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CD1a expression in HER2-positive breast carcinoma tissues and its prognostic implications

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ABSTRACT

Aims: Dendritic cells are key players in initiating the primary immune response. Many studies have investigated the role of antigen-presenting cells in breast carcinoma, revealing associations between dendritic cell density, their spatial distribution within the tumor, and prognosis. CD1a is a glycosylated type I transmembrane protein that is frequently used as a dendritic cell marker in human tumors. This study aims to detect CD1a expression using immunohistochemical methods in a cohort of HER2-overexpressing breast carcinoma patients. It also analyzes the correlation of CD1a expression with prognostic parameters and overall survival outcomes.

Methods: Patient records of individuals diagnosed with invasive breast carcinoma between 2003 and 2009 were retrieved from the digital pathology archive of İstanbul University İstanbul Faculty of Medicine Pathology Department. From this dataset, 48 cases were selected based on the following inclusion criteria: HER2 positivity confirmed. We applied cd1a immunohistochemically to all of these cases and compared the staining with prognostic data.

Results: Any level of CD1a positivity was considered when evaluating the association between CD1a expression and survival/prognostic factors. No statistically significant relationship was found between CD1a positivity and age, tumor size, lymph node involvement, or recurrence. No correlation was identified between CD1a positivity/negativity and the neoadjuvant status of the tumour. However, a significant association was observed between nuclear grade and CD1a positivity. No statistical correlation was found between 5-year total and disease-free survival and CD1a staining.

Conclusion: Considering that HER2-positive tumors account for only 25–30% of breast carcinomas, our study focused on a particular and homogeneous patient group. A lower survival rate was expected because HER2 positivity is a known poor prognostic factor, and our cohort consisted of non-early-stage cases. Therefore, while a proportional relationship between CD1a positivity and survival was observed in HER2-positive cases, statistical significance was not achieved. Future studies should include larger patient populations or more heterogeneous cohorts in terms of prognostic features to obtain more conclusive results. In our study, CD1a positivity was significantly associated only with higher nuclear grade.

Keywords: CD1a, HER2, breast carcinoma, dendritic cell

INTRODUCTION

Dendritic cells (DCs) are key players in initiating the primary immune response. Originating from the bone marrow, these cells process antigens and present them to T cells. CD34+ myeloid progenitor cells, under the influence of GM-CSF and TNF-α, differentiate into two distinct types of DCs—CD1a+ and CD14+—by day 5 of development. These two subtypes mature into typical DCs by day 12, enter circulation, and reside as immature cells in peripheral organs.[1] They are predominantly located in barrier tissues such as the skin, nasal mucosa, respiratory tract, and gastrointestinal system.[2]

Immature DCs undergo a three-step maturation process involving antigen capture, migration, and antigen presentation to T cells.[1,3,4] Mature DCs are CD83-positive and express high levels of MHC class II molecules, CD40, CD80, and CD86. In contrast, immature DCs are CD1a-positive and show low expression of CD40, CD80, and CD86.[5]

CD1a is a glycosylated type I transmembrane protein that exhibits structural homology with MHC class I and II molecules.[6] It is frequently used as a dendritic cell marker in human tumors. In the lymphoreticular system, CD1a expression is limited to a subset of DCs and some thymic cells.[7]

Numerous studies have demonstrated a correlation between dendritic cell density in tumor tissues and clinical outcomes

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across various tumor types.[6,8-12] The earlier perception of breast cancer as a non-immunogenic tumor has been challenged. The presence of antibodies specific to breast carcinoma antigens and the expansion of tumor-reactive T-cell clones among tumor-infiltrating lymphocytes support the immunogenic nature of breast cancer.[13]

Many studies have investigated the role of antigen-presenting cells in breast carcinoma, revealing associations between dendritic cell density, their spatial distribution within the tumor, and patient prognosis.[6,13] Since mature DCs are typically observed only in lymphoid organs close to T cells, the appearance of mature DCs in peritumoral regions suggests that tumor-specific immune responses may be initiated in these areas.[13]

However, the origin of tumor-infiltrating DCs remains controversial. Some studies propose that these and Langerhans cells arise from distinct lineages.[14] In contrast, lymphoscintigraphic studies have demonstrated the migration of Langerhans cells from the skin of the breast into breast tissue and subsequently to the axillary lymph nodes.[7] Supporting this view, other reports have shown that CD1a+ Langerhans cells exhibit increased CD1a expression following 24-hour in vitro incubation and lose Birbeck granules—a hallmark of Langerhans cells—during this process.[15]

