

Case Report

# A challenging case of pigmented Bowen's disease and differential diagnosis of pagetoid pigmented skin lesions

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## Summary

Differentiation of pagetoid cutaneous neoplasms can be very challenging on hematoxylin and eosin-stained sections.

We report a singular case of pigmented pagetoid Bowen's disease showing transitional features between extramammary Paget's disease and in situ squamous cell carcinoma.

## Key words

Pigmented • Pagetoid • Bowen's disease • In situ squamous cell carcinoma

## Introduction

Pigmented Bowen's disease (BD) is an uncommon type of intraepidermal squamous cell carcinoma, representing less than 2% of all cases of cutaneous Bowen's disease (BD) <sup>1</sup>.

The most common clinical presentation is as pigmented papules or plaques located on sun-exposed areas like face, neck, trunk and extremities, even if cases involving the umbilicus and the perianal area have been reported <sup>2</sup>.

Among cutaneous squamous cell carcinomas in situ, only 5% show a nested growth pattern, referred to as pagetoid BD <sup>3,4</sup>.

We report a case of pigmented pagetoid BD (PPBD) of the back, clinically mimicking in situ malignant melanoma, and histopathologically characterized by an unusual immunohistochemical profile.

## Case report

A 74-year-old woman presented with a slowly and gradually enlarging solitary heavily pigmented lesion of the back, present since more or less for one year.

The patient reported a history of repeated sunburns and sun exposure.

The physical examination revealed a solitary dark brown, ill-defined flat lesion, measuring 1.5 x 1 cm in size, clinically suspicious for melanoma (Fig. 1). A wide surgical excision was performed and there has not been evidence of recurrence after 10 months of follow-up.

## Materials and methods

The biopsy was formalin fixed and paraffin embedded. Hematoxylin-eosin stained slices were observed at light microscopy, then immunohistochemical reactions for Cam5.2, CK pool, CK7, CK5/6, CK20, CK19, CK 34 $\beta$  12, EMA, CEA, BerEP4, S100, Melan A, CD117, p63, p16 (Ventana Medical System, Tucson, Arizona) were performed according to the peroxidase-antiperoxidase technique. Histochemical stains for Alcian Blue, PAS and PAS-D were done.

## DNA EXTRACTION

The commercial QIAamp DNA Mini Kit (Quiagen, Hilden, Germany) was used according to manufacturers' protocol.

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**Fig. 1.** A slowly and gradually enlarging solitary heavily pigmented lesion of the back.

#### PCR AMPLIFICATION

Real-time PCR is based on the detection of the fluorescence produced by a reporter molecule which increases, as the reaction proceeds. This occurs due to the accumulation of the PCR product with each cycle of amplification. The commercial Biogen HPV-HR kit (Biodiversity, Brescia, Italy) was used according to manufacturers' protocol. This is an automated qualitative real-time PCR test for detection of DNA from 12 high-risk HPV types (16, 18, 31, 33, 35, 45, 52, 53, 56, 58, 66, 73).

#### PATHOLOGIC FINDINGS

Light microscopy revealed a thickening of the involved epidermis, with foci of parakeratosis. The lesion was characterized by an increased amount of melanin-rich epidermal cells in the basal layer and by a significantly increased number of dendritic melanocytes scattered throughout the full epithelial thickness and in intimate association with atypical epithelioid cells. The atypical cellular component was characterized by a moderate amount of pale cytoplasm containing dusty melanin pigment and by malignant appearing nuclei, with coarse chromatin and prominent nucleoli, showing a pagetoid nested intraepithelial growth pattern, with typical and atypical mitotic figures (Fig. 2).

The dermis did not show neoplastic invasion and was characterized by focal dense lymphocytic infiltrate admixed with melanophages. No glandular structures or adenoid growth pattern was evident. The presence of intracytoplasmic mucin was excluded by negative staining for Alcian Blue. PAS and PAS-diastase gave negative staining. The atypical cells resulted strongly positive with cytokeratin AE1/AE3, CK 34 $\beta$  12, CK

19, EMA, CK5/6 and p63, weakly and focally positive for CK7, while cam 5.2, CK20, CEA, BerEP4, S100, Melan A were negative (Fig. 3). There was strong nuclear and cytoplasmic p16 immunoreactivity in both neoplastic cellular population of the tumor and in melanocytes present in the lesion and at the periphery, in the adjacent skin (Fig. 4). CD117 immunoreactivity resulted intensely positive in melanocytes both intralésional and of peripheral epidermis, while resulted slightly less intensely positive in intralesional keratinocytes and in neoplastic cells, but negative in adjacent non neoplastic keratinocytes (Fig. 4).

