Diagnostic utility of Ki-67 and Cyclin D1 immunostaining in differentiation of psoriasis vs. other psoriasiform dermatitis

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ABSTRACT

Background: Differentiation of psoriasis from non-psoriasis psoriasiform dermatitis (NPPD) may be difficult for dermatopathologists, as lack of distinctive histopathological features in a subset of cases may cause confusion in diagnosis.

Objective: As the prototype of psoriasiform dermatitis, psoriasis is a hyperproliferative skin disorder with increased epidermal turnover compared with NPPD, we investigated the role of proliferation markers, Ki-67 and Cyclin D1 as diagnostic tools to differentiate psoriasis from other psoriasiform dermatitis.

Methods: Histopathological specimens of psoriasis (n = 35) and NPPD (n = 36, 14 pityriasis rubra pilaris, 12 pityriasis rosea and 10 lichen simplex) cases were reviewed and immunohistochemically stained for Ki-67 and Cyclin D1. Ki-67 and Cyclin D1 positive cells were counted for suprabasal, and total epidermal immunostaining per mm^2.

Results: Suprabasal and total epidermal cell counts for Ki-67 were found to be significantly higher in the psoriasis group compared with the NPPD group ($p < 0.05$). An important and interesting feature was the presence of a cut-off value for the suprabasal/total epidermal cell count ratio of 75% for Ki-67 immunostaining, which was higher in all patients having psoriasis (range, 77.1% - 92.4%) and lower in all NPPD cases (range, 21.0% - 73.3%). However, suprabasal Cyclin D1 cell counts were higher in the psoriasis group compared with the NPPD group ($p < 0.05$), total epidermal Cyclin D1 cell counts were not statistically significant in either group ($p = 0.167$), and a cut-off value for suprabasal/total epidermal cell count ratio to distinguish these two entities was not detected using this immunostain.

Conclusions: We suggest that Ki-67 is a more sensitive marker than Cyclin D1 in terms of having a cut-off value of 75% for the suprabasal/total epidermal immunoreactive cell count ratio, which we believe could be useful for dermatopathologists in differentiating psoriasis from other psoriasiform dermatitis.
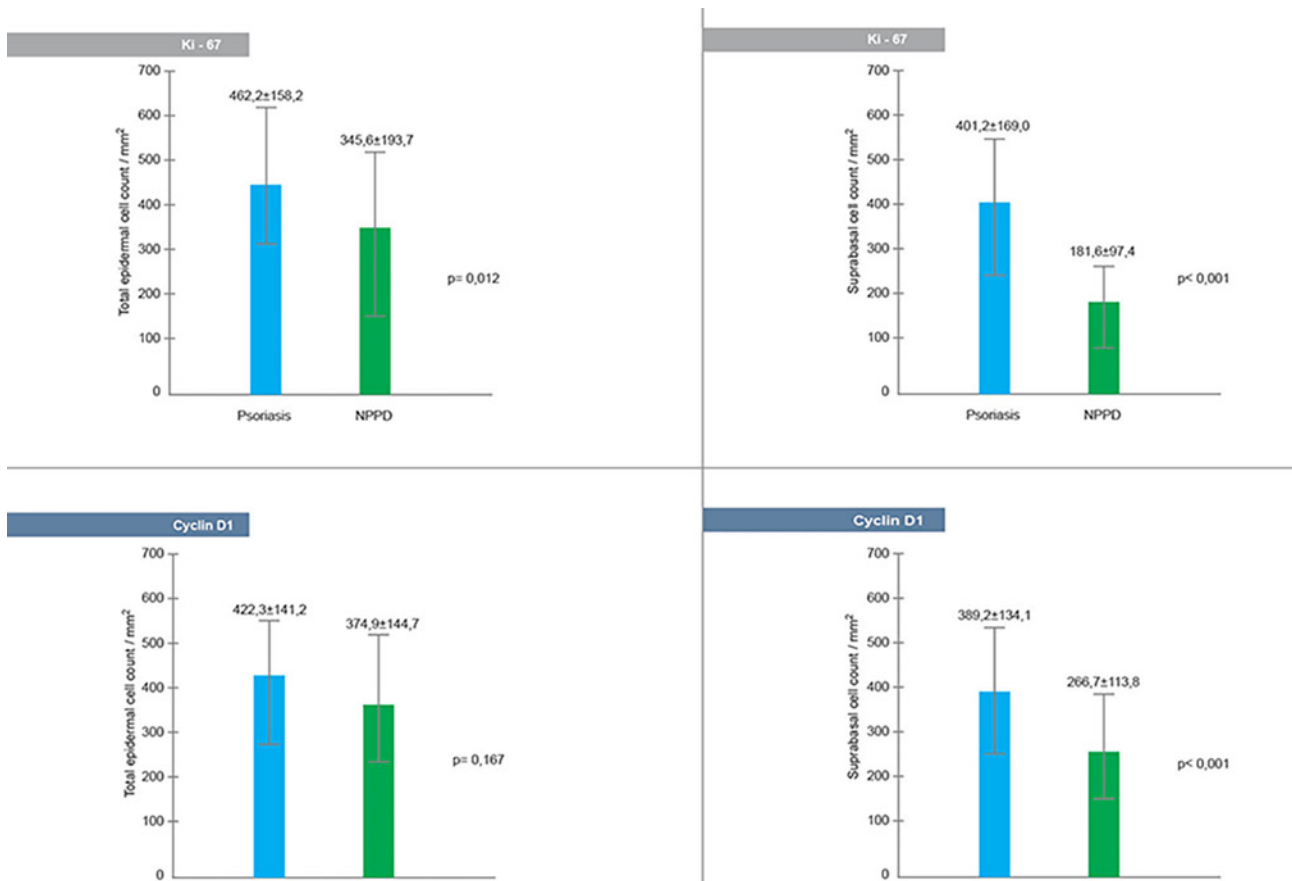
Figure 1. Total epidermal and suprabasal cell counts/mm² for Ki-67 and Cyclin D1 immunostaining; NPPD, Non-psoriasis psoriasiform dermatitis. [Copyright: ©2015 Sezer et al.]

