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Pagetoid Bowen Disease: A Simulator of Clonal Seborrheic Keratosis, Case Report

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ABSTRACT

Seborrheic keratosis (SK) and Bowen disease (BD) are different entities in dermatopathology. Differentiating between these two is important and can sometimes be a challenge for the pathologist, who may need to rely on complementary techniques. To obtain a reliable distinction, several immunohistochemistry markers have been explored such as p16 and Ki67, being positive in Bowen disease and negative in Seborrheic keratosis. Ki-67 is a non-histone protein associated with ribosomes and a well-known marker of cellular proliferation, overexpressed in Bowen disease. In addition, it has been related to a greater expression of antigens associated with the growth and differentiation of keratinocytes. P16 is a tumor suppressor gene that inhibits cyclin-dependent kinases 4 and 6. His inactivation leads to a unregulated proliferation of the cell cycle. A greater expression was found in Bowen Disease compared to Seborrheic Keratosis. Immunohistochemistry allows the distinction between entities that may be appear similar both clinically and histopathologically. This is of utmost relevance since proper treatment depends on a precise diagnosis.

KEYWORDS: Squamous cell carcinoma in situ, Seborrheic Keratosis, Bowenoid pattern, Ki67, p16

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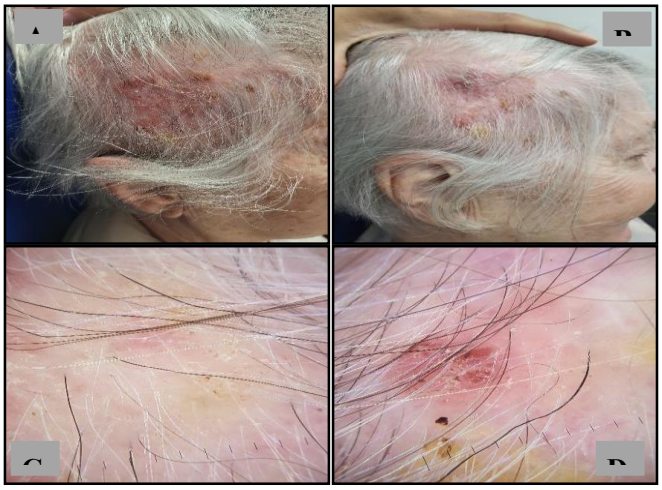
INTRODUCTION

Seborrheic keratosis (SK) and Bowen disease (BD) are common diagnoses in dermatopathology. There are numerous histological patterns of Seborrheic Keratosis, among which are acanthotic, mixed, hyperkeratotic, irritated, melanoacanthoma, reticulated, adenoid and clonal. Clonal seborrheic keratosis is a variant characterized by nests of "basaloid" cells, which can mimic the nests of "atypical keratinocytes" seen in pagetoid Bowen disease. Seborrheic keratosis present clonal nests as numerous tiny collections in which individual cells can be found in a pagetoid matrix, a configuration we refer to as "microclonal" seborrheic keratoses. Differentiating these two patterns is important and sometimes can be challenging for the pathologist, who tends to rely on ancillary techniques. The characterization of the immunoprofile of both entities is still evolving. In the search for a reliable distinction, various immunohistochemical markers have been explored, such as p16 and Ki67, being positive in Bowen disease and negative in Seborrheic keratosis.

CASE REPORT

An 80-year-old female patient, originally from Villahermosa, Tabasco, and resident of Mexico City. She was attended due a dermatosis developed over 9 years of evolution with gradual growth and completely asymptomatic.

Located on the head affecting the scalp in the right temporal region. Described by a raised neoformation 5 centimeters in diameter, light brown to yellow in color and red-orange in the center, surface with fine whitish, non-adherent scale, with regular and well-demarcated edges (Figure 1. Image A and Image B).



Dermoscopy with polarized light (10X)
(DermLite II Hybrid M Dermatoscope) showed areas with different patterns, on the one hand areas with yellowish scale, horny plugs and white background without structure that suggested seborrheic keratosis (Figure 1. Image C). On the other hand, there were alternating areas with erythema, bloody crust and white scale that indicated squamous cell carcinoma (Figure 1. Image D).

Figure 1 Clinical appearance: macroscopic and dermoscopic photographs lesions. Image A and B: Raised neoformation 5 cm in diameter, light brown, yellow and red-orange in color in the center, surface with fine white scale, non-adherent, with regular and well-defined edges. Image C. Yellowish scale, horny plugs, and white bottom without structure. Image D: Erythema, bloody crust, and white scale.

