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CK 8/18: the key to differentiating intracutaneous lesions with pagetoid features

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Abstract

Introduction: Neoplasms with pagetoid features are a category of rare lesions defined by the presence of atypical cells at different levels of the epidermis. The most important diseases within this category are mammary Paget disease (MPD), extramammary Paget disease (EMPD), Bowen's disease, *in situ* melanoma, and pagetoid reticulosis. *Aim*: The aim of this analysis was to describe the importance of the cytokeratin 8/18 (CK 8/18) immunostaining in diagnosing MPD and EMPD and differentiating them from other lesions. *Materials and Methods*: A retrospective study was employed, based on the histopathological and immunohistochemical (IHC) characteristics of 30 cases that presented pagetoid features. The cases were processed and analyzed at the Department of Pathology, Mureş Clinical County Hospital, Târgu Mureş, Romania, from 2017 to 2020. *Results*: Five MPD cases, one EMPD case, one pagetoid reticulosis case, 10 Bowen's disease cases, and 13 *in situ* melanoma cases were collected. Under Hematoxylin–Eosin staining, cells presented pale cytoplasm in MPD, EMPD, and in 25% of the melanoma cases. Hyperchromasia with nuclear enlargement was seen in all cases. Immunostaining with CK 8/18 was positive in all MPD and EMPD cases. Tests for CK7, p63, and CK AE1/AE3 were positive in MPD, EMPD, and Bowen's cases. Tests for S100, SRY-box transcription factor 10 (SOX10), human melanoma black 45 (HMB45), and Melan A were positive in melanoma cases, while cluster of differentiation (CD)3, CD4, and CD8 tests were positive in the pagetoid reticulosis case. *Conclusions*: CK 8/18 is an IHC marker that can help establish the diagnosis of MPD and EMPD and differentiate them from other pagetoid neoplasms, ensuring the proper diagnosis and prognosis are provided.

Keywords: cytokeratin 8/18, intraepidermal neoplasia, pagetoid neoplasm, cutaneous, immunohistochemistry.

Introduction

Neoplasms with pagetoid features are rare lesions characterized by the presence of atypical cells at different levels of the skin epithelium. The cause of mortality and morbidity in such lesions is determined by the type of neoplasm involved. Currently, the most common lesions in this category are mammary Paget disease (MPD), extramammary Paget disease (EMPD), Bowen's disease, *in situ* melanoma, and pagetoid reticulosis.

MPD is uncommon, representing 1–4% of all breast neoplasia. While it primarily affects females, in rare cases, it can affect males and has a peak incidence level during the sixth decade of life [1–3]. The prognosis of MPD is primarily dependent on the underlying lesion, as it is typically associated with invasive ductal carcinoma. When developed without this association, MPD has a good prognosis. However, surgical therapy and radiation of the breast will improve patient outcomes. Patients with associated carcinoma have a 5-year survival rate of 76%, 10% lower than patients without associated carcinoma. The histopathology of the lesion is characterized by the presence of single or multiple malignant Paget cells in the epithelium. Paget cells are larger in size, with pale or eosinophilic cytoplasm, enlarged nuclei, and prominent nucleoli. The lesion can mimic melanoma, squamous cell carcinoma (SCC), and pagetoid reticulosis. Immunohistochemically, markers such as cytokeratin (CK) AE1/AE3 (keratin cocktail), CK7 (cytoplasmic marker expressed in many normal epithelia and epithelial tumors), and epithelial membrane antigen (EMA) (a transmembrane protein expressed in glandular or luminal epithelial cells) are frequently used to confirm the diagnosis of MPD. CK AE1/AE3 and CK7 are epithelial markers that stain the cytoplasm of cells [4–6].