Real-time PCR genotyping for HPV gave negative result.

The periphery of the tumor showed features of pigmented reticular solar keratosis, characterized by narrow, pigmented trabeculae, with progressive merging between the two lesions.

#### Discussion

We have described a case of PPBD. Pigmented BD is an uncommon form of in situ squamous cell carcinoma (IS-SCC), that, according to Ragi et al., represents less than 2% of all BD<sup>1</sup>. Moreover, a pagetoid growth pattern has been reported to occur in only 5% of cutaneous in situ squamous cell carcinomas<sup>3,4</sup>. Pigmented BD is characterized by increased deposition of melanin pigment in the epidermis or papillary dermis, in addition to the typical histopathological features of BD, while pagetoid BD shows an intraepithelial nested growth pattern simulating Paget's disease.

Assessment of pigmented lesions is an everyday challenge both for dermatologists and dermatopathologists.

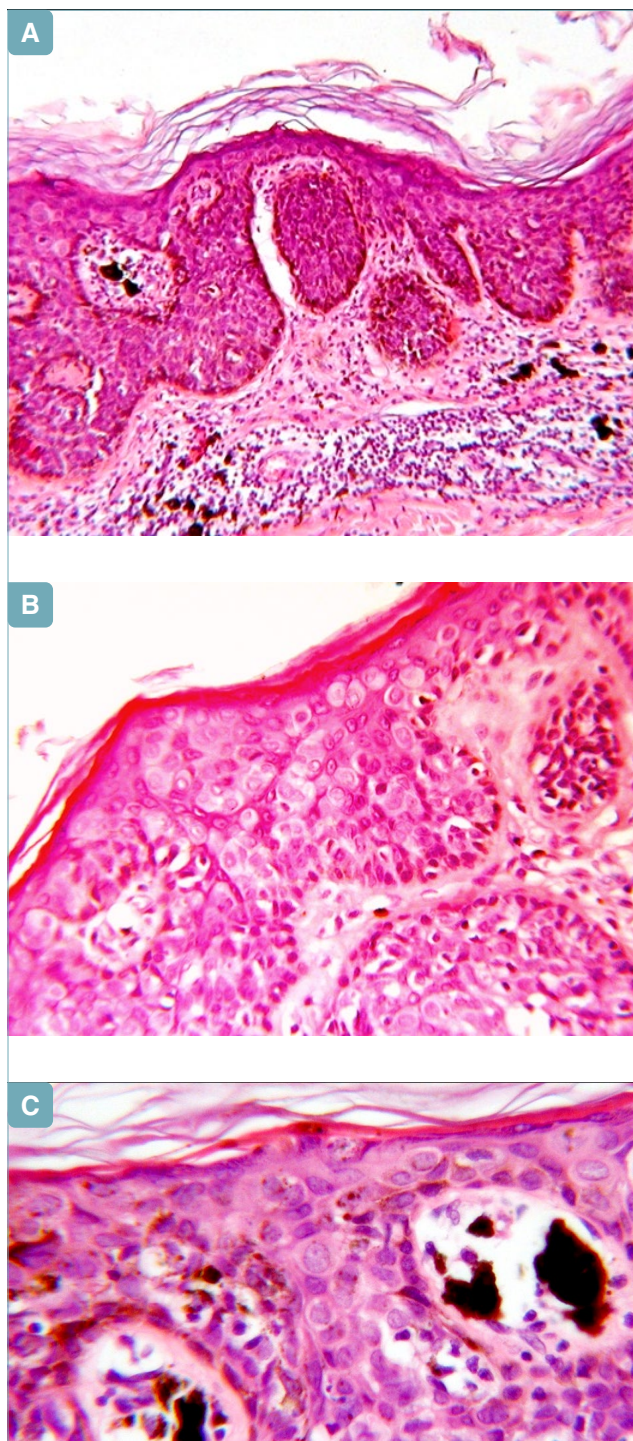
The clinical and histopathological differential diagnosis of pigmented BD includes clonal seborrheic keratosis, in situ melanoma, pigmented malignant hydroacanthoma simplex, and pigmented extramammary Paget's disease (Tabs. I, II)<sup>5-11</sup>.

