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Original Research Article

Evaluation of cortical contour of suspicious axillary lymph nodes using ultrasound among various molecular subtypes of breast cancer

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ABSTRACT

Background: In this study, we assessed specific morphological features of axillary lymph nodes, including the longitudinal axis to short axis ratio, distortion of the corticomedullary interface, cortical contour, nodal core sign, and perinodal hyperechogenic ring using a high-frequency linear probe. Among these features, the p-value was significant for cortical contour, warranting special emphasis. This focus on cortical contour may help reduce the need for immunohistochemistry in the future, proportionately lowering associated costs.

Aims and Objectives: To evaluate B-mode ultrasound features of suspicious axillary lymph nodes in histopathologically proven cases of breast cancer and assess whether these features vary between different molecular subtypes of breast cancer.

Materials and Methods: A total of 74 patients with histopathologically confirmed breast cancer, complete immunohistochemistry data, and proven metastatic axillary lymph nodes were evaluated. The sonomorphological characteristics of these metastatic axillary lymph nodes were subsequently correlated with the molecular subtype of breast cancer. Radiologists performed the ultrasound assessments, while pathologists confirmed histopathological diagnoses.

Results: Among all morphological features, only the cortical contour of the lymph node showed an association with the immunohistochemistry subtype of breast cancer, making our study unique in its ability to assess specific features of abnormal lymph nodes in relation to molecular subtypes of the disease.

Conclusion: Our study highlights a positive correlation between abnormal cortical contour and specific molecular subtypes of breast cancer. A concentric pattern predominates in the Luminal A subtype and HER2 neu-enriched subtype; an eccentric pattern is most common in the triple-negative basal-like subtype; and a focal pattern of cortical thickening is notably present in the Luminal B HER2+ subtype.

1. Introduction

The most significant indicator of overall recurrence and survival in patients with breast cancer is axillary lymph node metastases. Axillary US, MRI, and US-guided biopsy can all be used to assess the nodal disease burden, which is increasingly thought to be a crucial part of axillary imaging in order to guide multidisciplinary therapy decision-making. Patients with carcinoma breast have a 5-year survival rate of 98.8%; those with regional lymph node metastases have a 5-year survival rate drops to 85.8%.[1]

According to GLOBAL CANCER OBSERVATORY data 2022, breast cancer is the most common cause of cancer in India, accounting for 10.7% of all causes of death and 13.6% of newly diagnosed malignancies. The axillary lymph nodes are the common site of breast cancer metastasis, and the presence or absence of these nodes is predictive of early-stage breast cancer.[2]

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Molecular subtyping categorizes breast cancer according to distinct molecular profiles, providing insightful information about the biology of tumors and directing individualized treatment plans. The Luminal A subtype denotes tumors that are positive for estrogen receptor (ER) and/or progesterone receptor (PR), and negative for human epidermal growth factor receptor 2 (HER2), with low proliferative activity. Luminal B subtype tumors are ER and/or PR-positive, but they demonstrate increased proliferative activity in comparison to Luminal A tumors. Additionally, these tumors can be categorized further as either Luminal B HER2-positive or Luminal B HER2-negative based on their HER2 expression. HER2-positive breast cancer is characterized by the overactive expression or increased amplification of the HER2/neu oncogene. Triple-negative breast cancer (TNBC) does not express the ER, PR, and HER2 receptors. This subtype is linked to a less favorable prognosis because of the limited treatment choices available compared to other types of breast cancer.[3,4]

B-mode ultrasound serves as a cornerstone in axillary lymph node imaging due to its ability to capture detailed grayscale images. In B-mode ultrasound, a suspicious axillary lymph node is characterized by changes in shape—such as a round or irregular morphology—and cortical thickening, which often indicates the presence of metastatic disease. Key features that suggest malignancy on B-mode ultrasound include alterations in nodal shape, loss of the normal fatty hilum, and increased cortex-to-hilum ratio. These morphological changes assist in the non-invasive staging of axillary nodal disease and are particularly useful in distinguishing benign from malignant nodes across different molecular subtypes of breast cancer.[5,6]

Axillary lymph node evaluation is crucial in breast cancer management as it provides valuable prognostic information and guides treatment decisions. Breast cancer staging is essential for prognosis determination and treatment planning. The axillary lymph nodes play a vital role in this staging process due to their anatomical nearness to the breast tissue. The presence of metastasis in axillary lymph nodes has a significant impact on disease staging, treatment planning, and patient outcomes. Historically, surgical procedures like sentinel lymph node biopsy or axillary lymph node dissection have been used to assess the status of axillary lymph nodes. However, technological advancements in imaging, especially ultrasound, have made it possible to evaluate axillary lymph nodes non-invasively, providing a less invasive and more accessible method.[7,8]

