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ORIGINAL ARTICLE

Reliability of sonoelastography in predicting pediatric cervical lymph node malignancy

Ossama M. Zakaria[1,2] · Ahmed Mousa[1,3] · Reema AlSadhan[1] · Tamer A. Sultan[4] · Ahmed F. Eid[5] · Mohamed Y. Daoud[1] · Asmaa Al-Taher[1] · Hazem M. Zakaria[6] · Krishna Swaroop[1] · Amr M. El-Gibaly[7] · Haytham Al-Arfaj[1] · Essam M. Abdelbary[1]

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Abstract

Purpose Controversy exists as regards the best non-invasive diagnostic tool for pediatric cervical lymphadenopathy. The current work aimed to evaluate the reliability, sensitivity, specificity, and accuracy of sonoelastography in diagnosing benign and/or malignant pediatric cervical lymphadenopathy.

Methods Prospective study took place over a period of 4 years from January 2013 to December 2016. A total of 177 lymph nodes (LNs) in 128 children with an age ranging from 11 months to 12 years were recruited in this study. Patients were 77 males and 51 females with a ratio of 3:2. All patients underwent a thorough history taking and clinical examination of the neck focusing on the cervical lymph nodes. After that, a B-mode sonography, Color Doppler ultrasound, and Sonoelastography were performed. Elastographic patterns of 1–5 were evaluated, whereas patterns of 3–5 (firm to hard) were suspected to have a malignant nature. Sonographic-guided aspiration cytology took place in 107 lymph nodes and excisional biopsy in 102 lymph nodes, whereas 13 lymph nodes responded adequately to conservative treatment. They proved to be benign reactive hyperplasia.

Results The majority of LNs (87%) were of the malignant type that showed an elastographic pattern of 3–5. The same patterns were observed in only 6 (3.4%) of the benign LNs. Sonoelastography showed a sensitivity of 85.9%, specificity of 100%, PPV of 100%, NPV of 75.96%, and overall accuracy of 90.23% in distinguishing benign from malignant lymph nodes. Using the B-Mode ultrasound, an abnormal hilum was seen in 75%. The accuracy of color Doppler US reached 82.7%.

Conclusions Sonoelastography may be superior to other US modalities in elucidating different cervical lymph node biopsy helping to distinguish benign from malignant lesions. This may replace the lymph node biopsies in the future. Moreover, its use in the follow-up of patients with cervical malignancies may reduce the number of future biopsies. Further studies with more patients may be needed for a better assessment of results.

Keywords Sonoelastography · Lymph node · Malignancy · FNAC · Lymphoma

✉ Ossama M. Zakaria
ossamaz2004@gmail.com

1 Departments of Pediatric Surgery, Surgery, Radiology, Pathology, College of Medicine, King Faisal University, Al-Ahsa, Saudi Arabia

2 Division of Pediatric Surgery, Department of Surgery, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

3 Department of Vascular Surgery, Faculty of Medicine for Males, Al-Azhar University, Cairo, Egypt

4 Division of Pediatric Surgery, Faculty of Medicine, Menoufia University, Menoufia, Egypt

5 Medical Imaging Department, King Abdul-Aziz Hospital, Health Affairs of the Ministry of National Guard, Al-Ahsa, Saudi Arabia

6 Department of Surgery, Imam Abdulrahman Bin Faisal University, College of Medicine, Dammam, Saudi Arabia

7 Department of General, Visceral, Thoracic and Vascular Surgery, Hanse Klinikum Stralsund, University Medicine of Greifswald, Greifswald, Germany

Introduction

Accurate diagnosis of pediatric cervical lymphadenopathy still poses a challenge to pediatricians with a considerable controversy as regards the best diagnostic tools. Moreover, distinguishing benign from malignant cervical lymphadenopathy is a major dilemma. A proper diagnosis is of great importance to help in drawing the best treatment plan [1]. In the absence of any signs of inflammation or a congenital lesion, a pediatric lateral neck lymphadenopathy must be considered as lymphoma or a metastatic carcinoma until proven otherwise [2, 3]. In diagnosing the probable causes of cervical lymph node enlargement, US constitutes a superior feasibility in comparison to other imaging modalities because of its high resolution, low cost, good-discriminative soft-tissue ability, and a high accessibility [4, 5]. Recently, a new concept in imaging has been introduced based on the elasticity (hardness) that is a mechanical characteristic of the tissues, which prevents them from displacement under pressure aiming to non-invasively discriminate and distinguish between different pathologic states such as inflammation or malignancy. Measuring the degree of tissue distortion due to the application of an external source, which is known as "palpation by imaging", is the main concept of the sonoelastographic imaging techniques [6–8]. The main principle of the technique is to receive digitized radiofrequency echo lines from tissues; then, it slightly compressed the tissues via the transducer along the radiation access inducing some displacement, followed by receiving a post-compression digitized radiofrequency echo line of the same tissue. After processing the two echo lines, an ultimate sonoelastographic image appears on the monitors. Both gray-scale and color US elastography are used. Nevertheless, the colored type of sonoelastogram can detect any increase in tissue hardness in the form of an ascending manner of red, yellow, green, and blue. The assessment of nodal strain elucidated by sonoelastography can be performed either by grading the appearance of a scoring system (elasticity score—ES) or calculating the strain ratio (*S*/*R*) [9]. The current work aimed to evaluate the accuracy and reliability of sonoelastography in distinguishing malignant pediatric cervical lymphadenopathy from their benign counterparts.

