Surgical and Experimental Pathology

RESEARCH Open Access

Role of GATA3 as a potential adjunct marker in the differential diagnosis of Paget's disease of the nipple

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Abstract

Aims: Paget's disease of the nipple (PDN) is a rare type of cancer of the nipple-areola complex. We examined GATA3 protein expression in PDN to determine its potential value as an adjunct marker in the differential diagnosis with other nipple lesions.

Methods and results: Chart review documented clinicopathological data. H&E slides were re-evaluated and immunohistochemistry (IHC) for GATA3 was performed. Amongst 3614 breast cancer patients, 74 had PDN and 41 cases were selected for our study (mean age, 55 years). Amid PDN cases, 4 (10%) patients showed PDN alone, 22 (65%) had an underlying ductal carcinoma in situ and 15 (37%) had invasive breast carcinomas (IBC), including 11 invasive carcinoma of no special type, 2 lobular, 1 mucinous and 1 micropapillary carcinoma. Additionally, 9 cancers were classified as luminal B, 4 as HER2 overexpression and 2 as luminal A. GATA3 expression was detected in all 41 PDN cases and in all underlying cancers. Furthermore, IHC for S-100, HMB45 and Melan-A was performed in PDN-only, ensuing negative results. Positivity for cytokeratin 7 or AE1/AE3 was demonstrated in all cases and HER2 overexpression was seen in 2/4 lesions. GATA3 expression was noted in all lesions, including one CK7-negative case.

Conclusion: Our findings indicate that GATA3 is consistently expressed in PDN. Although not entirely specific, positivity for GATA3 reinforces the non-melanocytic nature of PDN and its mammary origin, thus representing a potential adjunct tool for the diagnosis of PDN in tricky situations, particularly PDN variants or unusual lesions.

Keywords: Paget's disease of the nipple, Breast cancer, GATA3, Immunohistochemistry, Nipple skin lesions: definitive diagnosis

Background

Paget's disease of the nipple (PDN) is a disorder of the nipple-areola complex, first described by Sir James Paget in 1874 as an unusual type of cancer affecting approximately 1 to 4% of breast cancer patients (Karakas, 2011; Hoda et al., 2014). It is characterized by the presence of malignant glandular epithelial cells within the epidermis of the nipple and/or areola and is usually associated with underlying ductal carcinoma in situ (DCIS) or invasive breast carcinoma (IBC), nearly always as invasive carcinoma of no special type (IBC-NST), in 92 to 100% of cases (Karakas, 2011; Hoda et al., 2014). Most frequently, it affects women at post menopause with a mean age at diagnosis of 57 years. However, cases diagnosed in adolescents and younger patients have been reported (Karakas, 2011). Clinically, PDN presents as an eczematous,

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red or sometimes pigmented, oozing and often crusted skin lesion (Song et al., 2015). The affected area is usually limited to the nipple, although it may extend to the areola and rarely to the surrounding skin in advanced cases. Of note, these lesions might be clinically occult and identified only upon microscopic examination. Histologically, malignant epithelial cells arranged singly or in clusters are seen spreading through the epidermis, mainly in the basal region (Fig. 1). Paget's cells have abundant, pale and amphophilic cytoplasm, pleomorphic nuclei, and prominent nucleoli (Fig. 2). Also, neoplastic cells can contain cytoplasmic mucin and melanin (Schnitt & Collins, 2009). Regarding the immunophenotype, Paget's cells show expression of epithelial membrane antigen (EMA) and low-molecular weight cytokeratins, such as cytokeratin 7 (CK7), CAM5.2 and AE1/AE3. Furthermore, they regularly exhibit human epidermal growth factor receptor 2 (HER2) protein overexpression and may also express estrogen receptor and progesterone receptor, gross cystic disease fluid protein-15 (GCDFP-15) (Lundquist et al., 1999; Yao et al., 2002). The differential diagnosis of PDN includes malignant melanoma, Bowen's disease of the skin (squamous cell carcinoma in situ), Toker cell hyperplasia, and benign keratinocytes with cytoplasmic clearing (Kohler et al., 1998). In challenging cases, immunohistochemistry may be necessary to reach a definitive diagnosis (Schnitt & Collins, 2009).

