



INTERNATIONAL MEDICAL SCIENTIFIC JOURNAL

ART OF MEDICINE



Art of Medicine

International Medical Scientific journal

ART of MEDICINE

**International Medical Scientific
Journal**

Volume 3, №4 August 2023

Art of Medicine
International Medical Scientific journal

Founder and Publisher **Pascual Izquierdo-Egea**
Published science may 2021 year. Issued Quarterly.
Internet address: <http://artofmedicineimsj.us>
E-mail: info@artofmedicineimsj.us
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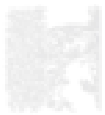
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**HISTOLOGICAL ALTERATIONS IN THE SKIN OBSERVED IN
DIFFERENT MANIFESTATIONS OF ACTINIC KERATOSIS**

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Abstract: Histological analysis was conducted on 90 patients with different clinical presentations of actinic keratosis (AK). The most prevalent forms were hypertrophic (45 cases) and bowenoid (20 cases) AK. The acanthotic form of AK was observed least frequently (2 cases). The results of the study indicated that the most common histological changes in AK involved the epidermis, which could be considered pathognomonic for AK. These changes included dysplasia of epidermal cells, presence of atypical keratinocytes in the basal and spinous layers, abnormal mitotic activity, and disruption of keratinocyte stratification. On the other hand, phenomena such as acanthosis, hypergranulosis, and epidermal atrophy were considered reactive rather than specific to AK.

Keywords: actinic keratosis (AK), histological changes in actinic keratosis

The diagnosis of actinic keratosis is suspected in most cases and is made on the basis of a clinical and dermatoscopic picture, but the "gold standard" for excluding its transition to SCC is morphological examination. In countries where evidence-based medicine prevails, a skin biopsy of lesions is carried out in each case. Thus, doctors are suspicious of each case and try not to miss the malignant process. In the classical course, the histological picture of AK is represented by hyperkeratosis of varying severity in combination with parakeratosis, violation of keratinocyte stratification and single pathological mitoses in the epidermis. Due to the fact that AK occurs in open areas of the body, the main histological feature in the dermis are solar elastosis, basophilic degeneration of papillary collagen and perivascular lymphocytic infiltrate with an admixture of histiocytes and in some cases plasmocytes. Atypical keratinocytes usually manifest in more pronounced, chronic lesions and are represented by large pleomorphic hyperchromic nuclei [1,2]. Histological classification of hypertension takes into account an important factor, such as the transition, or evolution into squamous cell cancer, characterized by the proliferation of atypical keratinocytes.

Histological variants of AK have been described in detail, and now there are 7 basic and 2 additional [3]:

-hypertrophic - the main histological signs are acanthosis, papillomatosis, hyper (para)keratosis, solar elastosis;

-atrophic - atrophy, a small number of atypical pleomorphic keratinocytes and parakeratosis are observed in the epidermis;

- bowenoid - the histological picture is very similar to Bowen's disease. Pronounced polymorphism and polychromasia of keratinocytes are observed in the epidermis. In the dermis - elastosis, perivascular and interstitial infiltrate from lymphocytes;

-acantholytic - resembles Darve's disease; suprabasal cleavage of keratinocytes, acantholysis, dyskeratosis are the main pathomorphological signs. Signs of acantholysis can be observed along the appendages;

-pigmented - acanthosis, hyper/parakeratosis, increased melanization of atypical keratinocytes and dermal macrophages;

-lichen-like - apoptosis of keratinocytes, vacuole dystrophy of epidermal cells, and streaky lichenoid infiltrate, consisting mainly of lymphocytes, distinguishes this type of AK from other variants;

-epidermolytic - characteristic granular changes are observed in the epidermis due to the cleavage of keratinocytes from each other.

Both AK and SCC contain atypical keratinocytes with loss of polarity, nuclear polymorphism, disordered maturation and an increase in the number of mitoses [4]. AK and SCC often come into contact with each other. In the study of SCC on sun-damaged skin, it was revealed that histological signs of actinic keratosis are also noted along the periphery of lesions in almost 100% of cases [5,6]. Follicular involvement is the key to severe UV damage and a potential histopathological criterion for determining high-risk lesions. However, in our opinion, follicular involvement is difficult to assess in a "differentiated" model.