Introduction

Psoriasiform dermatitis histopathologically indicates the presence of epidermal hyperplasia with elongation of the rete ridges in a regular manner. However psoriasis is the prototype of psoriasiform dermatitis, various skin disorders such as pityriasis rubra pilaris, lichen simplex chronicus and pityriasis rosea may reveal psoriasiform epidermal hyperplasia and cause confusion in histopathological diagnosis.

Although characteristic and distinctive histopathological features such as Munro's microabscesses and tortuous, dilated capillaries in psoriasis; alternating horizontal and vertical parakeratosis in pityriasis rubra pilaris; mounds of parakeratosis with extravasation of erythrocytes in pityriasis rosea; and dermal, thickened vertical collagen bundles with orthokeratosis resembling acral skin in lichen simplex help us reach a specific diagnosis, unfortunately such is not the case in every instance, forcing the dermatopathologist to report as "non-specific psoriasiform dermatitis."

Because psoriasis is a hyperproliferative skin disorder with increased epidermal turnover rate and mitotic index, we investigated the role of proliferation markers Ki-67 and Cyclin D1 as diagnostic tools to differentiate psoriasis from non-psoriasis psoriasiform dermatitis (NPPD).

Materials and Methods

Histopathological specimens of psoriasis (n = 35) and control NPPD (n = 36, 14 pityriasis rubra pilaris, 12 pityriasis rosea, and 10 lichen simplex) cases were reviewed by a Board Certified Dermatopathologist (E.S.) from the histopathology archives of the Acibadem University School of Medicine. Immunohistochemical staining for Ki-67 and Cyclin D1 was performed on all specimens for microscopic analysis.