HER2 is a transmembrane protein which possesses tyrosine kinase activity. HER2 is expressed at low levels in normal mammary epithelium, where only a single copy of the gene exists. In approximately 25–30% of breast carcinomas, HER2 gene amplification—often without changes in chromosome 17 copy number—results in overexpression of the receptor protein. Activation of these overexpressed receptors triggers intracellular signaling cascades that enhance tumor cell survival and proliferation.[16]

This study aims to detect CD1a expression using immunohistochemical methods in a cohort of HER2-overexpressing breast carcinoma patients. It also analyzes the correlation of CD1a expression with prognostic parameters and overall survival (OS) outcomes.

METHODS

Ethics

The study protocol has been approved by the İstanbul University Clinical Researches Ethics Committee (Date: 04.01.2013, Decision No: 2012/1504-1231). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Sample Selection

This retrospective study retrieved patient records of individuals diagnosed with invasive breast carcinoma between 2003 and 2009 from the digital pathology archive of İstanbul University İstanbul Faculty of Medicine Pathology Department. From this dataset, 48 cases were selected based on the following inclusion criteria: HER2 positivity confirmed either as strongly positive (+++) by immunohistochemistry (IHC) or moderately positive (++), with additional verification of HER2 gene amplification via the silver-enhanced in situ hybridization (SISH) technique in five of these cases. Cases that were HER2-negative or scored moderately positive but lacked confirmed positivity by SISH, cases with cell blocks unsuitable for immunohistochemical analysis, and those with unavailable prognostic data were excluded from the study.

Among the 48 tumor samples included in the study, 24 were pre-treatment biopsy specimens, while the remaining 24 were obtained from resected tumor tissues following neoadjuvant therapy. For each case, when both pre-treatment tru-cut biopsy and post-neoadjuvant resection specimens were available, the excised tissue was preferred due to its higher tumor volume and better cellularity. However, in cases where the resection specimen showed marked regression or insufficient viable tumor cells following trastuzumab-based therapy, the pre-treatment biopsy was used for CD1a immunohistochemical evaluation. All cases were reviewed on hematoxylin and eosin (H&E) stained slides, and corresponding paraffin blocks were retrieved from the departmental archives.

All selected patients had stage III breast carcinoma and received neoadjuvant treatment regimens that included trastuzumab. In accordance with the AJCC (8th edition) staging criteria, stage III breast carcinoma encompasses tumors with larger size and/or regional lymph node involvement, including T3N1, T2N2, or T4 lesions, but without distant metastasis (M0). Of the 48 cases included in the study, pathological regression data after neoadjuvant therapy were available for 47 cases. Pathological complete response (pCR) was identified in 12 of these 47 cases (25.5%). Prognostic information was collected from the patient records archived at the Oncology Institute of the İstanbul University İstanbul Faculty of Medicine. Data regarding treatment protocols and recurrence were obtained by reviewing clinical files. Additional survival information was gathered by directly contacting patients or their relatives using details from the institution's digital patient database. Both OS and disease-free survival (DFS) times were recorded. Histologic grading was assessed using the Modified Bloom-Richardson grading system.[17] Due to the use of tru-cut biopsies in some cases, only nuclear grade was assessed based on a modified Bloom-Richardson system for standardization.

Immunhistochemical Staining Method

In accordance with the datasheet recommendations of the primary antibody, non-tumoral thymic tissue was used as the positive control. Additionally, Langerhans cell histiocytosis tissue was included as a tumor-related positive control to ensure staining quality and reproducibility. Negative control staining was performed in parallel by omitting the primary antibody, confirming the specificity of CD1a immunoreactivity.

From each paraffin block, two sections were prepared—one for H&E staining and one for IHC—each cut at 3-micrometer thickness. IHC sections were mounted on positively charged slides and incubated overnight at 37°C.

For deparaffinization, the slides were immersed in xylene for 30 minutes, followed by treatment with absolute and 96%

ethanol for 15 minutes each. The slides were then rehydrated in distilled water.

Antigen retrieval was conducted using 2 ml of Envision Flex Target Retrieval Solution (50x), High pH (DM 828, Lot No:00096056, Dako), diluted in 98 ml of distilled water. The slides were placed into this solution and heated in a Dako pressure chamber at 1.5 atmospheres for 25 minutes, then allowed to cool at room temperature for 20 minutes. After retrieval, slide borders were outlined with a hydrophobic pen, followed by phosphate-buffered saline (PBS) rinses. The slides were treated with 3% hydrogen peroxide for 20 minutes to block endogenous peroxidase activity. Non-specific binding was prevented using a 15-minute protein block (ScyTek Super Block, Logan, Utah, USA; Ref No: AAA125, Lot No: 21292).