EMPD is an adenocarcinoma where the prognosis depends on whether the lesion is invasive or non-invasive EMPD in areas where apocrine glands are present in increased numbers, such as the vulva (the most commonly affected site), perineal region, and scrotum. EMPD is very rare, representing 6% of all Paget diseases of the cutaneous area, with a peak incidence rate during the sixth decade of life. There is a significant and important association between EMPD and underlying malignancies. Therefore, a detailed investigation of each patient is required. From a histopathological (HP) perspective, EMPD tumors consist of Paget cells, which show the same characteristics as in MPD. Mitosis of the cells is a constant feature. The cells are located across the entire thickness of the epidermis.

In rare cases, the cells can invade the dermis or can extend into the epithelium of the eccrine ducts and hair follicles. Regarding the immunohistochemistry of the cells, they return positive test results for CK AE1/AE3, EMA, and carcinoembryonic antigen (CEA) (an epithelial marker that demonstrates strong immunostaining in adenocarcinomas). Usually, the only treatment option is surgical resection [7, 8].

Bowen's disease, also known as SCC *in situ*, is a lesion with no detectable cause or effect yet can be linked with a series of factors, from ultraviolet exposure to human papillomavirus (HPV) infection. Bowen's disease is not common; however, its exact incidence is unknown. It primarily affects people above 60 years of age and affects both genders equally. HP examination reveals acanthosis and atypical keratinocyte cells. These cells are present in the entire thickness of the epithelium. The cytoplasm is strongly eosinophilic and may show vacuolization; the nuclei are enlarged, and mitoses are present. Immunohistochemistry of the cells demonstrates positivity for the keratin cocktail, p63 nuclear immunomarker (which stains tumoral squamous cells), and, in some cases, CK7. The lesion rarely becomes invasive, only becoming so in 3–5% of cases. Typically, surgical removal is the only therapeutic option [9].

Pagetoid reticulosis, also known as Woringer–Kolopp disease, is a very rare variant of mycosis fungoides. From a HP perspective, the tumor consists of atypical mononuclear cells that infiltrate the epidermis. These cells have pale, eosinophilic cytoplasm, and atypical, large nuclei with prominent nucleoli. Inflammatory cells are typically present in the dermis. Immunohistochemically, the cells express a range of membrane markers, including cluster of differentiation (CD)3 (specific T-cell marker), CD4 (T-helper cell marker), and CD8 cells (cytotoxic T-cell marker) [10].

The most aggressive type of tumor is melanoma *in situ*. If discovered early, the 5-year survival rate can reach up to 98%. However, this neoplasm has a high rate of mortality due to its fast rate of invasion and high rates of recurrence and metastasis. Consequently, only a small percentage of cases manage to be diagnosed in an early stage. The histological examination for these tumors shows cells of various sizes, with pale or eosinophilic cytoplasm and enlarged, pleomorphic nuclei with prominent eosinophilic nucleoli. The immunohistochemical (IHC) profile of these tumors demonstrates positivity for a range of markers, including S100 (nuclear marker), SRY-box transcription factor 10 (SOX10) (nuclear marker, highly specific for melanoma), human melanoma black 45 (HMB45) (cytoplasmic marker), and Melan A (cytoplasmic marker) [11].

Diagnosing these lesions solely using Hematoxylin–Eosin (HE) staining is difficult due to the features of these lesions. Therefore, immunohistochemistry has become a crucial diagnostic tool.

Aim

The aim of the current study was to highlight the role of CK8 and CK18 in the diagnosis and differentiation of MPD and EMPD from other pathologies with morphological similarities. Due to the significant differences in the prognosis and treatment of patients affected by different lesions, understanding the role of these will help ensure the appropriate diagnosis, prognosis, and treatment is received. By comparing the characteristics of each tumor with one another and analyzing the existing literature, it is clear that some possess a higher capacity for invasion and progression into extremely aggressive tumors that may endanger the life of an individual. Therefore, a clear, accurate diagnosis is critical for the patient and for determining further treatment.

Materials and Methods

A retrospective study design was employed by selecting 30 neoplasm cases that displayed pagetoid migration features. These cases were originally processed and analyzed at the Department of Pathology, Mureş Clinical County Hospital, Târgu Mureş, Romania, from 2017 to 2020. This selection represented all cases with pagetoid features that were diagnosed in the Department. Of the 30 cases, there were five cases of MPD, one of EMPD, one of pagetoid reticulosis, 10 of Bowen's disease, and 13 of melanoma *in situ*.

