Dermatology Practical & Conceptual

Might Necrotic Keratinocytes Contribute to the Diagnosis and Pathogenesis of Psoriasis?

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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory skin disease that can pose challenges for histopathological diagnosis. Recent research has emphasized the importance of necrotic keratinocytes, meaning keratinocytes undergoing programmed cell death, for diagnosing psoriasis. It has also become increasingly evident that programmed cell death pathways play a significant role in psoriasis's pathogenesis, development, and progression, including via a recently identified programmed cell death mechanism called "PANoptosis."

Objectives: In our study, we aimed to investigate the significance of necrotic keratinocytes in both the diagnosis and pathogenesis of psoriasis.

Methods: We analyzed the number of necrotic keratinocytes in 135 samples of psoriasis, 57 samples of psoriasiform spongiotic dermatitis, and 71 samples of normal skin. We additionally assessed the distribution of necrotic keratinocytes in the upper, middle, and lower thirds of the epidermis.

Results: Our findings revealed a significant difference in the total number of necrotic keratinocytes and their distribution within epidermal regions between patients with psoriasis and both the psoriasiform spongiotic dermatitis and control groups ($p < .001$). In particular, necrotic keratinocytes were predominantly found in the upper epidermis (77.5%) in patients with psoriasis. We also observed a strong correlation between Psoriasis Area and Severity Index scores and the total count of necrotic keratinocytes in patients with psoriasis ($r = .72$).

Conclusions: Our results highlight the role of necrotic keratinocytes, resulting from programmed cell death, as important marker cells in both the diagnosis and pathogenesis of psoriasis.

Introduction

Psoriasis, a chronic inflammatory skin disease that occurs worldwide, is associated with multiple systemic complications that significantly impact patients' quality of life as well as physical and mental health [1]. Many efforts have been devoted to understanding the primary pathogenic mechanisms and cellular components responsible for the onset of psoriasis [2], the pathogenesis of which is known to be influenced by factors including the environment, genetics, and the dysfunction of immune cells such as T cells and dendritic cells as well as nonimmune cells such as keratinocytes [1]. In the longstanding debate on the pathogenic role of keratinocytes in psoriasis, extensive research has indicated that the hyperproliferation and abnormal differentiation of keratinocytes are secondary effects triggered by immune activation. While the immune hypothesis, which focuses on the pathogenic functions of dendritic cells and T cells, has been supported by the efficacy of immune-targeting treatments, psoriasis is recognized as being not only a T-cell-dependent disease. On that count, it is now widely acknowledged that keratinocytes play a pivotal role in initiating early pathogenic events and sustaining the disease's chronic progression [2]. In psoriasis, the breakdown of the epidermal barrier heightens the susceptibility of keratinocytes to external harmful substances, which can result in cell damage or death [3].

Programmed cell death (PCD) is a vital process during development that plays an important role in maintaining homeostasis and defending against various pathogens and stimuli. PCD has specific genetically encoded requirements [4]. PANoptosis, a recently defined form of PCD that has become a new focus of research [5], is regulated by the PANoptosome complex, which entails the substantial interaction and coordination of pyroptosis (P), apoptosis (A), and/or necroptosis (N) [4,6]. Although the relationship between PANoptosis and psoriasis remains largely unclear, mounting evidence suggests that PANoptosis is implicated in pathogenesis's psoriasis [5,7]. Programmed apoptosis, necrosis, and pyroptosis have also been shown to be associated with inflammation in psoriasis [5]. Previous research has additionally demonstrated that the presence of necrotic keratinocytes, meaning keratinocytes undergoing PCD, which are not typically seen in the classical histopathology of psoriasis, is significant for the disease's diagnosis [8].

Objectives

In our study, we aimed to investigate the role of necrotic keratinocytes, which we believe indicate PANoptosis, in psoriasis's pathogenesis and diagnosis.