Seborrheic keratosis is a very common lesion developing in middle aged and elder patient, that appears as a warty plaque, occasionally intensely pigmented, so that can clinically mimic melanoma<sup>12</sup>.

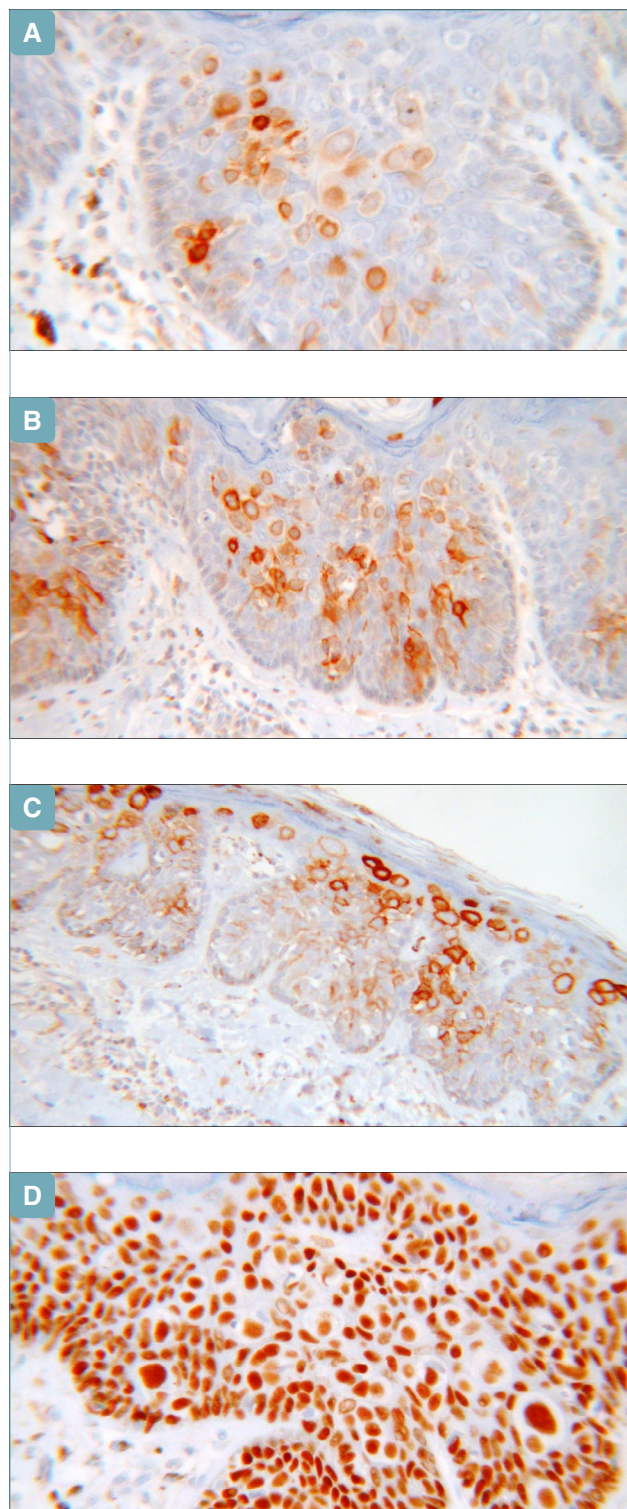
This lesion has been demonstrated to be monoclonal, representing more a benign tumor rather than an hyperplasia<sup>13</sup>.

In clonal seborrheic keratosis (CSK), tumor cells appear as circumscribed nodules of basaloid cells with an intrepidermal nested growth pattern, the Borst-Jadassohn appearance, but without evidence of cytologic malignancy as in our case<sup>14,15</sup>.

