Original Article

Immune hyperplasia patterns in lymph nodes draining breast cancer: A correlation with histomorphological parameters

Sheena Khetarpal, S. K. Mathur, Divya Sethi, Rajeev Sen

Department of Pathology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

ABSTRACT

Background: Lymph nodes serve as site of immunologic expansion of lymphocyte populations. Enlargement of nodes may be caused by spread and growth of cancer cells or it can be due to reactive hyperplasia of lymph nodes. **Aim:** To study the pattern of reaction in involved and uninvolved lymph nodes draining breast carcinoma and correlate different patterns of hyperplasia with other morphological parameters in modified radical mastectomy (MRM) specimens. **Material and Methods:** Histopathological examination of 734 lymph nodes isolated from MRM specimens over a period of 2 years was performed on routine microsections. **Results:** Mixed pattern of hyperplasia was the most widespread followed by the diffuse pattern, the follicular hyperplasia, sinus histiocytosis, and paracortical hyperplasia in decreasing order. Follicular hyperplasia was seen in 23.44% of the ductal carcinomas and 36.36% of the malignant phylloides tumor. Sinus histiocytosis was seen in 23.53% of the metaplastic carcinomas, 22.22% of the medullary carcinomas with a decline to 12.10% amongst the ductal carcinomas. However, mixed pattern of hyperplasia was seen in 28.57% of the papillary carcinomas, 26.31% of the lobular and 27.41% of the ductal carcinomas. The incidence of sinus histiocytosis increased from 10.96 to 23.68% with the grade of tumor. There was a decline in the incidence of sinus histiocytosis, paracortical hyperplasia with the increase in the size of the tumor. **Conclusions:** The assessment of the reactive behavior of lymph nodes serves as an indicator to the histologic immunostaging of malignant tumors. This data indicate that the lymph node reaction to cancer and their incidence and prognostic significance may vary depending upon the stage and type of tumor.

Key words: Ductal carcinoma, hyperplasia, sinus histiocytosis

INTRODUCTION

Breast carcinoma is the second most common type of cancer after lung cancer worldwide (10.4% of all cancer incidence, both sexes counted) and the fifth most common cause of death due to cancer.[1] Peak incidence of breast cancer is seen in 45-60 years of age and is rare in patients younger than 25 years and above 80 years of age.[2] Lymph nodes are the most common site of metastatic malignancy and sometimes constitute the first clinical manifestation of the disease. Lymph nodes constitute a substantial component of the immune system strategically located in various areas of the body. Lymph nodes serve as areas of antigen retention and a site of immunologic education and expansion of lymphocyte populations. They also represent a site where differentiation of plasma cells or immunoglobulin secreting cells takes place, and they are thus major organs of antibody synthesis and secretion. Lymph nodes are also considered the site in which tumor-specific T cells are located, where their numbers and phenotype correlate to tumor prognosis.[3]

Breast carcinoma is now considered to be a systemic disease even at the time of detection and treatment is directed to both local control and eradication of occult systemic micrometastasis. In many cases, the regional nodes serve as effective barriers to further dissemination of tumor, at least for a time. Conceivably the cells, after being arrested within the node, may be destroyed by a tumor specific immune response. Drainage of tumor cell debris or tumor antigens or both, also indicate reactive changes within the nodes. Thus enlargement of nodes may be caused by

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Address for correspondence: Dr. Sheena Khetarpal, Department of Pathology, Post Graduate Institute of Medical Sciences, Rohtak - 124 001, Haryana, India. E-mail: sheenakhetarpal@yahoo.com

spread and growth of cancer cells or reactive hyperplasia of lymph nodes. Therefore, nodal enlargement in proximity to a cancer does not necessarily mean dissemination of the primary lesion.[3] In this study pattern of reaction in the involved and uninvolved lymph nodes draining breast carcinoma was evaluated. Different patterns of hyperplasia with other morphological parameters such as size of the tumor, histological type of the tumor, histologic grade of the tumor, Nottingham Prognostic Index (NPI) of the modified radical mastectomy (MRM) specimen were correlated.

MATERIALS AND METHODS

The study was conducted over 734 lymph nodes isolated from 50 MRM specimens over a 2 year period submitted for histopathological examination. After gross examination of the specimens and proper sampling, the tissues were processed by routine histological technique for paraffin embedding and sectioning at 4 μm thickness. Histopathological diagnosis was established on routine hematoxylin and eosin (H and E) staining of the sections. Special histochemical stains like reticulin stain, periodic acid-Schiff (PAS), Van-Gieson's, toluidine blue wherever necessary were also applied as per the standard techniques.