On ultrasound, a suspicious axillary lymph node is characterized by change in shape, such as round or irregular, or abnormal cortical thickening. These changes often indicate the presence of metastatic disease in the lymph node. Assessment of axillary lymph node is done through various methods, which are physical examination, imaging techniques like ultrasound and MRI, as well as histopathological examination of lymph node tissue obtained via biopsy or sentinel lymph node dissection.[9]

2. Materials and Methods

Following approval by the Institutional Research Ethics Committee, the study was initiated as an ambispective study, including cases diagnosed between January 2021 and June 2024. A total of 74 cases with histopathologically confirmed breast cancer with immunohistochemistry data and metastatic axillary lymph nodes were included. Radiological assessment of lymph nodes was performed by a radiologist trained in breast imaging. Data of these patients was retrieved from the Picture Archiving and Communication System (PACS), and ultrasound (USG) features were analyzed retrospectively to determine the sonomorphological characteristics of metastatic lymph nodes.

2.1. Radiological assessment

Both axillae were assessed for suspicious axillary lymph nodes, studied based on size (long-axis diameter), cortical thickness, cortical contour (uniform or non-uniform cortical thickness), distortion of the corticomedullary interface, nodal core sign, and perinodal hyperechogenicity. For ultrasound examination, the lymph node with the most suspicious features was selected for detailed morphological study, and fine needle aspiration (FNA) was performed on this node during the same session. Slides prepared from the FNA sample were sent for cytological evaluation.

2.2. USG report archival & retrieval

Ultrasound reports were archived within the PACS system and systematically recollected for retrospective review and analysis. All the data was carefully documented, and images were retained within the electronic records to enable consistent retrospective evaluation.

2.3. Inclusion criteria

1. Patients with histopathologically confirmed invasive mammary carcinoma.
2. Availability of immunohistochemical subtype data.
3. Suspicious axillary lymph nodes with a cortical thickness greater than 3 mm on USG, subsequently proven to be metastatic on FNA.

2.4. Exclusion criteria

1. Cases without complete immunohistochemistry data.
2. Patients with proven breast cancer with normal axillary lymph nodes on ultrasound/mammogram.
3. Patients with no FNA reports for axillary lymph nodes.

2.5. Ultrasound characteristics evaluated

The following specific USG features of suspicious axillary lymph nodes were diligently assessed:

1. Cortical thickness: Only lymph nodes with a cortical thickness greater than 3 mm were included. The cortex appears hypoechoic on ultrasound, and if thickened (>3 mm), it may be concentric, eccentric, or focal. The medulla appears echogenic, and its distinctness or indistinctness was evaluated by examining the cortex-to-medulla ratio, reflecting any distortion of the corticomedullary interface.
2. Nodal core sign: Evaluated based on the presence or absence of the hilum and medulla, indicating whether the nodal core sign was complete or absent.
3. Distortion of corticomedullary interface: This was assessed as an indicator of metastatic involvement if distorted.
4. Perinodal hyperechogenic ring and nodal matting: These features were examined to assess potential perinodal soft tissue involvement.

2.6. Statistical analysis

Data entry and descriptive analysis were performed using Google Sheets. Statistical analysis was conducted using the Chi-square test in SPSS software to assess whether one or more USG variables differed between the molecular subtypes of breast cancer.

3. Results

A total of 74 female patients with proven breast cancer with complete histopathology report (including immunohistochemistry) with suspicious axillary lymph nodes proven to be metastatic were included in the study during the period of January 2021 to June 2024. Luminal B HER2 + was the most common immunohistochemical subtype followed by Triple negative basal like, Luminal B HER2 -, HER2 neu enriched and Luminal A (Table 1).

3.1. Individual variables with their frequency in our study subjects

3.1.1. Longitudinal axis to short axis (l/s ratio)

Most (57 out of 74) cases showed longitudinal to short axis ratio <2 suggesting, the lymph node shape as round (Table 2).

3.1.2. Distortion of cortico medullary interface

Most of the cases (51 out of 74) showed distinctive cortex and medulla, suggesting there was no distortion of corticomedullary interface. 23 out of 74 cases showed distortion of corticomedullary interface (Table 3).