Methods

This prospective study took place over a period of 4 years from January 2013 to December 2016, after getting the approval of the study protocol by our institute researcher board (IRB). The inclusion criteria of patients were all infants and children, who presented with clinically palpable, non-tender cervical lymph nodes (LNs) with an uncertain diagnosis having no specific clinical features and signs of infection that have not been yet diagnosed nor received any treatment. The exclusion criteria were patients

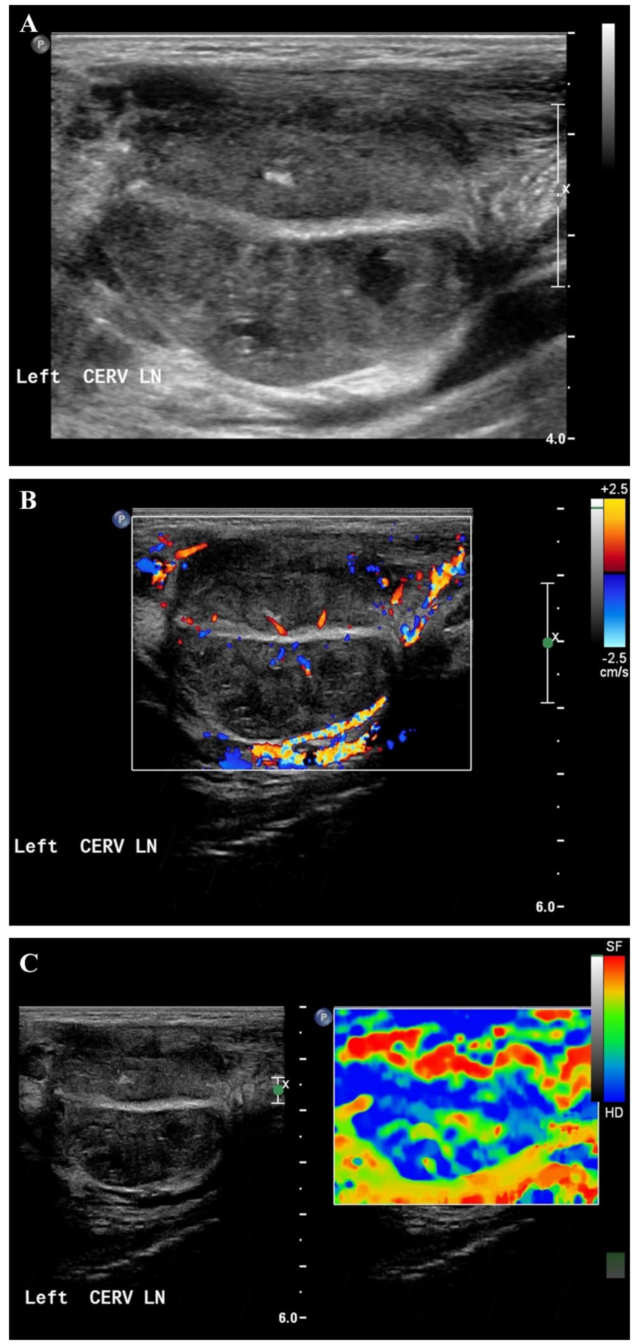

Fig. 1 **a** B-Mode US of an enlarged cervical lymph node with loss hyperechoic hilum, markedly thickened hypoechoic cortex suggestive of malignancy. **b** Color Doppler US of a malignant LN showing markedly increased peripheral and central vascularity. **c** Elastographic US of a malignant LN shows large blue area(s); total blue area ≥45% indicate increased hardness with strain ratio: 6.5