The method used for immunostaining was the streptavidin-biotin-amplified system. The slides were submitted to subsequent steps of deparaffinization and rehydration. Sections were sliced (6 μm thick) and air-dried for 30 minutes. Then the sections were fixed in cold acetone for 10 minutes. After blocking endogenous peroxidase using 0.2% sodium azide for 5 minutes, they were washed with phosphate buffered saline for 15 minutes. Subsequently, the sections were incubated with primary antibodies for 1 hour. The primary antibodies were Ki-67 (Dako, Düsseldorf, Germany) and Cyclin D1 (Dako, Düsseldorf, Germany) with a dilution of 1:100. After incubation, the sections were rinsed with distilled water and tap water. The tissue was counterstained with Mayer's hematoxylin. All slides were covered with a cover slip.
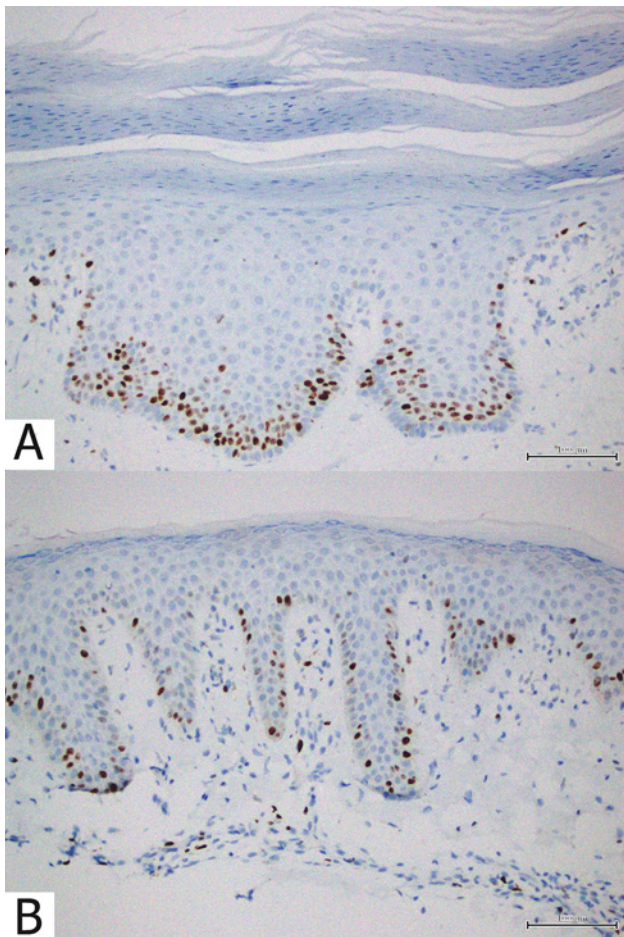
Figure 2. Overall Ki-67 cell count was marked in the psoriasis group (A) compared with that of the NPPD group (B). [Copyright: ©2015 Sezer et al.]
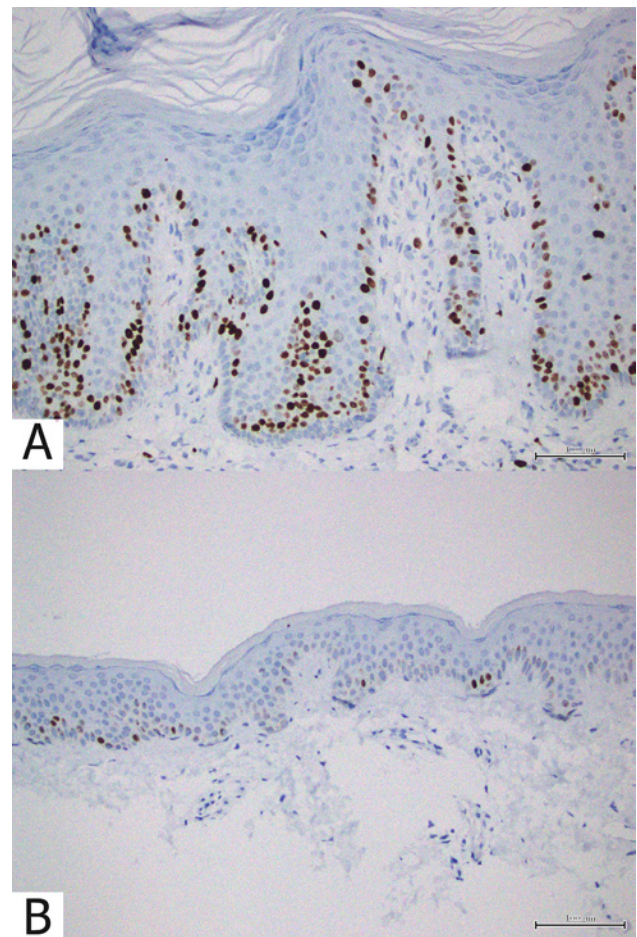

Figure 3. Predominance of suprabasal Ki-67 immunostaining cells was observed in the psoriasis group (A) compared with the NPPD group (B), which shows marked basal layer staining. [Copyright: ©2015 Sezer et al.]