3.1.3. Cortical contour

Most (48 out of 74) cases showed concentric cortical thickening in our study subjects. 15 out of 74 cases showed focal cortical thickening. Rest of the cases had eccentric cortical contour (Table 4).

3.1.4. Nodal core sign

53 out of 74 (71.6%) cases showed complete nodal core, suggesting presence of both hilum and medulla. 21 out of 74 (28.4%) cases showed absent nodal core suggesting neither hilum nor medulla noted (Table 5).

3.1.5. Perinodal hyperechogenic ring

Most (72 out of 74) cases showed no perinodal hyperechogenic ring, suggesting there is no perinodal soft tissue infiltration. However, its absence did not rule out the lymph node infiltration (Table 6).

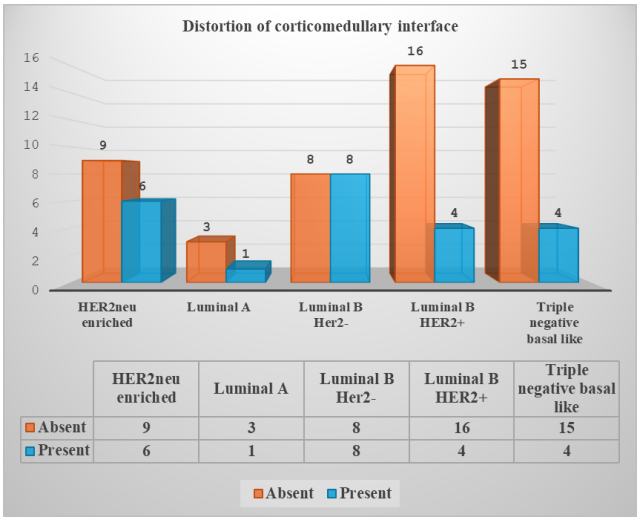
3.2. Imaging features of FNAC positive axillary lymph nodes were evaluated with proven histological subtypes of breast cancer and the results are as follows

3.2.1. Longitudinal axis to short axis ratio (l/s ratio

Of 15 cases with HER2 neu enriched molecular subtype, 13 (86.6%) of cases showed L/S ratio of greater than 2, conveying most of them were of oval morphology. All 4 (100%) cases with Luminal A subtype showed L/S ratio of less than 2, conveying all of them were of rounded morphology. Of 20 cases with Luminal B HER 2 +, 14 (70%) cases showed L/S ratio of less than 2. 11 (68.7%) out of 16 of the Luminal B HER 2 - subtype showed L/S ratio less than 2. 15 (86.6%) of the cases with Triple negative basal like subtype showed L/S ratio of less than 2. Overall 57 out of 74 cases (77%) showed L/S ratio less than 2 suggesting rounded morphology of the lymph node. However, no association between L/S ratio and molecular subtype is noted ($p = 0.346$) (Table 7).

3.2.2. Distortion of corticomedullary interface

Our study revealed, 9 (60%) out of 15 cases showed mainatined corticomedullary interface in most of the HER2 neu enriched subtype. 1 (25%) out of 4 cases showed distortion of corticomedullary interface in Luminal A subtype. 16 (80%) out of 20 cases showed maintained corticomedullary interface in most of the cases of Luminal B HER2+ subtype. 8(50%) out of 16 cases showed distortion of corticomedullary interface in Luminal B HER2- subtype. Most of the cases (78.9%, n=15) showed maintained corticomedullary interface in Triple negative basal like subtype. However, p value was 0.26 suggesting no association between this variable and the molecular subtype of breast cancer (Chart 1).

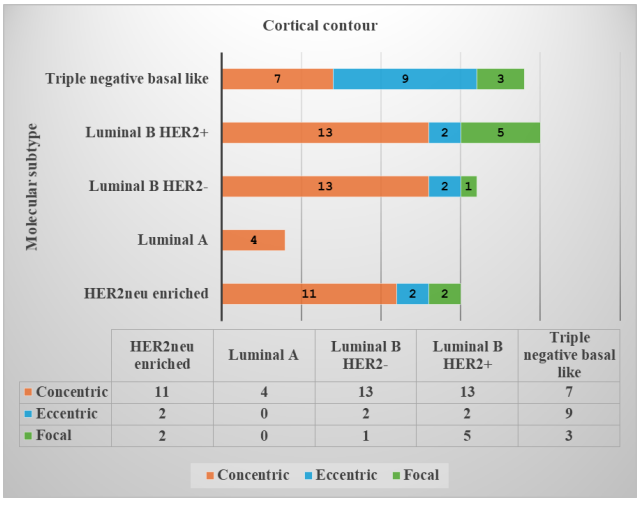


	HER2neu enriched	Luminal A	Luminal B Her2-	Luminal B HER2+	Triple negative basal like
Absent	9	3	8	16	15
Present	6	1	8	4	4

Chart 1: Bar chart showing distortion of corticomedullary interface of a lymph node in our study subjects.