Due the extension of the lesion, it was not possible to remove it, so spindle biopsies were taken from the different areas.
The histological sections show a fragment of skin that presents an intraepidermal neoformation composed of islands of enlarged keratinocytes, with an epithelioid and basaloid appearance, with moderate pleomorphism, nuclei with slight hyperchromasia and an open chromatin pattern, evident nucleoli, and some isolated figures of mitosis. (Figure 2. Image A).
These atypical cells form well-defined nests that are located above the basal layer and lead to acanthosis. In the papillary dermis and reticular dermis, a perivascular inflammatory infiltrate of lymphocytes and melanophages is observed. (Figure 2. Image B, C and D).

Immunohistochemistry studies show that atypical epithelial cells are nuclear positive for p16 in more than 75% of the cell nest population, and with the cell proliferation index measured with Ki-67, more than 60% are observed in the same nests. Both immunostainings present a lower expression in the epidermis without alterations. (Figure 3. Image A and B)

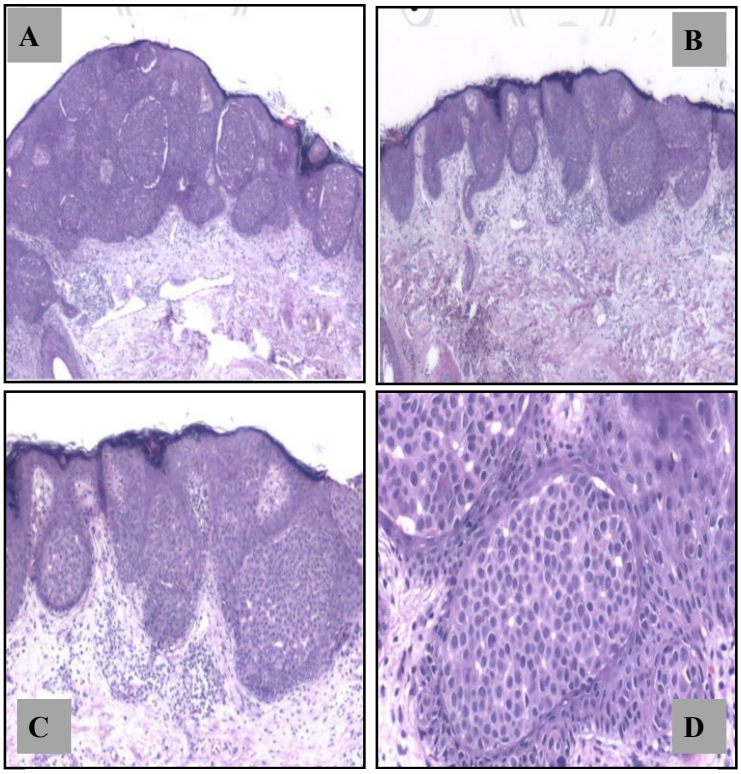


Figure 2 Histological appearance Hematoxylin and Eosin staining (H&E) *Image A and B: Intraepidermal neoformation composed of islands of enlarged keratinocytes, epithelioid and basaloid in appearance, with moderate pleomorphism, nuclei with slight hyperchromasia and open chromatin pattern, evident nucleoli, and some isolated mitosis figures. (H&E 20x).*
Image C: Atypical cells that form well-defined nests, which are found above the basal layer and cause acanthosis. (H&E 20x).
Image D: Histopathological characteristics of a Microclonal Seborrheic Keratosis. Clonal nests comprise small collections of keratinocytes with pale cytoplasm. (H&E 40x)

