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Significance of Immune Response Patterns in Lymph Nodes Draining Breast Carcinoma

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Abstract:

Background: Axillary lymph node enlargement in breast cancer may be caused by metastasis or may be due to reactive hyperplasia. It is assumed that the histological analysis of the patterns in the regional lymph nodes draining the tumor could elucidate the immunological host-tumor relationship and provide additional information on patient survival.

Material and Methods: Retrospective study on lymph nodes received with mastectomy specimens. The lymph nodes both involved and uninvolved by metastasis were selected. The morphological responses in the uninvolved lymph nodes were classified into groups comprising of either a single predominant pattern i.e., lymphocyte predominance, germinal centre predominance, or sinus histiocytosis according to the WHO proposal. The tumor size, grade, stage and the ER/PR and HER2-neu status were recorded and correlated with the patterns.

Results: Forty six cases were studied with a total of 551 lymph nodes. Out of these, 123 lymph nodes had metastatic carcinoma & 428 lymph nodes had no metastasis. The patients were in the age range 22-78years. Most of the cases had a tumor size of 2-5 cms. Maximum cases had a microscopic grade of II and pathological TNM stage II. Sinus histiocytosis was the common pattern in all the patients followed by Germinal Centre Predominance and Lymphocyte Predominance. The predominance of the sinus histiocytosis pattern was found to be statistically significant, but there was no association with the pattern and tumor size, grade, stage, ER/PR and Her2-neu status.

Conclusion: Reactive patterns in the regional lymph nodes could be helpful in providing information on patient prognosis

Keywords: ***Breast, carcinoma, lymph node patterns, sinus histiocytosis.***

Introduction:

Breast carcinoma accounts for over 20% of all female cancers.[1] Axillary lymph node involvement in breast cancer is very common. Enlargement of the lymph nodes may be caused by the metastasis or may be due to reactive hyperplasia in response to tumor-associated antigens.

The role of host defence against a tumor has been gaining increasing attention. The various lymphoid cell populations within the lymph nodes react in various ways, giving rise to different reactive morphologic patterns which can be observed in the lymph nodes.[2] Only a few studies have investigated the possible correlations between the various reactive patterns and the prognosis in breast and other carcinomas.[2,3,4,5,6] More extensive studies on lymph node immune response patterns will be helpful in providing information on patient prognosis.

This study was done to observe the morphological patterns in the axillary lymph nodes from cases of carcinoma breast and to correlate these patterns with the tumor size, tumor grade, pathological TNM stage and biomarker status.

Material and Methods:

Study Design: Retrospective assessment of slides of axillary lymph nodes from mastectomy specimens of cases with carcinoma breast available in the archives of the Department of Pathology over a one-year period.

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Study Population: Patients diagnosed to have carcinoma breast that were admitted to the Medical College Hospital and underwent mastectomy.

Sampling method: Convenience sampling.

Inclusion criteria: All slides with lymph node from cases of mastectomy done for carcinoma breast and histologically found to be Invasive Carcinoma, No Special Type (NST).

Exclusion criteria: Lumpectomy specimens (as the lymph nodes are not removed) and histological types other than Invasive Carcinoma, NST.

Data Collection Procedure and Methodology:
According to the routine procedure, mastectomy specimens are sent to the Department of Pathology in 10% formalin and are grossed according to the standard protocol prescribed by the CAPS (College of American Pathologists and Surgeons). The tissue bits are paraffin-embedded and the sections were stained with Haematoxylin and Eosin.

The slides were retrieved from the archives and those slides from the lymph nodes found were carefully scrutinized. The lymph nodes involved (positive) and uninvolved (negative) by metastasis were segregated. The morphological responses in the negative lymph nodes were classified into five groups comprising of the predominant pattern (lymphocyte predominance [LP], germinal centre predominance [GCP], sinus histiocytosis [SH], lymphocyte depletion [LD], granulomatous reaction) according to the WHO proposal.[2,5] In cases where the pattern was mixed, the predominant pattern was recorded.

