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CASE REPORT

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A review of nonpigmented premalignant skin and mucosa lesions with cases: Case series

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Abstract

This study aimed to present conditions such as actinic keratosis, Bowen's disease, keratoacanthoma, and leukoplakia not only within a theoretical framework but also from a holistic perspective with actual cases diagnosed in our clinic. Four examples of non-pigmented premalignant skin and mucosa lesions were included in the study. These cases are, respectively: a keratoacanthoma presenting as a cutaneous horn under the right eye, Bowen's disease diagnosed from an erythematous plaque that had persisted for about eight years on the dorsum of the hand, actinic keratosis diagnosed from a rapidly growing lesion on the anterior forearm for one month, and a leukoplakia identified by a biopsy from the floor of the mouth. As a result, the early detection of these precursor lesions and their effective management, considering individual factors, provides the opportunity to intervene in the cancerization process in a timely and correct manner.

Keywords: Actinic keratosis, Bowen's disease, keratoacanthoma, p53, premalignant

Introduction

Non-melanoma skin cancers have the highest incidence rate among all malignant tumors [1], and one of the most important members of this group, squamous cell carcinoma (SCC), unlike the often spontaneously arising basal cell carcinoma (BCC), originates from precursor lesions to a significant extent. These precursor lesions represent the final stage before a tumor gains the potential for deep tissue invasion and metastasis. Due to these characteristics, they offer an invaluable opportunity for early intervention in dermatologic oncology. The most dominant factor in the development of this process is the lifelong exposure to ultraviolet (UV) radiation. UV rays cause typical mutations in the TP53 gene, which plays a key role in maintaining cellular health [2]. In addition, other risk factors include immunosuppression or exposure to chemical agents such as arsenic [2]. Our aim in this study is to discuss the four main lesions that are precursors to SCC, along with their reflections in our clinical practice, supported by theoretical knowledge. For this purpose, we will concretize the subject by presenting four different cases diagnosed in our clinic. Through these cases, we will specifically focus on the increasing role of immunohistochemistry (IHC) in overcoming diagnostic challenges and determining the risk of the lesion.

Case Presentation

Four case samples were included in this study. Each of these cases has a different premalignant lesion diagnosis and consists of biopsy cases evaluated and diagnosed in the pathology clinic. Necessary permissions were obtained from the patients for these cases. Separate ethics committee approval was not required.

Case 1

An 88-year-old female patient had a lesion excised from under her right eye with a clinical preliminary diagnosis of cutaneous horn, and the material was sent to our clinic. On macroscopic examination, a tissue fragment 0.9 cm thick was observed with a 1.2x0.7 cm ellipse of skin on it. On the skin, a brownish,

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irregularly shaped lesion measuring 0.6x0.3 cm, which was not raised from the skin, was observed at a distance of 0.5 cm from the nearest surgical margin. In the microscopic evaluation, a cup-shaped appearance with buttressing on both sides, dysplastic appearance in the epidermis within this cup, and a dense keratin plug were noted. There was no suspicious invasive area. The case was reported as keratoacanthoma (KA) (Figure: 1A, 1B).

