Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.202291213-220

Architectural Patterns and PD1 Expression in Partially Effaced Tumor Draining Lymph Nodes of Breast Carcinoma: A Small-Scale Preliminary Study on 50 Patients

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ARTICLE INFO

Received:
6 December 2021
Revised:
12 March 2022
Accepted:
22 March 2022

Keywords:
Tumor draining lymph nodes (TDLN), histology, PD1 immunohistochemistry, breast carcinoma

ABSTRACT

Background: Metastasis in tumor draining lymph nodes (TDLNs) is correlated with poor prognosis in breast cancers. It is associated with local immune suppression, which can be partly due to the higher expression of check point inhibitors in immune cells. The morphological manifestation of the underlying immunomodulation of TDLNs has been less investigated. Here, we present the histomorphological changes and PD1 expression pattern in metastatic and non-metastatic TDLNs in breast cancer patients.

Methods: A total of 248 metastatic or non-metastatic TDLNs from 50 breast carcinoma samples were examined histologically and for PD1 expression in the present study. We assessed the immune response in these TDLNs as per histomorphological patterns on H&E stained slides, categorizing them into lymphocyte predominance, germinal center predominance and an un-stimulated pattern. Anti-PD1 immunohistochemistry was performed on all lymph nodes. The results were analyzed using SPSS version 23 and P value <0.05 was considered to be significant.

Results: The lymph node metastasis in breast carcinoma was significantly higher at younger age, patients with higher tumor grade and lympho-vascular invasion in the primary tumor. The metastatic lymph nodes showed significantly higher densities of germinal centers with abnormal shapes, as compared to non-metastatic ones. There was significantly higher expression of PD1 in the immune cells of metastatic TDLNs.

Conclusion: The identification of PD1 immunohistochemical profile along with histological changes of TDLNs should therefore be considered as a possible prognostic and predictive marker for lymph node metastasis. The patients with higher densities of germinal center with abnormal shape and increased PD1 expression should benefit from immune-check point inhibitor therapy.

INTRODUCTION

Breast carcinoma is the most prevalent malignant disease in women across the globe representing 24% of all new cancer cases and 15% of cancer deaths.[1] The diagnosis as well as the treatment of breast cancer have improved but controlling tumor progression is still challenging.[1] The regional lymph nodes are an effective barrier to the dissemination of tumors and malignant cells may be destroyed by the immune response. The drainage of tumor cell debris or antigen may initiate reactive changes in lymph nodes.[2] Thus, the increase in the size of the nodes may take place

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due to the spread and growth of cancer cells or reactive hyperplasia of the lymph node. According to the type and amount of stimulus, different components of lymph node (e.g., marginal zone, germinal center, mantle zone, etc.) may expand or diminish. These morphological changes reflect different types of underlying immunomodulation occurring in tumor draining lymph nodes (TDLN).[3,4] Thus, apart from the absolute count of metastatic lymph nodes among the total lymph nodes harvested in the mastectomy specimen, different histological patterns of hyperplasia in lymph nodes may also provide further insight into the clinical outcome.[3]

PD-1 (programmed cell death protein-1)/PD-L1 (programmed cell death ligand-1) is a well-recognized immunomodulatory pathway which contributes to peripheral tolerance.[5,6] PD-1 is expressed by T lymphocytes and other immune cells, functioning as a coregulatory cell surface membrane protein. Research suggests that the expression of PD-1 is significantly upregulated on cancer specific T lymphocytes.[7,8] As a ligand of PD-1, PD-L1 is often expressed by antigen-presenting cells (APCs), like macrophages, in addition to tumor cells and B lymphocytes. When PD-1 combines with PD-L1, it can compromise the immunity effects of lymphocytes, resulting in exhausting the immune function and tumor progression.[5]

The immune checkpoint inhibitors, including the anti-PD-L1 antibody and the anti-PD-1 antibody block the interaction between PD-1 and PD-L1 and produce good anti-tumor responses. Researchers have investigated PD-1/PD-L1 expression in various malignancies, including lymphoma, melanoma, colorectal cancer as well as lung cancer. However, little information exists on the expression of PD-1 and PD-L1 in breast cancer and TDLN.[8,9]

Thus, this study was carried out to determine morphological changes in different compartments of TDLNs after being stimulated by tumor antigens in different histological types and grades of breast cancers. We also evaluated the PD-1 expression status in the TDLNs of breast carcinoma cases.