Methods

Our study included patients diagnosed with psoriasis and psoriasiform spongiotic dermatitis who were monitored at our hospital's Dermatology Clinic from September 2021 to December 2022. We recruited 135 patients diagnosed with psoriasis, 57 patients with psoriasiform spongiotic dermatitis, and 71 individuals with normal skin who were matched for age and gender. Psoriasis and psoriasiform spongiotic dermatitis skin biopsies were compiled from archival specimens, whereas normal skin biopsies were prospectively obtained as a control group. The samples of the control group were obtained from the skin tissue materials accepted to the pathology laboratory that did not contain any skin lesions. For the group of patients with psoriasis and psoriasiform spongiotic dermatitis, no systemic drugs, phototherapy, or externally applied drugs were administered in the month prior to sample collection. The patients' records contained systematically organized data, including age, gender, family history, clinical type(s) of psoriasis, specific areas affected (e.g., scalp, nails, face, genital area, inverse area, and joints), duration of disease, and details about the biopsy's location. The Psoriasis Area and Severity Index (PASI) was used to assess the severity of the disease.

Samples of psoriasis, psoriasiform spongiotic dermatitis, and normal skin were analyzed. Slides stained with hematoxylin and eosin were used to examine necrotic keratinocytes, which were characterized as intraepidermal cells with pyknotic nuclei and hypereosinophilic cytoplasm. The total number of necrotic keratinocytes present in three consecutive sections was calculated, and each necrotic keratinocyte within the epidermis was noted as being located in the lower third, middle third, or upper third. The research protocols followed the principles of the Declaration of Helsinki, while an ethics committee of a tertiary hospital approved the study (Ethical Approval No.: 19.04.2021-109/01).

The collected data were transferred to a computer and analyzed using SPSS (version 15.0). The normal distribution of the data was assessed using the Kolmogorov–Smirnov test. For data that did not follow a normal distribution, analysis was performed using the Mann–Whitney *U* test, Kruskal–Wallis test, Spearman's correlation test, and logistic regression analyses.

Results

The group of patients with psoriasis included 87 males and 48 females, the group of patients with psoriasiform spongiotic dermatitis had 36 males and 21 females, and the control group consisted of 45 males and 26 females. Statistical analysis showed that all three groups were comparable.

The average age of patients with psoriasis was 44.7 years (age range: 11–85 years), of patients with psoriasiform spongiotic dermatitis was 49.19 years (age range: 17–83 years), and of the control group was 46.79 years (age range: 11–83 years). No statistically significant difference in age emerged between the three groups. The general characteristics of the study group are presented in Table 1.

We evaluated the quantities of necrotic keratinocytes in the upper, middle, and lower thirds of the epidermis. When assessing the total number of necrotic keratinocytes and the number of necrotic keratinocytes in each of the three epidermal regions in patients with psoriasis (Figure 1), a significant difference arose between the psoriasiform spongiotic dermatitis ($p < .001$) (Figure 2) and control groups ($p < .001$) (Figure 3). The results of our quantitative analysis of necrotic keratinocytes in the psoriasis, psoriasiform spongiotic dermatitis, and control groups appear in Table 2, while Table 3 presents the quantities of necrotic keratinocytes based on their locations in the epidermis for all three groups.

No significant relationship surfaced between the involvement of specific areas and the number of necrotic keratinocytes in the psoriasis group ($p > .05$). Similarly, no significant association was observed between the presence or absence of a family history of psoriasis and the number of necrotic keratinocytes ($p > .05$). The duration of the disease also showed no significant relationship with the number of necrotic keratinocytes ($p > .05$).

Among patients with psoriasis, the quantity of necrotic keratinocytes was significantly higher in each of the three regions of the epidermis than among patients with psoriasiform spongiotic dermatitis ($p < .001$).

A significant difference was also observed between the psoriasiform spongiotic dermatitis and control groups in terms of the quantity of necrotic keratinocytes in the upper epidermis ($p < .001$). However, no significant differences were found in the quantities of necrotic keratinocytes in the middle ($p = .184$) and lower thirds of the epidermis ($p = .479$). The results of logistic regression analyses showed that individuals with psoriasis were 923 times more likely to have necrotic keratinocytes, whereas ones with psoriasiform spongiotic dermatitis were 5.4 times more likely to have necrotic keratinocytes than patients without those conditions.

Table 1. General Characteristics of the Study Group.