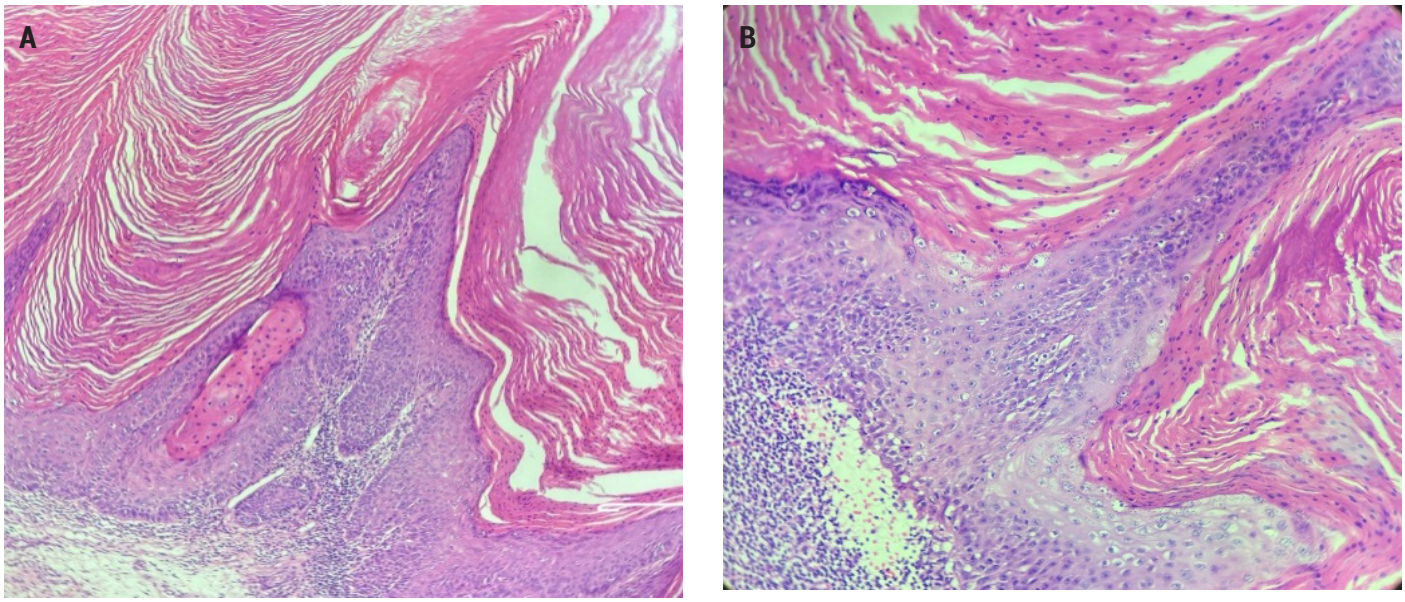

Figure 1. (A) A cup-like structure is seen with dysplasia (abnormality) in the cells forming this structure (H&E, x100), (B) Dysplasia and the dense keratin accumulation in the upper part are seen in detail (H&E, x200)

Case 2

A biopsy sample from a 51-year-old male patient's erythematous plaque, approximately 1 cm in diameter, which had been observed on the dorsum of his hand for about 8 years, was sent to our clinic. On macroscopic examination, a skin-subcutaneous tissue fragment 0.3 cm deep with a 0.5x0.5 cm ellipse of skin on it was observed. In the microscopic evaluation, keratinocytes were seen to be atypical throughout the full thickness, from the basal layer to the uppermost layers. These atypical cells had nuclear enlargement, hyperchromasia, and pleomorphism, and a scattered arrangement described as "wind-blown" was noted (Figure: 2A). In the IHC study, Ki-67 positivity was not limited to the lower layers of the epidermis but continued throughout the full thickness from the basal layer to the uppermost layers (Figure: 2B). P53 expressed mutant or wild type. In this case mutant type staining (strong nuclear staining) was observed with p53. It was noted that p53 positivity was not confined to the basal layer. The staining continued through almost the entire thickness of the epidermis, from the basal layer at the bottom to the granular layer closest to the surface (Figure: 2C). With all findings, the case was reported as Bowen's Disease.

Case 3

A biopsy sample from a rapidly growing lesion on the anterior surface of the arm of a 58-year-old female patient for one month was sent to our clinic. Macroscopic examination revealed a skin-subcutaneous tissue fragment 0.4 cm deep with a 0.6 cm diameter skin ellipse on it. In the microscopic evaluation, findings of atypia in keratinocytes limited to the lower part of the epidermis, the presence of parakeratosis, and prominent solar elastosis in the dermis were observed (Figure: 3A, 3B, 3C). Mutant type staining with p53 appeared to be predominantly limited to the basal layer of the epidermis and the few suprabasal layers immediately above it. The Ki-67 staining pattern indicated an increased proliferation rate and the extension of this proliferation into the suprabasal area. The case was reported as actinic keratosis (AK).

Case 4

A biopsy sample from the floor of the mouth of a 43-year-old female patient was sent to our clinic. On macroscopic examination, multiple cream-colored tissue fragments were observed, the largest being 0.7 cm and the smallest 0.2 cm. In the microscopic examination, the sections appeared very superficial with no subepithelial stroma in most areas, and there were areas where nuclear details could not be clearly distinguished due to cautery artifact, as well as areas of mild to moderate dysplasia in the epidermis (Figure: 4A, 4B, 4C). The case was reported as leukoplakia with foci of mild to moderate dysplasia.