MATERIALS AND METHODS

After approval by institutional ethics committee (Institutional Ethics Committee, Burdwan Medical College, Purba Barddhaman), the study was conducted on 50 patients who were diagnosed with breast carcinoma and had undergone modified radical mastectomy at the Department of Surgery in our institution. The inclusion criteria were the existence of axillary lymph nodes and the absence of neo-adjuvant or anti–hormonal therapy prior to resection. The clinical history and histological features like tumor size, WHO subtype, grade, lymph node involvement and lympho-vascular invasion were evaluated. Immunohistochemistry (IHC) for hormonal receptors was not included in the present study, as for most of the patients IHC was done in trucut biopsies during initial diagnosis. To assess lymph nodes, all the nodes were thinly sliced along the long axis of the nodes at 2 mm and all slices were submitted for microscopical examination. After processing and preparation of paraffin blocks sections of 3-5 micrometers were evaluated. Light microscopic examination of H&E stained slides was performed by two independent observers. Immune response in the TDLNs (metastatic or non-metastatic) was assessed as per histomorphological features highlighted in previous studies.[10-12] A simplified diagrammatic representation of the study design is shown in Figure 1.

Morphology of the TDLNs may represent certain parameters of the patient's immune response which are associated with humoral and cell mediated immunity.[11] We identified three histological patterns of TDLNs: lymphocyte predominance, germinal center predominance and an unstimulated pattern. Sinus histiocytosis may coexist with all these changes. So, it was not considered as a notable response in this study by itself.

Paracortical hyperplasia signifies a large number of small lymphocytes throughout the paracortex (T cell Zone), indicating the lymphocyte predominant pattern in lymph nodes. Follicular hyperplasia shows an increased number of B lineage lymphocytes after being antigenically stimulated. So, an increase in the number of follicles with active germinal canters represents the germinal center predominant pattern. The lymph nodes were categorized as an unstimulated pattern when the cortex was thin, germinal canters were inconspicuous and the deep cortex was ill-defined.[4,10] The shape of germinal centers in TDLNs was also studied. Previous studies have correlated ill-defined, fused, non-circular germinal centers of lymph nodes with immune dysregulation.[3,13] In the present study, all of them were classified as the abnormal shape of the germinal center (Figure 2 a-d). Unless the great bulk of a lymph node was replaced by a metastatic tumor (completely effaced lymph nodes), no problem occurred in evaluating a lymph node with metastases for its morphological pattern of the immune response.

All lymph nodes including metastatic and non-metastatic were evaluated by PD-1 stain using anti-PD1 antibody (PATH-N SITU, Clone EP239 RTU) according to the manufacturer's protocol. The staining intensity was scored as follows: negative (score=0), weak (score =1) and strong (score=2). The lymph nodes with >1% positive lymphoid cells of any staining intensity were considered to be positive.[8]

