JSSN 2016; 19 (1)

Original Article

Value of ultrasound in evaluation of cervical lymphadenopathy: correlation with FNAC / histopathology

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Abstract

Introduction: The role of high-resolution ultrasound in evaluation of cervical lymph nodes is well established. The aim of this study was to determine its accuracy in differentiating benign and malignant cervical lymphadenopathy. The objectives were to study various sonographic features applicable in routine clinical practice to identify and differentiate various types of cervical lymphadenopathy.

Methods: The study was done at the Pathology and Radiology department of Manipal teaching hospital (MTH) from Jan 2015 to Dec 2015. Seventy cervical nodes in 70 patients (17-reactive, 23-tuberculous, 9-lymphoma and 21-metastatic) were evaluated by high resolution ultrasound (7.5-10MHz). Shape (S:L ratio), (maximal short to maximal long axis ratio diameter) nodal margins, hilar echogenicity, vascular pattern, distribution, size, echogenicity, calcification, posterior enhancement, eccentric cortical hypertrophy, matting and soft tissue edema were assessed. Confirmed diagnosis was either made by USG guided FNAC on the largest node or by open biopsy. The first four parameters had the most significant differences between benign and malignant lymph nodes and were evaluated to calculate the accuracy of ultrasound in their differentiation. Individual groups were compared and optimal sonographic features in differential diagnosis were determined.

Results: The common useful sonographic features to identify different types of cervical lymph nodes were S:L ratio, nodal margins, hilar echogenicity, vascular pattern, matting, soft tissue edema, echogeneity, intranodal necrosis, displaced hilar vascularity, eccentric cortical hypertrophy and posterior enhancement. Vascularity was the most accurate parameter (86%) when used in isolation and when combined parameters were used ultrasound had accuracy of 97% in diagnosing benign or malignant cervical lymphadenopathy.

Conclusion: This study showed that high resolution ultrasound has a high degree of accuracy in differentiating benign and malignant cervical lymphadenopathy and assists in differentiating various causes of lymphadenopathy.

Key words: Benign; high resolution ultrasound; lymph nodes; malignant.

Introduction

Lymphadenopathy, which is defined as an abnormality in the size or character of the lymph node, is caused by invasion or propagation of either inflammatory cells or neoplastic cells into the node. Among the serious illnesses that can present with lymphadenopathy, perhaps the most concerning to the patient and physician alike, is the possibility of underlying malignancy.[1]

Cervical lymphadenopathy may be either an important clue to an underlying disease process or a specific clinical syndrome. It can be both benign and malignant in nature.[2] The most common benign causes include granulomatous lymphadenitis and reactive lymphoid hyperplasia, while the most common malignant causes include lymphoma and metastatic cancers.[3, 4]

For patients with known primary disease, the single most important factor in determining prognosis is whether nodal metastasis is present or not and the presence of a metastatic node to one side of the neck reduces the 5-year survival rate to 50%, and the presence of a metastatic node in both sides of the neck reduces the 5-year survival rate to 25%.[5] Metastatic nodes are site-specific, and nodal metastasis of a particular head and neck cancer in an unexpected level indicates that the neoplasm is more biologically aggressive.[6]

Cervical lymph nodes are also common sites of involvement in Non- Hodgkin's lymphoma of the head and neck region.[7] Such nodal involvement is often difficult to differentiate from metastatic nodes of squamous cell carcinomas and, as the treatments of lymphoma and metastatic squamous cell carcinomas differ, differentiating between the two is essential. Tuberculous lymphadenitis remains a diagnostic dilemma and lymph nodes in the head and neck regions are common sites of this infection.[8] The complex array of lymph nodes of the head and neck are considered in anatomic groupings based on the lymph drainage patterns.[2] Although lymph node biopsy is the final method to differentiate between benign and malignant nodes, several investigations are known to be helpful, including ultrasound and CT of the nodes.[4,] Lymph nodes < 5 mm in diameter are difficult to detect by CT, [2] whereas high resolution sonography can detect lymph nodes as small as 2 mm in diameter.[9] Nodal shape on CT and MRI does not have any value in differentiating reactive from malignant nodes, because axial scans are commonly performed on CT and MRI, which only demonstrate the nodes in the transverse plane where they tend to appear round or oval.[4, 10] However in USG, free manipulation of transducer allows the operator to obtain a scan plane for accurate determination of nodal shape. MRI does not easily detect nodal calcification, [5] which may be important in differential diagnosis of the primary site.