The inclusion criteria were male or female patients who displayed intracutaneous lesions with pagetoid features and were of adult age (20–80 years old).

Tissue samples were collected and processed using a routine HP technique. Samples were fixed in 10% neutral buffered formalin and embedded in paraffin prior to undergoing HE staining. IHC analysis was performed on 4 μm-thick sections prepared from formalin-fixed paraffin-embedded tissue, using an automated immunostainer (Benchmark GX, Ventana Medical Systems, Inc., Tucson, AZ, USA). All reagents and incubation times were chosen based on the directions given on the antibody package inserts. Slides were developed using the OmniMap 3,3'-Diaminobenzidine (DAB) detection kit (Ventana Medical Systems, Inc.) and were counterstained with Hematoxylin (Table 1).

Table 1 – ***Antibodies used for IHC reactions***

Antibody (clone)	Source	Reactivity		Dilution
CK AE1/AE3 (PCK26)	VMS, Inc.	Epithelial cells	Cytoplasm	RTU
CK 7 (SP52)	VMS, Inc.	Epithelial cells	Cytoplasm	RTU
CK 8/18 (B22.1&B23.1)	VMS, Inc.	Epithelial cells	Cytoplasm	RTU
p63 (4A4)	VMS, Inc.	Myoepithelial cells	Nucleus	RTU
S100 (polyclonal)	VMS, Inc.	Melanocytic cells	Nucleus	RTU
HMB45 (anti-melanosome)	VMS, Inc.	Melanocytic cells	Nucleus	RTU
Melan A (A103)	VMS, Inc.	Melanocytic cells	Cytoplasm	RTU
SOX10 (SP267)	VMS, Inc.	Melanocytic cells	Nucleus	RTU
CD3 (2GV6)	VMS, Inc.	T-lymphocytes	Membrane	RTU
CD4 (SP35)	VMS, Inc.	T-lymphocytes	Membrane	RTU
CD8 (SP57)	VMS, Inc.	T-lymphocytes	Membrane	RTU

CD: Cluster of differentiation; CK: Cytokeratin; HMB45: Human melanoma black 45; IHC: Immunohistochemical; RTU: Ready-to-use; SOX10: SRY-box transcription factor 10; VMS: Ventana Medical Systems.

Results

Of the 30 cases, 16 (53%) were female patients, and 14 (47%) were male patients. All five MPD cases (100%) were in female patients and involved the nipple. The single case of EMPD (100%) also belonged to a female patient; however, it involved the vulva. Of the Bowen's disease cases, four (40%) were female patients, and six (60%) were male patients. Six (46%) of the melanoma *in situ* cases were female patients, and seven (54%) were male patients. The single case of pagetoid reticulosis (100%) belonged to a male patient.

Four of the five (80%) MPD cases were associated with underlying ductal carcinoma. The radiological suspicion of the presence of a malignant tumor led to a sectorectomy in two (40%) cases and mastectomy in three (60%) cases.

The treatment for all the cases of EMPD, Bowen's disease, melanoma *in situ*, and pagetoid reticulosis was surgical removal through excisional biopsy.

Under HE staining, tumoral cells with clear cytoplasm were present in 100% of MPD and EMPD cases and in in 25% of melanoma cases (Figure 1).

Nuclear enlargement and hyperchromasia were observed in all 30 cases. In the melanoma *in situ* cases, the presence of prominent eosinophilic nucleoli was observed in seven (53.84%) out of the 13 cases.

Nesting was detected in six (46.15%) melanoma cases, four (40%) Bowen's cases, two (40%) MPD cases, and one EMPD case (100%). Neoplastic cells were isolated in all pagetoid reticulosis cases (Figure 2).