We examined 90 patients (50 women and 40 men) with various forms of AK aged 45 to 80 years. All patients underwent diagnostic skin biopsy followed by histological examination. Based on the results, skin biopsies were divided into 6 histological subtypes: hypertrophic (n = 45), bowenoid (n = 20), atrophic (n = 10), lichenoid (n = 5), proliferative (n = 3) and acantholytic (n = 2), respectively. In the epidermis with hypertrophic form of AK (see Fig. 1) the following signs were observed: local hyperkeratosis (n = 25/45, 55.5%), diffuse hyperkeratosis (n = 20/45; 44%), uniform acanthosis (n = 25/45; 55.5%), irregular acanthosis (n = 20/45; 44%), local hypogranulosis (n = 15/45; 33%), epidermal cell dysplasia in stage KIN 2 (n = 3/45; 7%), in stage KIN 3 (n = 7/45; 15.5%), inflammatory lymphocytes in the basal layer in stage KIN 2 (n = 3/45; 7%), in stage KIN 3 (n = 7/45; 15.5%), atypical keratinocytes in the basal layer in the KIN 2 stage - in 2 out of 45 (4.4%), in the KIN 3 stage (n = 8/45; 18%), atypical keratinocytes in the basal layer in the KIN 2 stage (n = 2/45; 4.4%), in the KIN 3 stage (n = 8/45; 18%), pathological mitoses in the KIN 3 stage (n = 10/45; 22%) and violation of keratinocyte stratification in the KIN 2 stage (n = 3/45; 6.6%), in stage KIN 3 (n = 7/45; 15.5%).

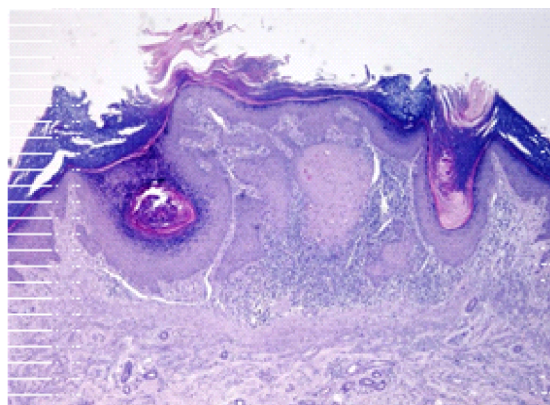


Fig. 1. Actinic keratosis, hypertrophic form. Orthohyperkeratosis, hypergranulosis, and irregular acanthosis are seen in the epidermis.. Perivascular infiltrate and interstitial infiltrate, consisting mainly of lymphocytes, are noted in the dermis. Stained with hematoxylin and eosin. x100.

Histological examination of the second largest group of AK (bowenoid variant) showed the following results in the epidermis (see Fig. 2): local hyperkeratosis (n = 5/20; 25%), diffuse hyperkeratosis (n = 15/20; 75%), uniform acanthosis (n = 5/20;

25%), irregular acanthosis (n = 15/20; 75%), local hypogranulosis (n = 5/20; 25%), cell dysplasia epidermis in stage KIN 2 (n = 2/20; 10%), in stage KIN 3 (n = 8/20; 40%), inflammatory lymphocytes in the basal layer in stage KIN 2 (n = 5/20; 25%), in stage KIN 3 (n = 5/20; 25%), atypical keratinocytes in the basal layer in the KIN 2 stage (n = 5/20; 25%), in the KIN 3 stage (n = 5/20; 25%), atypical keratinocytes in the spinous layer in the KIN 2 stage (n = 2/20; 10%), in the KIN 3 stage (n = 8/20; 40%), pathological mitoses in the KIN 3 stage (n = 10/20; 50%), and violation of keratinocyte stratification in the KIN 2 stage (n = 5/20; 25%), in the KIN 3 stage (n = 5/20; 25%) (see Fig. 3).