In the last decade, the anti-GATA3 antibody has been widely reported as a valuable immunohistochemical marker in both urothelial and breast carcinomas (Miettinen et al., 2014; Osman et al., 2016). GATA3 is a transcription factor important in the differentiation of breast epithelia, urothelia, and subsets of T-lymphocytes. Even though not 100% specific, the anti-GATA3 antibody is considered a highly sensitive and specific tumor marker for primary or metastatic breast cancer. GATA3 protein expression has been described in the majority of luminal IBCs and also in triple-negative breast cancers, though at a lower rate (Deftereos et al., 2015; Asch-Kendrick & Cimino-Mathews, 2016). Its sensitivity in metastatic breast carcinomas is higher than GCDFP-15. In contrast, metastatic melanomas do not show GATA3 expression (Davis et al., 2016). Interestingly, Morbeck and colleagues have recently demonstrated GATA3 immunohistochemical positivity in 13 cases of Paget's disease of the vulva (Morbeck et al., 2017).

In the present study, we sought to assess GATA3 protein expression in Paget's disease of the nipple to determine its potential value as an adjunct marker in the differential diagnosis of nipple skin lesions.

Methods

Patient selection

Patients with a documented history of PDN submitted to surgical treatment at A. C. Camargo Cancer Center between 2014 and 2016 were identified amongst medical archives and Pathology files of the Department of Anatomic Pathology. Cases with no specimen slides and/

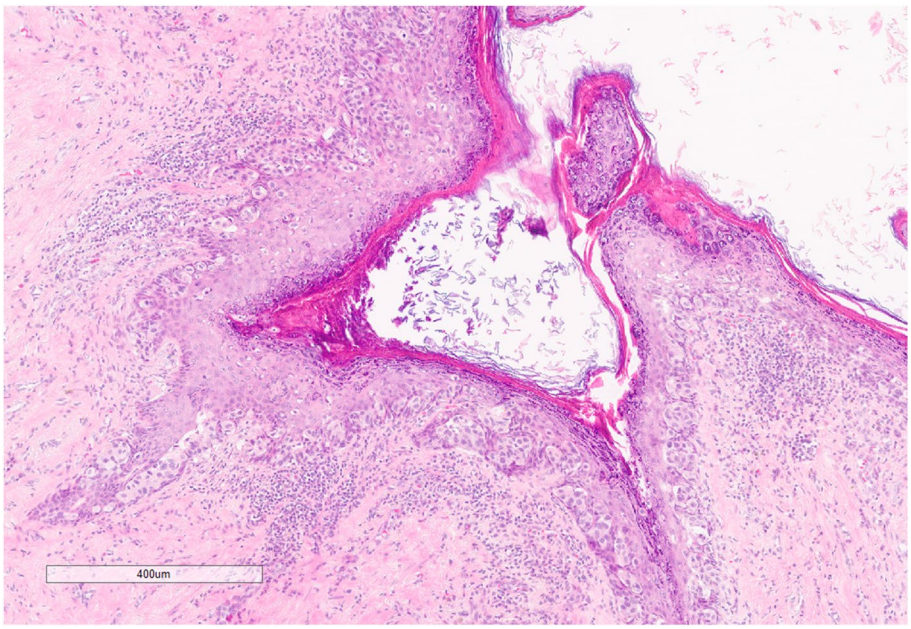

Fig. 1 Detail of Paget's cluster pools in the epidermis and dermo-epidermal junction. HE. (100x)