The H and E stained sections were systematically examined and the pattern of reaction in the lymph nodes was studied with regard to the size of tumor, histological type of tumor, grade of tumor, and size of lymph nodes. Also, granulomatous foci, hyalinization, and amyloid changes as well as metastases in the nodes were noted. Histological grading of the tumor was done according to Nottingham modification of Bloom-Richardson score.[4]

OBSERVATION AND RESULTS

Forty-two percent (21 cases) of the patients examined belonged to the age group of 41-50 years. Only 6% (three cases) of the patients were above the age of 70 years. Eighteen percent (nine cases) were in the age group of 31-40 years and 16% (eight cases) in the age group of 51-60 years. The youngest patient was 26-year-old and the oldest was 80-year-old. Only one (2%) case was from a 70-year-old male patient who presented with ductal carcinoma of the breast.

Fifty-four percent (27) of the cases had metastatic deposits in lymph nodes draining the breast cancer, whereas 46% (23) of the cases had lymph nodes revealing reactive hyperplasia. Of the 734 lymph nodes isolated, reactive hyperplasia was seen in 87.6% (643) of the lymph nodes while 12.39% (91) showed metastatic deposits. Out of the 643 reactive lymph nodes, 25.74% (189) had mixed pattern and 25.34% (186) had diffuse pattern of hyperplasia. Sinus histiocytosis was seen in 12.39% (91) lymph nodes. Follicular hyperplasia comprised 23.70% (174) and paracortical hyperplasia comprised 0.40% (three) lymph nodes [Table 1].

Ductal carcinoma was the most commonly isolated tumor constituting 68% (34) of the cases, with medullary comprising only 10% (five) of the cases. Metaplastic and malignant phylloides constituted only 2% (one) of the cases. Eight percent (four) of the cases identified belonged to the category of lobular carcinomas. Mucinous and papillary constituted 6% (three) and 4% (2) of the cases, respectively. Thirty-two percent (16) of the ductal carcinomas patients were node negative and 36% (18) were node positive cases. Medullary carcinoma constituted 10% (five) of the cases, with 6% (three) node negative and 4% (two) node positive cases. Six percent (three) of the lobular carcinoma patients showed metastatic deposits in lymph nodes. All the cases identified with papillary carcinoma had metastatic deposits in lymph nodes. Both metaplastic carcinoma and malignant phylloides was node negative.

Of the 529 lymph nodes isolated from ductal carcinoma, 91.3% (483) revealed reactive hyperplasia with 27.78% (147) and 27.41% (145) being constituted by diffuse and mixed pattern of hyperplasia, respectively; whereas only 23.44% (124) revealed follicular hyperplasia. Sinus histiocytosis comprised only 12.01% (64) and paracortical hyperplasia was seen in only 0.56% (three). However, 8.69% (46) of the lymph nodes isolated from ductal carcinoma showed metastatic deposits. Fifty-seven lymph nodes isolated form lobular carcinoma were studied. Reactive hyperplasia was seen in 59.64% (34) and 40.35% (23) showed metastatic deposits. Of these, 26.31% (15) of the lymph nodes showed mixed pattern of hyperplasia and 14.03% (eight) showed follicular hyperplasia. Of the lymph nodes isolated from malignant phylloides tumor, diffuse pattern of hyperplasia was the commonest and amongst the lymph nodes draining metaplastic carcinomas, follicular hyperplasia and mixed pattern constituted 29.41%. Of the lymph nodes isolated from medullary carcinoma; 92.59% (50) were negative for metastasis, whereas only 7.40% (four) of them showed metastatic deposits. Amongst the lymph nodes isolated from mucinous carcinoma, 28.94% (11) showed follicular

Table 1: Distribution of lymph nodes according to the pattern of hyperplasia in reactive lymph nodes

Number of lymph nodes	Pattern of hyperplasia in reactive lymph nodes									
	FH		SH		PCH		Mixed		Diffuse	
	No.	%	No.	%	No.	%	No.	%	No.	%
734	174	23.70	91	12.39	3	0.40	189	25.74	186	5.34

FH: Follicular hyperplasia, SH: Sinus histiocytosis, PCH: Paracortical hyperplasia

hyperplasia. For the papillary carcinomas, lymph nodes revealed follicular hyperplasia and mixed patterns in 28.57% (eight) each [Table 2, Figures 1-5].

Of the metastatic lymph nodes isolated from mucinous carcinoma; 31.58% (12) showed mixed pattern of hyperplasia, whereas amongst ductal carcinomas only 4.53% (24) of the metastatic lymph nodes revealed mixed pattern of hyperplasia. Sinus histiocytosis was seen in 3.50% (two) lymph nodes of the lobular and 1.13% (six) lymph nodes isolated from the ductal carcinomas [Figures 6-9].