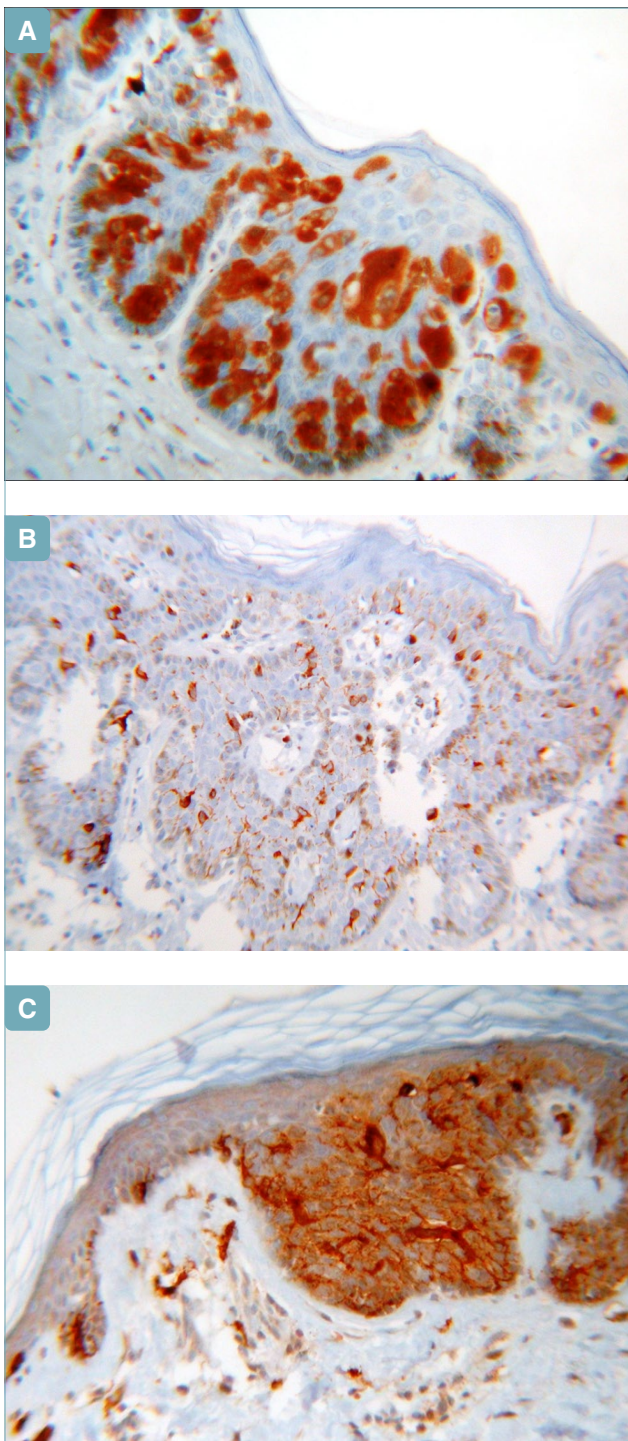
In situ melanoma (IS-M) arising within seborrheic ker-



**Fig. 2.** (A) The lesion was characterized by thickening of the epidermis, with foci of parakeratosis and by an increased amount of melanin-rich epidermal cells in the basal layer (HE, 10x); (B) the lesion had a pagetoid nested intraepithelial growth pattern (HE, 20x); (C) atypical cells characterized by a moderate amount of pale cytoplasm containing dusty melanin pigment and by malignant appearing nuclei, with coarse chromatin and prominent nucleoli (HE, 40x).



**Fig. 3.** Neoplastic cells were focally positive with CK7 (Fig. 3a; P-AP technique, 40x), strongly and diffusely positive with CK19 (Fig. 3b; P-AP technique, 40x), EMA (Fig. 3c; P-AP technique, 40x) and p63 (Fig. 3d; P-AP technique, 40x).