3.2.3. *Cortical contour*

Our study revealed that the concentric pattern is predominant across most molecular types, especially in all 4 (100%) cases with Luminal A subtype and 11 (73.3%) out of 15 cases of HER2 neu enriched subtype, while the eccentric pattern is most common in 9 (47.3%) out of 19 cases with Triple neg basal like subtype. The focal pattern of cortical thickening is notably present in 5 (25%) out of 20 cases of Luminal B HER2+ subtype. There was a significant association between cortical contour and molecular subtype of breast cancer (p = 0.03). (Chart 2)

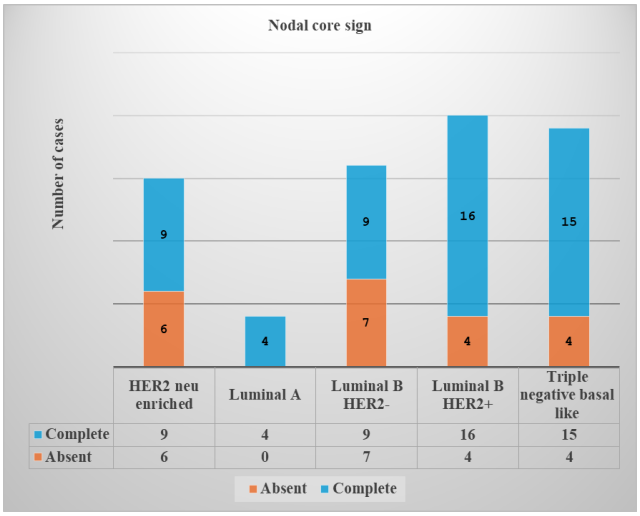


	HER2neu enriched	Luminal A	Luminal B HER2-	Luminal B HER2+	Triple negative basal like
Concentric	11	4	13	13	7
Eccentric	2	0	2	2	9
Focal	2	0	1	5	3

Chart 2: Bar chart showing nodal core sign in our study subjects

3.2.4. *Nodal core sign*

Of 74 cases, 53 (71.6%) cases showed complete nodal core sign suggesting, the hilum and the medulla are present. 21 (28.4%) out of 74 cases showed absent nodal core suggesting neither hilum nor medulla noted. 16 (80%) of 20 cases with Luminal B HER2+ subtype showed complete nodal core sign. 9 (56.2%) out of 16 cases of Luminal B HER2- subtype showed complete nodal core sign. 7 (43.7%) out of 16 cases of Luminal B HER2- subtype showed absent nodal core sign. None (n=0, 0%) of the cases of Luminal A subtype showed absence of nodal core sign. 15 (80%) of 19 cases of Triple negative basal like subtype showed complete nodal core sign. 9 (60%) of 15 cases of HER2 neu enriched subtype showed complete nodal core sign. However, p value was 0.09 suggesting no association between this variable and the molecular subtype of breast cancer. (Chart 3)



	HER2 neu enriched	Luminal A	Luminal B HER2-	Luminal B HER2+	Triple negative basal like
Complete	9	4	9	16	15
Absent	6	0	7	4	4

Chart 3: Bar chart showing nodal core sign in our study subjects

3.2.5. *Perinodal hyperechogenic ring*

1(6.6%) out of 15 cases of HER2 neu enriched subtype and 1 (6.2%) out of 16 cases of Luminal B HER2 – subtype showed perinodal hyperechogenic ring in our study subjects. 72 (97.2%) of 74 cases showed no perinodal hyperechogenic ring (Table 8).