The demographic details of the patients, the tumor size, the tumor grade, tumor stage and the hormone receptor status (Estrogen and Progesterone Receptor positivity) and HER2/neu positivity status were also recorded. The immunohistochemistry was done using Estrogen receptor alpha, clone EP1, RTU, PathnSitu, Progesterone receptor, clone EP2, RTU, PathnSitu and HER2/neu (c-erB-2 oncoprotein), clone EP3, RTU, PathnSitu. The detection system used was PolyExcel HRP/DAB detection system. The morphological patterns in the lymph nodes with regard to the tumor size, the grade, the pathological TNM stage and the hormone receptor and HER2/neu status were studied.

Statistical Tool: Application of Cross-tabulation and Pearson Chi Square Test using SPSS package version 23.

Ethical clearance: The study was done after obtaining permission from the Institutional Ethics Committee (IEC).

Results:

During this study period 46 cases of invasive carcinoma, NST, were selected according to the inclusion/exclusion criteria. The ages of the patients ranged from 22 to78. The patients were divided into 3 groups viz., <30 years - 4 (8.6%), 30-50 years - 21 (45.7%) and >50 years - 21 (45.7%). The number of patients in the age groups 30-50 years and >50 years were equal.

Most of the cases had a tumor size of 2-5 cms. Maximum cases had a microscopic grade of II and pathological stage II.

A total of 551 lymph nodes were identified. Out of these, 123 lymph nodes had metastatic carcinoma (positive nodes) & 428 lymph nodes had no metastasis (negative nodes). The total number of lymph nodes studied in the individual cases was divided into categories according to the TNM staging. In most of the cases (n=29) more than 10 lymph nodes were isolated. In 13 cases there were 4-9 lymph nodes (20 positive & 46 negative), & in 4 cases, less than 3 lymph nodes (all negative) were identified. The maximum number of positive lymph nodes in a single case were 18 in the >10 lymph nodes group and 8 lymph nodes in the 4-9 group.

Immunohistochemistry was done for the hormone receptors (estrogen [ER] and progesterone [PR]) and HER 2/neu [ERBB2]). The immunohistochemical findings were as follows: ER+, PR+, HER 2/neu +, 14 (30.5%) cases; ER-, PR-, HER 2/neu +, 5 (10.9%)cases; ER+, PR+, HER 2/neu -,12 (26.2%) cases; & ER-, PR-, HER 2/neu -, 15 (32.7%) cases.

The reactive patterns in the lymph nodes observed were Sinus Histiocytosis (SH) Germinal Centre Predominance (GCP), and Lymphocyte Predominance (LP). Sinus histiocytosis was the common pattern (Figure 1) in all the patients followed by GCP and LP. Granulomatous reaction and LD pattern were not observed. SH pattern was the most common pattern irrespective of patient's age, tumor size, microscopic tumor grade, pathological TNM stage and hormone (estrogen and progesterone) receptor status and the HER2-neu positivity. The findings are shown in Table 1.

Table 1: Showing the reactive patterns in the various groups

	Reactive patterns		
	GCP	**SH**	**LP**
Age group	4 (0.9%)	**21 (4.9%)**	0
<30 years (n=4)	47 (11%)	**157 (36.7%)**	31 (7.2%)
30-50 years (n=21) >50 years (n=20)	43 (10%)	**99 (23.1%)**	26 (6.1%)

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Tumor size			
<2 cms (n=3)	12 (2.8%)	**15 (3.5%)**	0
2-5 cms (n=31)	71 (16.9%)	**182 (42.5%)**	35 (8.2%)
>5 cms (n=12)	12 (2.8%)	**78 (18.2%)**	23 (5.4%)
Grade I (n=9)	7 (1.6%)	**56 (13.1%)**	5 (1.2%)
Grade II (n=29)	79 (18.5%)	**179 (41.8%)**	29 (6.8%)
Grade III (n=8)	10 (2.3%)	**42 (9.8%)**	21 (4.9%)
Stage I (n=3)	0 (0)	**15 (3.5%)**	13 (3%)
Stage II (n=28)	89 (20.8%)	**183 (42.8%)**	20 (4.7%)
Stage III (n=15)	7 (1.6%)	**77 (18%)**	24 (5.6%)
ER/PR	70 (16.4%)	**238 (55.6%)**	31 (7.2%)
HER2/neu	30 (7%)	**49 (11.4%)**	10 (2.3%)