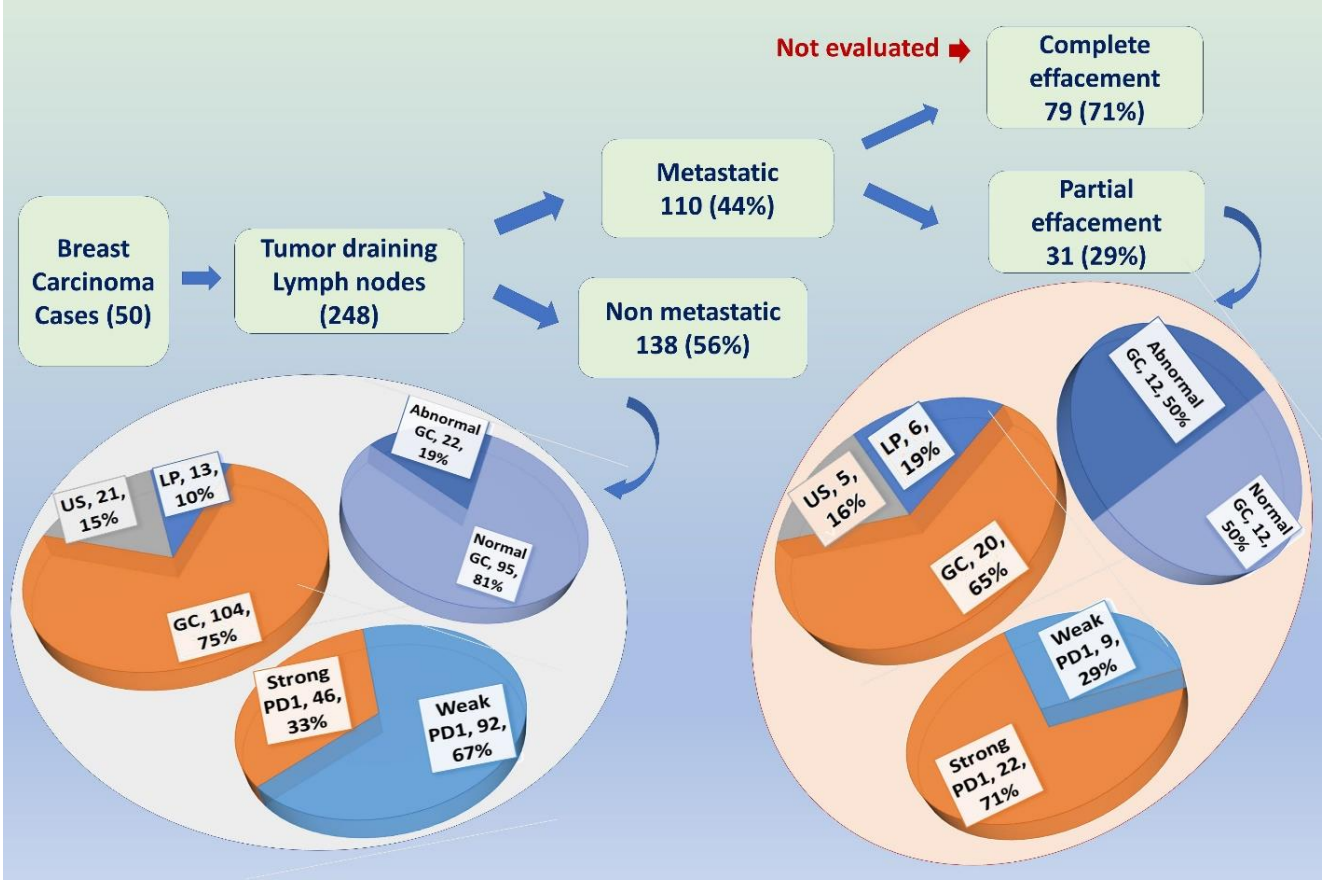

Figure 1. Simplified diagrammatic representation of the study design (GC= Germinal center predominance pattern, LP= Lymphocyte predominance pattern, US= unstimulated pattern.)

The results were analyzed using appropriate statistical methods (Pearson's Chi Square test), by SPSS version 23 software. An alpha level of 5% was considered, i.e., any P-value less than 0.05 was taken to be significant.

RESULTS

From 50 cases of breast carcinoma, 248 axillary lymph nodes were evaluated. Among these 248 lymph nodes, 110 (44%) lymph nodes showed metastatic deposit and 138 (56%) lymph nodes were negative for malignancy. Out of 110 metastatic lymph nodes, 79 (71%) lymph nodes showed complete effacement of nodal architecture by malignant cells, whereas 31 (29%) lymph nodes showed partial effacement. As no residual lymph nodal architecture was present to categorize them into specific immune morphological pattern in completely effaced lymph nodes, they were not assessed further. Clinico-pathological parameters of primary tumor were correlated with axillary lymph node metastasis. In younger patients (less than 50 years of age), the percentage of lymph node metastasis was higher (52%) compared to that of the elderly patients (27.2%). The lymph node metastasis did not vary much in different histological types of tumor. However, larger tumors, higher grade and those showing lympho-vascular invasion were more associated with lymph node metastasis (Table 1).