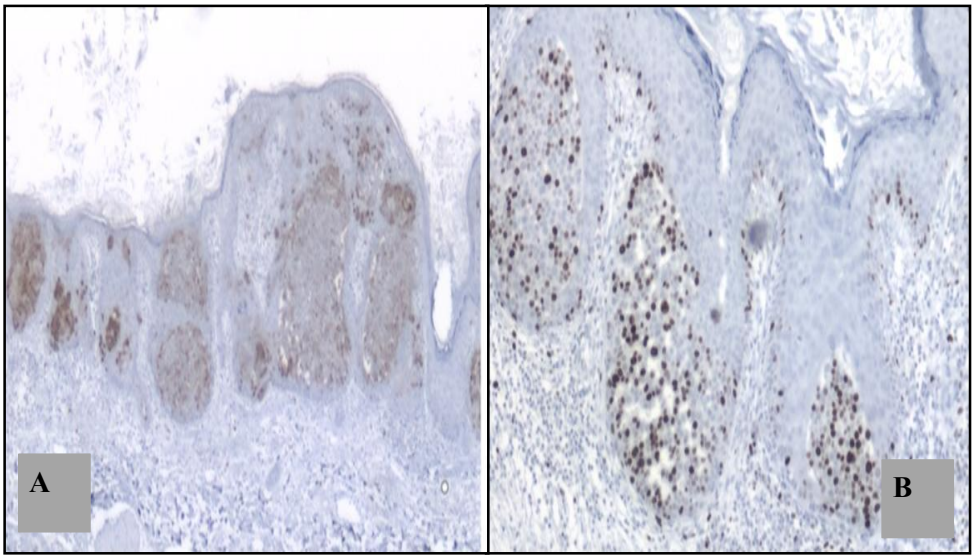


Figure 3 Immunohistochemistry studies
Image A: P16 positive in nests.
Image B: Ki-67 positive in nests.

DISCUSSION

Bowen disease and seborrheic keratoses are completely different entities. The first one is a malignant lesion, and the second one is a harmless lesion, which leads to radically different management.

Seborrheic keratoses are benign tumors that occur frequently, they affect people over 30-years-old, may appear on any part of the skin, but their most frequent location is on the torso and head. His etiology is unknown; however, several theories have been postulated such as: FGFR3, PIK3CA, KRAS and EGFR mutations, sun exposure and the presence of Human Papillomavirus. They are asymptomatic but sometimes can cause itching or irritation. As it is a benign lesion, it does not require treatment.[1,2]

Bowen Disease is an epidermoid carcinoma in situ, it can appear on any mucocutaneous surface including the nail bed, but it predominates in regions exposed to the sun such as the head, neck, and arms. They usually appear as well-defined erythematous-scaly plaques. It frequently affects men, especially those over 60 years of age. Its etiology is related to exposure to UV radiation, genetics, and DNA repair defects. The treatment is surgical, achieving a good future prognosis.[3]

One of the similarities between pagetoid Bowen Disease and seborrheic keratosis is the Borst–Jadassohn phenomenon, which is a histological term that describes lesions that present well-defined nests of typical or atypical cells within the epidermis. The mechanism of formation of these nests is unknown, although it is postulated that epidermal growth factor plays an important role in their development. Few studies related to the immunoprofiling of entities that comprise this phenomenon have been recorded with limited data on the specific immunohistochemical distinction between Pagetoid Bowen Disease and Clonal Seborrheic Keratosis.[4]

Ki-67 is a non-histone protein associated with ribosomes and a well-known marker of cell proliferation, which demonstrated overexpression in Bowen disease. Also, it has been related to a greater expression of antigens associated with the growth and differentiation of keratinocytes.[5,6]

P16 is a tumor suppressor gene that inhibits cycle-dependent kinases 4 and 6. His inactivation causes unregulated proliferation of the cell cycle. A higher expression was found in Bowen Disease. [7]

The histological parameters showed a significant difference with the positive immunostaining of nests between Bowen Disease and Clonal Seborrheic Keratoses, which means growth and proliferation of keratinocytes.[8] These findings are relevant to achieve an adequate diagnosis and, therefore, appropriate treatment.

Pagetoid Bowen Disease represents only 5% of all histological variants of Bowen Disease.[5] Despite an extensive literature search, we were unable to identify a previous publication of pagetoid Bowen disease in the Mexican population.

We consider the case of interest due it represents a strange histological variant, and physical examination, dermatoscopy, and conventional histopathology did not clearly show data suggestive of malignancy.

Finally, biopsies were taken from different sites of the lesion, in addition to performing immunohistochemistry studies with Ki67 and P16 to achieve the definitive diagnosis. Although the lesion has been evolving for a long time and one area appeared to be a benign lesion (Seborrheic keratosis), the presence of extensive erythema did not coincide with the clinical suspicion.

CONCLUSION

Seborrheic keratosis usually mimics other dermatological diagnoses, which is why it sometimes requires the support of

histopathological study, which is the gold standard for its definitive diagnosis. However, on some occasions it can represent a diagnostic challenge for the pathologist.

Immunohistochemistry is an extremely useful tool for distinguishing diagnosis that may be similar clinically and histopathologically.

This is of utmost importance due the treatment of the entity depends on the histological diagnosis and in cases like ours, where it was hard to distinguish the cells arranged in nests and cell proliferation, an adequate diagnosis was achieved using Ki67 and P16, to carry out adequate and timely treatment.

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