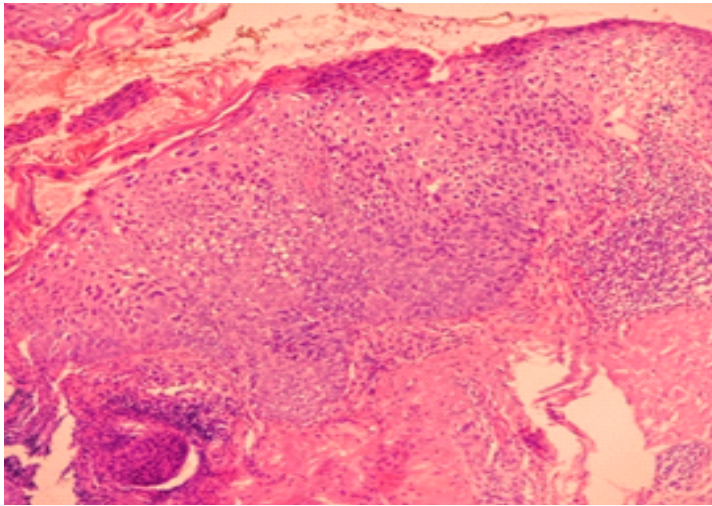


Fig. 2. Actinic keratosis, bowenoid form. Hyperkeratosis, diffuse hypogranulosis, uniform acanthosis, violation of the stratification of keratinocytes of the spinous layer are observed in the epidermis.

Stained with hematoxylin and eosin. X 200

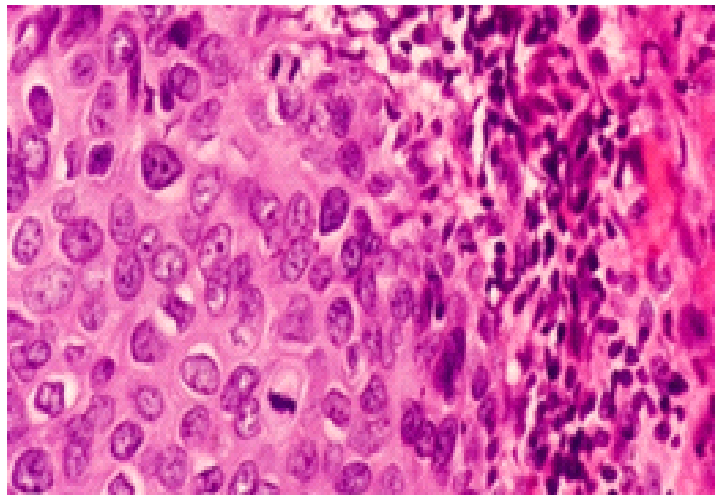


Fig. 3. Actinic keratosis, bowenoid form. The histological preparation reveals large atypical cells, pathological mitoses and cellular pleomorphism. Stained with hematoxylin and eosin. x400.

The atrophic variant of AK is represented in the epidermis by local hyperkeratosis (n = 5/10; 50%), scab (n = 2/10; 20%), local atrophy (n = 7/10; 70%), diffuse atrophy (n = 8/10; 80%), local hypogranulosis (n = 5/10; 50%), epidermal cell dysplasia in the KIN 3 stage (n = 10/10; 100%), inflammatory lymphocytes in the basal layer in the KIN 3 stage (n = 10/10; 100%), atypical keratinocytes in the basal

layer in the KIN 2 stage (n = 3/10; 30%), in the KIN 3 stage (n = 7/10; 70%), atypical keratinocytes in the spinous layer in the KIN 2 stage (n = 2/10; 20%), in the KIN 3 stage (n = 8/10; 80%), pathological mitoses in the KIN 3 stage (n = 10/10; 100%) and stratification disorders in the KIN 3 stage (n = 10/10; 100%) (see Fig. 4).