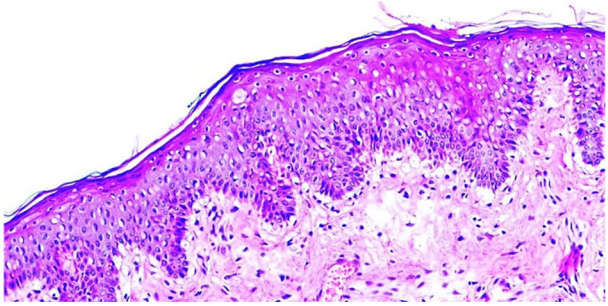

Figure 1 – ***MPD: tumoral cells are reaching the granular layer of the epidermis; these cells are large and present abundant clear cytoplasm along with enlarged, irregular nuclei. HE staining, ×50. HE: Hematoxylin–Eosin; MPD: Mammary Paget disease.***

Pigmentation was observed in one MPD case (20%), one Bowen's case (10%), and 11 (84.61%) melanoma cases.

One of the parameters analyzed was the distribution of tumoral cells across the entire epidermis. The only lesions that demonstrated differences in tumoral cell distribution were in melanoma and MPD cases. For the MPD cases, in three (60%) specimens, the tumoral cells involved the entire thickness of the epidermis, and in two (40%) cases, the pagetoid cells had extended towards the granular layer (Figure 3).

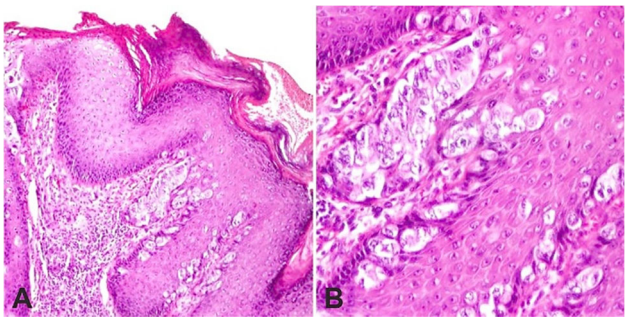

Figure 2 – ***EMPD: (A) Tumoral cells are observed in this section in the lower side of the epidermis, organized in nests but also isolated; the cells present atypia, with clear, vacuolated cytoplasm and enlarged, irregular nuclei; perilesional, we can observe inflammatory cells; (B) Tumoral cells showing high atypia. HE staining: (A) ×50; (B) ×400. HE: Hematoxylin–Eosin; EMPD: Extramammary Paget disease.***

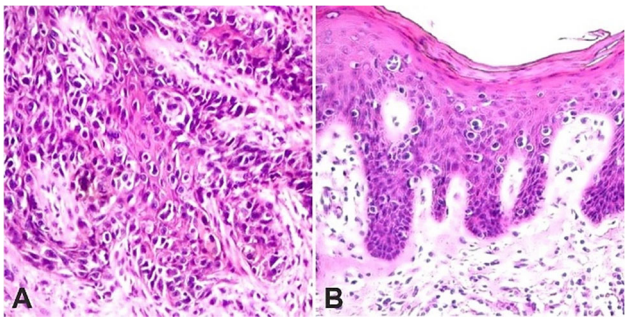

Figure 3 – ***Melanoma in situ: (A) Tumoral cells with clear/pale eosinophilic cytoplasm; the nuclei present hyperchromasia and enlargement; some of the cells show prominent nucleoli; (B) Tumoral cells reaching the upper side of the squamous layer of the epidermis; inflammatory cells are observed in the papillary dermis. HE staining: (A) ×200; (B) ×100.***

All cases of Bowen's disease and EMPD demonstrated tumoral cells in all epithelial layers. In the single pagetoid reticulosis case, the neoplastic cells extended into the granular layer. Six (46.15%) melanoma cases involved all the epithelial layers. In three (23.07%) cases, the neoplastic cells reached the spinous layer, while in two (15.38%) cases, the cells extended towards the granular layer. In the remaining two (15.38%) melanoma cases, isolated pagetoid cells reached the *stratum corneum* (Table 2).