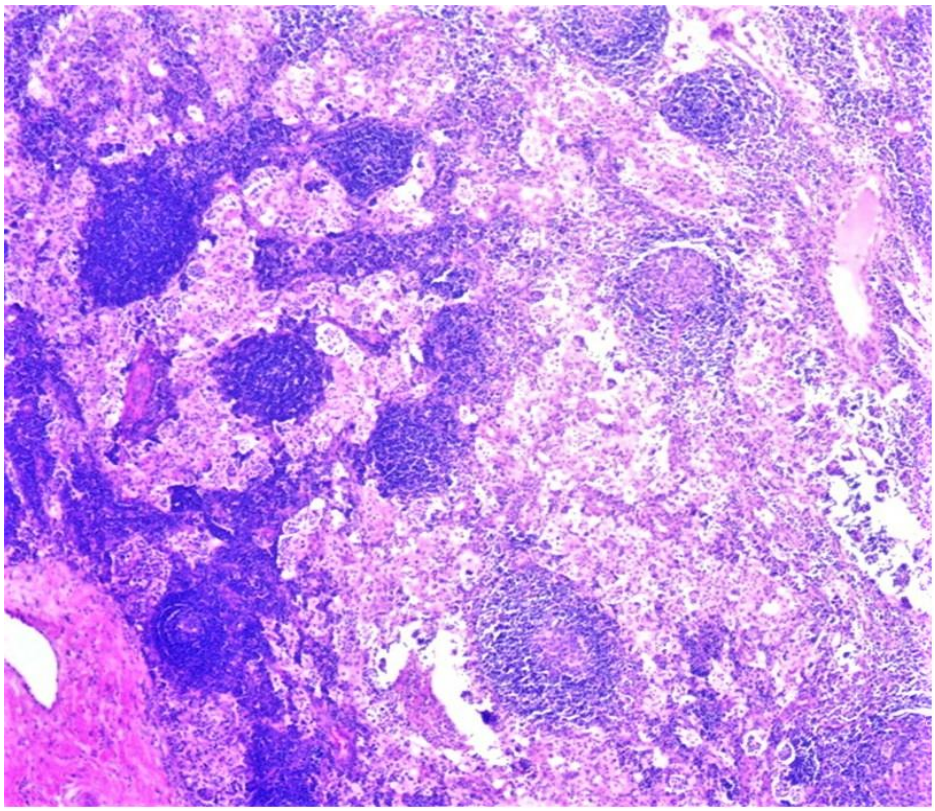

Figure1: Lymph node showing extensive reactive Sinus Histiocytosis (H&E,40x)

There was no correlation with the lymph node reaction patterns and the patient's age, tumor size, microscopic tumor grade, pathological TNM stage and hormone (estrogen and progesterone) receptor status and the HER2-neu positivity. However, the predominance of the SH pattern over other patterns was found to be statistically significant ($p<0.05$).

Discussion:

Breast carcinoma causes significant morbidity and mortality. There are several parameters used for predicting the prognosis in these patients.[1,7] 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. These prognostic indicators serve as guides for clinical decisions and estimates of outcome.[3]

The prognosis of breast carcinoma is related to a number of clinical, pathologic and molecular factors. The clinical factors include patient's age, pregnancy, early diagnosis, tumor stage, local recurrence and type of therapy. It has been found that the relative survival declines with age and is particularly low in women over the age of 50 years.[7]

The various factors assessed during histopathological examination of the breast include site and size of the tumor,

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cytoarchitectural type, microscopic grade, types of margins, presence or absence of invasiveness, tumor necrosis, stromal reaction, microvessel density, elastosis, fibrotic foci, lymph node metastasis, surgical margins, skin and nipple invasion, Paget disease, and lymphatic and blood vessel emboli.[7]

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.[7]

Cancer management and prognosis depend to a great extent on the presence and degree of tumor metastasis. These are evaluated by staging tumors according to the internationally accepted tumor-node-metastasis (TNM) system. Of all the various criteria used as prognostic factors, the most powerful prognostic factor is the description of the anatomic spread according to the TNM staging. Each successive stage in the TNM system indicates a significant decrement in the prognosis. The diagnosis of lymph node tumor metastasis is therefore essentially important for cancer therapy. This consists not only of establishing the presence of lymph node metastasis but also of evaluating the site of the primary tumor and its degree of histologic differentiation and determining the tumor cell phenotype and prognostic indicators of tumor cell behaviour.[10]