Seventy-six percent of the tumors (38) studied were of grade II which belongs to the category of moderately differentiated tumors according to the Modified Bloom

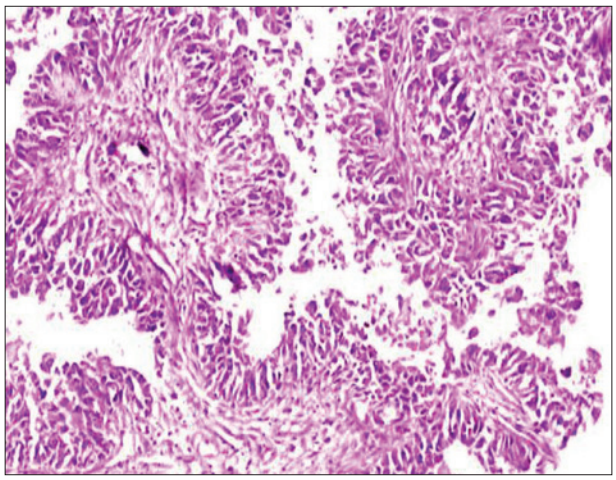

Figure 1: Photomicrograph of papillary carcinoma breast (H and E, ×200)

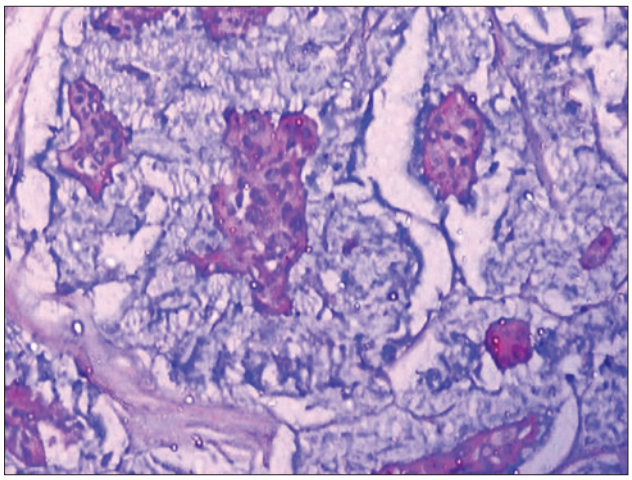

Figure 2: Photomicrograph of mucinous carcinoma breast (H and E, ×200)

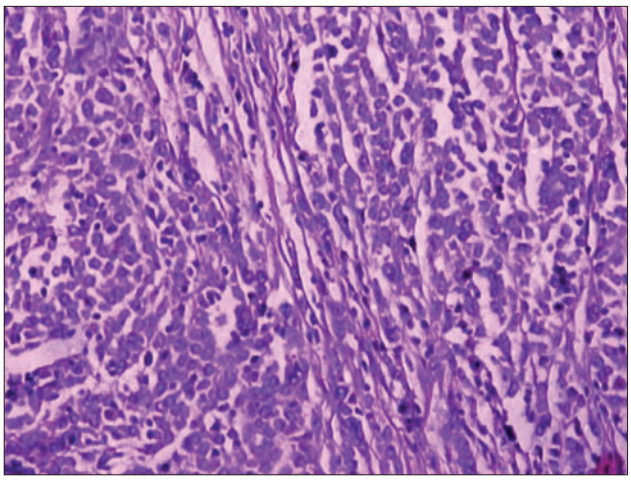

Figure 3: Photomicrograph of lobular carcinoma breast (H and E, ×200)

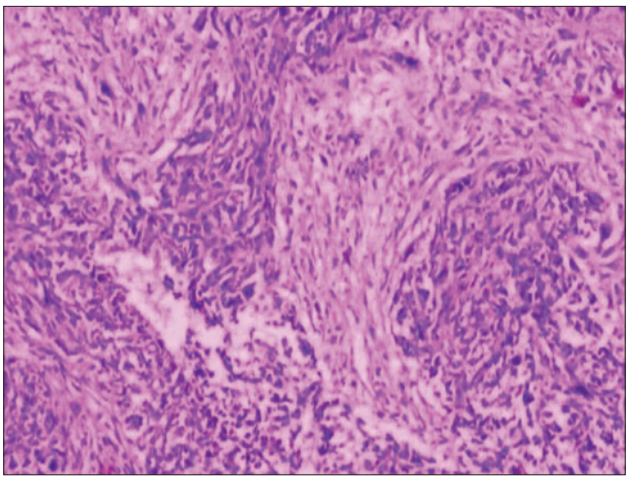

Figure 4: Photomicrograph of metaplastic carcinoma breast (H and E, ×100)

Table 2: Hyperplasia patterns in reactive lymph nodes classified according to the various histologic types of the tumor

Histologic type of the tumor	Number of lymph nodes	Pattern of hyperplasia in reactive lymph nodes									
		FH		SH		PCH		Mixed		Diffuse	
		No.	%	No.	%	No.	%	No.	%	No.	%
Lobular	57	8	14.03	3	5.26	0	0	15	26.31	8	14.03
Medullary	54	14	25.92	12	22.22	0	0	13	24.07	11	20.37
Metaplastic	17	5	29.41	4	23.53	0	0	5	29.41	3	17.64
Mucinous	38	11	28.94	4	10.52	0	0	2	5.26	7	18.42
Ductal	529	124	23.44	64	12.10	3	0.56	145	27.41	147	27.78
Papillary	28	8	28.57	4	14.28	0	0	8	28.57	4	14.28
Malignant phylloides	11	4	36.36	0	0	0	0	1	9.09	6	54.54
Total	734	174	23.70	91	12.39	3	0.40	189	25.74	186	25.34