Table 4: Patterns and frequency of cortical contour in our study subjects

Cortical contour	Number of cases	Percentage
Concentric	48	65%
Eccentric	11	15%
Focal	15	20%

Table 1: Number and frequency of molecular subtype of breast cancer in our study subjects

	HER2 neu enriched	Luminal A	Luminal B HER2-	Luminal B HER 2+	Triple negative basal like
Total	15	4	16	20	19
Percentage	20.2%	5.4%	21.6%	27%	25.6%

Table 2: Longitudinal axis to short axis ratio in our study subjects

L/S Ratio	Number of cases	Percentage
<2	57	77%
>2	16	22%

Table 3: Distortion of corticomedullary interface in our study subjects

Distortion of corticomedullary interface	Number of cases	Percentage
Present	23	31%
Absent	51	69%

Table 5: Frequency of nodal core sign in our study subjects

Nodal core sign	Number of cases	Percentage
Complete	53	71.6%
Absent	21	28.4%

Table 6: Frequency of perinodal hyperechogenic ring in our study subjects

Perinodal hyperechogenic ring	Number of cases	Percentage
Present	2	2.7%
Absent	72	97.3%

Table 7: Longitudinal axis to short axis ratio in various molecular subtypes of breast cancer

L/S ratio	HER2 neu enriched	Luminal A	Luminal B HER2-	Luminal B HER 2+	Triple negative basal like
<2	13	4	11	14	15
>2	2	0	5	6	4
Total	15	4	16	20	19

Table 8: Perinodal hyperechogenic ring in various molecular subtypes of breast cancer

	HER2 neu enriched	Luminal A	Luminal B HER2-	Luminal B HER 2+	Triple negative basal like
Present	1	0	1	0	0
Absent	14	4	15	20	19
Total	15	4	16	20	19

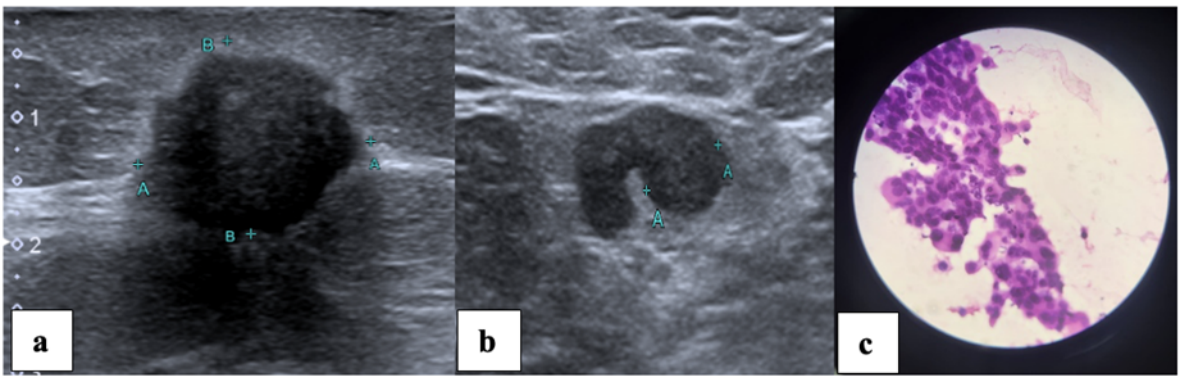


Figure 1: High resolution B mode ultrasound of BI-RADS 5 mass (**a**), and eccentrically thickened lymph node (**b**), with HPE (**c**) of the metastatic lymph node in a case of Luminal A molecular subtype of breast cancer

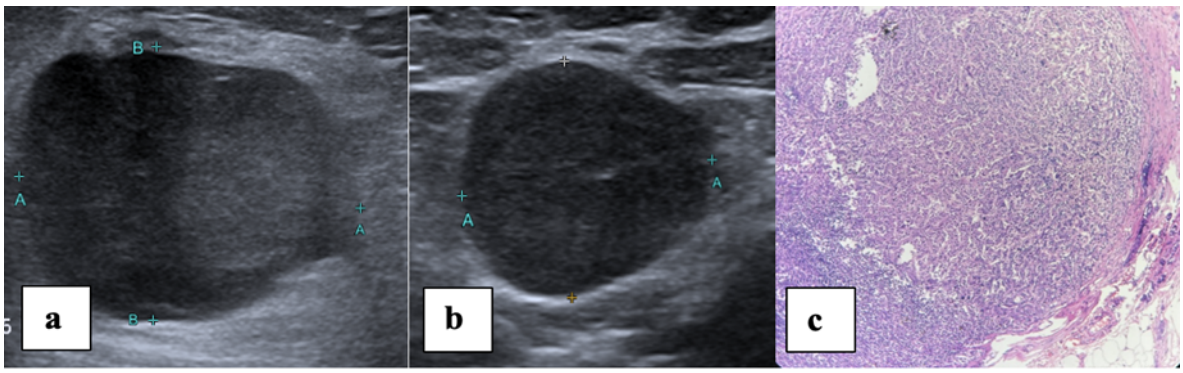


Figure 2: High resolution B mode ultrasound of BI-RADS 4c mass (**a**), and concentrically thickened lymph node with loss of fatty hilum (**b**), with HPE (**c**) of the metastatic lymph node showing metastatic deposit inthe subcapsular space in a case of Triple negative molecular subtype of breast cancer