Hormone receptor (estrogen and progesterone receptors) positive tumors, whether determined biochemically or immunohistochemically, have a longer disease-free survival than the others. Overexpression of HER2/neu oncogene as determined either by immunohistochemistry or FISH is an excellent predictor of response to trastuzumab but a weak predictor of response to chemotherapy. It identifies a subset of patients with poor prognosis, particularly when lymph node metastases are present, and correlates closely with tumor grade.[7]

The lymph nodes form a major part of the lymphatic system and drain the lymphatics from various anatomic regions. This process involves not only mechanical filtration of the foreign substances present in the lymph but also the recognition and processing of foreign antigens. The lymph nodes exhibit a complex architecture in which the various cell populations are arranged in distinct compartments. This provides a favourable environment suitable to process antigens, and generate the immune response.[2,8]

Normal lymph nodes are not palpable. They become detectable as a result of intense immunological reactions or due to the presence of a primary tumor or tumor metastasis. The lymphatic sinuses carry the lymph from the afferent lymphatics on the surface of the lymph node through the lymphoid parenchyma into the efferent lymphatics in the lymph node hilus. The phagocytic apparatus of the sinuses filters the lymph, retaining foreign bodies, and plays an important role in antigen binding. The passage of lymph and cells from one chain of lymph nodes to the next is a means by which the immune response is conveyed from the peripheral to the more central lymph nodes.[2,8]

Regional lymph nodes draining tumor-bearing organs are considered effective barriers to tumor spread. They are also the site where specific immune responses between tumor antigens and reacting lymphoid cells take place. The primary antitumor function of lymph nodes is not only filtration but also immunologic tumor surveillance.[2,9] Tumors spread to regional and distant lymph nodes occurs via lymphatic vessels. Consequently, the regional lymph nodes are commonly enlarged as a result of reactive lymphadenopathy, tumor metastasis, or both.[10]

The involvement of lymph nodes by metastatic spread of tumors signifies the start of a new phase in the progress of a cancer. It indicates that through a succession of molecular changes, the cancer cells have acquired phenotypes that enable them to invade, colonize, and disseminate. Establishing the presence of metastatic tumor in lymph nodes is essential for the management and prognosis of cancer. Lymph node status is the most important indicator of clinical outcome.[7,10] The anatomic location and the number of lymph nodes involved are also important indicators of the process.[7]

Lymph nodes play an essential role in the control of tumor progression. In response to the antigenicity of tumor cells, regional lymph nodes may initiate and develop complex immune reactions. The lymph nodes may entrap circulating tumor cells that have originated in their territories, acting as efficient barriers, the lymph nodes may be able to destroy invading tumor cells completely, or at least stop their dissemination temporarily.[10]

Axillary lymph node metastasis is one of the most important prognostic parameters. There a sharp difference in survival rates between patients with positive and negative nodes, and the survival rate also depends on the level of axillary node involved (low, medium, or high), the absolute number (fewer than four versus four or more), the amount of metastatic tumor, the presence or absence of extranodal spread, and the presence or absence of tumor cells in the efferent vessels. For prognostic purposes, the best grouping seems to be the following: negative nodes, one to three positive nodes, and four or more positive nodes lymph node metastases.[1,7]

In response to tumor-associated antigens, the various cell populations of regional lymph nodes react in different ways, giving rise to a multitude of morphologic patterns. The term

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tumor-reactive lymphadenopathy is used which is defined as reactive, enlarged, regional lymph nodes draining tumors.[11]

Numerous studies have been devoted to the analysis of such reactions, in an effort to understand the mechanisms of lymph node metastases. Some studies have correlated various histologic patterns of reactive lymph nodes with the dissemination of tumors in cancers of various organs. Tumor-associated antigens, shed by tumor cells or released by cell death, in addition to viable tumor cells, are carried by lymph to the draining lymph nodes, providing constant nonspecific and specific stimulation. Thus, various defence reactions may be triggered.[11] It is assumed that the histological analysis of the patterns in the regional lymph nodes draining the tumor could elucidate the immunological host-tumor relationship and provide additional information on patient survival.[2]

