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Role of high-resolution colored-doppler ultrasound in the differentiation between benign and malignant cervical lymphadenopathy

Shahad D. Ali [(1)]*, Taghreed F. Zaidan [(2)], Fadhil Al-Janabi [(3)]
[1] *Department of Oral Medicine, College of Dentistry, University of Baghdad*
[2,3] *College of Dentistry, University of Baghdad, Baghdad*

Abstract

Background: The role of high-resolution color Doppler ultrasound (CDUS) in the differentiation between benign and malignant cervical lymphadenopathy remains unclear. Lymphadenopathy results from a wide range of disease processes, including infections, autoimmune disorders, malignancies and unusual conditions. The continuous advancements of techniques have led to an increasing sensitivity of the imaging modalities in the examination of lymph nodes. This study was aimed to differentiate between bengin and malignant cervical lymphadenopathy using CDUS and to correlate these findings with cytology or histopathology findings in patients with clinical cervical lymphadenopathy.

Methods: The study was carried out at Al-Sadder Teaching Hospital in AL-Najaf, Iraq, from November 2017 to May 2018. it involved 81 patients with cervical lymphadenopathy. An informed consent was obtained from patients before launch of study. Following clinical examination of the enlarged cervical lymph nodes, forty patients were clinically suspected to have malignant cervical lymphadenopathy; whereas the remaining 41 patients were clinically suspected to have benign cervical lymphadenopathy. All the patients were subjected to CDUS and histopathological examination via ultrasound-guided FNAC and biopsy. FNAC or biopsy and its histopathological appearance were considered for their correlation with CDUS features of all LNs of the same group.

Results: The age of patients ranged from 5 to 75 years (45 males and 36 females). Regarding clinical evaluation and consistency, 13 hard LNs were malignant and 1 was benign. In addition, 27 rubbery LNs were malignant and 40 soft LNs were benign. Also, the results revealed that 41 LNs were fixed (40 were malignant and 1 was benign) and 40 LNs were not (which under histopathological evaluation appeared benign). CDUS detected color flow signals in 81 LNs. Of these LNs, 39 LNs showed central color flow signal; 36 nodes showed hilar signal, which suggested a benign nature, but 3 were malignant. Of the 81 LNs, 13 showed peripheral flow (10 nodes were malignant and 3 were benign LNs). The LNs that showed mixed vascularity were 29 (27 were malignant and 2 were benign.

Conclusions: High-resolution CDUS provides information that is useful in making a correct diagnosis. Also, nodal vascularity is important in the diagnosis and differentiation of malignant from benign LNs.

Keywords: Lymphadenopathy, malignant, benign, histopathology, vascularity, CDUS.

INTRODUCTION

Cervical lymphadenopathy is the most common finding in head and neck diseases. More than half of patients examined each day may have enlarged lymph nodes (LNs) in the head and neck region [1]. Cervical lymphadenopathy may be the only clinical finding or one of several nonspecific findings and the recognition of enlarged cervical LNs will often raise the spectrum of serious diseases [2]. The common causes of lymphadenitis are bacterial, viral, protozoan, and fungal infections, autoimmune disorders, use of drugs such as phenytoin and certain vaccines [3]. Most patients have benign lymphoid hyperplasia or reactive lymphadenitis, however, it may be a serious disease in few cases. Therefore, patients with serious illness must be differentiated from others with benign lymphadenopathy. High-resolution color doppler ultrasound (CDUS) is a noninvasive procedure that shows the morphologic and vascular characteristics of lymphadenopathies [4]. The current method of evaluating vascular structures and morphology may have an important role in the differential diagnosis of reactive and malignant LNs [5]. For ultrasonographic examination, LNs were categorized to eight regions depending on their cervical localization: submental, submandibular, parotid, upper cervical (above the hyoid, along the internal jugular vein), middle cervical (between the hyoid bone and cricoid cartilage, along the internal jugular chain), lower cervical (under the cricoid cartilage, along the internal jugular vein), supraclavicular and posterior (accessory chain) [6]. The aim of current study was to differentiate between bengin and malignant cervical lymphadenopathy using CDUS and to correlate these findings with cytology or histopathology findings in patients with clinical cervical lymphadenopathy.