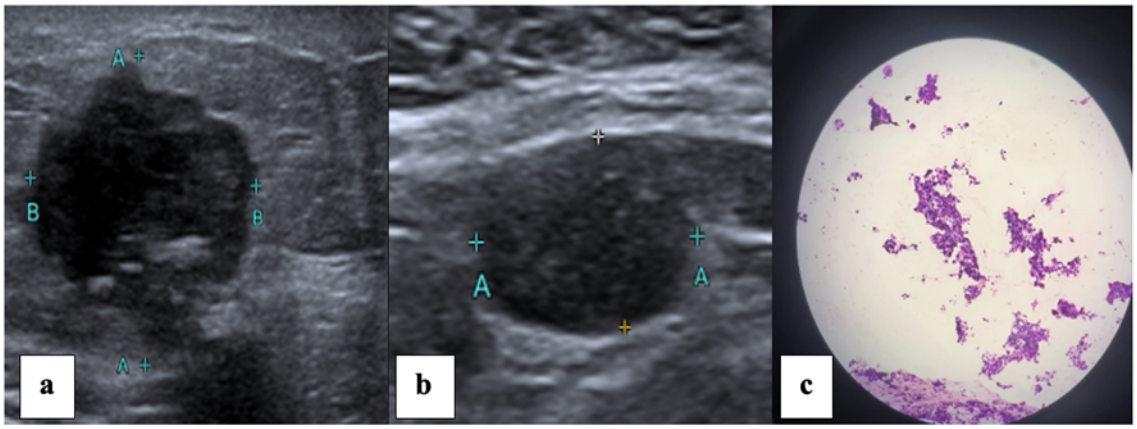


Figure 3: High resolution B mode ultrasound of BI-RADS 5 mass (**a**), and concentrically thickened lymph node with loss of corticomedullary differentiation (**b**), with HPE (**c**) of the metastatic lymph node in a case of HER 2neu enriched molecular subtype of breast cancer

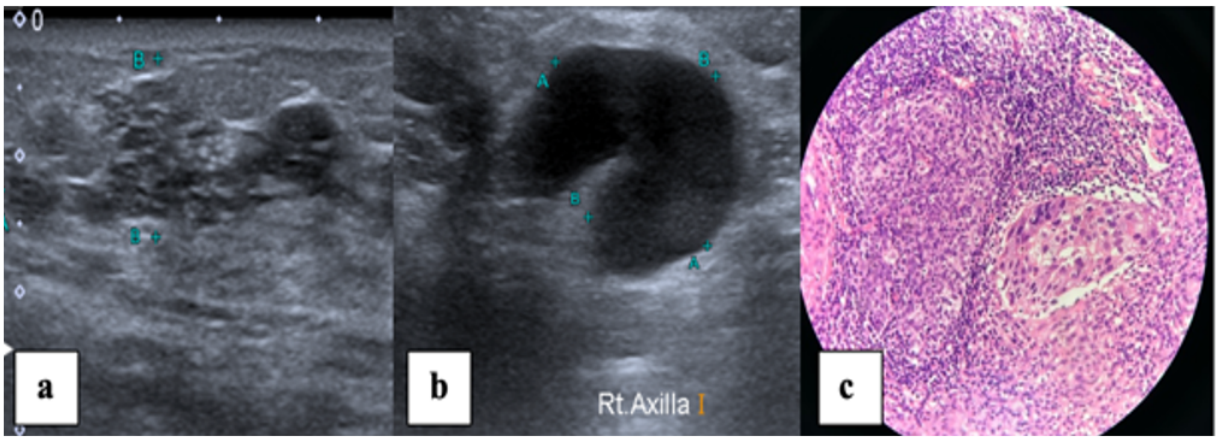


Figure 4: High resolution B mode ultrasound of BI-RADS 4a mass (**a**), and concentrically thickened lymph node (**b**), with HPE (**c**) of the metastatic lymph node showing metastatic deposit in atypical cells forming glandular pattern in subcapsular space in a case of Luminal B HER2 + molecular subtype of breast cancer