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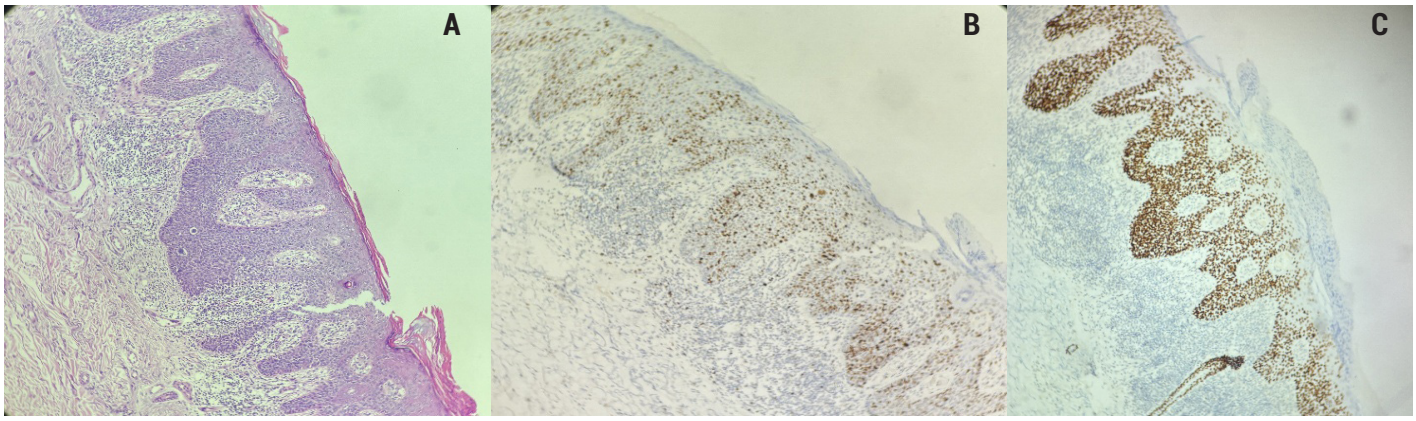

Figure 2. (A) Atypical cells extending through the full thickness are seen. These cells show a scattered arrangement described as "wind-blown"(H&E, x100), (B) Ki-67 positivity is seen extending through the full thickness of the epidermis, from the lower layers to the top. Positive cells are scattered irregularly at all levels of the epidermis (DAB, x100), (C) This image shows the mutant expression of p53 (expression is seen throughout the entire epidermis) (DAB, x100)

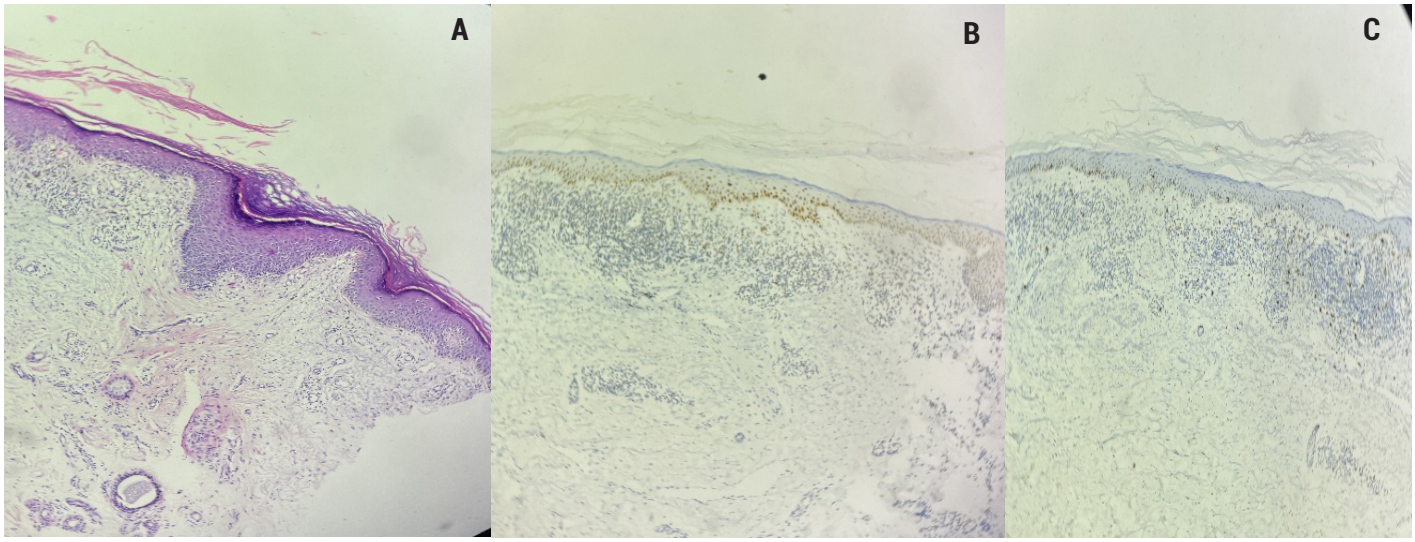

Figure 3. (A) Atypia limited to the lower part of the epidermis, parakeratosis, and prominent solar elastosis in the underlying dermis are observed (H&E, x100), (B) This image shows the mutant type expression of p53 (DAB, x100), (C) Ki-67 positivity indicates an increased cell proliferation rate and the extension of this proliferation into the suprabasal area (DAB, x100)