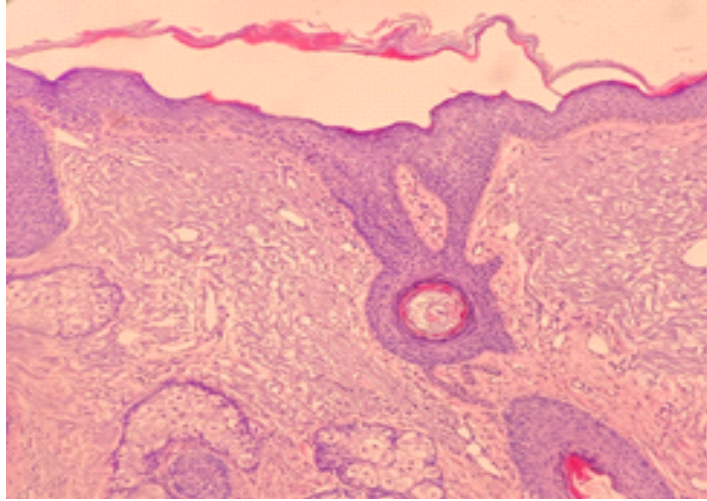


Fig. 4. Actinic keratosis, atrophic form. Compact orthokeratosis and flatness of the epidermal-dermal junction are observed in the epidermis. Dense perivascular infiltrate and interstitial infiltrate of lymphocytes with an admixture of histiocytes are noted in the dermis. Stained with hematoxylin and eosin. x200.

Changes in the epidermis in lichenoid type of AK are represented by the following histopathological signs: local hyperkeratosis (n = 3/5; 60%), scab (n = 1/5; 20%), uniform acanthosis (n = 2/5; 40%), irregular acanthosis (n = 2/5; 40%), local spongiosis (n = 5/5; 100%), inflammatory lymphocytes in the basal layer in stage KIN 1 (n = 5/5; 100%), in stage KIN 2 (n = 1/5; 20%), violation of keratinocyte stratification in stage KIN 2 (n = 2/5; 40%), in stage KIN 3 (n = 3/5; 60%), respectively (see Fig. 5).

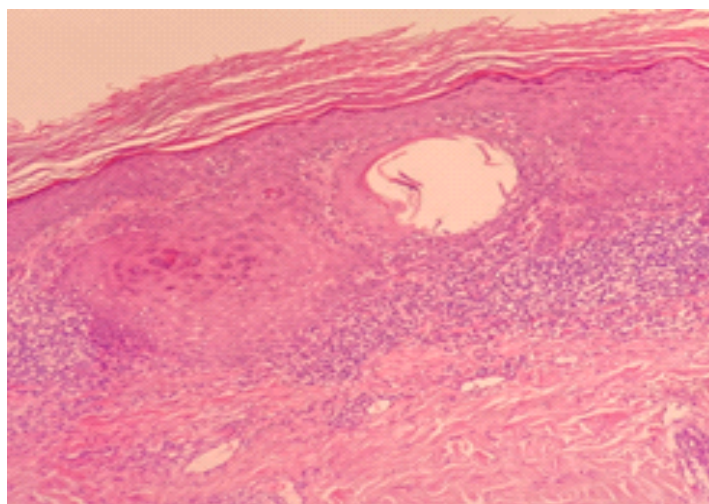


Fig. 5. Actinic keratosis, lichenoid form. Compact orthokeratosis, irregular acanthosis, smoothness of the epidermal-dermal junction are seen in the epidermis. Dense perivascular infiltrate and interstitial infiltrate of lymphocytes with an admixture of histiocytes are noted in the dermis.

Stained with hematoxylin and eosin. x400

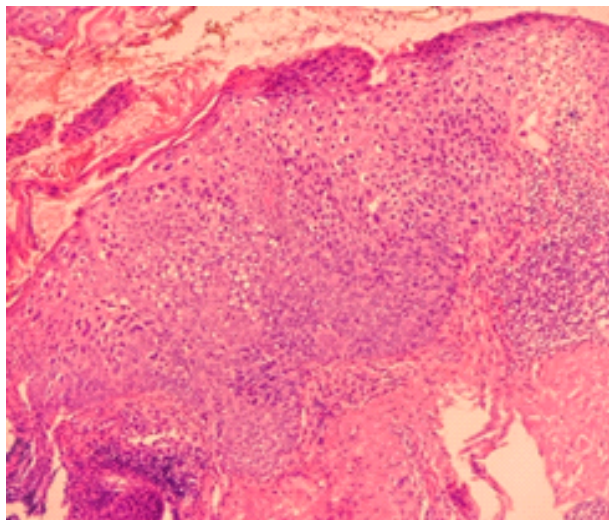


Fig. 6. Actinic keratosis, proliferative form. Compact orthokeratosis, irregular acanthosis and smoothness of the epidermal-dermal juncture are seen in the epidermis. Dense perivascular and interstitial infiltrate of lymphocytes with an admixture of histiocytes is noted in the dermis. Stained with hematoxylin and eosin. x400.