Most of the TDLNs showed germinal center predominance. About 64.5% of the positive lymph nodes and 75.3% of negative lymph nodes showed this pattern, which was statistically significant (P<0.001) (Table 2a). The germinal center shape could be assessed in 24 metastatic lymph nodes and 117 non-metastatic lymph nodes, as most of the TDLNs with unstimulated pattern lacked active follicle with a germinal center. Presence of abnormal germinal centers and non-circular follicles was significantly higher in metastatic lymph nodes (50%) compared to non-metastatic lymph nodes (19%) (P= 0.001) (Table2b). The PD1 staining was evaluated in 31 metastatic lymph nodes (showing partial metastasis) and all 138 non-metastatic lymph nodes (Table2c).

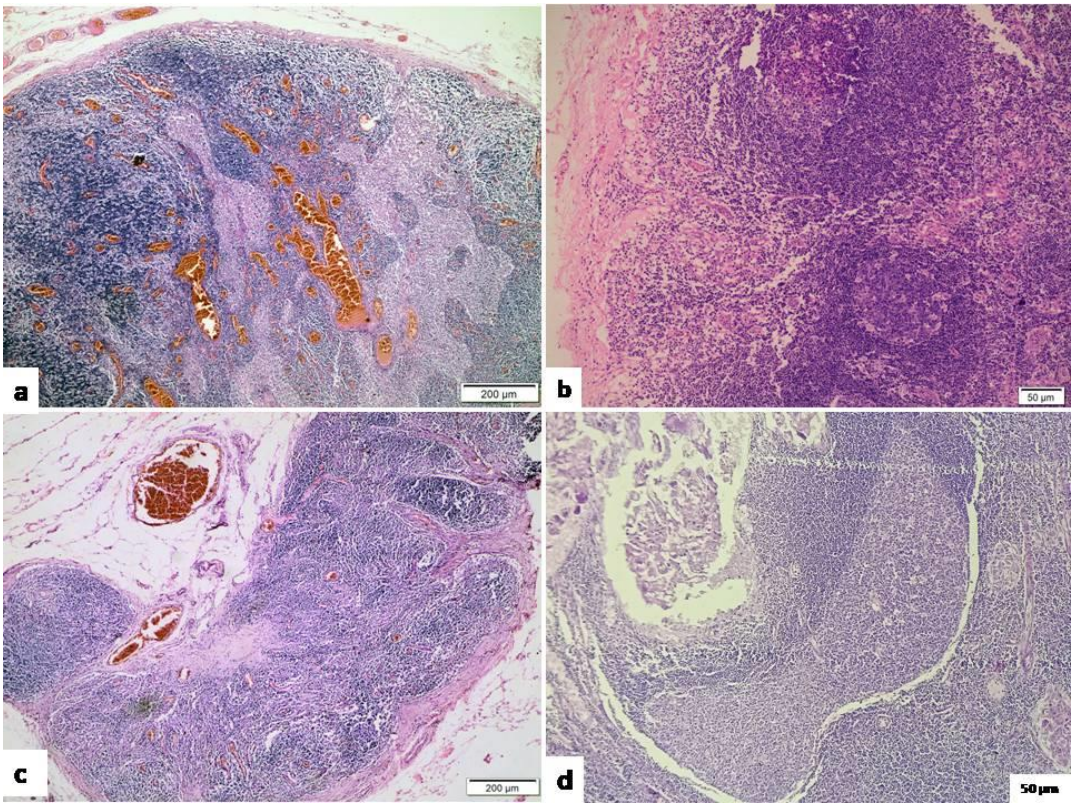

Figure 2. Different histological patterns in four metastatic tumor draining lymph nodes of breast carcinoma. (a) Lymphocyte predominance pattern (b) Germinal center predominance pattern (c) Unstimulated pattern (d) Abnormal (fused) shape of germinal center (H & E stain).