Inflammatory cells, represented by lymphocytes, were observed in 10 (76.92%) of the melanoma *in situ* cases, in four (40%) Bowen's disease cases, and in the single EMPD.

A panel of antibodies were used, including CK AE1/AE3, CK7, CK 8/18, p63, S100, SOX10, HMB45, Melan A, CD3, CD4, and CD8 (Table 3). Each was chosen based on their specificity for the analyzed lesions.

Table 2 – ***Distribution [%] of tumoral cells in the depth of the epithelial layers***

Diseases	All	Spinous	Granular	*Stratum corneum*
MPD	60%	0%	40%	0
EMPD	100%	0	0	0
Bowen's disease	100%	0	0	0
Melanoma	46.15%	23.07%	15.38%	15.38%
Pagetoid reticulosis	0	0	100%	0

EMPD: Extramammary Paget disease; MPD: Mammary Paget disease.

MPD and EMPD both demonstrated high expression levels of CK 8/18 in all the analyzed specimens (Figure 4). The IHC reaction with p63 marker was positive in 10 cases of Bowen's disease (100%), one case of EMPD (100%), and one case of MPD (20%).

CK7 was positive in one EMPD case (100%), four (80%) MPD cases, and one Bowen's disease case (10%).

The immunostaining for S100, Melan A, HMB45, and SOX10 markers was positive in all 13 cases of melanoma. In the pagetoid reticulosis cases, only CD3, CD4, and CD8 were positive under immunostaining.

Table 3 – ***The immunohistochemistry expression of the intraepidermal lesions***

IHC markers	MPD	EMPD	Bowen's disease	Melanoma	Pagetoid reticulosis
CK AE1/AE3 (cytoplasmic marker)	+	+	+	-	-
CK7 (cytoplasmic marker)	+	+	+	-	-
CK 8/18 (cytoplasmic marker)	+	+	-	-	-
p63 (nuclear marker)	+	+	+	-	-
S100 (nuclear marker)	-	-	-	+	-
HMB45 (cytoplasmic marker)	-	-	-	+	-
Melan A (cytoplasmic marker)	-	-	-	+	-
SOX10 (nuclear marker)	-	-	-	+	-
CD3 (membrane marker)	-	-	-	-	+
CD4 (membrane marker)	-	-	-	-	+
CD8 (membrane marker)	-	-	-	-	+

CD: Cluster of differentiation; CK: Cytokeratin; EMPD: Extramammary Paget disease; HMB45: Human melanoma black 45; IHC: Immunohistochemical; MPD: Mammary Paget disease; SOX10: SRY-box transcription factor 10.

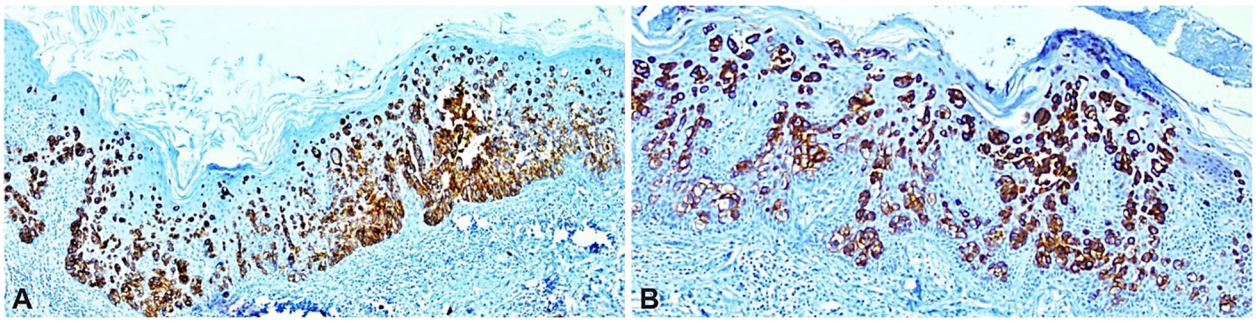

Figure 4 – ***CK 8/18 immunoexpression: (A) MPD, intense cytoplasmic immunostaining of the tumoral cells; (B) EMPD vulvar area, intense cytoplasmic immunostaining of the tumoral cells. Anti-CK 8/18 antibody immunomarking: (A) ×50; (B) ×100. CK 8/18: Cytokeratin 8/18; EMPD: Extramammary Paget disease; MPD: Mammary Paget disease.***