The primary anti-CD1a antibody (Clone EP3622, Cell Marque) was diluted 1:50 and applied to the sections, followed by overnight incubation at 37°C. The following day, slides were rinsed with PBS and incubated with a biotinylated secondary antibody (ScyTek SensiTek Anti-Polyvalent, Biotinylated Antibody; Ref No: ABF125, Lot No: 21020) for 40 minutes. After another PBS wash, streptavidin-conjugated horseradish peroxidase (ScyTek SensiTek HRB; Ref No: ABG125, Lot No: 21026) was applied for 25 minutes. Slides were then stained with aminoethyl carbazole (AEC) chromogen solution (ScyTek Bulk Pack AEC Chromogen/Substrate System; Lot No: 15923), prepared by mixing 20 ml of AEC chromogen with 1 ml of AEC substrate and applied for 15 minutes.

After staining, slides were rinsed in distilled water, counterstained with Mayer's hematoxylin for 5 minutes, rinsed again, and neutralized in ammonia water. Mounting was completed using an aqueous-based mounting medium (Vision Mount, Thermo Scientific/Lab Vision; TA-060-UG, 60 ml).

Evaluation of CD1a Staining

CD1a-positive DCs were identified based on both immunoreactivity and characteristic morphology: intermediate-sized cells with irregular nuclear contours, delicate cytoplasm, and occasional dendritic extensions. In excisional specimens, CD1a-positive cells were manually counted in 50 consecutive HPFs selected from viable tumor regions, excluding necrotic or stromal areas. In small-volume core biopsies, all viable tumor areas were included in the count due to limited tissue availability. This approach was consistent with methods reported in previous studies such as Coventry et al.[6] and Hillenbrand et al.[7] To enhance consistency and reduce observer bias, all cases were jointly evaluated by two pathologists who reached consensus on all immunohistochemical findings. Although formal interobserver variability analysis was not conducted, this collaborative approach helped ensure the reproducibility of results.

The distribution pattern (homogeneous vs. heterogeneous), relationship of DCs with tumor cells, and presence of DCs in the surrounding non-tumoral tissue were also examined.

Statistical Analysis

Descriptive data and immunohistochemical findings were analyzed using SPSS version 16. Relationships between variables were evaluated using Pearson's Chi-square and Fisher's exact tests. OS and DFS analyses were conducted using the Kaplan–Meier method. A p-value <0.05 was considered statistically significant.

RESULTS

All patients included in the study were female, with a median age of 52 years (range: 30–80 years). The majority (43 cases; 89.5%) were diagnosed with invasive ductal carcinoma, while 2 cases (4.16%) had invasive lobular carcinoma, and 3 cases (6.25%) had mixed-type carcinoma with both ductal and lobular components.

All patients had received neoadjuvant chemotherapy due to stage III disease.

The tumors were either strongly HER2-positive (+++) by IHC or moderately positive (++) with HER2 overexpression confirmed by SISH. All patients received trastuzumab, a tyrosine kinase inhibitor, as part of their neoadjuvant regimen. Demographic data and prognostic indicators for patients are summarised in **Table 1**.

Table 1. Prognostic features

Feature	Value
Gender (n=48)	All female
Age (n=48)	Median 52 years (range 30–80 years)
Tumor type (n=48)	Invasive ductal: 43 (89.5%) Invasive lobular: 2 (4.16%) Mixed type: 3 (6.25%)
Tumor size (n=44)	Mean: 3.85 cm Range: 0–18 cm >2 cm: 26 (59.1%) ≤2 cm: 18 (40.9%)
Axillary lymph node status (n=48)	Positive: 26 (54.2%) Negative: 22 (45.8%)
Nuclear grade (n=48)	Grade 3: 37 (77.1%) Grade 2: 11 (22.9%)

CD1a-positive dendritic cell counts in 50 HPFs ranged from 0 to 150, with a median of 7 and a mean of 17.3 cells. No staining was observed in 16 cases (33.3%), while variable levels of CD1a-positive DCs were detected in 32 cases (66.7%). In 15 of these (46.8%), DCs were evenly distributed throughout the tumor tissue; in 17 cases (53.2%), staining was patchy and clustered. In all cases with CD1a positivity, DCs were intermingled with tumor cells, and no DCs were observed in the adjacent non-tumoral tissue (**Figure**). Notably, five cases with CD1a positivity also showed prominent peritumoral lymphocytic infiltration. Data related to CD1a staining are summarised in **Table 2**.