presenting with lymph nodes that are clearly clinically diagnosed as inflammatory; for example, abscess or suppurative nodes. An informed written consent was obtained from the children guardian/s. Patients underwent a complete history taking and full clinical examination. Following that, B-Mode US assessment was performed using Toshiba Aplio MX (Tokyo, Japan) with a 7–12-broadband linear array transducer to assess the different cervical groups of lymph nodes. With the help of B-Mode US scoring of all LNs, the size, shape, border, echogenicity, as well as the hilum in each group (Fig. 1a) were evaluated per each region [10–12]. For a better accuracy, the shape is expressed by a ratio of short-to-long-access diameters (*S*/*L* access). To differentiate between benign (reactive) and malignant nodes, a criterion assessing characteristics of LNs as seen by color Doppler has been applied. Benign LNs are small in size, have normal margin and echogenicity, preserved fatty hilum with central normal vascularity, or matted together with surrounding soft-tissue edema with markedly increased vascularity on color Doppler. While malignant LNs are multiple and discrete with loss of the normal shape as it may be rounded rather than oval, irregular outer margin, loss of fatty hilum, peripheral vascularity on its capsule, or focal loss at its pole, or have a mass effect on the normal blood vessels [13]. Sonoelastography evaluation technique took place by repeating light pressure compression and decompression until having a stable picture (Fig. 1c). The monitor revealed the compression frequency of a special scale. The pattern and scoring system of the sonoelastography findings was previously described (Table 1) [14]. Fine-needle aspiration cytology (FNAC) is an accurate and useful method in the evaluation of pediatric cervical lymphadenopathy [15]. Histological assessment of all the examined lymph nodes took place through FNAC to compare the histology results with the US features weather B-Mode, Doppler, and US elastography (Fig. 2a–c). The radiologist was blind to the result of the FNAC.

Statistical analysis

Statistical analysis was done to compare the sensitivity, reliability, and specificity of the different US tools in relation to the histopathological findings using Statistical Package for the Social Science (SPSS) computer program version 23.0 (IBM Corporation, Armonk, New York, USA). Data are expressed as mean and standard deviation (±SD). Differences were considered significant at $p < 0.05$.

Results

One hundred and seventy-seven LNs in 128 children were evaluated. Patients' age ranged from 0.92 to 12 years (M ± SD = 5.7 ± 3.3). They were 60% males ($n = 77$) and 40% females ($n = 51$) with a male-to-female ratio of 3:2. The majority of the histopathologically examined lymph nodes 87% ($n = 154$) proved to be malignant. Lymph nodes were firm in consistency. We categorized the lymph nodes according to the final pathological diagnosis into two groups: Group I ($n = 23$) including 13 (7%) with reactive hyperplasia, acute lymphadenitis in 8 (5%), and tuberculous lymphadenitis in 2 patients (1%), (Fig. 1c). Group II ($n = 154$) included lymphoma in 103 (58%) patients (Fig. 2b) and 51 (29%) with metastasis (Fig. 2a, Table 2). Malignant LNs had absence of the hilum (100%), ill-defined borders (73%), heterogenicity (100%), and regular shape (60%). While benign LNs had a present hilum (75%), well-defined borders (75%), heterogenicity (67%), and regular shape (75%). A sonoelastographic pattern of 3–5 was recorded in all the histopathologically proved malignant LNs. Yet, the same pattern was observed in only 26% ($n = 6$) of the benign lymph nodes. The majority (74%) ($n = 17$) of benign lymph nodes showed sonoelastographic pattern of 1–2 sites of the assessed cervical LNs included: 27 (15%) in the submental region, 58 (33%) at the submandibular region, 12 (7%) at the parotid region, 39 (22%) at the upper cervical group, and 27 (15%) at the middle cervical, while 7 (4%) were present at the lower cervical and the remaining 7 (4%) were located at the posterior triangle. Malignant lymph node showed

Table 1 Patterns and scoring system on sonoelastographic findings

Pattern	Score	Description	Sonoelastographic diagnosis
1	2	Absent or very small blue area(s)	Benign
2	4	Small scattered blue areas, total blue area < 45%	Benign
3	6	Large blue area(s), total blue area ≥ 45%	Malignant
4	8	Peripheral blue area and central green area, suggesting central necrosis	Malignant
5	10	Blue area with or without a green rim	Malignant