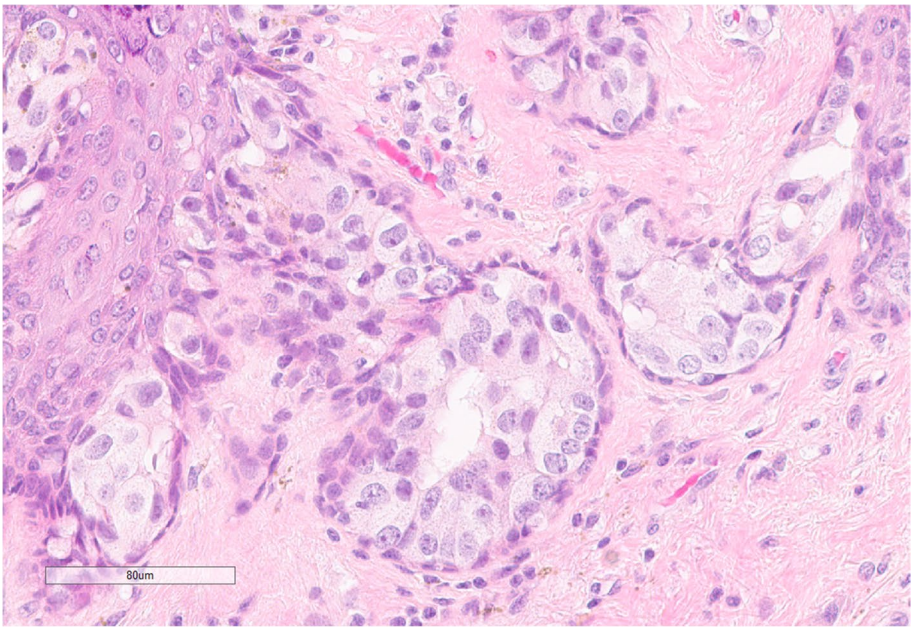

Fig. 2 Detail of Paget's cells: cluster of cells with abundant, pale and amphophilic cytoplasm, pleomorphic nuclei, and prominent nucleoli. H.E. (400x)

or paraffin blocks available for pathology review were excluded.

Clinicopathological data

Electronic medical records were reviewed for data collection comprising age and gender.

Original routine hematoxylin and eosin (H&E) stained sections representative of PDN and the remaining surgical specimen were reviewed by three pathologists (CBTO, SMB, TJNS) who evaluated all slides independently to assess the subsequent findings: presence of intraepidermal neoplastic cells characteristic of PDN (Figs. 1 and 2); DCIS and/or associated IBC (histological grade and type); IBC immunophenotype and molecular subtype as defined by the Saint Gallen consensus surrogate clinical definitions and ASCO/CAP guidelines (Gnant et al., 2015; Gnant & Harbeck, 2017; Wolff et al., 2018; Allison et al., 2020) adapted to our service, as follows: luminal A-like (estrogen receptor 'ER' strong, moderate or weakly positive; progesterone receptor 'PR' strong, moderate or weak and greater than 20%; human epidermal growth factor receptor type 2, 'HER2' negative 0 or 1+; Ki67 < 15%); luminal B-like (either ER strong, moderate or weakly positive, PR strong, moderate or weak and greater than 20%, HER2 negative 0 or 1+, Ki67 high > 20%; or ER strong, moderate or weakly positive, PR strong, moderate or weak and less than 20%, HER2 negative 0 or 1+, any Ki67; or ER strong, moderate or weakly positive, any PR, HER2 positive, any Ki67); HER2 overexpression (ER negative; PR negative; HER2 positive) or gene amplification by ISH; and triple negative breast cancer (ER negative; PR negative; HER2 negative). Breast cancer histologic classification was based on the recommendations by the World Health Organization (WHO) Classification of Tumors of the Breast, 2019 (Tan et al., 2020). Tumor histologic grade was assessed using the Bloom & Richardson scoring system modified by Elston & Ellis, the so-called Nottingham system (Elston & Ellis, 1991).

