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Original Article

Dysplastic Change Rate in Cases of Actinic Cheilitis: A Retrospective Study of 33 Cases

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Abstract

Background: Chronic lip inflammation is the characteristic feature of actinic cheilitis (AC), a precancerous lesion that can develop into squamous cell carcinoma (SCC). Early detection and education of individuals at higher risk for AC can reduce the likelihood of developing SCC. This retrospective study sought to assess the demographic and clinicopathological attributes of 33 patients diagnosed with AC.

Methods: Thirty-three cases were retrieved from the archive of the Department of Pathology of Sina Hospital, Hamadan, Iran, between 2009 and 2019. All information was recorded from the submission forms, including gender, age, anatomical location of the lesions, size, duration, outdoor occupation, and clinical aspects.

Results: There were 29 males and 4 females. The mean age was 62 ± 14 years. Nine cases of older patients (>62 years) showed mild, moderate, and severe grades of dysplasia (3 cases for each degree). Fisher's exact test indicated a significant difference between the presence of dysplasia and the age of the patients ($P<0.001$). In addition, a statistically significant distinction emerged concerning the presence of dysplasia and the size of the lesion (Fisher's exact test, $P<0.001$). Likewise, a significant difference was found between the presence of dysplasia and the type of occupation regarding exposure to the sun ($P<0.001$). Finally, there was a significant difference between the presence of dysplasia and the duration of the disease (Fisher's exact test, $P<0.003$).

Conclusion: The clinicopathologic profile observed in the series of patients with AC revealed that patients were more frequently males, aged ≤ 62 years. The predominant clinical features were erythematous and atrophic lesions. However, in cases with dysplasia, ulceration emerged as the most frequent clinical finding. Further research with larger sample sizes is imperative to explore the potential role of smoking and other environmental factors in the development of AC and its potential malignant transformation.

Keywords: Actinic cheilitis, Dysplasia, Lip neoplasms, Precancerous conditions

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Background

Chronic lip inflammation is the characteristic feature of actinic cheilitis (AC), a precancerous lesion that can develop into squamous cell carcinoma (SCC) (1). The primary causal factor is believed to be prolonged exposure to solar ultraviolet radiation, especially ultraviolet B. SCC development has also been linked to tobacco use and/or alcohol consumption (2). AC has a variety of clinical symptoms, such as swelling, erythematous or white patches, ulcers, crusts, atrophy, pallor, and/or scaly lesions, in addition to dryness (3). On histological examination, the epithelium shows atrophy or hyperplasia, hyperkeratosis, and different grades of dysplasia. Furthermore, an amorphous, basophilic substance known as solar elastosis may be evident in the underlying connective tissue. Malignancy can occur in 3.07%–16.9% of AC cases, according to earlier investigations (4). Early detection and education of individuals at higher risk for AC can reduce the likelihood of developing SCC (1). SCC on the lips has a four times higher metastatic rate than cutaneous SCC (4). The importance of this lesion and its timely diagnosis is highlighted by these findings. This retrospective study seeks to assess the demographic and clinicopathological attributes of 33 patients diagnosed with AC.

Materials and Methods

This was a cross-sectional, retrospective study based on the analysis of the pathology records of patients diagnosed with AC. Thirty-three cases were retrieved from the archive of the Department of Pathology of Sina Hospital, Hamadan, Iran, between 2009 and 2019. All information was recorded from the submission forms, including age (in years), gender, anatomical location of the lesions, size (greatest diameter of the lesion in millimeters), outdoor occupation, duration, and clinical aspects. To validate the prior diagnosis rendered by an anatomical pathologist, an oral and maxillofacial pathologist conducted a comprehensive review of all microscopic slides, meticulously documenting histological attributes. The grading of epithelial dysplasia followed the World Health Organization classification (2017), encompassing categories such as no dysplasia, mild dysplasia, moderate dysplasia, and severe dysplasia (5,6). Statistical analyses were performed employing both Chi-square and Fischer's exact tests to establish associations. Additionally, the correlation among variables was assessed utilizing Spearman's test. Statistical significance was determined by a P value less than 0.05 ($P \leq 0.05$).