FH: Follicular hyperplasia, SH: Sinus histiocytosis, PCH: Paracortical hyperplasia

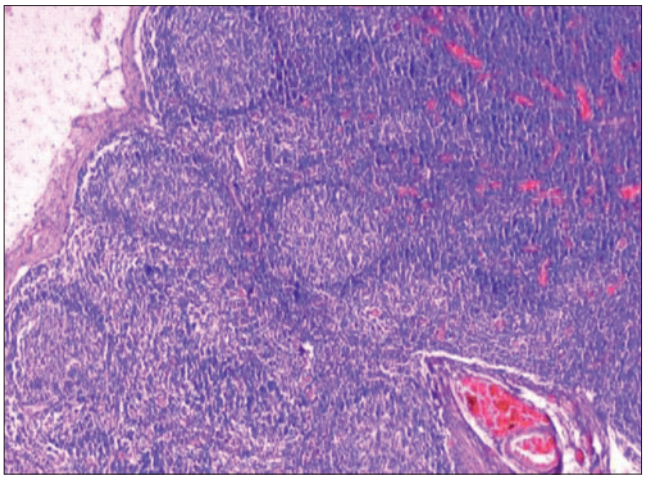

Figure 5: Photomicrograph of follicular hyperplasia; lymph node (H and E, ×100)

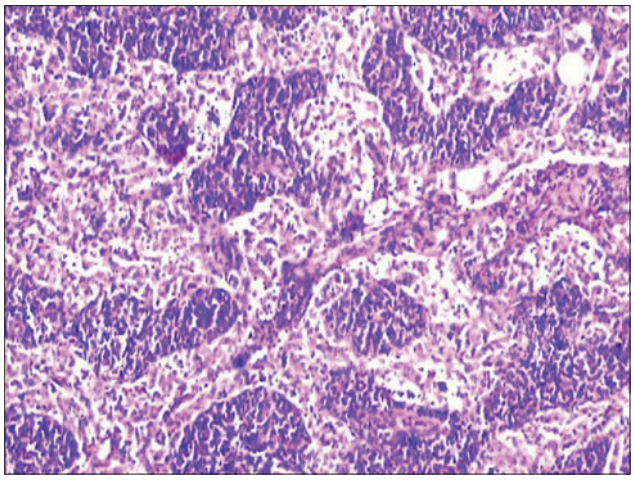

Figure 6: Photomicrograph of sinus histiocytosis; lymph node (H and E, ×200)

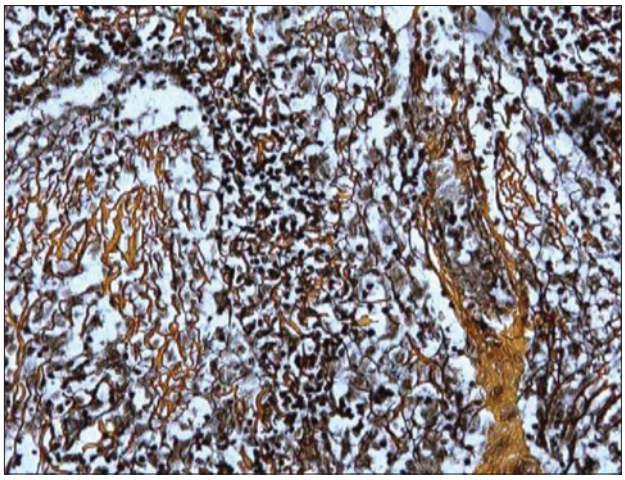

Figure 7: Photomicrograph of sinus histiocytosis; lymph node (reticulin stain (RETIC), ×200)

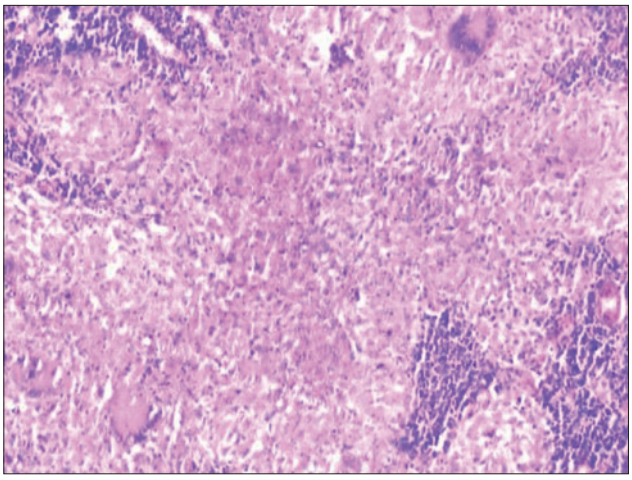

Figure 8: Photomicrograph showing granulomatous reaction in a lymph node draining carcinoma breast (H and E, ×100)