**Fig. 4.** (A) strong nuclear and cytoplasmic p16 immunoreactivity in neoplastic cells (P-AP technique, 40x); (B) Melan-A revealed a significantly increased number of dendritic melanocytes scattered throughout the full epithelial thickness and in intimate association with atypical epithelioid cells (P-AP technique, 20x); (C) CD117 immunoreactivity in both neoplastic cellular population of the tumor and in melanocytes present at the periphery (c; P-AP technique, 10x).

**Tab. I.** Clinical features in differential diagnosis of cutaneous pigmented pagetoid lesions.

	Type of lesion	Site	Sex	Age
CSK	Round/oval hake Flat/scaly surface May itch	Face, chest Shoulders, back	No sex predilection	Middle aged people
MIS	flat Irregular borders	Head, neck, upper and lower extremities	Females  Males	Young adults-until 49 y Over 49 y
PMHS	Nodular/ verrucous/ Hyperkeratotic plaque Ulcerated	Lower extremities Trunk	Slight male predilection	Sixth-Eighth decade
PEPD	Flat/scaly plaques	Genital/ axillary region	Female predilection	Sixth-Eighth decade
PPBD	Scaly patches or plaques	Sun exposed and covered areas	No sex predilection	Sixth-Eighth decade

atosis has been described as a relatively rare entity, although separately they have been well characterized both clinically and histopathologically<sup>16</sup>.

If clinical diagnosis is challenging, histology is confirmatory, revealing usual features of seborrheic keratosis and a concomitant proliferation of atypical melanocytes, immunoreactive to S100, HMB45 and melan-A, with a nested and pagetoid intraepidermal growth pattern. On the contrary, our case could be easily distinguished immunophenotypically from malignant melanoma by the expression of epithelial markers and lack of melanoma markers.

Pigmented variant of malignant hydroacanthoma simplex (PMHS) is a very rare entity. Only few cases are reported in the literature, all arising within benign pigmented hydroacanthoma simplex<sup>17 18</sup>.

This tumor appears as a nodule or a verrucous hyperkeratotic plaque or an ulcerated lesion with predilection for the lower extremities and the trunk of elderly patients, more frequently males, clinically mimicking seborrheic keratosis or Bowen's disease. Malignant hydroacanthoma simplex is characterized by the intraepidermal proliferation of basaloid cells with clear cytoplasm and various degrees of nuclear atypia, sharply demarcated from surrounding keratinocytes. These cells contain moderate amounts of glycogen, resulting invariably PAS positive and PAS negative after diastase digestion, although the diagnostic feature of porocarcinoma are the eccrine ductal formation and intracytoplasmic lumina, better highlighted by

Tab. II. Immunohistochemical profile in differential diagnosis of cutaneous pigmented pagetoid lesions.

	Cam5.2	CKAE1-AE3	CK5/6	CK7	CK19	CK20	CK34β E12	EMA	BER EP4	CEA	Melan A	S100	CD117	p63	p16	HER2 NEU
CSK	+	+	+	·	·	·	+	+	·	·	·	·	·	+	+	·
MIS	·	·	·	·	·	·	·	·	·	·	+	+	·	·	+	·
PMHS	+	+	+	+	+	·	·	+	+	+	·	·	+	+	+	·
PEPD	+	+	-/+	+	+	·	·	+	+	+	·	·	+	·	·	+
PPBD	·	+	+	+/-	+	·	+	+	·	·	·	+/-	+	+	+	·

CEA and EMA immunostaining. The pigmented variant is characterized by all these features and by the colonization of dendritic pigmented melanocytes as in our case, while both PAS and immunoreactions to CEA gave negative results in the case we reported<sup>17 19</sup>.

However, the main and most challenging differential diagnosis is towards pigmented extramammary Paget's disease (PEPD)<sup>20</sup>, a rare entity described clinically by Culberson and Horn<sup>21</sup> and histopathologically by Ho et al.<sup>22</sup>.

Both share the presence of pale pagetoid cells containing fine melanin granules within their cytoplasm and of numerous interdigitating dendritic melanocytes. Only 4 well-documented cases were reported in literature, all occurring in the genital or axillary region, while in our case the lesion was located on the back<sup>23 24</sup>.

Immunohistochemistry, however, is still the most reliable method to outline a sharp demarcation between Paget's cells, which are usually strongly positive for CK7, and variably positive for Cam 5.2, CK19, EMA, CEA, Her-2/neu and squamous cells which are negative<sup>25</sup>.