In CT, dental fillings cause streak artifacts, which may also affect the visualization of the submandibular, subdigastric, and submental nodes. The shoulders may cause streak artifacts and obscure the supraclavicular and lower cervical nodes.[11] Moreover, CT involves radiation hazards and the use of intravenous contrast, and CT and MRI generally have a higher cost than ultrasound, and limited availability in developing countries. It is difficult and time consuming to perform guided fine-needle aspiration biopsy in conjunction with CT or MR imaging.[12] CT and MRI have the distinct advantage that they evaluate the primary tumor and evaluate nodes in areas such as oropharynx and nasopharynx which are inaccessible by ultrasound.

On the basis of sonographic findings, selection of additional imaging modalities including CT and MR imaging can be done more judiciously.[13] Sonography is now the first imaging modality after clinical examination. It is easily tolerated by patients without radiation and is inexpensive.[14]

The role of gray-scale sonography in evaluation of cervical lymph nodes is well established. Ancillary features such as matting and adjacent soft tissue edema are also assessed which are particularly helpful to identify tuberculous nodes. [15,16]

With the advance of technology and the introduction of Power Doppler sonography (PDS), assessment of the vascularity of lymph nodes by ultrasound has become more accurate.[17,18] In comparison to Color Doppler Sonography, PDS is more sensitive in detection of structures with low volume flow of fluid, and is less dependent on the direction of flow.[19]

The most accurate CT predictor of metastasis is the presence of central necrosis, which has been said to have 100% specificity.[20] Using all these combined CT criteria, a sensitivity of 87% and specificity of 94% per neck dissection specimen has been achieved.[20] Direct comparisons have shown CT to perform better than MRI even when using current technology.[21]

PET scanning provides sensitivities of up to 90% and specificities of up to 94% for individual lymph nodes and direct comparisons with CT, US and MRI have shown it to be at least as accurate.[22]

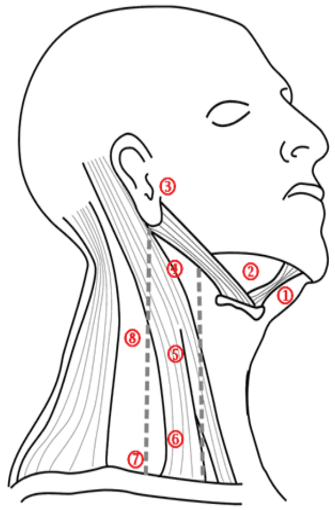
Ultrasound guided Fine-needle Aspiration Cytology (FNAC):

Ultrasound is a useful imaging modality in evaluation of cervical lymphadenopathy because of its high sensitivity (98%) and specificity (95%) when combined with FNAC.[23] It provides more accurate information than blinded FNAC .

USG guided FNAC can monitor the needle tip. Monitoring of the needle tip using ultrasound guidance prevents accidental puncture of vital structures such as the common carotid artery.[24] It is assumed that cases with definite benign or malignant FNA results are accurate unless proven otherwise by subsequent excision and histology (false-positive or false-negative).[25]

Lymph nodes in the neck are arranged in seven main chains. The most clinically important and readily accessible to USG are the anterior jugular, the parotid, and the submandibular chains. Normal lymph nodes have an axial diameter between 2 to 5 mm and are seldom visualized with USG because their echogenicity is similar to that of subcutaneous fat.[9]

In ultrasound examinations, the cervical lymph nodes are classified into eight regions according to their location in the neck. (Figure.1)



1. Submental
2. Submandibular
3. Parotid
4. Upper cervical (above the level of hyoid bone, and along the internal jugular chain)
5. Middle cervical (between the level of hyoid bone and cricoid cartilage, and along the internal jugular chain)
6. Lower cervical (below the level of cricoid cartilage, and along the internal jugular chain)
7. Supraclavicular fossa
8. Posterior triangle (accessory chain)

Figure.1: Ultrasound classification of cervical lymph node.