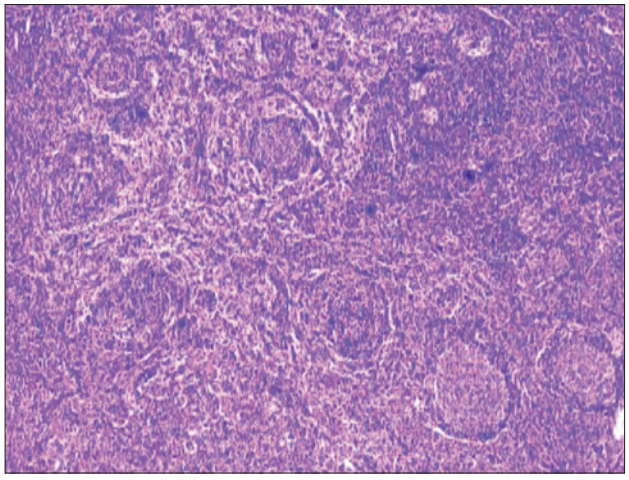

Figure 9: Photomicrograph of mixed pattern of hyperplasia (follicular hyperplasia + sinus histiocytosis); lymph node (H and E, ×100)

Richardson Score. Grade I tumors constituted 18% (nine) and only 6% (three) of the cases were poorly differentiated, that is, grade-III.

Thirty-six percent (18) of the moderately differentiated tumors (grade II) were node negative, whereas 40% (20) of these were node positive. Of the grade III tumors; 4% (two) were node positive, whereas only 2% (one) were negative for metastasis. Ten percent (five) of the node positive tumors belonged to grade I.

Seven hundred and thirty-four lymph nodes were isolated from 50 MRM specimens. Of these; 155 lymph nodes isolated were associated with grade I tumors, 87.74% (136) of which revealed reactive hyperplasia. Of these, 31.61% (49) of the lymph nodes revealed diffuse pattern of hyperplasia and 25.80% (40) showed follicular hyperplasia. Five hundred and forty-one lymph nodes were isolated from grade II tumors and 87.24% (472) of these tumors revealed reactive hyperplasia and 12.75% (69) had metastatic deposits. Of the 541 lymph nodes isolated from grade II tumors; 27.54% (149) revealed mixed pattern of hyperplasia, whereas diffuse pattern and follicular hyperplasia comprised 24.58% (133) and 22.92% (124), respectively. Of the 38 lymph nodes

isolated in the grade III category, 7.89% (three) of the lymph nodes showed metastatic deposits. Sinus histiocytosis was seen in 23.68% (nine) of the grade III tumors [Table 3].

Amongst the metastatic lymph nodes, mixed pattern of hyperplasia was seen in 22.69% (32) and diffuse pattern was seen in 5.36% (29) of the metastatic lymph nodes isolated from the grade II tumors. Amongst the grade I tumors; 6.45% (ten) and 2.58% (four) of the metastatic lymph nodes revealed mixed and diffuse pattern of hyperplasia, respectively. Mixed pattern was revealed by 5.26% (two) and diffuse pattern by 2.63% (one) of the metastatic lymph nodes isolated from the grade III tumors.

Seventy-four percent (37 cases) of the MRM specimens had tumor measuring in the range 2-5 cm, whereas only 6% (three) of the tumors measured more than 5 cm and 20% (ten) of the tumors measured less than 2 cm. There was an increase in the number of node positive cases with increase in the size of tumor. Thirty-four percent (17) of the node negative cases and 40% (20) of node positive cases were in the range of 2-5 cm. For tumors measuring less than 2 cm, node positive cases comprised 6% (three) and node negative cases were 14% (seven). Amongst tumors measuring more than 5 cm; 2% (one) were node negative, whereas 4% (two) were node positive.

With increase in the size of tumor, there was a decline in percentage of the reactive lymph nodes. Five hundred and seventy lymph nodes isolated were associated with tumors of the size 2-5 cm. Of these, 85.96% (490) lymph nodes had reactive hyperplasia and 14.04% (80) were positive for metastatic deposits. Out of 137 lymph nodes isolated from tumors measuring less than 2 cm; 96.3% (132) revealed reactive hyperplasia, whereas only 3.65% (5) had metastatic deposits. Amongst the tumors measuring more than 5 cm, reactive hyperplasia was revealed by only 77.77% (21). Reaction pattern in lymph nodes according to the tumor size, wherein 30.65% (42) of the lymph nodes with diffuse pattern of hyperplasia and 22.62% (31) with follicular hyperplasia were associated with tumors measuring less than 2 cm. Mixed pattern of hyperplasia comprised 27.01% (154) and follicular 23.68% (135) in tumors which measured in the range of 2-5 cm. For tumors measuring more than 5 cm, diffuse pattern was seen in 40.74% (11) of the lymph nodes and follicular hyperplasia in 29.62% (eight) of the lymph nodes [Table 4].