Results

There were 29 males and 4 females. The mean age was 62 years (ranging from 35 to 96 years). Tables 1 and 2 provide details on the demographic and clinical characteristics of 33 cases, respectively.

Nine cases of older patients (>62 years) showed mild, moderate, and severe grades of dysplasia (3 cases for each degree). Histologic findings of 33 cases of AC are reported in Table 3.

The results of Fisher's exact test demonstrated a significant difference between the presence of dysplasia and the age of the patients ($P<0.001$). In addition, a statistically significant distinction was found concerning the presence of dysplasia and the size of the lesion (Fisher's exact test, $P<0.001$). Similarly, there was a significant difference between the type of occupation regarding exposure to the sun and the presence of dysplasia ($P<0.001$). Further, a significant difference was observed between the presence of dysplasia and the duration of the disease (Fisher's exact test, $P<0.003$).

The literature was searched for previous case series. The detailed information of previous studies is provided in Table 4.

Discussion

AC occurs mainly on the lower lip and is often found in fair-skinned males (1,15). Chronic exposure to ultraviolet radiation is the main risk factor for its development (16). Based on our findings (Table 1), the majority of patients (87.9%) were males, and the lower lip was the primary site of lesions (90.9%). According to a study (16), AC lesions are most prevalent in females (55% vs. 44.6%). The use of lipstick or lip sunscreen may be the reason for the low

Table 1. Demographic Data of 33 Patients With Actinic Cheilitis

Clinical Parameters	No. (%)
Gender	
All patients	
Male	29 (87.9)
Female	4 (12.1)
Total	33
Gender	
Cases with dysplasia	
Male	18 (90)
Female	2 (10)
Total	20
Gender	
Cases without dysplasia	
Male	11 (84.6)
Female	2 (15.4)
Total	13
Age (y)	
All patients	
Mean age ± SD (range)	62 ± 14 (35-96)
≤62	17 (51.5)
>62	16 (48.5)
Age (y)	
Cases with dysplasia	
≤62	11 (55)
>62	9 (45)
Age (y)	
Cases without dysplasia	
≤62	6 (46.1)
>62	7 (53.9)
Size (mm)	
All patients	
Mean (range)	6.8 (3-25)
≤6.8	25 (75.5)
>6.8	8 (24.5)
Size (mm)	
Cases with dysplasia	
≤6.8	14 (70)
>6.8	6 (30)
Size (mm)	
Cases without dysplasia	
≤6.8	11 (84.6)
>6.8	2 (15.4)
Duration (month)	
All patients	
Mean (range)	8.5 (1-24)
≤8.5	17 (51.5)
>8.5	16 (48.5)
Duration (month)	
Cases with dysplasia	

Table 1. Continued.

Clinical Parameters	No. (%)
≤8.5	6 (30)
>8.5	14 (70)
Duration (month)	
Cases without dysplasia	
≤8.5	11 (84.6)
>8.5	2 (15.4)
Outdoor occupation	
All patients	
Yes	25 (75.7)
No	8 (24.3)
Outdoor occupation	
Cases with dysplasia	
Yes	15 (75)
No	5 (25)
Outdoor occupation	
Cases without dysplasia	
Yes	10 (76.9)
No	3 (23.1
Affected area	
All patients	
Lower lip	30 (90.9)
Upper lip	3 (9.1)
Affected area	
Cases with dysplasia	
Lower lip	17 (85)
Upper lip	3 (15)
Affected area	
Cases without dysplasia	
Lower lip	13 (100)
Upper lip	0

Note. SD: Standard deviation.

Table 2. Number (%) of Prominent Clinical Presentations of 33 Cases of Actinic Cheilitis and Duration of Lesions