Characteristics	Psoriasis (n) N=135	Psoriasiform Spongiotic Dermatitis (n) N=57	Control (n) N=71
Sex	87 M 48 F	36 M 21 F	45 M 26 F
Biopsy site			
Lower extremity	52	22	20
Upper extremity	36	24	19
Scalp	5	3	4
Back	23	6	12
Chest	2	-	-
Abdomen	17	2	16
Age, years	44.7	49.9	46.79
Family history			
Yes	39		
No	96		
Clinical type			
Plaque	126		
Guttate	9		
Specific area involvement			
Scalp	96		
Nail	65		
Face	44		
Genital area	52		
Joint	17		
Inverse area	28		
Disease duration, months (mean) (min-max)	137.88 (1-660)	171,32 (1-708)	
PASI, mean (min-max)	9.559 (0.6-55)		

M = male; F = female; PASI = Psoriasis Area Severity Index.

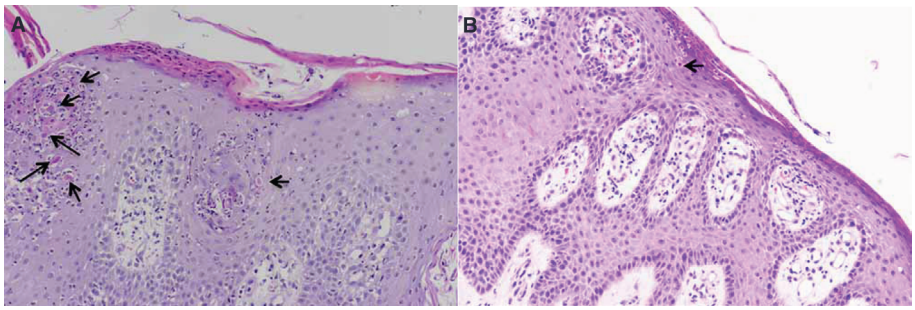

Figure 1. (A) Necrotic keratinocytes (black arrows) in upper and middle epidermis in psoriasis patient (PASI: 27.5; H&E, ×200). (B) Necrotic keratinocyte (black arrow) in upper epidermis in psoriasis patient (PASI: 2; H&E, ×200).

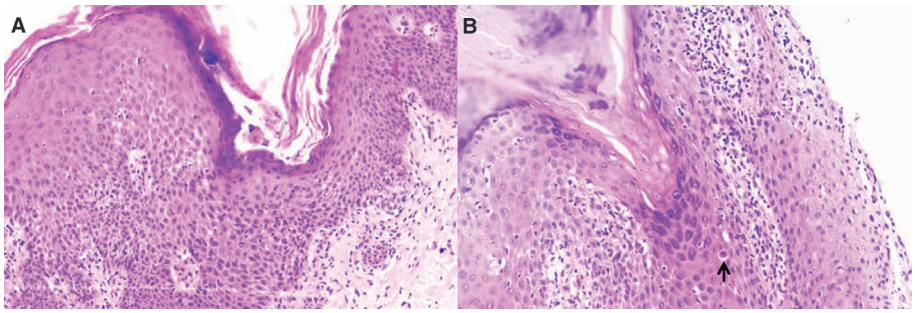

Figure 2. (A) Psoriasiform spongiotic dermatitis without necrotic keratinocytes (H&E, ×200). (B) Necrotic keratinocyte (black arrow) in middle epidermis in psoriasiform spongiotic dermatitis patient (H&E, ×200).

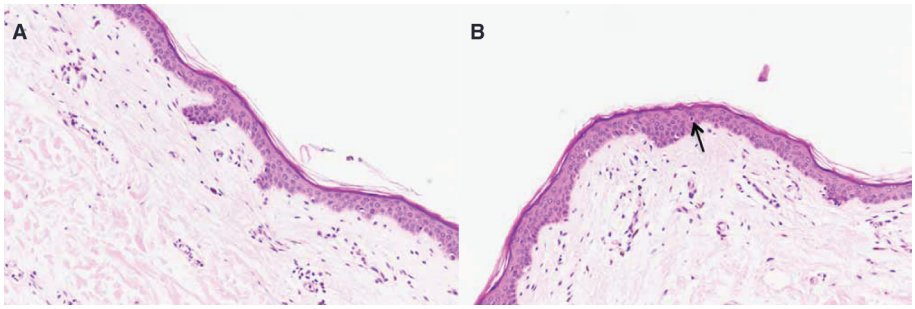

Figure 3. (A) Normal skin without necrotic keratinocytes (H&E, ×200). (B) Necrotic keratinocyte (black arrow) in middle epidermis in normal skin (H&E, ×200).