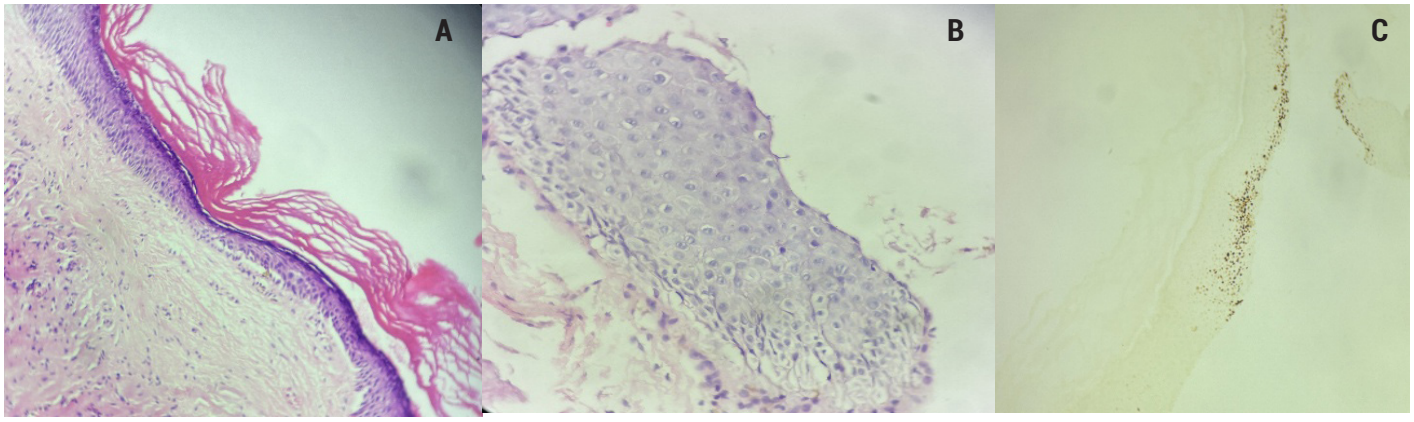

Figure 4. (A) Areas of mild to moderate dysplasia are seen (H&E, x200), (B) Areas of mild to moderate dysplasia are seen in greater detail (H&E, x400), (C) Ki-67 positive cells are seen ascending towards the upper layers of the epithelium. This is an indicator of increased cancerization potential (DAB, x200)

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Discussion

These non-pigmented precursor lesions we encounter on the skin or mucosa are not entirely separate diseases but rather different stages of a carcinogenesis process. The main trigger for this process is mostly the irreparable damage caused by years of exposure to the sun's ultraviolet rays to the TP53 gene, which is our cells' genetic shield [1]. The four different cases discussed in this study present the clinical and microscopic reflections of this molecular story, that is, the different stages of the process, as living examples.

If we evaluate the cases stage by stage, we first see AK, which can contain areas of low and high-grade dysplasia, where actinic changes are prominent and serve as the first warning sign. The lesion that grew rapidly on our 58-year-old female patient's arm for a month is a typical representative of this initial stage. When we look under the microscope, we see that the problem is still in its early stages; however, dysplasia that can extend to the full thickness of the epithelium may accompany the actinic changes. The risk of progression is related to the degree of dysplasia and can range from 1/10 to 1/1000. IHC stainings are what confirm the degree of dysplasia at a molecular level. The p53 protein, a sign of sun damage, accumulates in the lower layer, forming its characteristic pattern [3]. The Ki-67 marker, which indicates the proliferation rate of cells, also remains limited to these lower layers, indicating that it is not yet an advanced stage [4].

