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# Report of two cases of vacuolar interface dermatitis initially suspected as melanoma *in situ* and review of the literature

## *Relato de dois casos de dermatite de interface vacuolar, inicialmente diagnosticados como melanoma* in situ*, e revisão da literatura*

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## ABSTRACT

The diagnosis of melanocytic lesions can be challenging and immunohistochemical study is a valuable tool for dermatopathologists. We report two cases initially simulating melanoma *in situ*, reviewing the histopathological and immunohistochemical findings and the cases published in the literature with similar findings/results. We emphasize the importance of clinicopathological correlation in the evaluation of lesions with interface changes and in the "pseudomelanocytic nests", which may simulate melanoma *in situ*. We also highlight the importance of using a immunohistochemistry panel in addition to Melan-A, in the study of these lesions.

**Key words:** melanoma; MART-1 antigen; dermatitis.

## INTRODUCTION

Recent studies have emphasized the difficulties in distinguishing between epithelial pseudo-nests seen in interface dermatitis and true melanocytic nests[1-6]. This distinction has great impact on patients' care, since in the first scenario the treatment is conservative, and in the latter, surgery is the treatment of choice. In interface dermatitis there are changes at the dermo-epidermal junction where the basal keratinocytes undergo necrosis and vacuolization with subsequent formation of small clusters of cells with clear cytoplasm, often mimicking nests of *in situ* melanoma. Immunohistochemical staining may not be helpful, since the most widely used marker for melanocytic lesions, the Melan-A can label injured keratinocytes[4, 6].

Herein we report two cases, in which there was nonspecific labeling of basal keratinocytes by the immunohistochemical marker Melan-A/MART-1, leading to an initial erroneous diagnosis of melanoma *in situ* (lentigo maligna).

## CASE REPORT

### Case 1

A 47-year-old woman presented with a pigmented lesion on the left upper arm, without any other clinical information. The original pathology report described interface changes and suspected a primary melanocytic lesion at this site. The case was sent to us for consultation and to perform immunohistochemical tests. The epidermis showed slightly elongated rete ridges with pointed ends. There was extensive basal layer vacuolization and necrosis of isolated keratinocytes. Mild to moderate, perivascular and perifollicular lymphocytic inflammatory infiltrate was present. Numerous melanophages were seen in the papillary dermis. Solar elastosis was observed in the superficial reticular dermis (**Figure 1**). Immunohistochemical stain for Melan-A showed numerous positive cells in the basal layer of the epidermis and extending down within follicular epithelium (**Figure 2A**). Staining with anti-S100 antibody also showed increased number of

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melanocytes in the basal epidermal layer and labeled langerhans cells in the spinous layer (**Figure 2B**). Occasional cells at the dermo-epidermal junction labeled with human melanoma black (HMB45) (**Figure 2C**). Tyrosinase showed similar pattern of staining to that seen with HMB45 (**Figure 2D**). Periodic acid-Schiff (PAS) stain failed to demonstrate thickening of the basal membrane zone and alcian blue stain did not show increased dermal mucin. A diagnosis of vacuolar/interface dermatitis was concluded, favoring a fixed drug eruption.

## Case 2

A 34-year-old man, Fitzpatrick phototype IV, presented with an ill-defined, asymptomatic, 3 × 2 cm greyish brown plaque on the left forehead, which had increased in size over the past year (**Figure 3A**). Similar lesions were present on the right lateral neck and right ear lobe (**Figure 3B** and **3C**), containing scattered black papules. A greyish macule was observed on the lateral canthus of the left eye. The patient reported extensive sun exposure, playing beach soccer 3-4 days a week for years. A biopsy from the plaque on the left forehead was initially misdiagnosed histologically as "melanoma *in situ*". However, since the clinical presentation was incompatible, the dermatologist sent the case to us for a second medical opinion.

We received the original biopsy slides for review and also examined a second one, subsequently obtained by biopsy from the left forehead. The clinical differential diagnosis included lichen planus, solar lentigo, and nevus of Ota. Microscopic examination of both biopsies showed atrophic epidermis with mild basket-weave hyperkeratosis, extensive basal vacuolization, and frequent apoptotic keratinocytes (**Figures 4A** and **4B**). In the dermis, there was a superficial and deep, perivascular and periadnexal inflammatory infiltrate composed of lymphocytes and occasional plasma cells, associated with vascular ectasia and adnexal atrophy. Immunohistochemical staining with Melan-A/MART-1 revealed positivity in a large number of cells in the basal layer and within occasional clusters of cells and nests at the junction (**Figure 4C**). Based on the histopathologic findings along with clinicopathological correlation, a diagnosis of vacuolar interface dermatitis was concluded, which included entities, such as lupus erythematosus and erythema dyschromicum perstans (ashy dermatosis, lichen planus pigmentosus), in the differential diagnosis. The patient was treated with mometasone cream once a day for a week and photoprotection, which cleared the skin lesions in a few months. He remained without new lesions two years after the diagnosis.

