Small lesions of porokeratosis show a normal proliferation rate with MIB-1

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ABSTRACT

Aim: Cornoid lamella is the hallmark of the group of conditions encompassed by the term porokeratosis (PK). One of the characteristics of cornoid lamella is parakeratosis. Although these explanations are not universally accepted, dermatopathology suggests that parakeratosis is formed either by the acceleration of epidermopoiesis or the faulty maturation of keratinocytes. This study tested the proliferation rate of the cell population underneath the cornoid lamella.

Method: An immunohistochemical study was performed in four cases of PK (2 plaque type PK, 1 disseminated superficial actinic PK, and 1 linear PK) with the MIB-1 antibody. The lesions evidenced in the patients were all smaller than 2 cm.

Results: The epidermal cells beneath the cornoid lamella showed a proliferation rate that was similar to the one observed in the adjacent epidermal cells in all cases.

Conclusions: These findings support the premise that hyperproliferation of keratinocytes is not needed for the genesis of the cornoid lamella.

KEY WORDS

porokeratosis, MIB-1, Ki-67, proliferation rate, Mibelli, cutaneous basal layer

Introduction

The term porokeratosis (PK) encompasses a heterogeneous group of disorders that all have in common the presence of cornoid lamella. This is the result of a disorder in the normal keratinization of epidermal cells, which, among other things, turns into parakeratosis.

Taking into account many morphological studies dedicated to the subject, several hypothesis have been proposed to explain how the cornoid lamella would form. In dermatopathology, nevertheless, there are two main ways through which parakeratosis can be produced: either by an acceleration of the epidermopoiesis, or by faulty maturation of keratinocytes, although this latter concept is not universally accepted.

In order to test the proliferation rate of the epidermal cells beneath the cornoid lamella, 4 cases of PK were tested with the antibody MIB-1, which recognizes the protein Ki-67. Although this antibody is widely used on a daily basis in general pathology all over the world,

its use in the study of PK is only poorly represented in the literature, if at all.

Material and methods

Four cases that had been diagnosed as PK were recovered from our archives. In all of them, the slides plus clinical details were reviewed, and new sections for routine stain with hematoxylin and eosin were obtained. We performed an immunohistochemical study with MIB-1 in the four cases (DakoCytomation, monoclonal mouse anti-human antibody, clone MIB-1).

Results

The four cases were confirmed as PK. The morphologic characters of PK were evident in all biopsies with a typical cornoid lamella (Fig. 1). Two cases were clinically diagnosed as plaque type, one case as disseminated superficial actinic type, and the other as linear PK.

The details about the patients and the location of the lesions are shown in Table 1. The largest lesion was 2 cm in diameter, and so they would qualify as small PK skin lesions in all patients using the classification by Otsuka et al. (1).

The immunostain for MIB-1 showed that the proliferation was not increased under the cornoid lamella (Fig.2). The proliferation rate was similar to the areas of preserved epidermis that were adjacent to the lamella. The positive cells were mainly confined to the stratum basalis.

Discussion

Porokeratosis encompasses a heterogeneous group of disorders that have in common the histologic evidence of cornoid lamella (1). Among other characteristics, the cornoid lamella has a striking parakeratosis. In dermatopathology, parakeratosis is assumed to be the result of either one of two main pathogenic processes: the acceleration of epidermopoiesis or the faulty maturation of keratinocytes (2). This is not universally accepted; some think that rapid proliferation by itself does not cause parakeratosis (3).

There are many findings in the literature that give reason to think that the maturation of keratinocytes is somehow impeded in PK.

The epidermal cells underneath the cornoid lamella show signs of dyskeratosis and vacuolization, which correlates with the ultrastructural findings of degeneration of the keratinocytes (4), the condensation of tonofilaments in their periphery (5), autophagic vacuoles plus degraded organelles in them (6), and nuclear remnants (4). Some authors, on the other hand, have interpreted these findings as the outcome of rapid keratinization (7). Nevertheless, studies with the terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin nick-end labeling (TUNEL) reaction point to the premature degeneration via apoptosis of the keratinocytes as a mechanism for the formation of the cornoid lamella (8). Moreover, immunohistochemical findings show interruption of the loricrin expression underneath the cornoid lamella in cases of PK (8). However, there is a diffuse upregulation of involucrin in the epidermis in PK (7).