Table 1. Demographics of primary tumor and metastatic lymph nodes

variables		Number of patients (n=50)	Number of patients with Metastatic LN (36)	Total LN harvested (248)	Total Metastatic LN (110)	Total Non-Metastatic LN (138)
Age (years)	<50	36 (72%)	27	171	89 (52%)	82 (48%)
	≥50	14 (28%)	9	77	21(27.2%)	56 (72.8)
Breast tumor type	Invasive ductal carcinoma	40 (80%)	30	215	96 (44.6%)	119 (55.3%)
	Invasive Lobular carcinoma	6 (12%)	5	16	7 (43.7%)	9 (56.3%)
	Others	4 (8%)	1	17	7 (41.1%)	10 (58.8%)
Primary tumor size (cm)	1-2.5	5 (10%)	1	19	1(5.2%)	18 (94.8%)
	2.6-5	20 (40%)	15	109	51(46.7%)	58 (53.3%)
	>5	25 (50%)	20	120	58 (48.3%)	62(51.7%)
Grade	Grade 1	3 (6%)	2	18	3 (16.6%)	15 (83.4%)
	Grade 2	22 (44%)	16	94	46 (48.9%)	48 (51.1%)
	Grade 3	25 (50%)	18	136	61(44.8%)	75 (55.2%)
Lympho-vascular invasion	No	26 (52%)	20	145	47 (32.4%)	98 (67.6%)
	Yes	24 (48%)	16	103	63 (61.1%)	40 (38.9%)

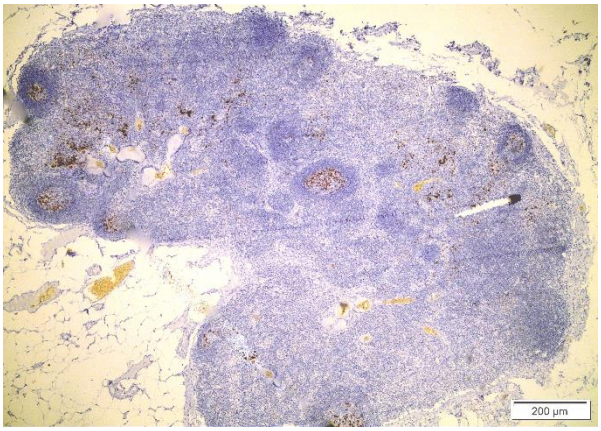

Figure 3. PD1 expression pattern (mostly staining germinal center lymphocytes) in non-metastatic lymph node (40x magnification).