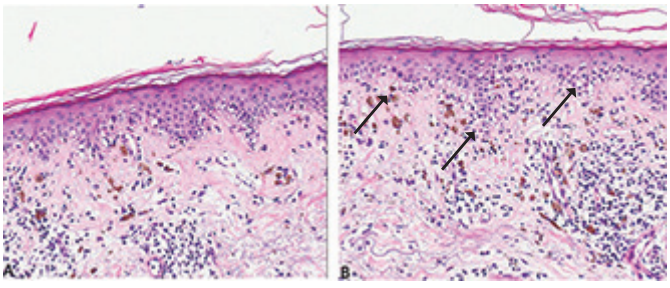

**FIGURE 1** – *Case 1: A) extensive vacuolization of basal keratinocytes resembling irregular proliferation of single melanocytes; B) in a few foci there is grouping of vacuolated keratinocytes mimicking melanocytic nests (arrows). Patchy lymphocytic inflammation and melanophages are present in the papillary dermis*

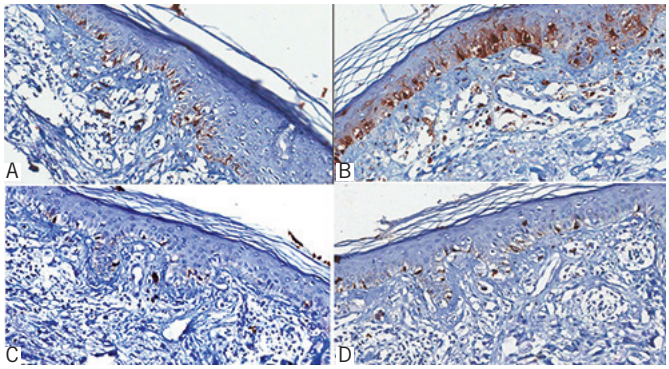

**FIGURE 2** – *Case 1: A) numerous isolated cells in the basal layer, in a continuous pattern, labeled with Melan-A, mimicking melanoma* in situ*; B) S100 stain highlighted junctional melanocytes as well as langerhans cells in the epidermis; C and D) a normal number of melanocytes labeled with HMB45 (C) and tyrosinase (D)*

*HMB45: human melanoma black 45.*

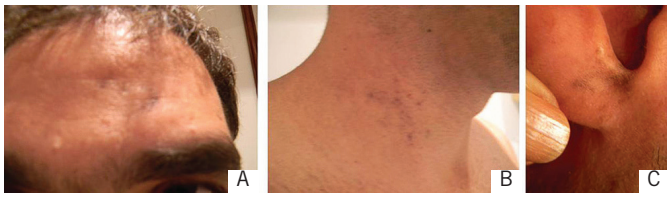

**FIGURE 3** – *Case 2: A) greyish brown plaque 3 × 2 cm on the left forehead; B) an ill-defined plaque on the right neck studded with numerous 2-3 mm black papules; C) brown papules and macules on the right ear lobe*

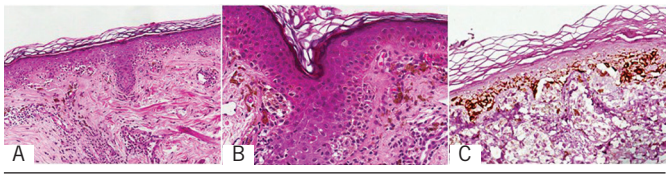

**FIGURE 4** – *Case 2: A and B) vacuolated basal keratinocytes, focally forming pseudomelanocytic nests; C) many individual cells and clusters of cells (pseudonests) at the dermo-epidermal junction showed strong positivity for Melan-A, which led to the original erroneous diagnosis of melanoma* in situ

## DISCUSSION

The most commonly used immunohistochemical markers in the diagnosis of melanoma are Melan-A/MART-1, S100, tyrosinase and HMB45[7, 8].

Melan-A/MART-1 is one of the most important melanocytic markers[1] labeling premelanosomes, which act as target for cytotoxic T lymphocytes, and is expressed by normal melanocytes and most melanomas[4, 5, 9].

The anti-S100 protein antibody is one of the most sensitive marker for melanocytes, but has low specificity, also labeling Langerhans cells in the epidermis and dermal dendritic cells, rendering identification of isolated melanocytes in the dermis particularly difficult. It is one of the melanocytic markers, in addition to nerve growth factor receptor (NGFR), SOX10 and, less frequently, MART-1/Melan-A expressed by desmoplastic melanoma cells[8, 10, 11].

HMB45 antibody is a cytoplasmic marker for the gp100 antigen, widely used for melanocytic lesions, and particularly useful for the evaluation of nevi maturation, showing strong positivity of superficial melanocytes (A type cells), and negativity of deeper cells (C type cells)[7, 8].

Recent publications have shown that Melan-A/MART-1 labels intraepidermal nonmelanocytic cells in lesions with interface damage, which may lead to an erroneous diagnosis of a melanocytic lesion, particularly melanoma *in situ*[1-7, 12].