Immunohistochemical study

Sequential slides obtained from the paraffin block most representative of PDN were deparaffinized in xylene, rehydrated in graded alcohol and stained with a commercially available primary antibody directed against GATA3 (Clone L50–823; Cell Marque; 1:1000 dilution, EDTA antigenic recovery for 32 minutes) following the supplier's specifications. The immunohistochemistry (IHC) reaction was performed using an automated method on a Ventana Autostainer based on the Bench-Mark XT protocol, catalog 390 M-16.

Cases were considered positive when nuclear staining was observed in PDN intraepidermal neoplastic cells (Fig. 3).

This study was approved by our ethics committee (number 2310/16 - Comitê de Ética em Pesquisa; cephcancer@accamargo.org.br).

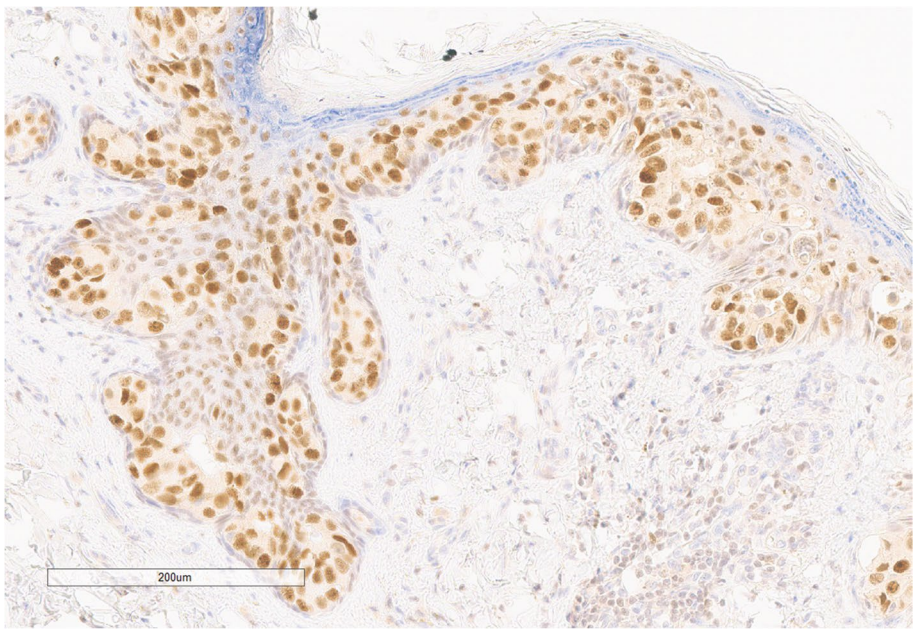

Fig. 3 Strong nuclear positive immunohistochemical staining of GATA3 in Paget's cells (200x)

Microscopic photographs were taken with Aperio AT2 Leica Biosystems.

Results

Patient selection

Our database search identified 3614 patients diagnosed with breast cancer who underwent breast surgery at our institution. Of those, a total of 74 patients had PDN and 50 were selected for our study, randomly. Due to not performing some immunohistochemical reactions because the patients removed the material from the institution, 9 cases were excluded, leaving 41 cases in our study.

Clinicopathologic characteristics

Mean age at PDN diagnosis was 55 years, ranging from 37 to 79 years, and all patients were female.

Amongst patients diagnosed with PDN, only 4 (9.7%) women showed PDN alone, whereas 22/41 (53.6%) had underlying DCIS only, 3/41 (7.3%) had underlying IBC only, and 12/41 (29,2%) had both IBC with associated DCIS. Of 22 PDN cases with DCIS only, 4/22 (18.2%) were classified as of intermediate nuclear grade and 18/22 (81.8%) as of high nuclear grade. Also, of 22 PDN cases associated with DCIS only, 20 had their immunophenotype assessed and 2/20 (10.0%) showed ER expression, 5/20 (25.0%) had PR expression, and 17/20 (85.0%) cases demonstrated HER2 overexpression (score 3+). Primary IBCs, either alone or with associated DCIS, were classified as IBC NST in 11/15 cases (73.3%), invasive lobular carcinoma in 2/15 (13.3%), invasive mucinous carcinoma in 1/15 (6.7%), and invasive micropapillary carcinoma in 1/15 (6.7%). Regarding histological grade, 4/15 (26.6%) were categorized as grade IIIand11/15 as grade II (73.3%). Moreover, 9/15 IBCs (60.0%) were classified as luminal B-like, 4/15 (26.6%) as HER2 overexpression and 2/15 (13.3%) cases as luminal A-like.