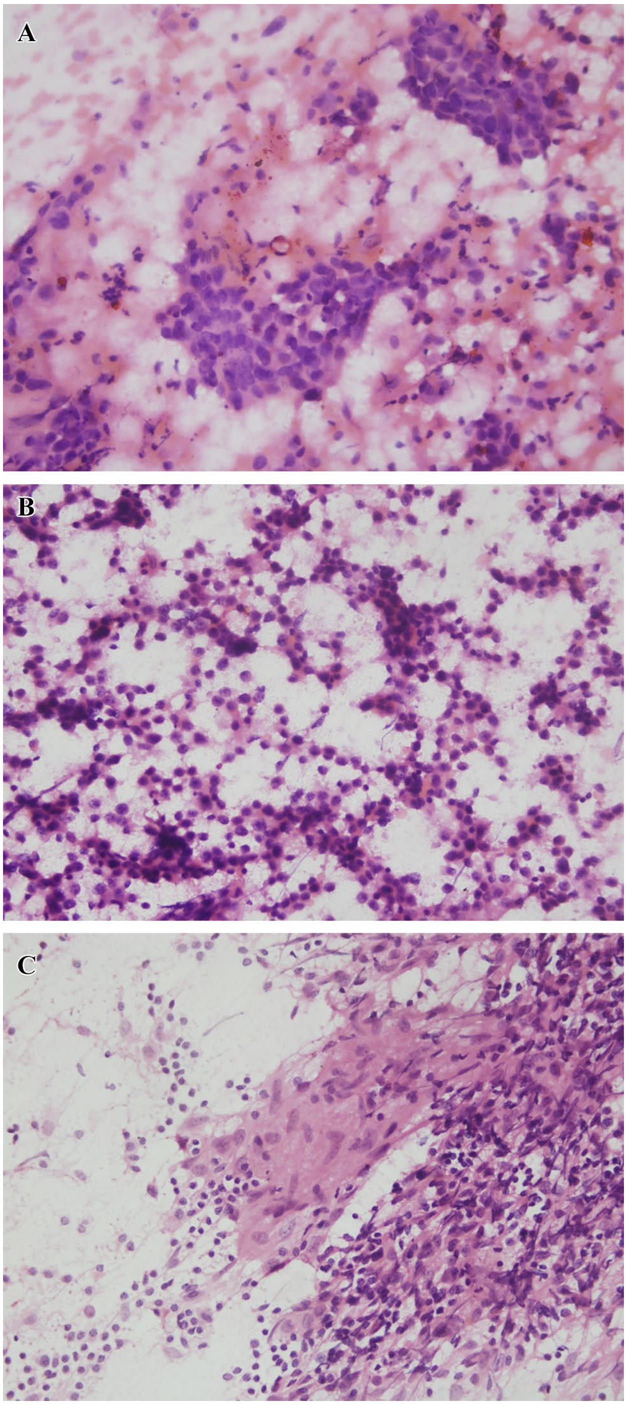

Fig. 2 **a** FNAC smear of a metastatic lymphadenopathy showing groups, clusters, and scattered pleomorphic cells with enlarged, irregular nucleus, and moderate amount of eosinophilic cytoplasm against a background of lymphocytes admixed with blood (400×H&E). **b** FNAC of a lymphoma showing a cellular aspirate and predominantly a monotonous population of malignant lymphoid series of cells with enlarged nuclei, coarse chromatin, and prominent nucleoli (400×H&E). **c** FNAC smear of a tuberculous lymphadenitis showing clusters of epithelioid cells with elongated slipper-shaped nuclei against a background of lymphocytes (200×H&E)

Table 2 Histopathological findings of LNs

Group I	*n*	%	Group II	*n*	%
Reactive hyperplasia	13	7	Lymphoma	103	58
Acute lymphadenitis	8	5	Metastasis	51	29
Tuberculous lymphadenitis	2	1			
Total = 177	23	13	154	154	87

higher B-Mode scores compared to their benign counterparts ($p = 0.009$). Table 3 represents the distribution of the elasticity pattern with its score for benign and malignant LNs. Table 4 shows the sensitivity, specificity, and accuracy of the different used US tools in comparison to each other.