Discussions

MPD is a rare neoplasm of the nipple first described in 1874 by James Paget. The lesion can affect both male and female patients; however, it is most often encountered in premenopausal females. In the current study, all MPD patients were females, and four out of the five cases were associated with underlying ductal carcinoma [12].

EMPD is an uncommon lesion that originates in the skin, and it is histologically characterized by Paget cells that present the same features as those seen in MPD. The primary locations of this neoplasm are the vulvar area, axillar region, perianal region, and scrotum, as these areas contain higher numbers of apocrine glands. EMPD is more common in females compared to males. The case included in the current study was a female patient and involved the vulva [13–15].

Various studies have highlighted the histological similarities between the lesions analyzed in the current study, particularly between melanoma, Bowen's disease, and MPD. The first author to note this resemblance was Bowen, while Ackerman stated: "no more deaths by melanoma" and first introduced the concept of *in situ* melanoma. *In situ* melanoma is now described as a pagetoid lesion due to its resemblance with MPD and EMPD [10, 16].

One of the most important features observed under HE staining is the cytoplasm of tumoral cells. Many studies have described the cytoplasm of Paget cells in MPD and EMPD as clear. The cytoplasm in Bowen's disease can be vacuolated, clear, or eosinophilic, while in melanoma, the cytoplasm of the tumoral cells can vary from clear to eosinophilic. In pagetoid reticulosis, most pagetoid cells have a clear cytoplasm. In the current study, the tumoral cells presented clear cytoplasm in the MPD and EMPD cases. In the specimens analyzed, the nuclei of the tumoral cells appear enlarged and atypical, concurrent with what has been described in the literature. The nesting phenomenon (term used to describe the group distribution of the cells along the dermoepidermal junction) was observed in all the lesion types examined, although the proportion of cases of each lesion type that displayed this phenomenon varied. This characteristic has been described in all pagetoid lesions, but in the current study, it was primarily observed in melanoma specimens. Even though the migrating cells of each lesion have different precursor cell origins, the histological appearances of the lesions were highly similar, further complicating the ability to differentiate each. Therefore, immunohistochemistry is a crucial tool for differentiating between the different types of lesions [17–19].

Keratins are specific markers for epithelial cells. CK18 is a type I intermediary filament protein which is packed together with CK8. Both are expressed in various neoplasms

and are considered low molecular weight CKs (LMWCKs). The most common lesions in which this CK18 immunostaining is observed are various types of adenocarcinomas, hepatocellular carcinoma, and large neuroendocrine carcinoma. In cases of SCC, which have developed in the oral cavity, the prognosis is poor [20].

Regarding MPD, numerous previous studies have evaluated the CK7 immunomarker, which has been found to be expressed in both Toker cells, which are precursors to Paget cells, and Paget cells. In the cases evaluated in the current study, CK7 was expressed in all the epithelial lesions targeted: Bowen's disease, EMPD, and MPD. Therefore, it cannot be considered specific for the EMPD or MPD. CK AE1/AE3 demonstrated the same results [21].

Previous studies have observed that LMWCKs show an increased expression in EMPD, which was confirmed by the high immunoexpression of CK 8/18 in this particular lesion in the current study [22].

While some studies about MPD have focused on molecular findings, such as human epidermal growth factor receptor 2 (HER2) immunoexpression, few studies have evaluated CK 8/18 as a diagnostic tool for MPD. This keratin is a newly used immunomarker for this lesion and was expressed in all the MPD cases evaluated in the current study, while immunostaining was negative in all cases of Bowen's disease, melanoma, and pagetoid reticulosis. Therefore, this CK could be used as a first option when having MPD or EMPD is suspected [23, 24].