MATERIAL AND METHODS

This study was carried out at Al-Sadder Teaching Hospital in AL-Najaf, Iraq, from November 2017 to May 2018. Eighty-one patients with cervical lymphadenopathy were selected in this study. After obtaining informed consent, the LNs were clinically examined for their location, number, size, consistency and fixity to decide whether the palpable node is benign or malignant. Forty patients were clinically suspected to have malignant cervical lymphadenopathy; whereas the remaining 41 patients were clinically suspected to have benign cervical lymphadenopathy. In cases of oral cancer, if the LN was larger than 1cm, then it was considered abnormal. Stony hard/indurated LNs were considered malignant; whereas soft nodes were considered benign. Fixation to underlying structures is a sign of malignancy; whereas mobile LNs were considered benign. LN tenderness was considered a sign of inflammatory process [7]. Cervical lymphadenopathy was diagnosed based on history and clinical examination. All the patients were subjected to CDUS and histopathological examination via ultrasound-guided FNAC and biopsy. For CDUS evaluation, a diagnostic ultrasound system (GE, USA) under high frequency linear transducer of 7.5 MHz was employed. The patient was placed in supine position with hyperextension of the neck. Settings for CDUS were standardized and the wall filters, pulse repetition frequency, color gain and focusing depth were set on the automatic mode. The technique used was continuous transverse and sagittal sweep covering all neck regions on both sides [8]. The examination began with a transverse scan of the submental area, followed by the submandibular area; parotid area; upper, middle, and lower cervical areas; supraclavicular fossa; and posterior triangle. CDUS was performed, and features and color Doppler flow patterns were studied. The distribution of LNs was classified into eight anatomic areas similar to the ones described by Hajek et al. [9]. The vascular pattern and displacement of vascularity of LNs were examined by CDUS. After CDUS, flow in LNs was stabilized or frozen. Moreover, color flow pattern was determined and resistive index (RI) and pulsatility index (PI) were measured. The vascular pattern of enlarged LNs was classified into the following four groups based on CDUS findings [10]:

- Central–Flow: signals directed radially from the center and the signals are not at the periphery of the nodes.
- Peripheral–Flow: signals at the periphery of LNs.
- Mixed–Flow: presence of central and peripheral flow signals.
- No flow: vascular signals are absent in LNs.

The cytological and/or histological diagnosis was obtained from the largest node. FNAC or biopsy and its histopathological appearance were considered for its correlation with CDUS features of all LNs of the same group. Only cases confirmed with clinically malignant/metastatic nodes were biopsied; whereas clinically confirmed/ suspected benign/ reactive LNs were confirmed cytologically with ultrasound-guided fine needle aspiration. A comparative study of clinical features, CDUS features and cytological/histological features of enlarged cervical LNs was conducted.

RESULTS

I. Clinical findings

1. Age: The age range of all participants 5–75 years. The mean age of patients significantly differed between the two studied groups. Patients with malignant cervical LNs were significantly older than those with benign ones as the mean age values were 44.17±2.65 and 22.21±1.92 years for the two groups of patients, respectively, (P<0.001; Table 1).

2. Gender: Gender distribution between the two groups of patients was not significantly different. The numbers (%) of male and female patients with malignant cervical LNs were 23 (57.5%) and 17 (42.5%), respectively; whereas those of patients with benign LNs were 22 (53.7%) and 19 (46.3%), respectively, (P>0.05; Table 2).

3. **Consistency of lymph node**: Among 81 patients, 13 LNs with hard consistency were malignant and 1 was benign. In addition, 27 rubbery LNs were malignant and 40 soft LNs were benign. All malignant lesions were either hard or rubbery and benign lesions were soft. A statistically significant difference was found between the consistency of LNs and histopathological findings (Table 3).

4. **Fixation to the underlying structure:** Clinically, 41 LNs were fixed to the underlying structures. Histopathological findings showed that 40 LNs were malignant and 1 was benign. Forty LNs were not fixed but benign. A statistically significant difference was found between fixation of LNs and their histopathological features (P<0.001; Table 4).