Various studies have suggested that the microscopic appearance (that is the pattern of lymph node reaction) of the regional node (lymphoid response and/or sinus histiocytosis) is an indication of the type of host response to the tumor and that it relates to prognosis. The issue however is incompletely studied.[7] The morphologic appearance of the lymph node reaction pattern 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.[3]

A relationship between immune deficiency and tumor occurrence and aggressiveness is generally well-documented. Not infrequently, markedly enlarged and firm lymph nodes removed as part of radical tumor excision reveal no tumor metastasis on microscopic examination. The morphologic changes of lymph nodes draining tumor-bearing organs provide evidence for anti-tumor immune reactivity. Recognition of the histologic patterns of lymph node reactivity to the presence of tumors is important in the study of biopsy and surgical specimens.[11] A number of studies have investigated possible correlations between patterns of lymph node reactivity and prognosis, so far without firm, conclusive results including breast[3,4] colon,[12,13,14,15,16] stomach,[17] oral cavity,[5,6] lung,[18,19] and cervix.[20]

Reactive lymph node hyperplasia is the enlargement of lymph nodes or other lymphoid tissue as a result of stimulation of the lymphoid cells by a variety of antigens. It is a benign, reversible process. The immune responses in lymph nodes may be predominantly of B-cell type, characterized morphologically by either follicular hyperplasia or plasmacytosis, or predominantly of T-cell type, with a characteristic pattern of T-cell hyperplasia.[21,22,23]

In general, lymphadenopathies tend to exhibit one of the four characteristic histologic patterns including follicular, sinusoidal, diffuse, or mixed. These patterns represent expansions of the normal follicular, paracortical, medullary, and sinusoidal lymph node compartments. The histologic patterns vary with the etiologic agent, as well as with the immune competence status of the host. Therefore, combined or mixed overlapping architectural features are a more common finding than clearly defined histologic patterns on biopsy specimens of lymph nodes without metastasis.[23]

A proposal for a standardized system of reporting human lymph node morphology in relation to immune reaction was published in 1973 by the World Health Organization. The authors recommended a topographic examination of the lymph node sections with separate descriptions of the functional areas: cortex with follicles and germinal centres, paracortex, sinuses, and medullary cords.[24] Studies of regional lymph nodes in tumors of various organs show histologic patterns of reactions, possibly with prognostic implications One of four major histologic patterns maybe seen, and more often combinations. The four major patterns include Lymphocyte Predominance (LP), Germinal Centre Predominance (GCP), Sinus Histiocytosis (SH) and Lymphocyte Depletion (LD). A Granulomatous Reaction has been described rarely.[11]

In lymphocyte-predominant tumor-reactive lymphadenopathy, lymph nodes are enlarged particularly because of the increased number of lymphocytes in the paracortical areas (T-cell zone). The lymphoid follicles are effaced, and the nonreactive germinal centres are mostly inapparent, whereas the paracortex is markedly thickened. Such lymphoid hyperplasia may or may not be associated with sinus histiocytosis. The pattern is thought to reflect changes related to cellular immunity and to be associated with an earlier diagnosis and a better prognosis.[11] This pattern has been observed in studies of lymph nodes in carcinomas of the breast [3,4] colon,[12,13,14,15,16] oral cavity,[17] lung,[18,19] and cervix.[20]

In germinal centre–predominant (follicular pattern) tumor-reactive lymphadenopathy, the lymph nodes are enlarged, but the increase in volume is caused by hyperplasia of follicles, particularly the germinal centres which is the B-cell zone. Reactive follicular hyperplasia, is the B-cell response to various antigens. A predominantly B-cell response is characterized by hyperplasia of germinal centres and therefore by a follicular pattern. Sinus histiocytosis may coexist with these changes, which are considered to be associated with humoral immunity. Also, follicles and germinal centres may remain reactive in lymph nodes largely replaced by metastatic tumor.[11] GCP pattern has been noted in studies of lymph nodes in carcinomas of the

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breast[3,4] colon,[12,13,14,15,16] oral cavity,[17] lung,[18,19] and cervix.[20]