Clinical Presentations	No. (%)	No. of Cases With Duration < 8.5 Months	No. of Cases With Duration > 8.5 Months
All patients			
White plaques	11 (33.3)	4	7
Ulceration	10 (30.3)	5	5
Scaly lesions	4 (12.1)	2	2
Erythematous and atrophic lesions	3 (9)	3	0
Areas of pallor	2 (6)	2	0
Dryness	2 (6)	1	1
Blurred demarcation of the vermilion border and skin	1 (3)	0	1
Cases with dysplasia			
Ulceration	9 (45)	4	5
White plaques	8 (40)	2	6
Scaly lesions	2 (10)	0	2
Blurred demarcation of the vermilion border and skin	1 (5)	0	1
Areas of pallor	0 (0)	0	0
Dryness	0 (0)	0	0
Erythematous and atrophic lesions	0 (0)	0	0
Cases without dysplasia			
White plaques	3 (23.1)	2	1
Erythematous and atrophic lesions	3 (23.1)	3	0
Scaly lesions	2 (15.4)	2	0
Areas of pallor	2 (15.4)	2	0
Dryness	2 (15.4)	1	1
Ulceration	1 (7.6)	1	0
Blurred demarcation of the vermilion border and skin	0 (0)	0	0

incidence of AC in women. The majority of outdoor jobs are dominated by males, and men tend to retire later than women. This observation supports the proposed idea that the lower lip, because it is everted, is more susceptible to chronic and direct sunlight exposure than the upper lip. This vulnerability could be attributed to the lower lip's thinner epithelium, which lacks the robust keratin layer found in the skin (17). The vermilion region of the lip is characterized by its unique characteristics, indicating a reduced presence or absence of the stratum corneum compared to the skin (18).

In agreement with the findings of a prior study, our results demonstrated more dysplastic changes in patients ≤62 years old, and there was a significant association between the presence of dysplasia and the age groups (11). However, in a previously published paper, the presence of dysplasia was not related to the age of the patient (9).

In the current series, "white plaque" was the most common clinical presentation (33.3%). Our results are in line with those of a prior paper, showing white plaques (33.6%) as the most frequent clinical feature (11,12). Conversely, loss of lip vermilion delineation was the most prevalent clinical presentation (77.1%) in some previous studies (14,19). Another study reported "dryness" as the most common clinical feature (9). These differences between the findings might be related to the clinical features of AC at the time of diagnosis and biopsy.

In our study series, the most prevalent clinical manifestation observed in cases with dysplasia was ulceration, followed by the presence of white plaques. This finding conforms to the results of the research conducted by Medeiros et al, where ulcers were identified in 100% of patients with moderate to severe cases. Interestingly, white plaques were documented in only 15.4% of individuals with moderate to severe conditions in their study (15). The progression of AC has been postulated to involve the development of focal chronic ulceration over time. Moreover, a prior study indicated a potential correlation between the consumption of pipes or cigarettes and the

Table 3. Histological Findings of 33 Cases of Actinic Cheilitis With or Without Dysplasia

Histologic Grading	No. (%)	Histologic Findings According to the Criteria Used for Diagnosing Dysplasia
Without dysplasia	13 (39.4)	Hyperplasia or atrophy, hyperkeratosis, mild inflammatory cell infiltrate, and elastosis (basophilic appearance of underlying connective tissue)
Mild dysplasia	4 (12.1)	Hyperplasia, hyperkeratosis, and dysplastic changes limited principally to the basal and parabasal layers: Basal cell hyperplasia, loss of basal cell polarity, irregular epithelial stratification, and drop-shaped rete ridges. Basophilic appearance of underlying connective tissue, angiogenesis and vasodilatation, and mild inflammatory cell infiltrate
Moderate dysplasia	6 (18.2)	Hyperplasia, hyperkeratosis, and dysplastic changes from the basal layer to the midportion of the epithelium: Basal cell hyperplasia, loss of basal cell polarity, irregular epithelial stratification, drop-shaped rete ridges, increased number of mitotic figures, abnormally superficial mitosis, cell and nuclear pleomorphism, hyperchromatism, increasing nuclear, and cytoplasmic ratio. Basophilic appearance of underlying connective tissue, angiogenesis and vasodilatation, and moderate inflammatory cell infiltrate
Severe dysplasia	10 (30.2)	Hyperplasia, hyperkeratosis, or a thin layer of keratin, and dysplasia changes can be observed from the basal layer to a level above the midpoint of the epithelium: Basal cell hyperplasia, loss of basal cell polarity, irregular epithelial stratification, dyskeratosis, drop-shaped rete ridges, increased number of mitotic figures, abnormally superficial mitosis, increased number and size of nucleoli, and hyperchromatism. Basophilic appearance of underlying connective tissue, angiogenesis and vasodilation, and moderate to severe inflammatory cell infiltrate