Immunohistochemical scoring

The Ki-67 and Cyclin D1 positive cells were counted for suprabasal and total epidermal immunostaining. For a more practical future use for the dermatopathologists, the immunostaining cells were counted per mm^2.

Statistical analysis

Data from microscopic analysis were expressed as mean ± standard error. The independent samples t test was used to determine the statistical significance of the cell count/mm^2 and the percentage of immunostaining suprabasal to the total epidermal cell ratio between psoriasis and NPPD. P values of less than 0.05 were considered statistically significant. The statistical analysis was performed by using SPSS statistical software (IBM, Armonk, NY, USA).

Results

Ki-67 and Cyclin D1 cell counts for psoriasis and NPPD are described in Figure 1. Total epidermal cell counts for

Ki-67 were found to be significantly higher in the psoriasis group ($462.2 ± 188.2$ cells/mm^2) compared with the NPPD group ($345.6 ± 193.7$ cells/mm^2) ($p = 0.012$, independent samples t test) (Figure 2). Suprabasal Ki-67 cell counts were also higher in the psoriasis group ($401.2 ± 169.0$ cells/mm^2) compared with the NPPD group ($181.6 ± 97.4$ cells/mm^2) ($p < 0.001$, independent samples t test) (Figure 3). Suprabasal/total epidermal cell count ratio for Ki-67 immunostaining was higher in the psoriasis group (mean: $86.0 ± 4.4$%) compared with the NPPD group (mean: $54.1 ± 13.8$%) ($p < 0.001$, independent samples t test). An important and interesting feature was the presence of a cut-off value for the suprabasal/total epidermal cell count ratio of 75% for Ki-67 immunostaining, which was higher in all psoriasis cases (range, 77.1% - 92.4%) and lower in all NPPD cases (range, 21.0% - 73.3%) (Table 1, Figure 3). These features highlight that suprabasal Ki-67 positive cells were more than three-fourths of the total epidermal Ki-67 positive cells in the epidermis (including basal and suprabasal cell population) in psoriasis group, whereas this ratio was lower than three-fourths in NPPD group (Figure 4). Figure 2A demonstrates that most of the Ki-67 positive staining cells were located on

	Psoriasis	NPPD	Cut-off value
Ki-67	77.1% - 92.4%	21.0% - 73.3%	75%
Cyclin D1	76.6% - 99.6%	46.5% - 96.1%	N/A

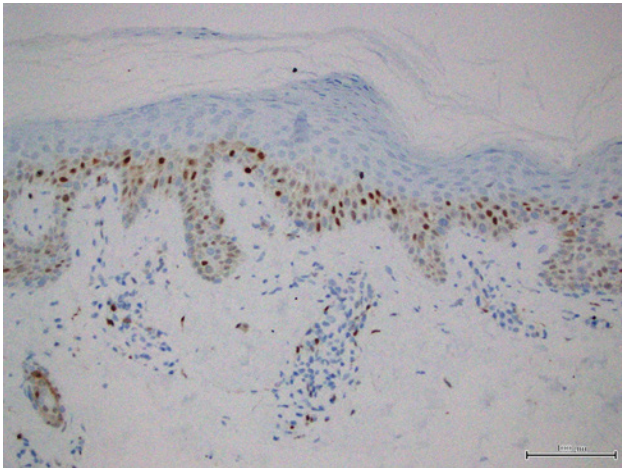NPPD, Non-psoriasis psoriasiform dermatitis; N/A, Not available.