Detailed information for each case of DCIS and IBC are demonstrated in Tables 1 and 2, respectively.

Expression of GATA3

Nuclear positive staining by GATA3 was detected in the intraepidermal neoplastic cells of all 41 (100%) cases of PDN included in our study. Of note, GATA3 expression was also observed in 22/37 (59.5%) of the underlying DCIS and in 15/37 (40.5%) of the underlying IBCs.

Furthermore, the 4 cases with PDN without underlying DCIS or IBC were investigated with additional markers to confirm the diagnosis of Paget's disease. To exclude malignant melanoma, antibodies against either S-100, human melanoma black (HMB45) and Melan-A were applied, ensuing negative results (Table 3; Additional file 1: Supplementary Figure 1). Plus, positivity for cytokeratin (either cytokeratin 7 or AE1/AE3) was demonstrated in all cases and HER2 overexpression was seen in 2/4 lesions. GATA3 expression was noted in all

Table 1 Age and pathological findings of cases of Paget's disease of the nipple with underlying ductal carcinoma in situ

Case	Age	Nuclear grade	ER Expression	PR Expression	HER2
1	70	High	Negative	Weak positive	Positive 3+
2	57	High	Negative	Weak positive	Positive 3+
3	37	High	Negative	Weak positive	Positive 3+
4	63	High	Negative	Negative	Negative
5	58	High	Negative	Negative	Positive 3+
6	57	High	Moderate 90%	Negative	Positive 3+
7	40	High	Negative	Weak positive	Positive 3+
8	74	High	Negative	Negative	Positive 3+
9	46	High	Strong 90%	Strong 90%	Negative
10	72	High	Negative	Negative	Positive3+
11	49	High	Negative	Negative	Positive 3+
12	56	High	NP	NP	NP
13	53	Intermediate	NP	NP	NP
14	39	Intermediate	Negative	Negative	Positive 3+
15	67	Intermediate	Negative	Negative	Positive 3+
16	60	Intermediate	Negative	Negative	Positive 3+
17	63	High	Negative	Negative	Negative
18	45	High	Negative	Negative	Positive 3+
19	33	High	Negative	Negative	Positive 3+
20	75	High	Negative	Negative	Positive 3+
21	64	High	Negative	Negative	Positive 3+
22	72	High	Negative	Negative	Positive 3+

Legend: *ER* estrogen receptor; *PR* progesterone receptor; *HER2* Human epidermal growth factor receptor, *NP* not performed

Table 2 Age and pathological findings of cases of Paget's disease of the nipple with underlying invasive breast carcinomas

Case	Age	Nottingham grade	Histologic Type	Molecular Subtype
1	55	3	Lobular	Luminal B-like
2	49	2	IBC-NST	HER2 overexpression
3	36	2	IBC-NST	Luminal B-like
4	50	3	IBC-NST	Luminal B-like
5	50	2	IBC-NST	HER2 overexpression
6	75	2	Mucinous	HER2 overexpression
7	40	2	IBC-NST	Luminal B-like
8	45	2	IBC-NST	Luminal A-like
9	44	2	IBC-NST	HER2 overexpression
10	57	2	IBC-NST	Luminal B-like
11	52	3	IBC-NST	Luminal B-like
12	61	2	IBC-NST	Luminal B-like
13	38	3	IBC-NST	Luminal B-like
14	79	2	Micropapillary	Luminal A-like
15	65	2	IBC-NST	Luminal B-like

Legend: *IBC-NST* invasive breast carcinoma of no special type

lesions, including one case that had been shown to be CK7-negative.