Any level of CD1a positivity was considered when evaluating the association between CD1a expression and survival/prognostic factors. No statistically significant relationship was found between CD1a positivity and age, tumor size, lymph node involvement, or recurrence. No correlation was identified between CD1a positivity/negativity and the neoadjuvant status of the tumor. However, a significant

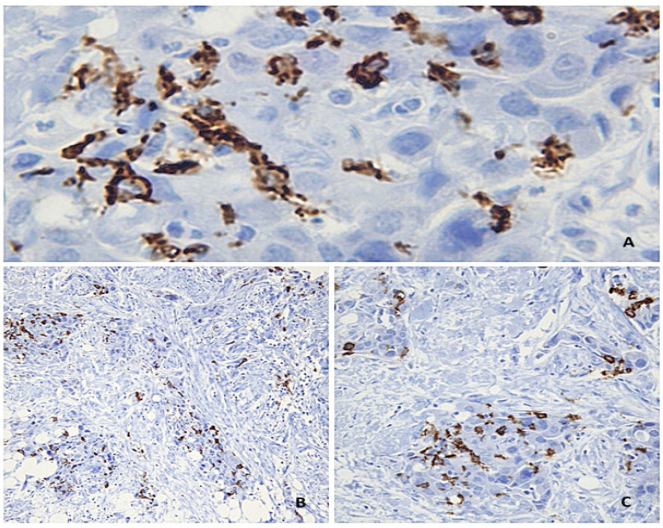

Figure. Immunohistochemical detection of intratumoral CD1a-positive dendritic cells in HER2-positive breast carcinoma. **A.** High-power field (×1000): Numerous CD1a-positive dendritic cells with intense membranous and cytoplasmic staining dispersed among tumor cells. **B.** Low-power field (×200): Diffuse distribution of CD1a-positive cells within tumor clusters. **C.** Intermediate magnification (×400): Focal accumulation of CD1a-positive dendritic cells within viable tumor areas.

Table 2. CD1a-positive dendritic cell distribution

Parameter	Value
CD1a-positive dendritic cell count (in 50 HPFs)	0 to 150
Median count	7
Mean count	17.3 cells
Cases with no staining	16 cases (33.3%)
Cases with CD1a-positive staining	32 cases (66.7%)

association was observed between nuclear grade and CD1a positivity.

CD1a positivity was observed in 36.4% of tumors with nuclear grade 2 and 75.7% of those with nuclear grade 3, indicating a significant correlation between higher nuclear grade and CD1a expression (p=0.015). When patients were grouped according to neoadjuvant therapy status, CD1a positivity was observed in 17 out of 24 patients who did not receive neoadjuvant therapy, and in 15 out of 24 patients who did (p=0.76; Chi-square test), indicating no statistically significant difference between the groups.

OS ranged from 6 to 108 months, with a mean of 55 months. DFS ranged from 1 to 108 months, with a mean of 48 months.

The five-year OS rate was 58% in CD1a-positive cases and 48% in CD1a-negative cases. Although survival appeared better in the CD1a-positive group, the difference was not statistically significant (p=0.73).

Using a cutoff of the median dendritic cell count,[7] the five-year OS was 57% in cases with high CD1a+ cell counts, compared to 52% in those with low or negative counts (p=0.89). ROC analysis was conducted to assess the ability of CD1a-positive cell count to predict DFS. The optimal cut-off determined by the Youden index was 16 cells; however, the AUC was 0.493, indicating no significant predictive value.

Additionally, multiple comparison correction was not applied due to the exploratory nature of the study and limited sample size, which may increase the risk of type I error.

Five-year DFS was 49% in CD1a-positive cases and 36% in CD1a-negative cases (p=0.9). When the threshold was set at 7 (median value) CD1a-positive cells, DFS was 49% in high-expression cases and 41% in low-expression cases. Although there was a proportional difference, it was not statistically significant.

DISCUSSION

This study analyzed 48 non-early-stage cases with HER2 positivity demonstrated by IHC or in situ hybridization. In this regard, the cases included in the study represent a specific subgroup among all breast carcinomas. The primary aim of our study was to evaluate the presence of DCs infiltrating the tumor and, thus, the impact of the immune response against the tumor based on the CD1a molecule in this particular subgroup.