This study was done to determine the accuracy of high-resolution ultrasound in differentiating benign and malignant cervical lymphadenopathy, considering FNAC/ histopathology as gold standard in diagnosis.

Methods

All adult patients with cervical lymphadenopathy referred to the Pathology/Radiology department from the outpatients/inpatients' Department of Manipal teaching hospital (MTH) for FNAC of cervical lymph nodes were included from Jan 2015 to Dec 2015.

Patients undergoing radiotherapy of the neck/on chemotherapy/Anti-Tubercular Treatment (ATT); patients with severe cervical disorders not capable of extending their neck for the examination or with extensive cervical soft issue scarring; age < 15 years; patients not willing to participate; restless or patients in distress not able to maintain a supine posture and those in whom pathological diagnosis was inconclusive/reports couldn't be traced or fell outside reactive, tubercular, lymphomatous or metastatic category were excluded from the study.

Seventy cervical nodes were evaluated by high resolution ultrasound (7.5-10MHz). commercially available real time scanner (GAIAMT 8800, Medison). (7.5-10MHz).

The sonographic features that were taken into consideration to evaluate cervical lymph nodes included S:L ratio, echogenic hilus, nodal border, vascular pattern, displaced vascularity, soft tissue edema, matting, posterior enhancement, calcification, eccentric cortical hypertrophy, intranodal necrosis and echogenicity.

A total of 100 patients underwent USG and USG guided FNAC, however; only 70 patients in whom the pathological diagnosis was confirmatory were included in the study. 30 patients were excluded from the study either because the FNAC results were inconclusive or not found during follow-up. Excision biopsy was done by the surgical team in 6 patients Confirmed diagnosis was either made by USG guided FNAC on the largest node or by open biopsy. The parameters that had the most significant differences between benign and malignant lymph nodes were evaluated to calculate the accuracy of ultrasound in their differentiation. Individual groups were compared and optimal sonographic features in differential diagnosis were determined.

Data obtained was analyzed using standard statistical software. SPSS 11.5 was utilized for data analysis and presentation. 'P value' <0.05 was considered statistically significant and ≥0.05 was considered insignificant. The significance of differences in USG features among different disease groups was assessed by the Fisher's exact test and Chi-square test.

Results:

A total of 70 nodes from 70 different patients with cervical lymphadenopathy were included in the study which consisted of 40 Benign (Tuberculous, 23; Reactive, 17) and 30 Malignant (9, Lymphomatous; 21, Metastatic) nodes.

Age of the patients ranged from 15-75 years, the mean age was 43.9 years. The largest age group comprised of 45-54 years (20%).

Out of 70, 33(47%) of patients were males and 37(53%) were female. (Figure 2)

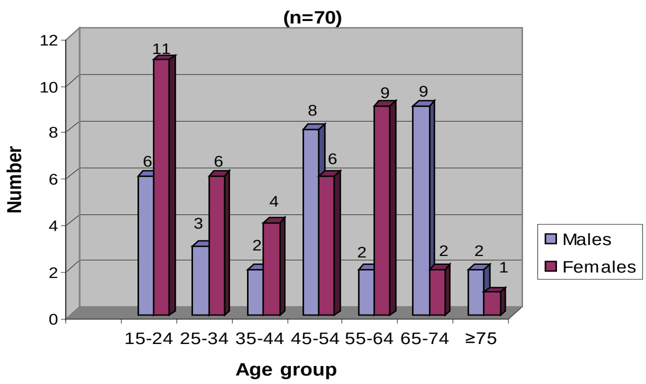


Figure 2: Age and sex distribution of cervical lymphadenopathy

Vascularity was the most accurate parameter to differentiate benign and malignant lymphadenopathy followed by nodal shape (S:L ratio).

The most common useful sonographic parameters to identity various types of cervical lymphadenopathy were as follows:

Reactive lymph nodes: Oval shape (S:L ratio <0.5), homogeneity, hilar vascularity, unsharp borders and absence of intranodal necrosis.