Discussion

The histological hallmark of the Paget's disease of the nipple is the presence of groups of large glandular epithelial cells within the epidermis, with atypical nuclei, prominent nucleoli, abundant and pale cytoplasm. Such clear cells may occasionally resemble those of other nipple skin lesions, specially malignant melanoma, thus representing a diagnostic challenge for pathologists in tricky situations, such as pigmented, bowenoid and anaplastic PDN (Sandoval-Leon et al., 2013). In the present study, we evaluated GATA3 expression in Paget's disease of the nipple and demonstrated that, interestingly, all 41 cases showed nuclear positivity for this biomarker.

Regarding PDN cases associated with DCIS, most lesions showed nuclear grade 3, negativity for hormone receptors and HER2 overexpression. Our results are similar to those described by Dixon and colleagues (Dixon et al., 1991). In that report, histological review of the operative specimen revealed in situ disease in 35 of 37 mastectomy specimens and all had high nuclear grade. Amongst PDN cases with subjacent IBC, most tumors were categorized as grade 3 IDC NSTs, as previously described in the literature (Chen et al., 2006).

In the present study, all 41 cases diagnosed as PDN expressed GATA3, both in the neoplastic intraepidermal glandular cells and in the underlying breast cancers. Expression of the GATA3 protein is observed in the nuclei of normal luminal epithelial cells of the mammary glands as well as in the most part of luminal breast cancers (Asch-Kendrick & Cimino-Mathews, 2016). Likewise, we demonstrated that 73.3% of IBCs associated with PDN were grade 2 or grade 3 tumors with a luminal immunophenotype and all of them displayed positivity for GATA3. It is worth to mention that no cases showed a triple negative immunophenotype. These findings are in part similar to those described by Wong et al. who evaluated a series of 1102 patients with Paget's disease of the nipple and associated IBC and noted that 63.5% of tumors had a high histological grade and 54.8% showed a luminal immunophenotype (Wong et al., 2015).

The pathogenesis of Paget's disease is still a rather controversial subject and two main theories have been proposed, the epidermotropic hypothesis versus the transformation hypothesis. The former postulates the origin of Paget's cells from ductal cancer cells that migrate along the basal membrane of the ductal system into the epidermis of the nipple, while the latter advocates that PDN cells originate from the malignant transformation of keratinocytes (Sandoval-Leon et al., 2013;

Table 3 Age and immunophenotypic characteristics of cases of Paget's disease without associated breast cancer

Case	Age	CK7	AE1AE3	S100	HMB45	HER2	MELAN A
1	54	NP	Positive	Negative	NP	NP	Negative
2	66	Positive	NP	Negative	NP	NP	NP
3	61	Negative	Positive	Negative	Negative	Positive 3+	NP
4	59	Positive	NP	Negative	NP	Positive 3+	NP

Legend: *CK* cytokeratin, *HMB45* Human Melanoma Black, *HER2* Human epidermal growth factor receptor, *NP* not performed

Adams & Kanthan, 2016; Kanitakis, 2007; Morandi et al., 2003; Marucci et al., 2002). The epidermotropic theory is supported by ours and prior studies in which an underlying breast carcinoma was detected in more than 90% of PDN cases (Tan et al., 2020).

GATA3 expression in all PDN cases of our series indicates that this biomarker may be useful in the differential diagnosis with other nipple skin lesions, particularly malignant melanoma. In problematic cases, IHC may be necessary to discriminate Paget cells from other cell types, particularly when PDN presents with an unusual, non-classic morphology. Anaplastic Paget's disease is a rare variant of PDN that imitates Bowen's disease (Sandoval-Leon et al., 2013). Also, Park et al. (2011) have reported a case of PDN, which mimicked malignant melanoma both clinical and histopathologically, hence the relevance of acknowledging pigmented PDN as an uncommon clinicopathologic variant of Paget's disease where Paget cells contain melanin pigment as a result of phagocytosis (Hida et al., 2012). S100 and Sox-10, two markers used to favor melanocytic lesions, can also be positive in a subset of breast carcinomas, further highlighting possible overlaps in immunohistochemical markers for both melanomas and PDN.