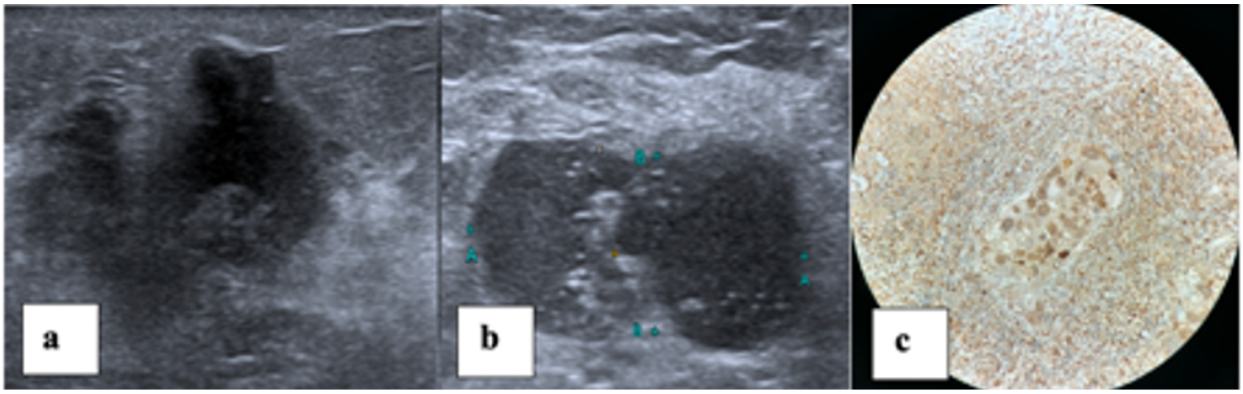


Figure 5: High resolution B mode ultrasound of BI-RADS 5 mass (**a**), and concentrically thickened matted lymph nodes (**b**), with immunohistochemistry showing GATA 3 positive for atypical cells conforming the primary origin from breast carcinoma in a case of Luminal B HER2 - molecular subtype of breast cancer (**c**)

4. Discussion

Ultrasound is the primary modality for imaging nodal involvement in breast cancer patients. In this study, we evaluated the B-mode ultrasound features of suspicious axillary lymph nodes that were confirmed to be metastatic on cytology, in histopathologically proven cases of breast cancer, to determine whether B-mode ultrasound features of axillary lymph nodes vary among different molecular subtypes of breast cancer.[10]

A total of 74 women with confirmed breast cancer and metastatic lymphadenopathy, referred to our department from January 2021 to June 2024, were included in the study. Each patient had complete histopathological and immunohistochemistry information available.

Previous studies, such as those by Alvarez et al., have demonstrated that ultrasound (US) has a sensitivity of 49%-87% and specificity of 55%-97% based on lymph node size, with 26%-76% sensitivity and 88%-98% specificity when using morphological criteria alone.[1] In our study, we evaluated specific lymph node variables beyond the commonly assessed long axis to short axis (L/S) ratio, including cortical thickness, nodal core sign, abnormal cortical contour, and others. Each of the variable was correlated with molecular subtypes of breast cancer to identify subtype-specific patterns.

In cases with suspicious axillary lymph nodes on ultrasound, histopathological confirmation was obtained via core biopsy or fine needle aspiration cytology (FNA). Our study demonstrated that FNA was generally used to confirm suspicious features, particularly where core biopsy posed challenges, while the choice between the two depended on clinical and technical considerations. This approach aligns with findings by Pamilo et al., who noted increased ultrasound specificity when coupled with FNA.[2]

The study assessed suspicious lymph node morphology on ultrasound imaging based on five variables, exploring their association with molecular subtypes of breast cancer.

L/S ratio: 77% of cases (57/74) had an L/S ratio below 2, indicating round lymph nodes. All cases of Luminal A subtype and the majority of Triple-negative basal and Luminal B HER2+ subtypes exhibited this morphology, although no significant association was found ($p = 0.346$).

Corticomedullary interface distortion: Distortion was absent in 68.9% of cases, particularly among HER2 neu-enriched subtypes. However, no significant association with molecular subtypes was observed.