Bowen's disease is a slow progressive neoplasm that can, in rare cases, demonstrate regression. Most of the tumoral cells in this lesion are modified keratinocytes that demonstrate a loss of orientation and numerous atypical features. The cells are similar to Paget cells and usually involve the entire epidermis. In the current study, the tumoral cells were distributed across the entire epithelium [25, 26].

A small proportion of Bowen's disease lesions demonstrated pigmentation, increasing the difficultly of a differential diagnosis with melanoma. The literature incriminates the loss of normal activity in the development of the lesion, and immunohistochemistry demonstrates the expression of certain keratins, such as CK AE1/AE3 and CK7, and the p63 myoepithelial nuclear marker. All Bowen's cases analyzed in the current study demonstrated positive immunostaining for each of the aforementioned markers. The negative immunostaining for CK 8/18 is the most critical element for establishing the diagnosis of Bowen's disease [27–29].

Melanoma is the most aggressive and deadly tumoral pathology of the skin. It is extremely important that this pathology be discovered in an early stage. The most significant characteristic of this is pagetoid migration, where neoplastic cells infiltrate the entire thickness of the epidermis or are present at different layers. In the current study, this distribution in different layers was observed. Almost half of the cases analyzed presented pagetoid migration into all the layers, while a lower proportion also reached the spinous layer. In an even lower number of cases, the granular layer or *stratum corneum* was reached by isolated cells. The neoplastic cells resemble Paget cells in their histological appearance; however, their origin is melanocytic. The most commonly incriminated genes in the appearance of this lesion are V-Raf murine sarcoma viral oncogene homolog B (*BRAF*) and *p53*. Melanoma *in situ* has a high rate of invasion. In the current study, seven out of 13 melanoma cases were associated with an invasive component.

Several previous studies the have examined the IHC expression of tumoral cells have compared the immunostaining of S100, HMB45, and CAM 5.2, highlighting the expression of the first two in melanoma and comparing them with Bowen's disease and MPD. In the current study, the specific "cocktail" of immunomarkers for melanoma *in situ* all showed positivity in the lesion (S100, SOX10, HMB45, and Melan A), confirming their specificity for the tumor. Based on the results, the immunomarker considered to be the most specific for melanoma detection was SOX10, while the least was Melan A. Although S100 alone is not solely specific for melanoma, as it is also specific in some neurogenic tumors, in cases of pagetoid diseases, it remains characteristic of this type of tumor. However, there have been cases reported in the literature where S100 positivity has been demonstrated in six out of 101 MPD cases. In the current study, none of the melanocyte-specific melanoma immunomarkers were positive for MPD, EMPD, Bowen's disease, or pagetoid reticulosis [30–32].

Pagetoid reticulosis is a type of cutaneous lymphoma characterized by the presence of a highly proliferative CD8 and CD3 T-cell lymphoma that creates a disaggregation of the epidermis. It is a very rare lesion which, as defined by the *World Health Organization* (WHO), is characterized by the presence of a monoclonal lymphoid infiltrate (atypical T-cells) in the epidermis. Along with melanoma and Bowen's disease, it is one of the most important neoplasms to differentiate from Paget disease. In the current study, the tumoral cells were clear, as described in the literature. Nuclear atypia was represented by hyperchromasia and nuclear enlargement. Immunohistochemistry confirmed the origin of the tumoral cells, demonstrating positivity for the CD3, CD4, and CD8 lymphocyte immunomarkers, which were all negative in the other lesions [33, 34].

Conclusions

The lesions presented in the current study are extremely important due to their histological similarities and patient prognosis differences. Immunohistochemistry has been proven to be the most important tool for certifying the existence of these lesions and differentiating them from one another. The results of the current study suggest that CK 8/18, an LMCK, is a very important IHC marker for differentiating MPD and EMPD from other pagetoid neoplasms. Furthermore, the high specificity of this molecule alone can enable an accurate diagnosis for patients.

Conflict of interests

The authors declare that they have no conflict of interests.

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