The presence and density of CD1a-positive immature DCs in breast carcinoma tissues vary across studies. Bell et al.[13] applied CD1a and Langerin to 32 breast carcinoma tissues and detected the presence of immature DCs in all cases. DCs ranged from 1 to 48 per 10 HPF, with a median of 7 and a mean of 12. Coventry et al.[6] investigated CD1a (+) DC density in 30 frozen invasive ductal carcinoma tissues and found DCs in half of the samples (0.00–6.05/HPF, 0.00–13.75/mm^2; mean 2.49/mm^2). In another study, Coventry et al.[18] found CD1a (+) DCs in 50% breast cancer tissues, with a mean of 5.5 cells/mm^2. Hillenbrand et al.[7] demonstrated CD1a(+) DCs in 84% of 52 invasive ductal carcinoma tissues. In our study, 32 cases (66.7%) showed variable densities of CD1a (+) DCs. The median number was 7, and the mean was 17.3, consistent with the median reported by Bell et al.,[13] though our mean was higher.

Studies have also examined the distribution and localization of immature DCs and reached similar conclusions. Bell et al.[13] showed that CD1a (+) immature DCs were closely associated with tumor cells, while CD83 (+) mature DCs were primarily found in peritumoral areas near lymphocytic clusters. Coventry et al.[18] observed CD1a (+) DCs loosely clustered in the tumor stroma and concentrated around ductal formations in well-differentiated tumors. Treilleux et al.[19] found close interaction between CD1a (+) and Langerin (+) cells and tumor cells in one-third of 152 patients. Hillenbrand et al.[7] reported higher CD1a (+) DCs in tumor areas than in non-tumor tissues. Similarly, our study found CD1a (+) DCs close to tumor cells. In contrast to the findings of Coventry et al.,[6] no prominent dendritic cell infiltration was observed in the tumor stroma, nor were CD1a (+) DCs present in the peritumoral tissues. The presence of specific mediators may explain this close relationship between DCs and tumor cells. Kradin et al.[20] demonstrated that granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-2 promote the migration of DCs into tumor areas. Notably, Szpor et al.[21] reported that intratumoral localization of CD1a+ DCs was significantly associated with improved progression-free survival in breast cancer patients, while peritumoral CD1a+

cells lacked such prognostic association. These findings support the potential clinical relevance of dendritic cell localization and align with our observation that CD1a+ cells were predominantly found within the tumor.

The impact of CD1a (+) DCs on overall and DFS has been associated with better prognosis in many cancer types. However, although a proportional association has been observed in breast carcinomas, statistical significance has not been achieved. Coventry et al.[6] studied 48 cases (42 invasive and 6 in situ ductal carcinomas) and found a mortality rate of 32% in cases with low CD1a (+) density, compared to 18% in cases with high density. Nonetheless, this difference was not statistically significant (p=0.331). Treilleux et al.[19] found no significant correlation between CD1a density and overall or DFS in 152 cases of non-metastatic primary breast carcinomas. However, they reported that CD208/DC-LAMP-positive mature DCs were strongly correlated with CD3 (+) T cell infiltration, tumor grade, and lymph node status.

In contrast, the number of immature DCs has been associated with favorable prognosis in many other cancer types. For instance, Furukawa et al.[8] in lung adenocarcinomas, Ambe et al.[22] in colorectal carcinomas, Goldman et al.[12] in tongue carcinomas, and Tsujitani et al.[9] in gastric carcinomas demonstrated this relationship. Eisenthal et al.[23] found that high CD1a (+) DC density reduced recurrence in ovarian carcinomas. Lewko et al.,[24] Lespagnard et al.,[25] and Iwamoto et al.[26] also investigated the prognostic role of immature DCs in breast cancer but found no significant association. However, they noted that CD83(+) mature DCs were related to clinical outcomes.[26]

Our study's 5-year OS rate was 58% in CD1a-positive cases and 48% in CD1a-negative cases. Although this difference was not statistically significant (p=0.73), a proportional trend favoring CD1a positivity was observed. Similar results were obtained using a cutoff of 7 CD1a (+) cells, where higher counts were associated with better outcomes.

Although neoadjuvant therapy has the potential to alter the tumor immune microenvironment, our analysis showed no statistically significant difference in CD1a expression between patients who received neoadjuvant treatment and those who did not (p=0.76). This suggests that neoadjuvant therapy may not markedly affect the presence of CD1a-positive DCs in HER2-positive breast carcinoma tissues, at least within the limitations of our sample size.