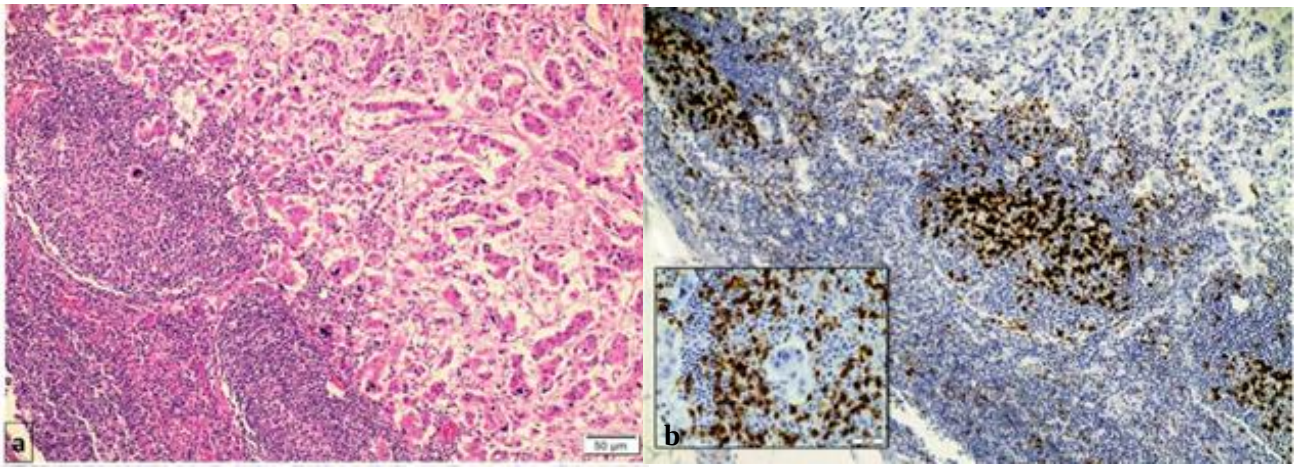

Figure 4. (a) Germinal center predominance pattern with abnormal (oval) shape of germinal centers in metastatic lymph node (H & E stain). (b) PD1 expression of the same node: strong PD1 expression is observed in germinal centers, at tumor and stromal interphase and in residual lymphoid cells [Inset: PD1 positive lymphocytes surrounding malignant cells, 400x magnification].

Table 2a. Distribution of tumor draining axillary lymph nodes according to predominant histomorphological patterns

	Lymphocyte predominant	Germinal center predominant	Unstimulated	Total	P value	Significance
Metastatic LN	6 (19.3%)	20 (64.5%)	5 (16.2%)	31*	.00001	significant
Non-Metastatic LN	13 (9.4%)	104 (75.3%)	21 (15.3%)	138		

*****out of 110 metastatic lymph nodes, 79 showed complete effacement; remaining 31 partially effaced nodes were available for evaluation.

Table 2b. Distribution of tumor draining axillary lymph nodes according to germinal center shape

	Germinal center shape				
	Normal	Abnormal	Total(141*)	P value	Significance
Metastatic LN	12 (50%)	12 (50%)	24	0.001	Significant
Non-metastatic LN	95 (81%)	22 (19%)	117		

*GC shape could be assessed in total 141 nodes, as most of the TDLNs with unstimulated pattern had lack of active follicle with germinal center

Table 2c. Distribution of PD1 expression in tumor draining axillary lymph nodes

	PD 1 expression				
	Weak	Strong	Total	P value	Significance
Metastatic LN	9 (29.03%)	22 (77.97%)	31	0.0001	Significant
Non metastatic LN	92 (66.67%)	46 (33.33%)	138		

In non-metastatic TDLNs, PD1 staining was mostly present in germinal centers (Figure 3). In cases of metastatic lymph nodes, strong PD1 expression was observed in germinal centers, at tumor stroma interphase and in residual lymphoid cells within the metastatic deposit (Figure 4). All the 20 GC predominant metastatic TDLNs showed strong PD1 expression (Table 2c). Strong PD1 expression was significantly higher in metastatic lymph nodes (77.9% cases) in comparison to non-metastatic lymph nodes (33.3% cases) (P<0.001) (Table 2c). The staining was mostly cytoplasmic in lymphoid cells; none of the malignant cells showed PD1 expression.The primary function of regional lymph nodes is not only to provide anatomic barrier to tumor metastasis, but also have a role in immunological surveillance.[3] The histomorphological patterns are the manifestation of underlying immune response of the host in draining lymph nodes. Several studies have correlated those patterns with patient survival.[10,11] The follicular hyperplasia and germinal center predominant pattern indicate an active immune response related to humoral immunity and paracortical hyperplasia may relate to T cell mediated immunity. The unstimulated pattern signifies the paucity or delay of immune response.[12] Recent studies have shown immune status of TDLN is suppressed in various cancer, partly mediated by regulatory T cells (T regs) and due to high expression of immune check point receptors (e.g., CTLA4 and PD1/PDL1) in immune cells.[8,14]