Table 1 Comparison of the age of patients with malignant and benign lymphadenopathy

Parameter	Histopathology		P value
	Malignant	Benign	
Age/years (Mean±SE)	44.17±2.65	22.21±1.92	<0.001

Table (2):- Number and percentage of male and female patients according to histopathology

Gender	Histopathology		Total	P value
	Malignant	Benign		
F	17	19	36	0.728
	42.5%	46.3%	44.4%	
M	23	22	45	
	57.5%	53.7%	55.6%	
Total	40	41	81	
	100.0%	100.0%	100.0%	

Table 3 Association between consistency of LNs and histopathological findings

Consistency	Histopathology		Total	P value
	Malignant	Benign		
Hard	13	1	14	<0.001
	32.5%	2.4%	17.3%	
Rubbery	27	0	27	
	67.5%	0.0%	33.3%	
Soft	0	40	40	
	0.0%	97.6%	49.4%	
Total	40	41	81	
	100.0%	100.0%	100.0%	

Table 4 Association between fixation of LN and histopathological findings

Fixation	Histopathology		Total	P value
	Malignant	Benign		
No	0	40	40	<0.001
	0.0%	97.6%	49.4%	
Yes	40	1	41	
	100.0%	2.4%	50.6%	
Total	40	41	81	
	100.0%	100.0%	100.0%	

II. CDUS findings

1**. Size**: The smallest LN detected by CDUS was 3mm × 8mm and benign; whereas the largest LN was 35mm × 25mm and malignant. The mean short axis diameters of malignant and benign nodes were 1.86±0.08 and 0.83±0.05cm, respectively, and the mean long axis diameters of malignant and benign nodes were 2.47±0.11 and 2.01±0.11cm, respectively. The short axis diameter of malignant nodes was significantly higher than that of other nodes; whereas the reactive nodes had the smallest short axis diameter. A statistically significant difference was found between the mean short axis, (P<0.001), and the mean long axis, (P<0.005), diameters among benign and malignant cervical LNs (Table 5).

2. Shape: The shape of LNs was determined by calculating the S/L ratio. When the ratio was >0.5, LNs were considered round; 38 (46.9%), out of 81, subjects had round nodes. When the ratio was<0.5, LNs were considered oval; 43 (53.1%), out of 81, subjects had oval nodes. The results of CDUS revealed that 38 patients with malignant LNs had round nodes; whereas only 2 cases demonstrated oval nodes. Among benign LNs, CDUS showed that they were all oval. Thus, the shape may provide a specific feature in cervical LAP and the difference in shape was statistically significant (P<0.001; Table 6).

3. Location of vascularity: The CDUS detected color flow signals in 81 LNs. Of these LNs, 39 showed central color flow signal (Figure 1), 36 nodes showed hilar signal (suggesting a benign nature) and 3 of these nodes were malignant. On the other hand, 13 nodes showed peripheral flow (Figure 2). Of the latter, histopathology confirmed that 10 nodes were malignant and 3 were benign. A total of 29 LNs showed mixed vascularity; 27 were malignant and 2 were benign. In this study, central flow for benign nodes and peripheral flow for malignant nodes were highly significant parameters (P<0.0001). A significant association was found between vascularity and histological findings. Benign lesions mostly exhibit central vascularity; whereas malignant lesions mostly exhibit mixed vascularity pattern (Table 7).

4. RI: In this study, the mean RI of the vessels of malignant LNs was 1.10±0.05; whereas that of benign LNs was 0.58±0.01 (Table 8). RI values were higher in malignant LNs than in benign LNs (Figure 3). The area under curve was 0.954 which indicated an excellent test cut-off value for RI of 0.71, sensitivity of 90% and specificity of 95.1% (Figure 4). This study showed statistically significant differences between the mean values of RI for benign and malignant nodes (P<0.001; Table 8).

5. PI: The mean PI from the vessels of malignant LNs was 2.68±0.17, whereas that from the vessels of benign LNs was 0.97±0.05 (Figure 5). PI values were higher in malignant LNs than in benign LNs. This study showed statistically significant differences between the mean values of PI for benign and malignant nodes (P<0.001; Table 8). The area under curve was 0.940 which indicated an excellent test cut-off value for PI of 1.73, sensitivity of 92.5% and specificity of 93.7% (Figure 6).

Table 5 Size of involved LNs measured by CDUS

Parameter	Malignant (N=40)	Benign (N=41)	P -value
	Mean±SE	Mean±SE	
Size (cm²)	2.15±0.098	1.44±0.099	<0.001
S. axis (cm)	1.86±0.08	0.83±0.05	<0.001
L. axis (cm)	2.47±0.11	2.01±0.11	0.005

Table 6 Association between shape of LN and histopathological findings

Shape	Histopathology		Total	P value
	Malignant	Benign		
S/L ratio	0.76±0.02	0.42±0.02		<0.001
Oval	2	41	43	<0.001
	5.0%	100.0%	53.1%	
Round	38	0	38	
	95.0%	0.0%	46.9%	
Total	40	41	81	
	100.0%	100.0%	100.0%	

Figure (1):- CDUS image of benign LN showing hilar/central vascularity.