Figure 4. A clear cut-off value for suprabasal/total epidermal cell count ratio could not be identified for Cyclin D1 immunostaining, such as in this example of NPPD specimen, in which a high suprabasal staining pattern was detected. [Copyright: ©2015 Sezer et al.]
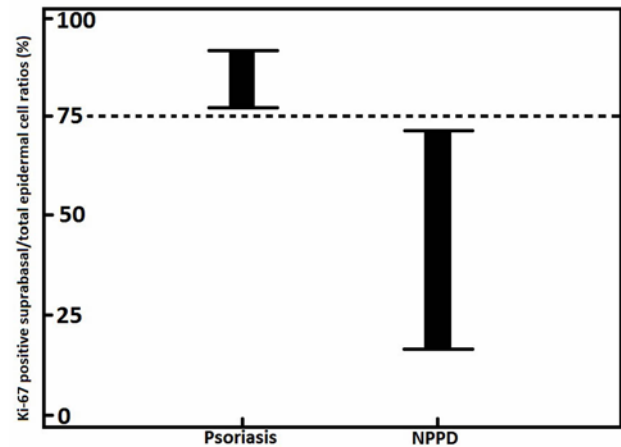

Figure 5. Suprabasal Ki-67 positive cells were more than 75% of the total epidermal Ki-67 positive cells in the epidermis (including basal and suprabasal cell population) in psoriasis group, whereas this ratio was lower than 75% in NPPD group. [Copyright: ©2015 Sezer et al.

suprabasal layer in psoriasis samples (i.e., Ki-67 positive 113 suprabasal and 29 basal cells with a suprabasal/total epidermal cell ratio of 79.6%) whereas most of the immunoreactive cells were located in basal layer in NPPD samples (i.e., Ki-67 positive 18 suprabasal and 53 basal cells with a suprabasal/total epidermal cell ratio of 25.5%) as highlighted in Figure 2B. We suggest that this phenomenon reflects the increased mitotic index in suprabasal layer of psoriatic lesions, related to hyperproliferative state.

Total epidermal Cyclin D1 immunostaining cell counts were not statistically significant in the psoriasis group (422.3 ± 141.2 cells/mm²) compared with the NPPD group (374.9 ± 144.7 cells/mm²) ($p = 0.167$, independent samples t test). Suprabasal Cyclin D1 cell counts were higher in the psoriasis group (389.2 ± 134.1 cells/mm²) compared with the NPPD group (266.7 ± 113.8 cells/mm²) ($p < 0.001$, independent samples t test). However, the suprabasal/total epidermal cell count ratio for Cyclin D1 immunostaining was higher in the psoriasis group (mean: 91.5 ± 5.0%) compared with the NPPD group (mean: 69.6 ± 14.1%) ($p < 0.001$, independent samples t test), a cut-off value to distinguish between these two entities was not detected (i.e., the Cyclin D1 ratio was as low as 76.6% in the psoriasis group and as high as 96.1% in the NPPD group) (Table 1, Figure 5).

Discussion

As the prototype of psoriasiform dermatitis, psoriasis is a chronic, relapsing, inflammatory skin disease characterized by epidermal hyperproliferation and disturbed differentiation of keratinocytes. Differentiation of psoriasiform dermatitis can be challenging for dermatopathologists, as the distinctive features may not be present in every histopathologic specimen. The characteristic histopathological features for psoriasis include collection of neutrophils within the parakeratotic stratum corneum (i.e., Munro's microabscesses), spongiform pustules beneath the keratin layer (i.e., Kogoj's pustules), thin suprapapillary plates and tortuous, dilated capillaries in the superficial papillary dermis. The diagnostic signs for pityriasis rubra pilaris are alternating orthokeratosis and parakeratosis in both vertical and horizontal directions, thick suprapapillary plates, broad epidermal ridges, and narrow dermal papillae [1]. The presence of thickened collagen bundles arranged in vertical streaks in the dermal papillae, marked hypergranulosis and a thick layer of compact orthokeratosis resembling that seen on normal palms and soles (i.e., hairy palm sign) leans toward a diagnosis of lichen simplex [2]. Angulated parakeratosis reminiscent of a teapot, pityriasiform vesicles, and extravasation of red blood cells is more characteristic of

pityriasis rosea [3]. However, these findings are exceedingly helpful for dermatopathologists in reaching a specific diagnosis, whereas a lack or overlap of these features may result in a nonspecific diagnosis of "psoriasiform dermatitis," which may cause confusion in accurate diagnosis.