Tubercular nodes: Round shape (S:L ratio ≥0.5), unsharp borders, matting, soft tissue edema, heterogeneity, intranodal cystic necrosis and displaced hilar vascularity.

Lymphomatous nodes: Round shape (S:L ratio ≥0.5), homogeneity, posterior enhancement, sharp borders, malignant vascularity (predominantly mixed) and absence of intranodal necrosis.

Metastatic nodes: Round shape (S:L ratio ≥0.5), sharp borders, malignant vascularity (predominantly peripheral), presence of intranodal necrosis and eccentric cortical hypertrophy.

Four sonographic parameters that were used to differentiate benign and malignant lymphadenopathy were hilar echogenicity, vascular pattern, nodal shape (S:L ratio) and nodal margins. Two by two tables were obtained to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positive rate (FPR), false negative rate (FNR) and accuracy for each of these parameters within 95% confidence interval. (Table 1)

Table 1: Summary of validity of USG in differentiating benign from malignant cervical lymphadenopathy

USG	SENSI-TIVITY	SPECI-FICITY	PPV	NPV	FPR	FNR	ACCURACY	P VALUE
Echoge-Nic Hilum	75	90	91	73	10	25	81	0.0000003
S:l Ratio	72	93	93	72	6	27	81	0.0000002
Vascu-Larity	85	87	89	81	13	17	86	0.00000004
Nodal Margins	75	90	73	91	10	25	81	0.0000003

Discussion

Ultrasound has high sensitivity when compared with clinical examination (92% and 70% respectively) and high specificity when combined with FNAC (95%).[26,29]

Gray scale ultrasound evaluates the size, shape and internal architecture of cervical lymph nodes.[26] PDS provides yet more information and is based on the fact that tumor larger than a few millimeters in diameter stimulate the growth of new vessels.[27,28]

Size of lymph nodes was used previously as an indicator of malignancy.[29] Using nodal size as the assessment criterion, one should note that when a lower cut-off point of nodal size is used, the sensitivity in differentiating malignant from benign nodes increases, whilst the specificity decreases.[30] A higher cut-off point yields higher specificity and lower sensitivity.

In this study, there was significant difference in the short axis diameter of lymph nodes between four disease groups and between benign and malignant nodes ($p < 0.05$). The shape of lymph nodes has been used to differentiate normal or reactive nodes from malignant nodes. Abnormal shape is a consistent finding in differentiating reactive nodes from other abnormal nodes.[9,10] Metastatic, lymphomatous and tuberculous nodes commonly appear round with an S:L ratio ≥0.5, whereas normal or reactive nodes are usually long, oval-shaped or flat with S:L ratio <0.5.[9,10,16] In this study, 94% of reactive lymph nodes were oval, whereas 65% of tuberculous, 90% of metastatic and 100% of lymphomatous lymph nodes were round ($p < 0.05$). In this study, the average S:L ratio of malignant nodes was 0.62 and was higher than that of benign nodes.

Malignant nodes (including metastases and lymphoma) tend to have sharp borders, whereas benign nodes (reactive and tubercular) usually have unsharp borders.[31] The presence of a central echogenic hilus within lymph nodes is usually considered as a sign of benignity and normality especially in large nodes.[32] Although metastatic, lymphomatous and tuberculous nodes tend to have absent hilus, they may present with an echogenic hilus in their early stage of involvement.[33]

Metastatic nodes are usually hypoechoic, except for metastases from papillary carcinoma of the thyroid, which tend to be hyperechoic.[34] In this study, all the tuberculous and lymphomatous nodes were hypoechoic .

Metastatic nodes may look homogeneous or heterogeneous.[35.36] Lymph nodes involved with Non-Hodgkin's lymphoma usually look homogeneous, and tuberculous nodes are commonly heterogeneous.[37,38]

In this study, tuberculosis was the most common disease with heterogenous lymph nodes (85%) followed by metastatic lymph nodes (47%).