Sinus histiocytosis is another pattern associated with a more favourable prognosis. A predominance of sinuses with proliferating histiocytes characterizes the morphologic pattern of sinus histiocytosis, which can occur in isolation or together with one of the preceding patterns. The lymph node is enlarged by markedly distended sinuses and hyperplasia of the sinus histiocytes. The pale staining of histiocytes and endothelial cells that line the branching lumina contrasts strongly with the dark staining of lymphocytic areas and produces the characteristic appearance of sinus histiocytosis.[11] In various studies of lymph nodes in carcinomas of the breast[3,4] as well as of the colon,[12,13,14,15,16] oral cavity,[17] lung,[18,19] and cervix,[20] the SH pattern has been observed. In the lymphocyte depletion pattern, the lymph node is of normal or diminished size, and the lymphocytic population is depleted. The loosely packed lymphocytes are separated by deposits of amorphous substance and areas of fibrocollagen. The vessels have thick walls, with hyaline deposits. Diffuse fibrosis and patchy deposition of hyaline involve both the cortex and medulla. These changes are considered to reflect an exhausted ("burnt out") lymph node and to be associated with metastases and a poor prognosis.[11]

Granulomatous reaction comprising of clusters of epithelioid histiocytes sometimes resembling non-necrotizing granulomas may be seen in draining lymph nodes. This pattern is rare.[11]

In various studies, different patterns of response in lymph nodes draining breast carcinomas were studied and correlated with other morphological parameters such as size of the tumor, the histological type of the tumor, and the histologic grade of the tumor. Significance of the pattern of reaction in the metastatic lymph nodes varies with regard to the histologic type of tumor, microscopic grade of the tumor, size of the tumor, and prognostic group of tumor in different studies.[3,4,11,25,26] However SH pattern was found to be more often seen in lymph nodes without metastasis.[25,26] 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.[3]

It has been found that in some studies certain patterns like sinus histiocytosis and lymphocyte predominance have a lower risk of metastasis while in some studies germinal centre predominance has a higher risk of metastasis. In studies of carcinoma of the oral cavity[5,6] GCP pattern was prognostically significant[5,6] while in carcinoma of the lung SH pattern was significant[18,19] carcinoma cervix LP pattern was important.[20]

In carcinoma of the breast sinus histiocytosis was the most common reactive pattern in lymph nodes[3,4,11,25,16] which was also found in our study. In some studies, the incidence of sinus histiocytosis declines with increase in the size of tumor.[3,25] In contrast another study conducted observed that the incidence of sinus histiocytosis increases with the tumor size.[4] However, in our study SH significantly predominated over other patterns but was not related to the size of the tumor.

According to one study, incidence of sinus histiocytosis increases with increase in the grade of tumor but another study suggests that higher grade of malignancy is associated with a decreased frequency of SH.[3] In our study, SH was the predominant pattern in all grades but there was no variation with increase or decrease of the microscopic tumor grade.

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 defence mechanism.[3,11] 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.[3]

When assessing the various histopathological parameters for predicting the prognosis in cancer patients, histological analysis of the patterns in the regional lymph nodes draining the tumor could elucidate the immunological host-tumor relationship and provide additional information on patient survival. Increasing size of the cancer, higher grade and stage of the malignancy are likely to show decreased number of reactive lymph nodes. It has been found that in some studies certain patterns have a lower risk of metastasis while in some other studies some patterns may indicate a higher risk of metastasis. However, more extensive studies on lymph node immune response patterns will be helpful in providing information on patient prognosis.

Conclusion:

Many parameters are used for predicting the prognosis in cancer patients. It is assumed that the histological analysis of the patterns in the regional lymph nodes draining the tumor could improve the understanding of the immunological host-tumor relationship and provide additional information on patient survival.

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The development of 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 type of tumor, the size of the tumor, the microscopic grade and the stage, as well as the expression of immunohistochemical markers. Routine examination of the lymph nodes without metastasis will also provide additional information on the prognosis of the tumor.

The present assessment of the reactive behaviour of the diverse lymph node compartments serves as a first pointer to histologic immunostaging of malignant tumors and further enhances the ability to predict the prognosis of the patient. This study is however limited by the small number of cases and more extensive studies are required for conclusive evidence.

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