Discussion

In humans, the head and neck contain nearly 60–70 LNs out of about 400–450 total body LNs. The reasons for pediatric lymphadenopathy include a myriad of benign as well as malignant conditions [14]. Elucidating the cause/s of pediatric cervical lymphadenopathy is crucial to plan the treatment modality. Clinical and investigatory tools come into play for this purpose. The US plays an indispensable role not only in diagnosing lymphadenopathy but also in anticipating the type of pathology whether benign or malignant [1, 10, 12, 16]. Sonoelastography is a recent, non-invasive US modality that helps to differentiate benign from malignant lymph nodes, and thus, it could decrease unnecessary biopsies [16]. The current study involved 177 LNs in 128 patients; they included 23 benign LNs and 154 malignant. Actually, low specificity and sensitivity of US diagnosis of lymphadenopathy were recorded when the examination is only based upon shape, S/L axis ratio (the ratio of the short axis diameter to the long axis diameter), hilum, echogenicity, and calcifications [17]. Nevertheless, some workers reported an ultrasound sensitivity of 85% by measuring the minimum and maximum axis diameter to distinguish benign from malignant lymph nodes [18]. Yet, in our study, the inflammatory lymph nodes were as large as their malignant counterparts, contradicting the previous reports, whilst in agreement with others [19–22]. In addition, the S/L ratio in our study failed to discriminate between benign and malignant LNs, coinciding with a previously published report [11], although others reported a 76% discriminative accuracy of S/L ratio [23]. Color Doppler sonographic assessment of LNs was reported to have an accuracy of 90% with a sensitivity of 83.3% and specificity of 100% [24, 25]. Our study showed a Doppler US sensitivity rate of 74%, an accuracy rate of 82.7%, and specificity of 100%, thus coinciding with previously published data that showed a high specificity and sensitivity 78.9% of Doppler US [19]. Sonoelastography showed a sensitivity of

Table 3 Sonoelastographic pattern and scoring for the studied cervical LNs

Elastography pattern	Elastographic scoring	Benign $N = 23$	Malignant $N = 154$	Total number	%
1	2	10	0	10	5.6
2	4	13	22	53	30
1, 2 (benign)	2, 4 (benign)			32	18
3	6	0	59	4	2.3
4	8	0	28	28	15.8
5	10	0	45	45	25.4
2, 3, 4 (malignant)	6, 8, 10 (malignant)			5	2.8
Total		23	154	177	100

Table 4 Collective statistical results of different sonographic tools

Item	TP	FN	TN	FP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
B-Mode US	157	20	23	20	88.7	53.5	88.7	53.5	81.82
Color Doppler US	131	46	89	0	74	100	100	65.93	82.7
ES Score	152	25	79	0	85.9	100	100	75.96	90.23

85.9% and a high accuracy of 90.23%, in agreement with a previously published data [12, 14, 16, 23]. Moreover, the true negative (TN) difference between the sonoelastography and histopathology of 44.6% was in accordance with other investigators, who showed a TN of 42.6% [26]. The true positive (TP) value in our study was 98.7%, coinciding with another group, reporting a sonoelastographic accuracy rate of 90%, reminiscent of our accuracy of 90.23% [26]. Conversely, other authors reported a sonoelastographic specificity of 75.1%, a positive predictive value (PPV) of 52.2%, and a negative predictive value (NPV) of 71% [13, 16]. The specificity of US elastography is generally reported to be high, not only in our study but also in many others [8, 13, 14, 17, 23]. In conclusion, the sensitivity and specificity of sonoelastography increase when combined with B-Mode and color Doppler US. However, the overall accuracy of any US technique is well known to depend on the operator's experience and the quality of the machine. Sliding motions during compression, especially in children, may represent another obstacle during the assessment, as do the neighboring vessel pulsations. Overall, sonoelastography might be considered as a future option to replace surgical lymph node biopsies in distinguishing benign from malignant pediatric cervical lymphadenopathy. A theoretical limitation thereof lies in the fact that the oncologists almost always need a histopathological statement for properly tailoring the chemotherapeutics. To what extent this is mandatory remains to debate. Yet, our method could help—at least in part—in primary screening sessions to rule out malignancy or in follow-up cases to check the early recurrence of malignancy, thus minimizing unnecessary operations. Our method also has a role in preventing unnecessary biopsies in LNs that has benign characteristics via sonoelastography. Moreover, it can differentiate tuberculous nodes from other benign lesions. Another promising potential lies in the opportunity of adequately performing the aspiration biopsy with the aid of sonoelastography exactly in the target tissue and not from the adjacent necrotic areas, hence increasing the yield and avoiding false negative results. Surgeons should be trained to perform sonoelastography of cervical lymphadenopathy in clinical setting to facilitate the time and resources and to provide patients with the proper management faster. It is always like anything novel in life; one is in need of adequate time to establish the idea, get acquainted with it and to finally polish it, bringing it to its ultimate glorious perfection. Further studies with larger number of patients may aid in paving the road for the establishment of sonoelastography as a routinely practiced tool for management of pediatric cervical lymphadenopathy. This may decrease the health care financial burden, especially in resource-challenged settings.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this article.

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