Mixed pattern of hyperplasia was seen in 11.11% (three) of the metastatic lymph nodes isolated from tumors measuring more than 5 cm in size. Of the metastatic lymph nodes in the range 2-5 cm size, 1.05% (six) revealed sinus histiocytosis and 3.70% (one) revealed sinus histiocytosis from metastatic lymph nodes isolated from tumors measuring more than 5 cm. Follicular hyperplasia and sinus histiocytosis was seen in 0.73% (one) of the lymph nodes isolated from tumors measuring less than 2 cm.

Maximum number of cases belonged to the intermediate prognostic group, 60% (30 cases). Sixteen percent of the cases were in the good prognostic group and 4% in the poor prognostic group, according to NPI.

Amongst the tumors in the intermediate prognostic group, 46% (23) were negative for metastasis and 14% (7) had metastatic deposits. Thirty percent (15) of the node positive cases and 2% (one) of the node negative cases were in the good prognostic group. However, 6% (three) of the node

Table 3: Hyperplasia patterns in reactive lymph nodes classified according to the various MRB grades of the tumor

MRB grade	Pattern of hyperplasia in reactive lymph nodes										
	No. of lymph nodes	FH		SH		PCH		Mixed		Diffuse	
		No.	%	No.	%	No.	%	No.	%	No.	%
Grade I	155	40	25.80	17	10.96	1	0.64	29	18.7	49	31.61
Grade II	541	124	22.92	65	12.01	1	0.18	149	27.54	133	24.58
Grade III	38	10	26.31	9	23.68	18	2.63	11	28.94	4	10.52
Total	734	174	23.70	91	12.39	3	0.40	189	25.74	186	25.34

FH: Follicular hyperplasia, SH: Sinus histiocytosis, PCH: Paracortical hyperplasia

Table 4: Hyperplasia patterns in reactive lymph nodes classified according to the size of the tumor

Size of tumor	Pattern of hyperplasia in reactive lymph nodes										
	Number of lymph nodes	FH		SH		PCH		Mixed		Diffuse	
		No.	%	No.	%	No.	%	No.	%	No.	%
<2 cm	137	31	22.62	24	17.51	2	1.45	33	24.08	42	30.65
2-5 cm	570	135	23.68	67	11.75	1	0.17	154	27.01	133	23.33
>5 cm	27	8	29.62	0	0	0	0	2	7.40	11	40.74
Total	734	174	23.70	91	12.39	3	0.40	189	25.74	186	25.34

FH: Follicular hyperplasia, SH: Sinus histiocytosis, PCH: Paracortical hyperplasia

negative cases and 2% (one) of the node positive cases belonged to the poor prognostic group.

Four hundred and ten lymph nodes were isolated from tumors in the intermediate prognostic group. Of these, 82.92% (340) revealed reactive hyperplasia and 17.07% (70) had metastatic deposits. Two hundred and sixty-six lymph nodes were isolated from tumors in the good prognostic group with reactive hyperplasia being revealed by 99.62% (265) lymph nodes and metastatic deposits in only 0.37% (one) lymph nodes. From tumors in the poor prognostic group, 65.51% (38) had reactive hyperplasia and 34.48% (20) had metastatic deposits. In the intermediate prognostic group, 22.92% (94) of the lymph nodes revealed follicular hyperplasia and 25.36% (104) of the lymph nodes showed mixed pattern of hyperplasia. Good prognostic group revealed diffuse pattern in 31.20% (83), mixed pattern in 27.06% (72), and follicular pattern in 26.69% (71) of the lymph nodes. Amongst the lymph nodes isolated from the poor prognostic group, 22.41% (13) of the lymph nodes revealed mixed pattern of hyperplasia [Table 5].

Of the 91 metastatic lymph nodes, 17.24% (ten) lymph nodes of the poor prognostic group were associated with mixed pattern of hyperplasia and 10.34% (six) showed a diffuse pattern. In the intermediate prognostic group; 8.29% (34) revealed mixed pattern, 6.83% (28) showed diffuse pattern, and 1.46% (six) showed sinus histiocytosis. Only one (0.37%) lymph node isolated from the tumor in the good prognostic group revealed follicular hyperplasia.

This suggests that with increase in the NPI of the tumor number of reactive lymph nodes declined, whereas there was an increase in the number of metastatic lymph nodes.

Out of 734 lymph nodes isolated, 643 revealed reactive hyperplasia and 0.27% (two) of these showed a granulomatous response.

DISCUSSION

The current overall 5-year survival for breast carcinoma is 60% for clinically localized disease and 34% for regional disease. These figures can be modified by a variety of clinical and pathologic factors.[5]

Prognostic indicators serve as guides for clinical decisions and estimates of outcome. Clinical follow-up studies have repeatedly demonstrated that features such as axillary lymph node status, histologic grade, histologic type, and lymphatic vessel invasion present powerful and independent prognostic indicators. Tumor size is a much weaker independent factor, but is strongly tied to other factors such as lymph node status and grade.[6] Axillary lymph node status is the single most important prognostic factor for patients with breast cancer and disease free survival, and the overall survival decreases as the number of positive lymph nodes increases.[6]

The diameter of the primary tumor is a sensitive indicator of prognosis, second only to the presence of nodal metastases in importance, and it is a prominent anatomic feature in staging.[7] With increase in the size of tumor, there was an increase in the number of metastatic lymph nodes and a decline in the number of reactive lymph nodes.