Some authors have claimed that PK is the result of hyperproliferation of keratinocytes, based on their find-

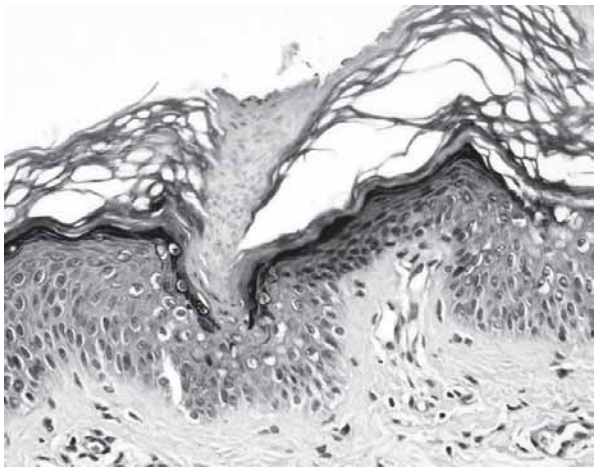

Figure 1. Morphologic character of PK in a biopsy of a typical cornoid lamella. The photograph was taken from the biopsy of case 3.

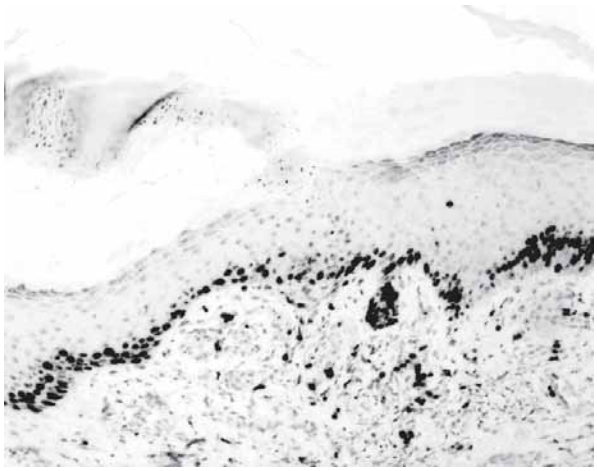

Figure 2. Immunostain for MIB-1 showing that proliferation was not increased under the cornoid lamella compared to the adjacent epidermis. Taken from the biopsy of case 3.

ings that gene expression profiling shows similarities between PK and psoriasis (9) but, as mentioned above, the phenotypic features of the cells in the cornoid lamella seem to be closer to a premalignant disease than to an inflammatory one (10).

In pathology, there is a very simple way to study the growing fraction of a cellular population through immunohistochemistry using, for instance, the MIB-1 antibody. It is well known that this antibody recognizes the nuclear protein Ki-67, which is mainly expressed during the active phases of the cell cycle (G1, S, G2, and M-phases), while it is not expressed by cells in resting phases (G_0) (11, 12).

Although several immunohistochemical studies of porokeratosis have been carried out (7, 10, 13), to the best of the author's knowledge there has been no emphasis on the immunostain for Ki-67 in PK. This is mainly due to the fact that many of the immunohistochemical studies on PK have focused on its premalignant potential, and thus on the expression of molecules such as p53 (13, 17). Other reports have focused instead on the inflammatory cells that might be involved in the pathogenesis of PK (18–20). It must be stated that some markers related to proliferation other than Ki-67 have been studied in PK. Some have tested the growth activation marker psi-3, and found it expressed by viable keratinocytes in all stages in the keratinocyte differentiation pathway in PK (10); again, however, this is interpreted by the authors more as an aberrant expression of molecules by the cells (21).

Some others have found an increase in cell proportions in the S and G2/M phase, when studying the nuclear DNA content from epidermal cells from PK lesions by fluorometry (22, 23).

Most of the tests for p53 in PK have demonstrated that expression of p53 is increased in cornoid lamella in comparison to either adjacent or subjacent epidermis (13, 16), and that this overexpression of the molecule is not related to gene mutation (24, 25). This agrees with the findings presented here because p53 arrests cells at G1 (26).

Table 1. Details of patients in whom porokeratoses were diagnosed.

Case	Sex	Age	Type of porokeratosis	Location of lesion(s)
1	Female	76	Plaque	Face
2	Male	73	Disseminated superficial actinic	Legs
3	Male	10	Linear	Trunk
4	Female	35	Plaque	Buttock

A normal proliferation rate might be interpreted as one more proof of an impeded maturation of keratinocytes as the main mechanism responsible for the parakeratosis that is observed in PK.

There is a very interesting report by Otsuka et al. from 1993, in which the authors demonstrated that large and small PK lesions might have different biological bases and behavior (1). They defined large lesions as those larger than 5 cm. These can appear as the outcome of the enlargement of a single lesion or by the coalescence of small ones. In this sense, in their first stages, it would be impossible to distinguish between small and large lesions on histopathological grounds alone. Large lesions would need years to develop, but they are not necessarily always the final stage of small lesions: some small lesions stay small forever. What these authors demonstrated was that large lesions presented a higher mitotic rate than small ones. Also, both DNA ploidy and DNA index values were higher in large lesions than in small lesions.

Considering these facts, our cases might all belong to the small lesion type rather than an early stage of large lesion type, owing to their non-increased proliferation rates. These findings also show that, even if large and small lesions are considered to be different in their biological behavior and nature, an increased proliferation rate is not necessary in the genesis of the cornoid lamella.

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