The first to describe these alterations was Maize *et al*. (2003)[1], reporting a case which had been initially misdiagnosed as regression of melanocytic neoplasia, based on the presence of lichenoid interface reaction associated with nests of Melan-A-positive cells along the dermo-epidermal junction. However, there was discordance between the clinical presentation and the histopathologic findings and the authors decided to include additional melanocytic markers. S100, B-cell lymphoma (bcl-2), tyrosinase and HMB45 were negative. With the help of this additional immunohistochemical panel correlated to the clinical and microscopic aspects of the lesion, the authors concluded that the most likely diagnosis would be discoid lupus erythematosus. The nests-like areas, marked by Melan-A, were determined to be false positive, and named by the authors as "pseudomelanocytic nests"[1].

Subsequently, other authors reported similar cases. Beltraminelli *et al*. (2009)[3] reported three cases of lichenoid eruptions with original erroneous diagnosis of melanoma *in situ*. There were increased Melan-A-positive cells along the dermo-epidermal junction, which subsequently proved to be negative for S100, HMB45. Based on new findings by additional immunohistochemical stains and clinicopathological correlation, the lesions were diagnosed as phototoxic reaction, lichen planus pigmentosus, and pigmented benign lichenoid keratosis respectively.

Nicholson *et al*. (2010)[4] reported two cases of what they interpreted as fixed drug eruption, initially misdiagnosed as melanoma *in situ* based on false positive immunostaining of keratinocytes for Melan-A. Nicholson *et al*. (2010)[4] and Silva *et al*. (2011)[6] proposed that cytoplasmic antigens of melanocytes can be transferred to or engulfed by non-melanocytic cells, such as keratinocytes and macrophages, which could explain the false positive cases.

More recently, Gavino *et al*. (2011)[5] studied 70 cases with clinical and histopathological features of lichen planus-like keratosis containing pseudmelanocytic nests on hematoxilin and eosin (HE) in order to assess whether or not MART-1 stains the pseudomelanocytic nests. All cases were subjected to immunostaining for Melan-A/MART-1 and those with MART-1 positive junctional nests along the dermo-epidermal junction (four cases) were subsequently immunolabelled with microphthalmia-associated transcription factor (MITF), resulting in similar positivity. The authors emphasized that there was no histopathologic suspicion of melanoma *in situ* in any of these cases. They concluded that the use of Melan-A/MART-1 should not be abandoned until larger cohorts are investigated. They also cautioned against its use alone and recommended the use of additional markers[5].

Kim *et al*. (2011)[13] studied immunostaining with Melan-A/MART-1, MITF, HMB45 and Mel-5 in skin samples of melanoma *in situ* and solar lentigo, using HE stained sections as gold standard. Through counting of labeled cells per square millimeter, the authors showed that more cells than just junctional melanocytes were marked by Melan-A/MART-1 compared to the others antibodies used. They suggested that the MITF is superior to Melan-A for quantification of melanocytic cells. In contrast, HMB45 and Mel-5 seemed to immunoreact with a smaller number of melanocytes than those present in HE stained sections.

In the first case described here, the histopathologic findings and the extent of positivity for Melan-A lead the original pathologist to consider the erroneous diagnosis of melanoma *in situ*. However, HMB45 and tyrosinase immunohistochemical stains labeled only melanocytes, which appeared to be in normal number and distribution in the basal layer of the epidermis. In comparison, Melan-A and S100 stained a higher number of cells other than

melanocytes, as Langerhans cells and keratinocytes. These findings could have been misinterpreted as melanoma *in situ* if a wider panel of melanocyitc markers had not been employed.

In the second case, the clinicopathological correlation, in addition to histopathologic examination, was crucial in achieving the correct diagnosis. The size, distribution and clinical appearance of the lesions were not those of melanocytic lesions, suggesting an inflammatory condition.

We emphasize the importance of clinicopathological correlation for the diagnosis of melanocytic lesions. Sending a detailed clinical description of the lesion and relevant differential diagnosis to the pathologist proves to be indispensable. Melan-A/MART-1 immunohistochemical stain should not be used alone for the diagnosis of melanocytic lesions in the background of interface dermatitis and damage to the dermo-epidermal junction.


## RESUMO

*O diagnóstico de lesões melanocíticas pode ser desafiador, e o estudo imuno-histoquímico é uma ferramenta valiosa para os dermatopatologistas. Relatamos dois casos inicialmente diagnosticados como melanoma* in situ*, avaliando os achados histopatológicos e imuno-histoquímicos e os casos publicados na literatura com resultados semelhantes. Ressaltamos a importância da correlação clinicopatológica na avaliação das lesões com danos na interface e nos "ninhos pseudomelanocíticos", que podem simular melanoma* in situ*. Destacamos também a importância da utilização de um painel de imuno-histoquímica, além do Melan-A, no estudo dessas lesões.*


***Unitermos:*** *melanoma; antígeno MART-1; dermatite.*

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