Proliferative type of AK was represented in the epidermis by local hyperkeratosis in 2 out of 3 (66.6%) patients, scab in 1 out of 3 (33%), uniform acanthosis in 2 out of 3 (66.6%), irregular acanthosis in 1 out of 3 (33%), local hypergranulosis in 3 out of 3 (100%), inflammatory lymphocytes in the basal layer in the KIN 1 stage in 1 of 3 (33%), in the KIN 2 stage in 1 of 3 (33%) and impaired keratinocyte stratification in the KIN 2 stage in 2 of 3 (66.6%) (Fig. 6).

The last, sixth, histological variant of AC - acantholytic type - is represented in the epidermis by local hyperkeratosis in 1 of 2 (50%) people, scab in 1 of 2 (50%), uniform acanthosis in 1 of 2 (50%), irregular acanthosis in 1 of 2 (50%), local hypogranulosis in 2 out of 2 (100%), local spongiosis in 1 out of 2 (50%), inflammatory lymphocytes in the basal layer in stage KIN 1 in 2 out of 2 (100%), in stage KIN 2 in 1 out of 2 (50%) and violation of keratinocyte stratification in stage KIN 2 in 2 out of 2 (100%) (see fig. 7). Other histological signs observed in this group of patients are shown in Table 1 and Figure 8.

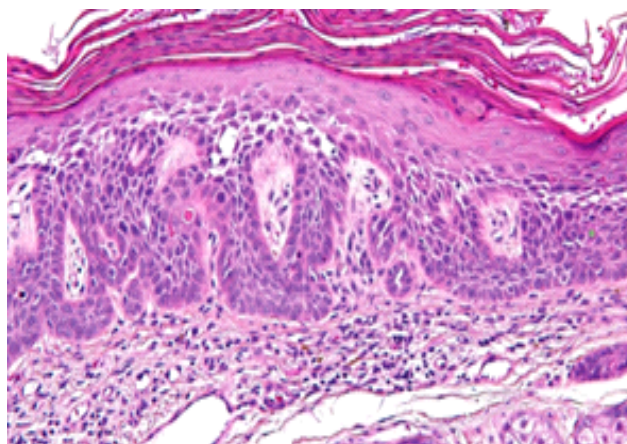


Fig. 7. Actinic keratosis, acantholytic form. In the epidermis, parakeratosis, irregular acanthosis, smoothness of the epidermal-dermal juncture, spongiosis, acantholysis of keratinocytes are observed. Dense perivascular infiltrate and interstitial infiltrate from lymphocytes are noted in the dermis. Stained with hematoxylin and eosin. x400

Table 1.
The ratio of histological signs of various types of actinic observed in the epidermis keratosis

Histological changes in the epidermis	Histological types of actinic keratosis											
	Hyperkeratotic*		Erythematous		Atrophic*		Erythematous		Proliferative		Acantholytic	
	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000
Local hyperkeratosis:	150	150	150	150	150	150	150	150	150	150	150	150
- diffuse	100	440	150	150	50	50	50	50	50	50	50	50
- focal	50	50	50	50	100	100	100	100	100	100	100	100
Acanthosis: + leukocytic	150	150	150	150	150	150	150	150	150	150	150	150
- atrophic	100	440	150	150	50	50	50	50	50	50	50	50
- parakeratotic	50	50	50	50	100	100	100	100	100	100	100	100
Atrophy: + hyperkeratosis	50	50	50	50	100	100	100	100	100	100	100	100
- focal	50	50	50	50	100	100	100	100	100	100	100	100
- diffuse	50	50	50	50	100	100	100	100	100	100	100	100

Extension of table 1.