According to a study conducted by Silverberg *et al.*, the incidence of sinus histiocytosis was virtually constant (approximately 30%) for all tumor with diameters up to 6.5 cm.[8] This figure fell to 18.5% in cases in which tumor measured 6.5 cm or greater. In our study also, the incidence of sinus histiocytosis declines with increase in the size of tumor. However, this is in contrast to a study conducted by Hartveit who observed that the incidence of sinus histiocytosis increases with the tumor size.[9]

Breast carcinoma presents in a great variety of histological patterns, including specific types which have useful clinical correlates and prognostic implications. A few special histologic types of invasive carcinoma pose a lesser risk of dissemination and death than do other types. These favorable forms are pure mucinous, pure medullary, and pure papillary carcinomas.[10]

The incidence of ductal carcinomas was the highest in this study. This is in agreement with the study conducted by Silverberg *et al.*, in a series of 366 modified radical

Table 5: Hyperplasia patterns in reactive lymph nodes classified according to the Nottingham prognostic index of the tumor

Prognostic index	Pattern of hyperplasia in reactive lymph nodes										
	No. of lymph nodes	FH		SH		PCH		Mixed		Diffuse	
		No.	%	No.	%	No.	%	No.	%	No.	%
Good	266	71	26.69	37	13.91	2	0.75	72	27.06	83	31.20
Intermediate	410	94	22.92	48	11.71	1	0.24	104	25.36	93	22.68
Poor	58	9	15.51	6	10.34	0	0	13	22.41	10	17.24
Total	734	174	23.70	91	12.39	3	0.40	189	25.75	186	25.34

FH: Follicular hyperplasia, SH: Sinus histiocytosis, PCH: Paracortical hyperplasia

mastectomies, wherein the predominant histological type was the infiltrating ductal carcinomas.[8]

Histologic grade of the tumor is an independent prognostic factor in patients with breast cancer. Higher grade of distant metastases and poorer survival in patients is associated with higher grade (poorly differentiated) tumors, independent of lymph node status, and tumor size. Histologic grade is found to increase with tumor size and advancing anatomic stage.[11] Poor histologic grade and nuclear grade may indicate responsiveness to adjuvant chemotherapy. Adjuvant chemotherapy produces a greater improvement in prognosis among node-positive and node-negative patients with poorly differentiated tumors.[7]

According to this study, incidence of sinus histiocytosis increases with increase in the grade of tumor. However, Wartman in 1959 suggested that higher grade of malignancy is associated with decreased frequency of sinus cell hyperplasia.[12]

According to a study conducted by Silverberg *et al*., the incidence of sinus histiocytosis is inversely related to tumor grade. Although only the difference between Grade I and III was statistically significant ($P < 0.05$).[8]

The NPI, based on histopathologic evaluation of tumor size, histologic grade, and lymph node stage, is a powerful and reproducible method of assessing prognosis. The higher the value for NPI, the worse the prognosis.[13] With the increase in the NPI of tumor, there was an increase in the incidence of metastatic lymph nodes.

The present study, wherein the pattern of hyperplasia is correlated with NPI of the tumor, helps in predicting the prognosis of patient. Predicted 15-year survival for patients in good prognostic group is 80%, whereas for those in the moderate prognostic group is 42% and is 13% for patients in the poor prognostic group.[13]

Microscopic appearance of regional lymph nodes is an indication of the type of host response to the tumor and it relates to the prognosis of patient.[4] The morphologic appearance of hyperplasia varies even if the stimulating agent is same, depending on the age of patient, past experience with the offending agent, time period following exposure to the stimulus, and the duration of exposure.[14]

Mixed pattern was the most frequently encountered pattern. This by and large comprised of follicular hyperplasia in combination with sinus histiocytosis. This was followed by diffuse pattern and follicular hyperplasia. Isolated sinus histiocytosis was also seen in reactive lymph nodes. This is in concordance with the study conducted by Wartman in 1959 suggesting that patients without metastases in the nodes showed sinus cell hyperplasia more frequently than the patients with metastases.[12] This was also proved by Hirschl *et al*., and Hartveit who found that the sinus histiocytosis positive response was most common in patients without lymph node metastasis.[9,15] In this study, the frequency of sinus histiocytosis was highest in metaplastic carcinomas followed by medullary carcinomas and then papillary carcinomas. However, Silverberg *et al*., observed that the incidence of sinus histiocytosis was highest with colloid carcinoma (38.1%) and in 30% cases it was associated with infiltrating lobular carcinoma.[8] Although this is in concordance with the study conducted by Culter *et al*., wherein the incidence of sinus histiocytosis was the highest in medullary carcinomas followed by papillary carcinomas.[16]

Sinus histiocytosis is a reactive change in the tissue of host and is associated with increased survival. It is termed as an expression of host resistance. The prominent role of the macrophage in both humoral and cell-mediated immune reactions supports the interpretation of sinus histiocytosis as an immune defense mechanism.