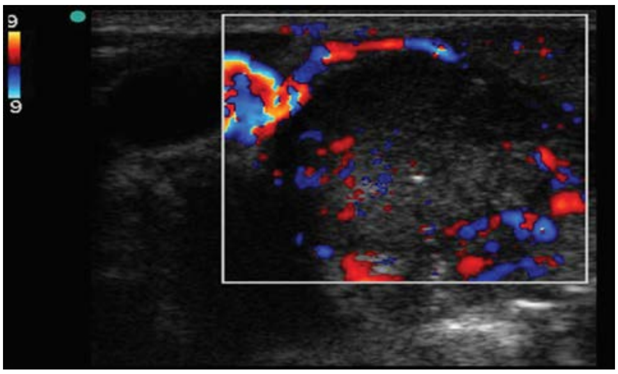

Figure 2 CDUS image of malignant LN showing mixed/peripheral vascularity

Table 7 Association between vascularity on CDUS and histopathological findings

Location of vascularity	Histopathology		Total	P-value
	Malignant	Benign		
Central	3	36	39	<0.001
	7.5%	87.8%	48.1%	
Peripheral	10	3	13	
	25.0%	7.3%	16.0%	
Mixed	27	2	29	
	67.5%	4.9%	35.8%	
Total	40	41	81	
	100.0%	100.0%	100.0%	

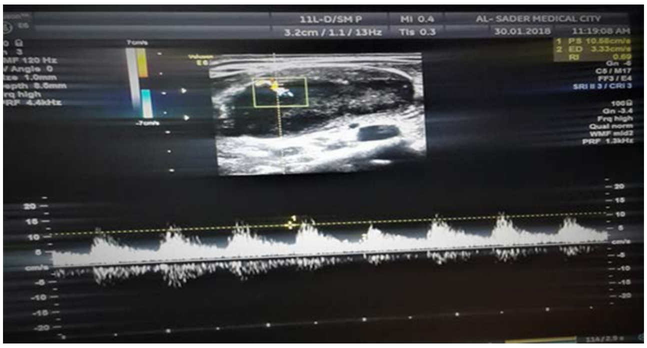

Figure 3 Measuring RI by CDUS

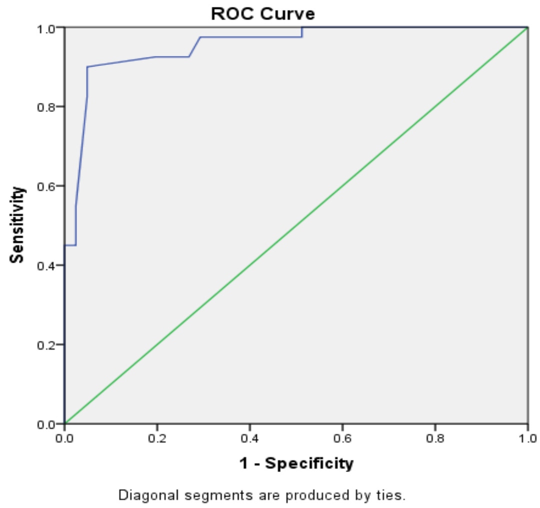

Figure 4 ROC curve for RI in diagnosing malignant LNs

Figure 5 Measuring PI by CDUS

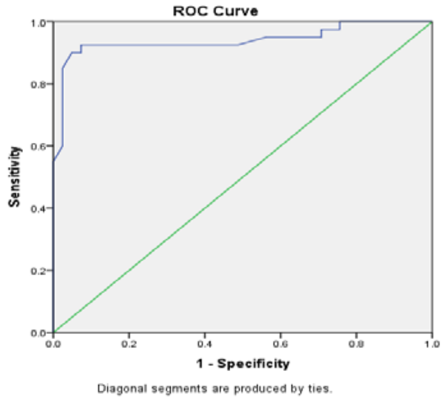

Figure 6 ROC curve for PI in diagnosing malignant LNs

Table 8 Mean of RI and PI in benign and malignant LNs

Parameter	Malignant (N=40)	Benign (N=41)	P- value
	Mean ±SE	Mean ±SE	
RI	1.10±0.05	0.58±0.01	<0.001
PI	2.68±0.17	0.97±0.05	<0.001