Table 2: Quantitative Analysis of Necrotic Keratinocyte (NK) in Psoriasis, Psoriasiform Spongiotic Dermatitis, and Control.

	Psoriasis	Psoriasiform Spongiotic Dermatitis	Control	P-Value
Total number of cases	135	57	71	
Cases with NK	134	25	9	
Percentage (%)	99.3%	43.9%	12.7%	<.001
Mean number of NK	5.27	0.58	0.13	<.001

(Note: Kruskal-Wallis test was used for analysis)

In the psoriasis group, a strong, significant correlation was observed between PASI score and the total number of necrotic keratinocytes (r = .72). When that correlation was evaluated separately for each of the three region of the epidermis, a strong, significant correlation also emerged between the number of necrotic keratinocytes in the upper epidermis and PASI score (r = .618). A significant correlation was also observed between PASI score and the total number

Table 3. Necrotic Keratinocyte (NK) Quantities Based on Epidermal Locations in All Study Groups.

Study Group	Psoriasis	Psoriasiform Spongiotic Dermatitis	Control
Total number of NK	712	33	9
NK in upper epidermis, n (%)	552 (77.5%)	23 (69.7%)	3 (33.3%)
NK in middle epidermis, n (%)	77 (10.8%)	7 (21.2%)	4 (44.4%)
NK in lower epidermis, n (%)	83 (11.7%)	3 (9.1%)	2 (22.2%)

(Note: Kruskal-Wallis test was used for analysis)

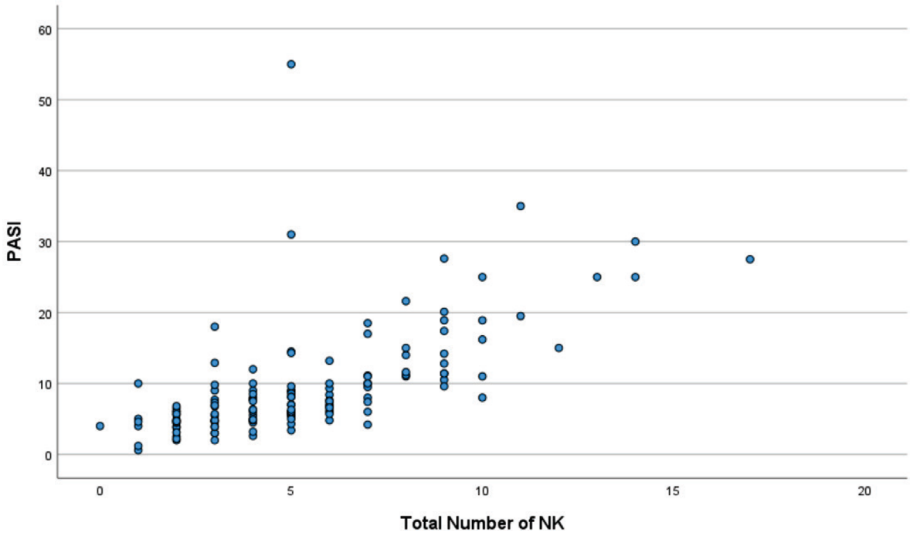

Figure 4: The correlation between the total number of necrotic keratinocytes and PASI
(Note: Spearman's correlation test was used for analysis)

of necrotic keratinocytes in the middle epidermis (r = .235). However, no significant correlation was found between the number of necrotic keratinocytes in the lower epidermis and PASI score. The correlation between the total number of necrotic keratinocytes and PASI score is illustrated in Figure 4.

Discussion

Psoriasis is a chronic inflammatory skin disorder characterized by the hyperproliferation and impaired maturation of keratinocytes, the increased infiltration of immune cells and blood vessel formation, and the accumulation of proinflammatory cytokines [3]. The diagnosis of psoriasis is supported both clinically and histopathologically [9], while the disease's severity is determined using various parameters, with PASI score being a primary indicator [10].

