and perinodal edema if presentedin patient without a history of radiotherapy in the neck are highly suggestive of CTLA.

Sonography alone cannot diagnose CTLA because of the interference between the sonographic criteria of CTLA and metastatic LN on one hand and between CTLA and reactive and nonspecific bacterial infection on the other hand , therefore other diagnosing modality is needed like histopathology, mycobacterial culture and polymerase chain reaction **PCR** [11]. In the present study we choose histopathology as a definite diagnosing tool. After excisional biopsy and histopathological examination 80% of the cases confirmed to be CTLA.

***Park & Kim*****(2014)** from Korea studied 79 patients retrospectively,40 patients (50.6%) proved to have CTLA either by histopathological, microbiological and PCR terms. [11]

When someone talking about the progress of situations and treatment evaluation, choosing a save, easy, cheap and repeatable imaging modality is mandatory.[8] In addition this modality should be sensitive in detecting minor changes. Therefore sonography is of great importance in follow up patients with CTLA.

In the present study the progression was different for each grey scale criteria and ranging from (53%-85%) of cases after 1.5 months of anti TB treatment.(table 4 ) The least progression is that of matting and the best is that of perinodal tissue edema after 46 days of treatment.

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## الخلاصة

الخلفية:لايزال مرض التدرن من الامراض الانتقالية الشائعة في العالم على الرغم من التقدم الصحي الهائل .الغدداللمفاوية وبالخصوص الغدد اللمفاوية العنقية هي الجزء الأكثر تعرضا للالتهاب التدرني خارج الرئتين .الحدس الطبي السريري هوالخطوة الأولى لتوقع المرض ثم اثباته بواسطة الفحوص المختلفة شعاعيا ونسيجيا .يعتبرالسونارالعادي والدوبلرهوالواسطة الأكثرحساسية لتشخيص المرض .
الهدف من الدراسة :الغرض من الدراسة هوتقيي مكفاءة السونارالعادي والدوبلرفي تشخيص ومتابعة عينة من مرضى التهاب العقد اللمفاوية التدرني تحت العلاج.
الأشخاص والطريقة :منذ تموز 2015 وحتى أيار 25 , 2016 مريضا 14) ذكوراو 11 اناث( تتراوح أعمارهم ( 50-6) سنة يعانون من تضخم الغدد اللمفاوية العنقية خضعوا للفحص السريري ثم الفحص بواسطة السونار , كما اجري الفحص النسيجي للعينات التي اخذت من الغدد اللمفاوية المتضخمة . تم إعطاءالعلاج اللازم للتدرن لاولئك المرضى الذين.
ثبت تشخيص التدرن لديهم واخضعوا للفحص الدوري والمتابعة بواسطة السوناربعد 46 يوما من بدء العلاج لنقارن نتائج الفحص بتلك التي اخذت في التشخيص الاولي .
النتائج :كانت نسبة 88% من المرضى ( 22/25) قد شخصت بواسطة السونارعلى انهاالتهاب الغدداللمفاوية العنقية التدرني ,بينما اثبت الفحص النسيجي ان 80% منهم ( 20/25) مصابين فعلا. وهذايعني ان السونارذوحساسية جيدة 100% وخصوصية 60% ودقة90% وبدون سلبية كاذبة و 8% معدل إيجابي كاذب . وفي متابعة المرضى بواسطة خصائص السونار وجد انه ناكفرق معتدبه لنفس المرضى قبل وبعد 46 يومامن العلاج .
الاستنتاج :وجد ان السونار يلعب دوراهامافي اكتشاف وتشخيص الغدد اللمفاوية العنقية التدرني وكذا في متابعة المرضى الذين هم تحت العلاج