Intranodal calcification is rarely found in cervical lymphadenopathy but it is common in metastatic nodes from papillary carcinoma and medullary carcinoma of the thyroid and in metastatic nodes after irradiation or chemotherapy.[32]

In this study, calcification was observed only in metastatic nodes from papillary carcinoma of thyroid (n=2), punctuate in type. Patients taking anti-tubercular treatment or undergoing chemotherapy/radiotherapy for metastatic disease were excluded from the study.

Lymph nodes with intranodal necrosis are considered to be pathologic. Cystic necrosis is commonly found in tuberculous nodes and metastatic nodes from squamous cell carcinomas and papillary carcinoma of the thyroid.[32,34] In our study, 78% of tubercular nodes exhibited intranodal necrosis, predominantly cystic (88%). Ancillary features that help to evaluate cervical lymphadenopathy are matting and adjacent soft tissue edema. Metastatic and granulomatous lymph nodes may produce adjacent soft tissue edema either due to tumor infiltration or as an inflammatory response to adjacent disease. Adjacent soft tissue edema and matting are common features in tuberculous nodes whilst these features are relatively less common in metastatic and lymphomatous nodes.[39] Matting of lymph nodes in tuberculous lymphadenitis is a useful feature in distinguishing tuberculosis from other diseases.

Normal and reactive lymph nodes tend to show hilar vascularity or appear apparently avascular.[40] However, metastatic nodes tend to have peripheral or mixed vascularity and mixed vascularity is also common in lymphomatous nodes.[7,17,41] Unlike metastatic nodes, peripheral vascularity alone is less common in lymphoma. As peripheral vascularity is not found in normal or reactive nodes, the presence of peripheral vascularity, regardless of sole peripheral or mixed vascularity, is highly suspicious of malignancy.[42] The vascular changes in malignant nodes are thought to be related to tumor angiogenesis and the associated thermoplastic reaction or recruitment of capsular vessels.[17,18,43]

On ultrasound, tuberculous nodes have varied vascular pattern, which simulates both benign and malignant conditions.[42] Peripheral vascularity was found in 31% of tuberculous nodes.[44] Apparent avascularity was also found in tuberculous nodes (19%) and may be related to the extensive intranodal cystic necrosis of tuberculous nodes, which destroys the blood vessels of the lymph nodes.[47] PDS, with its increased sensitivity, is consistently able to detect this abnormal vascularity and evaluate the distribution of vessels, thus differentiating histologically proven benign from malignant nodes with a high degree of accuracy (83-89% of sensitivity and 76-98% of specificity).[17,41]

In this study, approximately 78% of lymphomatous and 90% of metastatic lymph nodes demonstrated malignant vascularity (peripheral or mixed). Benign vascularity (hilar or absent) was observed in 100% and 69.6% of reactive and tuberculous lymph nodes respectively and none of the reactive nodes showed peripheral or mixed vascularity.

In a review of 730 enlarged cervical lymph nodes in 285 patients examined with ultrasound in 1995, S:L ratio was evaluated as a valid diagnostic parameter in the differentiation between benign and malignant nodal disease. Definite diagnoses of the nodes were obtained by histological examination following neck dissection. They concluded that the S:L ratio of lymph nodes provided an excellent criterion for differentiation between benign and malignant.[45]

In order to determination whether an enlarged cervical lymph node is metastatic or not 36 metastatic lymph nodes in head and neck and 24 non-metastatic nodes in benign disease were evaluated with a 10 MHz transducer and studied for size, shape, and internal echo.[46] Short axis diameter and shape of metastatic nodes were larger and rounder than those of non-metastatic ones. Internal echo findings and shape of lymph nodes was an important diagnostic tool, and the USG criteria of the lymph nodes were very useful for the differential diagnosis of the cervical lymph nodes.[46]

The shortest diameter, S:L ratio, margin and internal echo structure were critical indicators to differentiate between benign and metastatic nodes.[47]

Conclusion

High resolution ultrasound has a high sensitivity, specificity and accuracy in differentiating benign and malignant cervical lymphadenopathy when multiple parameters are used and assists in differentiating various causes of cervical lymphadenopathy. It is an invaluable tool in evaluating patients especially with known malignancy, to identify and obtain FNAC from clinically inaccessible nodes, which bears prime surgical as well as prognostic importance in patient management.

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