Pathologists usually refer to textbook descriptions of psoriasis, which emphasize the disease's important histological characteristics such as acanthosis, parakeratosis, reduced stratum granulosum, the presence of neutrophils in the superficial epidermis and stratum corneum, and increased vascularity in the papillary dermis [11]. While most biopsy specimens from individuals with psoriasis and eczematous dermatitis exhibit clear-cut features, a notable proportion presents with clinicopathologic overlap, which leads to challenges with diagnosis [12]. Recently, the significance of necrotic keratinocytes in diagnosing psoriasis has been emphasized in pathological studies [8,13]. In a study by Cloutier et al., for example, necrotic keratinocytes were found to be valuable in differentiating psoriasis from psoriasiform spongiotic dermatitis, which shares similar histopathological and clinical features with psoriasis [8]. In our study, we quantitatively evaluated necrotic keratinocytes in three groups: patients with psoriasis, patients with psoriasiform spongiotic dermatitis, and normal skin of the control group. Our results showed that the psoriasis group had a significantly higher total number of necrotic keratinocytes than both the psoriasiform spongiotic dermatitis and control groups. Those findings are consistent with the results of Cloutier et al., who also found significant results among patients with psoriasis [8]. The increased necrotic keratinocytes that we observed in patients with psoriasis in our study will be useful in differentiating spongiotic psoriasiform dermatitis, which has clinical and histopathological features similar to psoriasis's.

When comparing the quantitative values of necrotic keratinocytes between the groups in our study, we found that the mean number of necrotic keratinocytes was 10 and 50 times higher in the psoriasis group than in the psoriasiform spongiotic dermatitis and control groups, respectively. By contrast, Cloutier et al. reported a mean number of necrotic keratinocytes in the psoriasis group that was 1.5 and 7.5 times higher than in the psoriasiform spongiotic dermatitis and control groups, respectively [8]. Even so, our study and Cloutier et al.'s both revealed similar results in terms of mean necrotic keratinocytes when the psoriasiform spongiotic dermatitis and control groups were compared. According to the findings of both studies, the mean number of necrotic keratinocytes was approximately 4.5 times higher in the psoriasiform spongiotic dermatitis group than in the control group [8]. The discrepancy in the psoriasis group could be attributed to the fact that the mean PASI values of the patients with psoriasis in our study were as high as 9.6. By contrast, PASI values were not evaluated by Cloutier et al. [8].

Psoriasis is characterized by persistent inflammation, which leads to the uncontrolled proliferation and impaired differentiation of keratinocytes [14]. In our study, we reviewed the literature to understand the role of necrotic keratinocytes, which were increased in the skin biopsies of patients with psoriasis, in the development of the disease, largely because our findings showed the opposite based on decreased apoptosis in keratinocytes in psoriasis [15].

Our literature review identified several recently published articles implicating PANoptosis, a phenomenon newly described Kanneganti et al. in 2019 [16], in psoriasis's pathogenesis [4, 5, 7]. PANoptosis is an inflammatory PCD pathway regulated by the PANoptosome complex, which combines features of pyroptosis, apoptosis, and necroptosis and involves essential molecules from those three pathways [5].

Pyroptosis is executed by gasdermin family members through the inflammasome activation-mediated caspase-1 cleavage of gasdermin D (GSDMD), caspase-11/4/5- or caspase-8-mediated cleavage of GSDMD, caspase-3-mediated cleavage of gasdermin E, or granzyme A-mediated cleavage of gasdermin B. By contrast, apoptosis is executed by caspase-3 and 7 following the activation of upstream initiator caspases caspase-8/10 or -9. Last, necroptosis is executed by mixed lineage kinase-like (MLKL) oligomerization mediated by receptor-interacting serine threonine kinase-3 [17].