Out of the 734 lymph nodes isolated from 50 MRM specimens, 0.27% (two) of the reactive lymph nodes revealed a granulomatous reaction. This is in concordance with the case reported by Santini *et al*., who reported a case of invasive breast carcinoma with a granulomatous response in both breast carcinoma and axillary lymph node and deposition of stromal amyloid.[17] Sethi and Carter also described two cases of breast carcinoma with necrotic granulomas in axillary lymph nodes.[18] Coyne conducted a study wherein he described four such cases, one involving the tumor stroma and three draining lymph nodes. Noncaseating epithelioid granulomas were seen in lymph nodes draining carcinomas and less commonly within stroma of carcinomas.[19] Bhatia *et al*., concluded that carcinoma specially arising from breast, stomach, colon, and larynx can be associated with granulomatous response in the draining lymph nodes and should be included in the list of differential diagnosis of causes of granulomatous inflammation.[20]

A comparison of our study and various other studies revealed a number of differences with respect to certain parameters which can be attributed to different epidemiological factors. The key departure of this study was the realization that several lymphoid proliferative reactions could coexist in the lymph nodes of one patient. The morphologic appearance of hyperplasia varies even if the stimulating agent is the same, depending on the age of patient, past experience with the offending agent, time period following exposure to the stimulus, and the duration of the exposure. The onset of

germinal center hyperplasia in patients revealing a sinus histiocytosis response is brought about by a change in the nature of antigenic stimulus which reaches the lymph nodes. This change is related to some modification of the tumor cells as they become more malignant, or to a change in the physical form of tumor antigen presented to the lymph nodes. This evidence suggests that the physical form of antigen changes in a way that there is increase in its ability to stimulate germinal center hyperplasia. The formation of germinal centers within the follicles is stimulated by the presence of antigen. The main function of germinal centers is seen in the proliferation of specific antigen-reactive immunocompetent memory B cells. Germinal center hyperplasia reflects chronic local antigen stimulation.

Sinus histiocytosis is a manifestation of cell-mediated immune response to the carcinoma of breast. Marked sinus histiocytosis in the ipsilateral axillary lymph nodes is associated with an enhanced cellular response to autologous breast carcinoma and to clinically evident enlargement of contralateral axillary lymph nodes. The determination of sinus histiocytosis has been proven to be a highly subjective endeavor with considerable inter- and intraobserver variability.

Finally, while the evaluation of individual prognostic and predictive factors has value, there is pressing clinical need to develop a comprehensive profile of the biological and molecular characteristics of a tumor that may aid in the assessment of prognosis and the prediction of response to various therapeutic modalities. The tools of modern molecular biology, such as microarray technology, may ultimately provide such an assessment by permitting high throughput, parallel analysis of hundreds or thousands of parameters.

CONCLUSION

The lymph node reaction to cancer and attempted correlation led to the emergence of certain interesting patterns in lymph nodes draining breast cancer as follows:

- The development of germinal centers and plasmacytic reaction in tumor draining nodes are morphological expressions of active humoral immune responses that are specifically directed against the tumor. Their incidence and prognostic significance may vary depending upon the stage and type of tumor
- Sinus histiocytosis is an immunologically mediated nonspecific lymph node response
- Granulomatous reactions are signs of an immunologically mediated antitumor response of macrophages activated by T lymphocytes
- Paracortical hyperplasia, characterized by an increased population of lymphocytes and eventually immunoblasts, is an expression of an active T-cell reaction
- Lymphocytic depletion and nodular alteration of T-cell areas, with increased histiocytic infiltration, are reactions most often seen in the draining nodes of an advanced tumor.

The present assessment of the reactive behavior of diverse lymph node compartments serves as a first pointer to the proposed histologic immunostaging of malignant tumors. Mixed pattern of hyperplasia was the most widespread followed in decreasing order by diffuse pattern, follicular hyperplasia, sinus histiocytosis, and paracortical hyperplasia. Mixed pattern comprised most frequently of the follicular hyperplasia and sinus histiocytosis. Pertaining to the size of tumor, there was a decline in the incidence of sinus histiocytosis, paracortical hyperplasia with the increase in the size of the tumor. However, follicular hyperplasia showed an increase from 22.62 to 29.62%.

In relation to the prognostic group, there was a decline in the pattern of hyperplasia as presented by follicular, sinus histiocytosis, paracortical, mixed, as well as diffuse with the decline in the prognostic group. Not much statistically significant difference was seen in the pattern of reaction in the metastatic lymph nodes with regard to the histologic type of tumor, grade of tumor, size of tumor, and prognostic group of tumor.

This study will further enhance the ability to clinically stage the breast cancer and predict the prognosis of the patient.

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