Regarding DFS, although not statistically significant (p=0.9), CD1a-positive tumors again showed better 5-year DFS (49%) compared to CD1a-negative tumors (36%). A similar trend was seen with higher dendritic cell counts using the same cutoff.

While many studies suggest that high densities of CD83 (+) mature DCs positively affect survival, the presence of CD1a (+) immature DCs does not show statistically significant survival benefits in breast cancer. This may suggest a possible defect in the maturation of immature DCs in breast carcinomas. Some mediators secreted by tumor cells and the tumor microenvironment have been implicated in this dysfunction. Kradin et al.[20] suggested that IL-10 secreted by tumor cells may inactivate CD1a (+) immature DCs. Gabrilovich et al.[27] also reported VEGF-mediated DC maturation and function suppression.

Studies also investigate the relationship between the presence and density of CD1a (+) DCs and prognostic factors. Coventry et al.[6] found no significant associations with tumor size, grade, lymph node involvement, metastasis, or lymphovascular invasion. Hillenbrand et al.[7] also found no relationship between tumor grade and CD1a (+) cell count. In contrast, our study revealed a statistically significant association between higher nuclear grade and CD1a positivity (p=0.01), which differs from other published reports. No significant association was found with tumor size or axillary lymph node metastasis, consistent with Coventry et al.[6]

Limitations

One of the main limitations of our study is the inclusion of both pre-treatment biopsy specimens and post-neoadjuvant resection materials within the same cohort. Since all patients received trastuzumab-based neoadjuvant therapy, the potential effect of this treatment on CD1a expression remains unclear. This heterogeneity may have influenced the consistency of immunohistochemical findings and limited the comparability of CD1a positivity across subgroups.

While previous studies (e.g., Coventry et al.,[6] Hillenbrand et al.[7]) have assessed CD1a-positive DCs based on quantitative measures such as the number of positive cells per high-power field or per mm^2, an objective semi-quantitative scoring system has not been consistently adopted in the literature. We acknowledge this limitation and have recommended the development of standardized scoring systems in future studies. The absence of a universally accepted cut-off value for CD1a positivity in breast carcinoma posed a significant challenge in our analysis.

Assessing the entire tumor area in small biopsy specimens, while necessary due to limited tissue volume, may have introduced sampling variability when compared to larger excisional specimens. This potential bias is acknowledged as a limitation of the study.

The sample size was limited due to the highly specific nature of the study population. All cases were HER2-positive Stage III breast carcinoma, confirmed by IHC (and SISH when required), treated with trastuzumab-based therapy, and had available archival tissue blocks suitable for immunohistochemical analysis, along with complete 5-year clinical and radiological follow-up data accessible in our institutional records. Although extending the study period could have increased the number of eligible cases, older archival samples often pose challenges in immunohistochemical reliability due to tissue degradation or antigen loss. Therefore, prioritizing both technical feasibility and clinical consistency, we deliberately kept the sample size limited.

This study's retrospective and single-center design, along with variability in follow-up duration among patients, represent potential limitations that may influence the interpretation and generalizability of the findings.

Moreover, although trastuzumab is known to modulate the immune response through mechanisms such as antibody-dependent cellular cytotoxicity, no studies to date have specifically examined its direct effect on CD1a-positive DCs in breast cancer tissues. This lack of evidence limits the interpretation of CD1a expression levels in post-treatment specimens and represents an important area for future research.

CONCLUSION

The cases in our study were all HER2-positive. Considering that HER2-positive tumors account for only 25–30% of breast carcinomas, our study focused on a particular and homogeneous patient group. A lower survival rate was expected because HER2 positivity is a known poor prognostic factor, and our cohort consisted of non-early-stage cases. Therefore, while a proportional relationship between CD1a positivity and survival was observed in HER2-positive cases, statistical significance was not achieved. Future studies should include larger patient populations or more heterogeneous cohorts in terms of prognostic features to obtain more conclusive results. In our study, CD1a positivity was significantly associated only with higher nuclear grade (p=0.015). Thus, based on the data obtained, this specific subgroup warrants further investigation in a larger cohort.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol has been approved by the İstanbul University Clinical Researches Ethics Committee (Date: 04.01.2013, Decision No: 2012/1504-1231).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The data in this article are taken from the author's thesis titled "Investigation of HER3, CD1A, and Ki-67 expression in HER2-positive breast cancer tissues using immunohistochemical methods, determining the relationship of the results with prognostic parameters." This article is dedicated to the memory of my esteemed thesis advisor, Rıdvan İlhan.

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