Because, as a prototype of psoriasiform dermatitis, psoriasis differs from NPPD as being a hyperproliferative skin disorder with a 12-fold increase in the number of keratinocytes in cell cycling that results in a decreased turnover time for the epidermis from 13 days to 3 or 4 days, we hypothesized that proliferation markers such as Ki-67 and Cyclin D1 would be helpful in distinguishing psoriasis from NPPD [4]. Histopathologically, the presence of suprabasal mitotic figures leans toward a diagnosis of psoriasis in psoriasiform dermatitis [4]. Thus we designed the study protocol to investigate the suprabasal staining pattern with proliferation markers as well as suprabasal-to-total epidermal cell ratio as a diagnostic and practical approach to differentiate psoriasis from NPPD. Suprabasal Ki-67 and Cyclin D1 cell counts were found to be higher in the psoriasis group than in the NPPD. An important and practical finding for dermatopathologists in our research was the presence of a cut-off value for a suprabasal/total epidermal cell count ratio of 75% for Ki-67 immunostaining, which was higher in all psoriasis cases and lower in all NPPD cases. As far as we are aware, this phenomenon has not been described in the literature. However, suprabasal Ki-67 staining in the epidermis may also be observed in NPPD, resembling psoriasis, such as in the first and third rete ridges in Figure 2B, we suggest that the most reliable distinction between the two entities is the cut-off value for suprabasal/total epidermal cell count ratio of 75%, which is higher in all psoriasis and lower in all NPPD cases. We comment that this finding may be more useful for dermatopathologists in the differential diagnosis of psoriasis and NPPD, because evaluation of this feature is more practical compared with counting Ki-67 positive cells/mm^2. Increased keratin 16 and decreased keratin 10 expression in the suprabasal compartment of epidermis in psoriasis lesions also reflects the hyperproliferative state in this region, which supports the increased suprabasal Ki-67 immunostaining rate in our study. However, Ki-67 immunostaining was used as a prognostic tool to assess the efficacy of various treatment modalities for psoriasis such as acitretin, rambazole, ustekinumab, methotrexate, narrow band ultraviolet B phototherapy, photodynamic therapy, and topical tacrolimus, to the best of our knowledge, a study indicating the use of Ki-67 as a diagnostic tool to differentiate psoriasis from NPPD has not yet been reported [5-10]. In another study, hypoxia inducible factor 1 alpha (HIF-1 alpha), which is linked to inflammation through reciprocal interactions with several cytokines, was used as an immunohistochemical marker to differentiate psoriasis from NPPD [11]. However HIF-1 alpha immunoreactivity scores were higher in the psoriasis group than in the NPPD group, a cut-off point to obtain a clear differentiation as in our study could not be achieved in the reported research.

Overexpression of chemokines, interleukin-8 (IL-8) and GRO/melanoma growth-stimulatory activity (GRO-α) are known to stimulate proliferation of keratinocytes in psoriasis [12].

IL-8 is derived predominantly from keratinocytes and the associated neutrophils within the psoriatic plaques. GRO-α is an additional neutrophil chemoattractant. We suggest that the hyperproliferative state in psoriasis compared with NPPD may be related to the presence of neutrophils, which interact with these chemokines in keeping with the results of our study, as psoriasis is the only psoriasiform dermatitis with intraepidermal neutrophilic infiltration. Neutrophil elastase (NE), a 30-kD weight cellular toxic molecule produced by neutrophils is participated in the proliferation of keratinocytes by transforming growth factor-α (TGF-α). A recent study revealed enhanced expression of Ki-67 in a cultured transwell psoriasis organ model after NE treatment, thus strengthening the role of neutrophilic infiltration in the hyperproliferative state of psoriasis [13]. In contrast, TGF-β has an inhibitory effect on epithelial cell proliferation. Downregulation of its receptor in a psoriatic epidermis has the effect of diminishing this inhibitory influence, thus resulting in overproliferation [14]. T-cadherin, E-cadherin, P-cadherin, and protein kinase D expression also appears to play a part in the regulation of epidermal growth in psoriasis [15].