Histological changes in the epidermis	Histological types of actinic keratosis											
	Hyperkeratotic*		Erythematous		Atrophic*		Erythematous		Proliferative		Acantholytic	
	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000	n = 1000
Hyperkeratosis: + focal	50	50	50	50	50	50	50	50	50	50	50	50
- diffuse	50	50	50	50	50	50	50	50	50	50	50	50
Hyperkeratosis: focal	150	150	150	150	150	150	150	150	150	150	150	150
- diffuse	50	50	50	50	50	50	50	50	50	50	50	50
Acanthosis: + focal	50	50	50	50	50	50	50	50	50	50	50	50
- diffuse	50	50	50	50	50	50	50	50	50	50	50	50
Atrophy of keratinocytes:	0,2% 10	50	50	50	50	50	50	50	50	50	50	50
	0,2% 10	50	50	50	50	50	50	50	50	50	50	50
	0,2% 10	50	10, 10	50	50	50	50	50	50	50	50	50
Inflammatory lymphocytes in the basal layer:	0,2% 10	50	50	50	50	50	50	50	50	50	50	50
	0,2% 10	50	50	50	50	50	50	50	50	50	50	50
	0,2% 10	50	10, 10	50	50	50	50	50	50	50	50	50

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Extension of table 1.

Morphological changes in the epidermis		Morphological types of actinic keratosis											
		Hypertrophic		Bowenoid		Atrophic		Lichenoid		Proliferative		Acrolytic	
		Case (n)	Yes (%)	Case (n)	Yes (%)	Case (n)	Yes (%)	Case (n)	Yes (%)	Case (n)	Yes (%)	Case (n)	Yes (%)
Morphological keratinocytes in the basal layer	AK24 (n)	80	80	80	80	80	80	80	80	80	80	80	80
	AK24 (n)	20	4.4	20	20	20	20	20	20	20	20	20	20
	AK24 (n)	80	100	20	100	20	100	20	100	20	100	20	100
Morphological keratinocytes in the spinous layer	AK24 (n)	80	80	80	80	80	80	80	80	80	80	80	80
	AK24 (n)	20	4.4	20	20	20	20	20	20	20	20	20	20
	AK24 (n)	80	100	20	100	20	100	20	100	20	100	20	100
Morphological vessels	AK24 (n)	80	80	80	80	80	80	80	80	80	80	80	80
	AK24 (n)	20	4.4	20	20	20	20	20	20	20	20	20	20
	AK24 (n)	80	100	20	100	20	100	20	100	20	100	20	100
Impairment of the immunoreactive modification	AK24 (n)	80	80	80	80	80	80	80	80	80	80	80	80
	AK24 (n)	20	4.4	20	20	20	20	20	20	20	20	20	20
	AK24 (n)	80	100	20	100	20	100	20	100	20	100	20	100

After counting the histological signs observed in various forms of AK in the epidermis, we compared the percentages of symptoms observed in the dermis. 14 different morphological features were evaluated in the dermis. For example, the hypertrophic type was represented by solar elastosis (n = 30/45; 66.6%), basophilic collagen degeneration (n = 15/45; 33%), dilated vessels in the papillary layer of the dermis (n = 15/45; 33%), perivascular inflammatory infiltrate (n = 45/45; 100%) and interstitial inflammatory infiltrate (n = 45/45; 100%), consisting of lymphocytes (n = 45/45; 100%), plasmocytes (n = 3/45; 6.6%), histiocytes (n = 30/45; 66.6%), melanophages (n = 3/45; 6.6%), as well as exocytosis of lymphocytes (n = 7/45; 15.5%).

Solar elastosis (n = 15/20; 75%), basophilic collagen degeneration (n = 5/20; 25%), dilated vessels in the papillary layer of the dermis (n = 5/20; 25%), edema of the papillary layer of the dermis (n = 2/20; 10%), perivascular infiltration and interstitial inflammatory infiltrate (n = 20/20; 100%), consisting of lymphocytes (n = 20/20; 100%), plasmocytes (n = 3/20; 15%), histiocytes (n = 10/20; 50%), melanophages (n = 2/20; 10%), as well as exocytosis of lymphocytes (n = 8/20; 40%) were observed in the bowenoid type.