Previous studies have linked PANoptosis's components to the pathogenesis of psoriasis [3–5,7,18,19]. For example, one study showed that NLRP3 inflammasome-mediated pyroptosis was present in Imiquimod (IMQ)-induced psoriasis, similar to skin inflammation in mice [18]. Other studies have shown that the TNF-α-mediated NLRP3 inflammasome contributes to systemic inflammation in patients with psoriasis [19]. Meanwhile, Lu et al. pinpointed the close association between PANoptosis and the development of psoriasis and observed the activation of pyroptosis- and apoptosis-signaling pathways [5]. Similarly, Hu et al. identified the high activity of the PANoptosis pathway in psoriatic lesions [7]. In another study, Duan et al. found results suggesting that necroptosis in keratinocytes triggers psoriatic inflammation, which disrupts the epidermal barrier and thereby exposes keratinocytes to harmful stimuli and causes extensive necroptosis. Programmed necrosis-related proteins are primarily expressed in the epidermis, particularly in keratinocytes. Immunofluorescence and the immunohistochemical labeling of TUNEL, active caspase-3, RIPK1, and MLKL indicate that necroptosis primarily occurs in the upper epidermis in mice, as is consistent with results in patients with psoriasis [3]. Furthermore, Cloutier et al. reported that 89% of necrotic keratinocytes in patients with psoriasis were located in the upper two-thirds of the epidermis [8]. In our study, 88.3% of necrotic keratinocytes, which we believe may indicate PANoptosis, were located in the upper two-thirds of the epidermis, which supports the findings of both Duan et al. and Cloutier et al. [3,8].

The literature outlines the involvement of PANoptosis in psoriasis's pathogenesis and, on that count, indicates that elevated levels of circulating cytokines such as TNF and IFN-γ can synergistically induce PANoptosis. PANoptosis entails the activation of molecules associated with pyroptosis (i.e., GSDMD), apoptosis (i.e., CASP8/3/7), and necroptosis (i.e., pMLKL). Furthermore, those cytokines can activate JAK/STAT1/IRF1 signaling and nitric oxide production, which augments CASP8/FADD-mediated PANoptosis. That process leads to excessive cytokine production, which results in a cytokine storm that may perpetuate a positive feedback loop in psoriasis's progression [7]. Furthermore, the IL-23/IL-17 axis is closely associated with the PANoptosome complex. Taken together, those findings suggest that PANoptosis may be intricately linked to psoriasis's pathogenesis [5].

We additionally found a statistically significant correlation between the total count of necrotic keratinocytes and PASI score, an indicator of psoriasis's severity. Our results showing significantly increased necrotic keratinocytes in patients with psoriasis and their correlation with PASI might be an additional support for studies showing the relationship between necrotic keratinocytes in psoriasis known as PANoptosis. To our knowledge, our study was the first to provide evidence supporting previous animal and human studies on PANoptosis's role in psoriasis by showing its relationship with clinical severity.

Hu et al. conducted a study to investigate the diverse functions of hub genes involved in PANoptosis for drug prediction. Based on their experimental data, they found that disulfiram, a predicted drug, showed a significant ameliorative effect on IMQ-mediated psoriatic lesions. They also observed that disulfiram treatment, acting as an antagonist of

pyroptosis proteins, could reduce the cleavage of GSDMD in IMQ-mediated psoriatic lesions [7]. When considering studies that target PANoptosis, including the one conducted by Hu et al., together with our own study showing the increased presence of necrotic keratinocytes and their correlation with PASI scores, we support the idea that PANoptosis plays a role in psoriasis's pathogenesis.

Conclusions

Based on studies demonstrating the efficacy of drugs targeting PANoptosis, which has been shown to contribute to psoriasis's pathogenesis, drugs targeting necrotic keratinocytes might be able to improve the personalized treatment of psoriasis in the future [7]. At the same time, the exact function of necrotic keratinocytes in psoriasis's pathogenesis remains incompletely understood. In our study, we quantitatively demonstrated the presence of necrotic keratinocytes in the skin of patients with psoriasis. Understanding the correlation between those necrotic keratinocytes and PASI score may be useful in determining the pathogenesis of psoriasis. Also, the presence of superficially located necrotic keratinocytes serves as an additional diagnostic clue for psoriasis. Therefore, we look forward to further research on those intriguing cells and the role of PANoptosis in the future.

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