Cortical Contour: Concentric thickening was predominant in Luminal A and HER2 neu-enriched subtypes, while eccentric thickening was seen mainly in Triple-negative basal cases. This finding was statistically significant ($p = 0.03$), with Nariya Cho et al. supporting that eccentric thickening typically indicates malignancy.[11]

Nodal core sign: Complete nodal core was present in 71.6% of cases, especially within Triple-negative basal, Luminal B HER2+, and Luminal A subtypes. In Luminal B HER2- and HER2 neu-enriched subtypes, nodal core presence varied, with no significant association noted.

Perinodal hyperechogenic ring: This feature was rare, with only two cases each in HER2 neu-enriched and Luminal B HER2- subtypes showing this sign.

For patients with triple-negative basal breast cancer, a subset characterized by aggressive progression and limited treatment options, ultrasound findings often included eccentric cortical thickening. The role of histopathology was essential in further defining this group, with immunohistochemical analysis - including CD4+ and CD8+ T-cell evaluation, as recommended by Jagtap et al. supporting prognosis and therapeutic strategies.[12] Studies suggest that immune markers such as CD4+ and CD8+ T-cells can play a role in prognostication and potentially influence treatment decisions.

Histopathological analysis of triple-negative basal cancers revealed aggressive tumor behavior and high-grade

features. The absence of hormone receptors and HER2 expression limits targeted therapy options, underscoring the importance of adjunct markers like CD4+ and CD8+ T-cells for prognostication and therapeutic potential. Our study's findings align with Gábor et al., who emphasized that nodal involvement remains a key prognostic indicator in breast cancer. For such cases, evaluation of CD4+ and CD8+ T-cell levels could contribute to targeted immune-based therapies in the future. [13]

This study underscores the critical clinical implications of detailed axillary nodal assessment in breast cancer patients, emphasizing the value of ultrasound in preoperative staging and guiding therapeutic decisions. The detection of axillary nodal metastasis in 61.5% of cases aligns with findings from previous studies, such as Jagtap et al., [12] which highlight the frequent nodal involvement, particularly in aggressive variants like invasive lobular carcinoma (pleomorphic type) that often present with nodal metastasis. Accurate axillary staging is essential, as nodal status remains a strong prognostic factor influencing treatment outcomes. Given that our study observed a sensitivity of 87% and specificity ranging from 53-97% for ultrasound in detecting metastatic lymphadenopathy, integrating advanced techniques such as contrast-enhanced ultrasound (CEUS) or elastography could potentially enhance diagnostic accuracy by better differentiating benign from malignant nodes. These advanced imaging techniques could refine morphological evaluation, thus improving early detection and prognostication in breast cancer. [14,15]

5. Future Directions

Our study highlighted that cortical contour abnormalities in axillary lymph nodes on ultrasound imaging correlated significantly with molecular subtypes, a novel finding that suggests potential for subtype-specific imaging biomarkers. However, given the small sample size, further research is warranted to substantiate these associations.

6. Conclusion

Ultrasound imaging of the proven metastatic axillary lymph nodes plays an important role in planning initial surgery or neoadjuvant chemotherapy and guiding axillary management. Knowledge of various parameters of a suspicious lymph node on ultrasound imaging, plays an important role in identifying metastatic disease and guides further in planning FNA to rule out metastatic disease. In women, with histopatologically proven breast cancer, round morphology of the lymph node predominates across all molecular subtypes of breast cancer, with cortical thickening more than 3 mm. In our study, we have analyzed most specific imaging features - L/S ratio, distortion of corticomedullary interface, abnormal cortical contour, nodal core sign and perinodal hyperechogenic ring. The concentric cortical thickening is predominant across most molecular types, especially in all cases with Luminal A subtype and HER2 neu enriched subtype, while the eccentric pattern is most common with Triple negative basal like subtype. The focal pattern of cortical thickening is chiefly present in cases with Luminal B HER2+ subtype. Most of the cases showed long axis to short axis ratio <2, suggesting round shape of the lymph node. Hence, if suspicion for axillary lymph node metastasis is present in any one of the variables, it should raise a possibility for metastatic disease and it is crucial that all these patients should undergo ultrasound guided FNA. The study concluded that there was significant association between the cortical contour and the molecular subtype of breast cancer.

7. Ethical Approval

This Study was conducted after taking approval from the institute ethical committee with ref. no. CSP-MED/23/JAN/83/26.

8. Source of Funding

Nil.

9. Conflict of Interest

Nil.

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