In the next stage, as in the lesion our 51-year-old male patient carried on the dorsum of his hand for eight years, we encounter carcinoma in situ (Bowen's disease), a more advanced stage with full-thickness involvement [5]. Here, atypical cells have spread to all layers of the epidermis [6]. Generally, location, appearance, and age are helpful findings here. Clinically, it usually appears as a slowly growing, sharply demarcated, slightly crusted or scaly, erythematous (red) plaque. It can often mimic eczema or psoriasis [7]. If located on the breast, it can be confused with Paget's disease. In this case, IHC is very important. In an IHC study, cytokeratin7 (CK7) can be performed (Bowen's disease cells are typically CK7 negative, whereas Paget's cells are CK7 positive). If it has a pigmented appearance, melanocytic markers may be needed (e.g., SOX10, Melan-A) [8]. In addition to surgery, treatment methods such as cryotherapy, curettage, topical 5-FU, imiquimod, or photodynamic therapy (PDT) can be used depending on the size and location of the lesion [9]. In terms of progression, the risk of transformation into invasive SCC is 3-5%, with immunosuppression and anogenital location increasing the risk [9]. In IHC analysis, the continuous positivity of the cell proliferation marker Ki-67. We see mutant expression with p53. When we consider the two cases mentioned so far side by side and evaluate the degree of dysplasia, IHC and morphology can provide an objective assessment for differentiation.

The same basic principles apply to more sensitive surfaces such as mucosa. In our case of leukoplakia detected in a high-risk area for cancerization, such as the floor of the mouth of our 43-year-old female patient, the findings of mild-to-moderate dysplasia were accompanied by the ascent of Ki-67 positive cells towards the upper layers of the epithelium. This is an indicator of increased cancerization potential and supports the direct correlation established in the literature between dysplasia severity and Ki-67 spread [10]. Leukoplakia and erythroplakia are lesions usually seen on the oral mucosa. Leukoplakia is a white plaque that cannot be scraped off, while erythroplakia is a bright red, velvety patch. These plaques are more common in people who use tobacco and alcohol [11]. A biopsy is indicated when these plaques are seen. The degree of dysplasia can range from mild to severe, and this can also determine the risk of transformation into an invasive tumor. One of the factors that increases the risk is the location. Lesions located on the floor of the mouth and the lateral/ventral surfaces of the tongue have a higher risk of malignant transformation [12]. Erythroplakia has a much higher malignancy potential than leukoplakia. Speckled or nodular leukoplakias have a higher risk than homogeneous leukoplakias [13].

Oral leukoplakia is one of the most common oral potentially malignant disorders (OPMDs) and is recognized for its risk of malignant transformation. According to the WHO Classification of Head and Neck Tumours, 5th Edition, 2022, oral leukoplakia is defined as a lesion of the oral mucosa appearing as a predominantly white patch or plaque that cannot be clinically or pathologically classified as any other definable disease or disorder. Oral leukoplakia is associated with an increased risk of malignant transformation either at the site of the lesion or elsewhere in the oral cavity and head and neck region [14]. P53 and Ki-67 are guiding biomarkers. In terms of treatment and prevention, avoiding etiological causes and excision are necessary.

Another example of these cases is KA [11]. In the 2022 fifth edition of the WHO classification of skin tumors, keratoacanthoma has been reclassified as a subtype of “well-differentiated squamous cell carcinoma” due to its histological features of malignancy, despite its clinically benign behavior. As a result, a lesion that was previously regarded as benign is now considered malignant based on its biological potential. In line with this updated classification, KA may present clinically as an aggressive tumor by growing rapidly within a few weeks, yet it also has the surprising potential for spontaneous regression [15]. Our 88-year-old female patient had a lesion that appeared under her eye. While KA gives the impression of an aggressive tumor by growing rapidly within weeks, it also has the surprising potential to regress spontaneously [13]. Although there are clues under the microscope that suggest it is benign, such as cells with abundant pink cytoplasm or the cup-like architecture of the tumor, its distinction from a well-differentiated SCC is not always clear [12].

Finally, these cases remind us of a larger picture called "field cancerization". Especially in a patient with numerous AK lesions, the visible lesions are merely the most prominent signals of a

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large area of skin fatigued by years of sun damage [7]. Therefore, the modern approach increasingly recommends "field therapies" (e.g., photodynamic therapy or topical medications) that target the entire damaged area, rather than just destroying individual lesions [8].

Conclusion

The possibility of cancer can be eliminated from the outset when these precursor lesions are detected and necessary precautions are taken. These cases can be accurately diagnosed with the support of clinical experience, histopathological evidence, and immunohistochemical studies. The success of treatment depends on determining a personalized strategy by considering the biological character of each lesion, its location, and individual risk factors such as the patient's general health status. However, it should not be forgotten that the most effective way to prevent these lesions is to protect our skin from the harmful effects of the sun.

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Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Patient Informed Consent
Informed consent was obtained from the patients.

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