The atrophic variant of actinic keratosis was characterized by solar elastosis in 13 out of 15 (87%) patients, basophilic collagen degeneration in 15 out of 15 (100%), perivascular and interstitial inflammatory infiltrate in 15 out of 15 (100%), consisting of lymphocytes in 15 out of 15 (100%), plasmocytes in 2 out of 13 (13%), histiocytes in 5 out of 15 (33%) and exocytosis of lymphocytes in 10 out of 15 (66.6%) patients, respectively.

The fourth group consisted of skin biopsies obtained from patients with the lichenoid form of AK (n = 5). Solar elastosis (n = 2/5; 40%), basophilic collagen degeneration (n = 3/5; 60%), dilated vessels in the papillary layer of the dermis (n = 5/5; 100%), edema of the papillary layer of the dermis (n = 3/5; 60%), perivascular infiltrate and interstitial inflammatory infiltrate were noted in the dermis in (n = 5/5; 100%), consisting of lymphocytes (n = 5/5; 100%), eosinophils (n = 2/5; 40%), and exocytosis of lymphocytes (n = 5/5; 100%), respectively.

In the proliferative form of AK, the following signs were also observed: solar elastosis (n = 1/3; 33%), basophilic collagen degeneration (n = 2/3; 66%), dilated vessels in the papillary layer of the dermis (n = 1/3; 33%), papillary sclerosis (n = 3/3; 100%), perivascular infiltrate and interstitial inflammatory infiltrate (n = 3/3; 100%), consisting of lymphocytes (n = 3/3; 100%). No other cells were detected in the inflammatory

infiltrate.

The last histological group of AK was a rare acantholytic variant (n = 2). In the dermis of patients of this group the following signs were identified: solar elastosis (n = 1/2; 50%), basophilic collagen degeneration (n = 1/2; 50%), dilated vessels in the papillary layer of the dermis (n = 1/2; 50%), edema of the papillary layer of the dermis (n = 2/2; 100%), perivascular infiltration and interstitial inflammatory infiltrate (n = 2/2; 100%) consisting of lymphocytes (n = 3/3; 100%). The latter tended to penetrate into the epidermis (exocytosis of lymphocytes) (n = 2/2; 100%). A detailed percentage of the histological changes described above is presented in Table 2.

Table 2.

Percentage ratio of histological signs of various types of actinic keratosis observed in the dermis

Histological changes in the epidermis	Histological types of actinic keratosis											
	Hyperkeratosis (n=4/2)		Erythematous (n=2/2)		Acantholytic (n=1/2)		Lichenoid (n=1/2)		Bullous (n=1/2)		Atypical (n=2/2)	
	abs.	Per	abs.	Per	abs.	Per	abs.	Per	abs.	Per	abs.	Per
Solar elastosis	0	0%	1	50%	0	0%	0	0%	1	50%	0	0%
Basophilic collagen degeneration	1	50%	1	50%	0	0%	0	0%	0	0%	0	0%
Dilated vessels in the papillary layer of the dermis	1	50%	1	50%	0	0%	0	0%	0	0%	0	0%
Papillary layer edema	0	0%	2	100%	0	0%	0	0%	0	0%	0	0%
Papillary layer atrophy	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Perivascular inflammatory infiltrate	2	100%	2	100%	1	100%	1	100%	1	100%	2	100%
Interstitial inflammatory infiltrate	4	100%	2	100%	1	100%	1	100%	1	100%	2	100%
Neutrophils	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Lymphocytes	4	100%	2	100%	1	100%	1	100%	1	100%	2	100%
Macrophages	1	25%	1	50%	1	100%	0	0%	0	0%	0	0%
Monocytes	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Eosinophils	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Neutrophils	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Basophils	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Exocytosis of lymphocytes	2	100%	0	0%	0	0%	0	0%	0	0%	0	0%

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Thus, the study made it possible to determine the main morphological signs of actinic keratosis. It was revealed that the main changes are observed more often in the epidermis than in the dermis. As pathognomonic indications can be considered the following signs: dysplasia of epidermal cells, the presence of atypical keratinocytes in both the basal and thorny layers of the epidermis, pathological mitoses and violation of keratinocyte stratification. Meanwhile, signs such as acanthosis, hypergranulosis, atrophy of the epidermis are not specific and are of a reactionary nature.

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