DISCUSSION

Age and gender: Patients with malignant LNs were significantly older than patients with benign cervical LNs. This study agreed with Jayaraman et al. [11] who showed that malignant LNs are common in the age group of 35–65 years due to the high incidence of malignancy in older age groups. Also, results of current study were consistent with those of Richner and Laifer [12] who showed that the prevalence of malignancy is 0.4% in patients under 40 years old and 4% in those over 40 years in the primary care setting. The prevalence increased to 17% in referral centers [13]. This study showed that the number of male patients with cervical lymphadenopathy was higher than that of female patients. These findings were similar to those reported by [14].

Consistency: Current study revealed a significant association between consistency of LNs and malignancy where all malignant lesions were either hard or rubbery; whereas benign lesions were soft. These results were similar to those reported by Bazemore and Smucker [15].

Fixation to the underlying structures: This study showed a statistically significant difference between the fixation of malignant and benign LNs. Forty-one LNs were fixed, of which 40 were malignant and 1 was benign. Forty LNs were not fixed, yet they were benign. These results were similar to the findings of Leung and Davies [16] who showed that lymphadenopathy resulting from collagen vascular diseases and infections are usually freely movable in the subcutaneous region. Rubbery nodes are associated with lymphoma. Nodes that are associated with malignancy are often fixed to the skin or surrounding tissues.

Vascularity of LN

Several studies have evaluated the usefulness and efficacy of CDUS in the differentiation between malignant and benign lymphadenopathy [10]. Color and power Doppler equipment can readily examine LN vascularity. Reactive and normal LNs are generally either avascular or have vasculature confined to the hilum. Metastatic LNs have characteristically increased peripheral vascularity. Mixed vascularity has been shown to occur in lymphomatous nodes. These vascular differences in malignant LNs were believed to be due to tumor angiogenesis [17]. A study on 63 patients was conducted by Mirsa et al.[18] who evaluated cervical adenopathy via CDUS. A total of 178 nodes revealed vascularity and each was subjected to biopsy for histological diagnosis. Nearly 92% of reactive LNs demonstrated significant hilar vascularity and nearly 84% of all metastatic nodes showed peripheral vascularity. Approximately 79% of all lymphomatous nodes had mixed vascularity. Vascularity can be displaced either from tumor invasion or from cystic necrosis. The findings of current study were similar to those reported in previous investigations as results agreed that peripheral vascular pattern is associated with malignancy with high specificity and varying sensitivity. Tumor cells secrete angiogenic factors. As the central vessels become obstructed due to tumor infiltration, revascularization arises from peripheral and adjacent vessels [18]. Malignant LNs are usually characterized by a modification of the LN shape from oval to round by hilar and cortical deformation and by the development of new blood vessels (the latter is related to the formation of angiogenic factors by neoplastic cells). These new vessels are histologically characterized by a distorted pattern of growth, with appearance of abnormal arterial vessels and particular difference in the flow spectrum [19].

Vascular resistance

Doppler spectral analysis can measure vascular resistance (RI and PI) in LNs. Since the adoption of power Doppler sonography with Doppler spectral analysis, vascular resistance has been proposed to differentiate malignant LNs from reactive or normal ones. The theory is that malignant nodes are infiltrated by tumors which not only compress the internal structure and vasculature of the LN, thereby causing high vascular resistance, but also induce desmoplasia resulting in other structural changes to the LN and further increasing RI and PI [20]. Normal and reactive nodes that have high flow requirements without any disruption in the nodal structure have lower vascular resistance than malignant nodes. Data on the use of these parameters remain mixed depending on cut-off values assigned for RI and PI. Brnic and Hebrang [21] showed a statistically significant difference in RI and PI between reactive and metastatic LNs. The measurement of vascular resistance may be useful in distinguishing malignant LNs from normal or reactive cervical LNs. Current study showed higher PI and RI in malignant nodes than in benign ones.

CONCLUSIONS

High-resolution CDUS provides information that is useful in making a correct diagnosis. Nodal vascularity is important in the diagnosis and differentiation of malignant from benign LNs.

Ethical Clearance: Permissions for carrying out the study were obtained from the Research Ethics Committee at Al-Sadder Teaching Hospital in AL-Najaf Governorate, Iraq.

Financial Disclosure: There is no financial disclosure.

Conflict of Interest: None to declare.

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