Additionally, Ozerdem et al. have described 2 CK7-negative PDN cases, another tricky situation where it can be challenging to reach a final diagnosis without GATA3 as an adjunct staining to confirm the morphological hypothesis of PDN (Ozerdem et al., 2016). In our series, one PDN case with no underlying breast carcinoma showed CK7-negativity, but AE1/AE3, HER2 and GATA3 were positive in Paget cells. A recent work by Mertens et al. has described GATA3 expression in a wide variety of cutaneous epithelial neoplasms and demonstrated that GATA3 was constantly and usually strongly positive in several benign epidermal and cutaneous adnexal tumors as well as in basal cell carcinomas and squamous cell carcinomas (Mertens et al., 2015). Furthermore, Miettinen et al. have also shown that GATA3 is expressed in about 80% of squamous cell carcinomas and > 90% of basal cell carcinomas of the skin. Interestingly, all melanomas were negative (0/74) (Miettinen et al., 2014). In these cases, the classic morphology with the absence of cytoplasmic keratinization and the negativity for high molecular weight cytokeratins confirm the diagnosis of PDN (Yao et al., 2002).

We recognize the limitations of this series with regards to comparison of GATA3 expression, or lack thereof, in other nipple lesions that mimic PDN, and the retrospective nature of our study. Strengths of our work include a well-characterized patient population and central pathology review of all nipple skin lesions and breast primary tumors, with an independent cohort from previous studies in other centers that analyzed GATA3 expression in PDN.

Conclusions

In summary, our series of 41 cases further validates that GATA3 is consistently expressed in Paget's disease of the nipple. Even though not entirely specific, positivity for GATA3 reinforces the non-melanocytic nature of PDN and its mammary origin, thus representing a potential adjunct tool for the definitive diagnosis of PDN in intricate situations, particularly when dealing with PDN variants or lesions with unusual, non-classic morphology. Further studies are necessary to report specificity of this marker in the setting of nipple lesions.

Abbreviations

CK: Cytokeratin; CK7: Cytokeratin 7; DCIS: Ductal carcinoma in situ; EMA: Epithelial Membrane Antigen (EMA); GCDFP-15: Gross cystic disease fluid protein 15; GATA3: GATA binding protein 3; PDN: Paget's disease of the nipple; HMB45: Human melanoma black 45; IBC: Invasive breast carcinoma; IBC-NST: Invasive breast carcinoma of no special type; ISH: In situ hybridization.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42047-022-00125-7.

Additional file 1: Supplementary Figure 1. Melanoma cases with nested appearance (A) or pagetoid spread (B), both consistently negative for nuclear GATA3 expression in atypical melanocytes (C, D). Note that normal keratinocytes stain positively with GATA3 (C, D).

Additional file 2: Supplementary Table A.1. Antibodies, clones, dilutions, manufacturer, and city of manufacturer used.

Acknowledgements
Not applicable.

Authors' contributions
CABTO designed the study. TJNS selected the cases and performed the staining. TJNS wrote the manuscript and provide the pathological information. CABTO, SMB, VPA and FAS provided part of the cases. CABTO, SMB and TJNS rewiewed the cases and evaluated the immunostains. SRB and JVAC formatted the text. JVAC, SRB, SMB, CABTO and MDB critically read and revised the manuscript. CABTO and TJNS analyzed and interpreted the results. The authors read and approved the final manuscript.

Funding
This work was funded by the Department of Anatomic Pathology of A.C.Camargo Cancer Center.

Availability of data and materials
The data generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors have no competing interests to declare.

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Received: 29 June 2022 Accepted: 31 October 2022
Published online: 20 November 2022

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