DISCUSSION

In the present study, simultaneously morphology and PD1 expression were compared between metastatic and non-metastatic TDLNs in 50 breast cancer patients. A Total of 248 lymph nodes were included for analysis of which 110 nodes (44.3%) showed a metastatic deposit. Lymph node metastasis was higher among younger patients (less than 50 years), patients with a larger tumor size, higher grade and lympho-vascular invasion in the primary tumor. However, there was no relation between histological type of tumor and frequency of the positive axillary lymph node, similar to previously published studies.[15,16]

Several studies have reported immunological responses in breast cancer TDLNs are morpho-logically manifested mainly three histologic patterns, designated as "lymphocyte predominance," "germinal center predominance," and "unstimulated." Some authors have included the "lymphocyte depleted" pattern in their analysis. The correlation between the histologic pattern and survival showed that lymphocyte predominance was common in cases with a high survival rate. Also, this correlation showed that lymphocyte depletion was common in cases with a low survival rate, and that germinal center predominance and unstimulated patterns had an intermediate prognosis. Previous research has reported a relationship between these patterns of immune responses and cancer prognosis. [10,11] In the present study, most of the metastatic lymph nodes (64.5%) showed a germinal center predominance pattern and the result was highly significant (P<0.001). Yadav *et al.* also observed the preponderance of the 'germinal center predominance' pattern in the positive nodes.[12]

It is now well established that immune status of TDLN is suppressed in various cancers.[17,18] Unger *et al.* have demonstrated ill-defined, non-circular germinal centers in lymph nodes are histological hallmark of common variable immune deficiency.[13] Such abnormal germinal centers are also found in toxoplasma associated lymphadenitis, HIV related lymphadenitis and EBV associated tonsillitis.[19-21] Seidl *et al.* observed the abnormal shape of germinal center in breast cancer TDLNs. In the present study, metastatic lymph nodes showed a significantly more abnormal shape in germinal center (P= 0.001). We suggest the abnormal shape of the germinal center could be morphological evidence of immunomodulation in breast cancer TDLN, as a response to tumor antigenic challenge. Berlinger *et al.* described reactive follicles with germinal centers with a tendency to "fuse" in TDLNs of head and neck squamous cell carcinoma. We investigated expression of PD1 in lymphocytes, which could inhibit T cells and block anti-tumor immune response.[6,9,22] We found significantly higher expression of PD1 in metastatic lymph nodes (P<0.001). Recent studies have shown PD1 could suppress specific CD8+ T cell cytotoxicity via suppressor cytokine production in tumor and TDLN.[23,24] Shuang *et al.* have indicated that even though the tumor antigen could increase the number of activated T cells, the higher expression of PD-1 in T cells, especially CD4+ T cell, may suppress the capacity of CD4+ and CD8+ T cells.[21] These data suggest that anti–PD 1 therapy may retrieve the

immunosuppressed status of TDLN and induce antitumor immune response. In the same line, Adams *et al.* reported that anti PD1/PDL1 immunotherapy achieves an objective response rate between 12-21% in breast carcinoma patients.[25]

CONCLUSION

The present study showed that morphological evaluation of germinal center density, shape and PD1 expression status may give us some information on the immune status of TDLNs, developed in response to breast carcinoma. Future larger studies may identify patients with higher densities of germinal center with abnormal shape and increased PD1 expression, who should benefit from immune-check point inhibitor therapy.

ETHICAL CONSIDERATIONS

Institutional Ethics committee approval no. BMC 79; dated : 7-1-19.

LIMITATIONS

No follow up data is available.

ACKNOWLEDGEMENTS

The authors are thankful to Prof. Goutam Banerjee for his help and support.

FUNDING

None.

CONFLICT OF INTEREST

None.

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How to Cite This Article

Nayek S, Majumdar K, Sau S, Basu A, Bandyopadhyay A. Architectural Patterns and PD1 Expression in Partially Effaced Tumor Draining Lymph Nodes of Breast Carcinoma: A Small-Scale Preliminary Study on 50 Patients. Arch Breast Cancer. 2022; 9(2):213-220.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/495