There seems to be a significant immunophenotypic overlap between the case we described and extramammary Paget's disease, that share CK7, CK19 and EMA expression, while CEA and Alcian Blue stain for mucin gave negative results.

P63 positivity favors the diagnostic hypothesis of squamous cell differentiation. It belongs to the p53 gene family, in the skin it is expressed in the epidermis and sebaceous glands, not in eccrine and apocrine glands. It plays an essential role in regulating the proliferation and the differentiation of squamous cells and it seems a useful marker in differential diagnosis between pagetoid BD and extramammary Paget's disease<sup>26</sup>.

In conclusion, on the basis of both morphological and immunophenotypical features, the diagnosis was PPBD/IS-SCC.

In our opinion, Pagetoid IS-SCC, already considered a separate entity in other anatomic districts as esophagus or vulva, should be considered a distinct entity also in the skin<sup>27</sup>, different from BD or conventional IS-SCC, better characterized by neoplastic cells involving the whole thickness of the epidermis. In fact, it shares more immunophenotypical similarities and overlapping features with pagetoid actinic keratosis<sup>28</sup>.

Moreover, we think that if a focal pagetoid spread can be considered a feature in the context of conventional BD, a pure pagetoid pattern, characterizing the whole lesion, is much rarer, and could represent a neoplasm derived by a different cellular clone, since it has been argued that pagetoid IS-SCC arises from a bidirectional stem cell capable of both squamous and glandular differentiation<sup>29</sup>. Strong and diffuse expression of CK19 may probably be correlated with the retention of stem cell characteristics<sup>30</sup>.

P16 overexpression may be used as indirect indicator of integrated oncogenic HPV, so we tried to detect the presence of HPV DNA, which was not found. However, p16 overexpression may be due to non-HPV-induced mutation, and according to Conscience et al., it is significantly associated with the location in sun-exposed areas, suggesting a possible induction by UV radiation, and resulting in an increased proliferation<sup>31</sup>, which in our case involved both keratinocytes and melanocytes.

Pigmentation of pagetoid neoplastic cells still remains matter of debate. We argue that c-KIT/CD117 positivity of neoplastic cells, intralesional keratinocytes and melanocytes could support the hypothesis that chemotactic factors such as stem cell factor (SCF) and its receptor c-KIT/CD117 may play a role in colonization of the lesion by dendritic melanocytes and in aiding transfer of pigment from intralesional dendritic melanocytes to neoplastic cells<sup>32</sup>. In vitro studies reported the evidence that SCF stimulates the proliferation of human melanocytes<sup>33</sup> and

in xenografts of normal human skin<sup>34</sup>. It seems that SCF/c-KIT signaling could be involved in the pathway of melanocytic activation during UVB-induced pigmentation, probably accompanied by an increased expression of SCF both in keratinocytes and melanocytes<sup>32</sup>. Other studies demonstrated that c-KIT may play a role in the pathogenesis of some dispigmentary disorders like melasma and vitiligo<sup>35</sup>, as well as that KIT signaling is involved in hyperpigmentation of solar lentigo, resulting in increased melanogenesis of existing melanocytes and in increased large melanosome complexes in keratinocytes<sup>36</sup>.

In conclusion, differentiation of pagetoid cutaneous neoplasms can be very challenging on hematoxylin and eosin stained sections. We presented a singular case of pigmented pagetoid IS-SCC/PPBD, as far as we are aware, the first described in detail, expressing focally CK7 and strongly CK19, showing transitional features between extramammary Paget's disease and IS-SCC.

CK7 is a highly sensitive marker, although not specific, for Paget's cells, that may be focally or partially expressed in a subset of cutaneous SCCs, especially poorly differentiated tumors<sup>37</sup>.

In particularly challenging pagetoid pigmented cutaneous lesions, when more tools are necessary to distinguish SCC from other mimickers, diagnostic accuracy requires an expanded immunohistochemical panel comprising melanocytic markers together with at least CK7, CK19, p63 and CEA.

#### CONFLICT OF INTEREST STATEMENT

None declared.

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