Ki-67 is a cell-cycle-associated antigen, expressed in all parts of the cell cycle except in G_0 and early G_1, and therefore confined to the proliferative compartment of the epidermis [16]. Ki-67 has proven to be of value as a marker of cell proliferation by recognizing the cell cycle-dependent expression of the Ki-67 non-histone nuclear antigen [17]. Psoriatic lesions have been shown to reveal a higher Ki-67 index compared with normal appearing, nonlesional skin [18-20]. The Ki-67 activity rate was found to be higher in the inner margin of the lesions, followed by the center and outer margins [20]. Cyclin D1 is a component of cyclin-dependent kinase (CDKs) complexes, regulating the function of retinoblastoma susceptibility gene production, which is necessary for cell-cycle progression into mitosis [21]. Cell cycling and cell proliferation are regulated by sequential activation of CDKs, which are activated by specifically binding to cyclins: CDK4/6 links with Cyclin D1, and CDK2 with Cyclin E [22]. These complexes phosphorylate retinoblastoma proteins, thereby inducing a release of E2F transcription factors, and thus starting the G_1 phase [23]. We believe that Ki-67 is a more sensitive proliferation marker then Cyclin D1, because a cut-off value for the suprabasal/total epidermal cell count ratio could not be identified for Cyclin D1 and total epidermal immunostaining of Cyclin D1 in psoriasis and NPPD groups were statistically insignificant.

A study investigating the role of matrix metalloproteinases (MMPs) in the role of the proliferative status of psoriasis revealed that Ki-67 immunostaining for proliferative keratinocytes was particularly intense adjacent to the MMP-19 positive cells, mainly in the rete ridges, and was thought to be associated with remodeling of the extracellular matrix during inflammation [24]. The majority of T cells in established psoriatic plaques express cell-surface cutaneous lymphocyte-associated antigen (CLA). A correlation of CLA-positive T cells in evolving psoriatic skin with Ki-67 index was identified suggesting an additional function of the CLA-positive T lymphocytes in the proliferation of psoriatic epidermis [25]. This phenomenon also supports the context of decreasing Ki-67 activity in patients treated with ustekinumab, a human anti-IL-12 monoclonal antibody, as the cytokine IL-12 upregulates the CLA expression of activated T cells in vitro and its expression is increased in lesional psoriatic skin [7].

Another molecule showing correlation with Ki-67 activity in psoriatic lesions is 72 kDa heat shock protein 72 (Hsp72), which serves to protect cells from injury caused by oxidative stress, hypothermia, ultraviolet radiation, ionizing radiation, and metabolic poisons [26]. The damaged proteins produced by oxidative stress in psoriatic lesions have been thought to serve as stress signals in triggering Hsp72. Overexpression of src-family tyrosine kinases (SFKs) was demonstrated in skin biopsy specimens of psoriasis controlled with normal skin [27]. Because altered keratinocyte differentiation and hyperproliferation are associated with increased epidermal growth factor (EGF) receptor activity, and because SFKs are directly activated by EGF in human keratinocytes, stimulation of EGF receptor is believed to activate SFKs in psoriasis [27].

Suppression of apoptosis is also considered as the pathogenetic mechanism for the hyperproliferative state of psoriasis. Expression of survivin, a member of the inhibitor of apoptosis protein family, mediating the apoptosis suppressive function by inhibition of the caspase pathway and nuclear factor kappa β (a transcription factor also responsible for inhibition of apoptosis) was investigated, revealing overexpression of both markers in the psoriasis group [28].

Finally, we suggest that Ki-67 is a more sensitive marker than Cyclin D1 in terms of the presence of a cut-off value of 75% for the suprabasal/total epidermal cell count ratio, which we believe could be a useful tool for dermatopathologists to differentiate psoriasis from other psoriasiform dermatitis.

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