Table 4. Previous Studies on the Clinicopathological Profile of Actinic Cheilitis

Gender	Age (Years)	Most Common Clinical Feature (%)	Histological Findings	Reference
M (81.3%) F (18.7%)	62 61.2	No data	Dysplasia: Mild (52%), moderate (23%), severe (12.5%), carcinoma in situ (11.2%), and SCC (1.3%)	(7)
M (60; 92.3%) F (5; 7.4%)	53.2 51.4	Erosion and ulcer (47.7%)	Dysplasia: Mild: 18 (27.7%), moderate: 20 (30.8%), severe: 16 (24.6%), and SCC: 11 (16.9%)	(8)
M (72.41%)	75.86%>40	Dryness 29 (100%)	Dysplasia: Mild (10.34%), moderate (27.59%), and severe (62.07%)	(9)
No data	No data	Dryness (100%)	Dysplasia (100%)	(10)
M (30; 75%) F (10; 25%)	Overall: 80%≥40, 20%<40	White lesions (55%)	Without dysplasia (40%): Mild (25%), moderate (27.5%), and severe (7.5%)	(11)
M (128; 79.5%) F (33; 20.5%)	77.5%≥40 22.5%<40	White lesions (33.6%)	High risk (39.8%) and low risk (60.2%)	(12)
M (55; 80.9%)	53.1	No data	Without dysplasia (23.5%): Mild (30.9%), moderate (35.3%), and severe (10.3%)	(13)
M (43; 67.2%) F (21; 32.8%)	55.1 61.6	Loss of mucocutaneous limit (100%)	Dysplasia: Mild (13.6%), moderate (28.8%), and severe (57.6%)	(14)
M (29; 80.6%) F (7; 19.45)	Overall: 94.4%≥40, 5.6%<40	Blurred demarcation between lip and skin (88.95)	Without dysplasia (19.4%), mild (55.6%), moderate (16.7%), and severe (8.3%)	(15)

Note. F: Female; M: Male; SCC: Squamous cell carcinoma.

occurrence of ulcers. This study proposed that repetitive trauma stemming from these habits could potentially predispose the affected area to malignant transformation (20).

Concerning histologic classification, 42.4% of cases in our study showed some degree of dysplasia, and 18.2% of samples demonstrated SCC (18.2%) (Figure 1A-I). Kaugars et al found epithelial dysplasia in 98.7% of the cases. Further, they observed mild epithelial dysplasia and SCC in 52.0% and 1.3% of patients, respectively (7). Markopoulos et al reported mild epithelial dysplasia in 27.7%, while 72.3% showed moderate dysplasia to invasive SCC (8). De Santana Sarmento et al found mild, moderate, and severe dysplasia in 10.34%, 27.59%, and 62.07% of patients, respectively (10). In another study performed by Gonzaga et al, 76.5% of cases were graded as mild, moderate, and severe dysplasia (13). Additionally, Medeiros et al classified 55.6%, 16.7%, and 8.3% of samples as mild, moderate, and severe dysplasia, respectively (15). The variations observed among studies could stem from differences in the histological and cytological parameters considered during the assessment of epithelial dysplasia. In addition, these differences may reflect a delay in diagnosis at each center. Furthermore, in the early stages, some patients might erroneously attribute the lesion to aging, subsequently dismissing it until it progresses to a more advanced state.

Within the scope of our current study, a noteworthy correlation emerged between the presence of dysplasia and the duration of the condition. This observation lends credence to the notion that the passage of time plays a substantive role in the progression of AC toward epithelial dysplasia. Given the profound influence that dysplastic changes exert on the potential malignant transformation of pre-cancerous lesions, it is imperative to ascertain the presence and extent of epithelial dysplasia within the sampled specimens. It has been proposed that the first phase of epithelial dysplasia is the damage to the basal cell layer. Later, continued exposure to the sun and other environmental factors can cause acanthosis and hyperkeratosis. The severity of dysplasia is associated with acanthosis, hyperkeratosis, basophilic change of the connective tissue, perivascular inflammation, and inflammation within the connective tissue. The role of inflammation and inflammatory cells in malignant transformation has been documented in prior studies. For example, neutrophils promote cancer development through extracellular matrix remodeling,

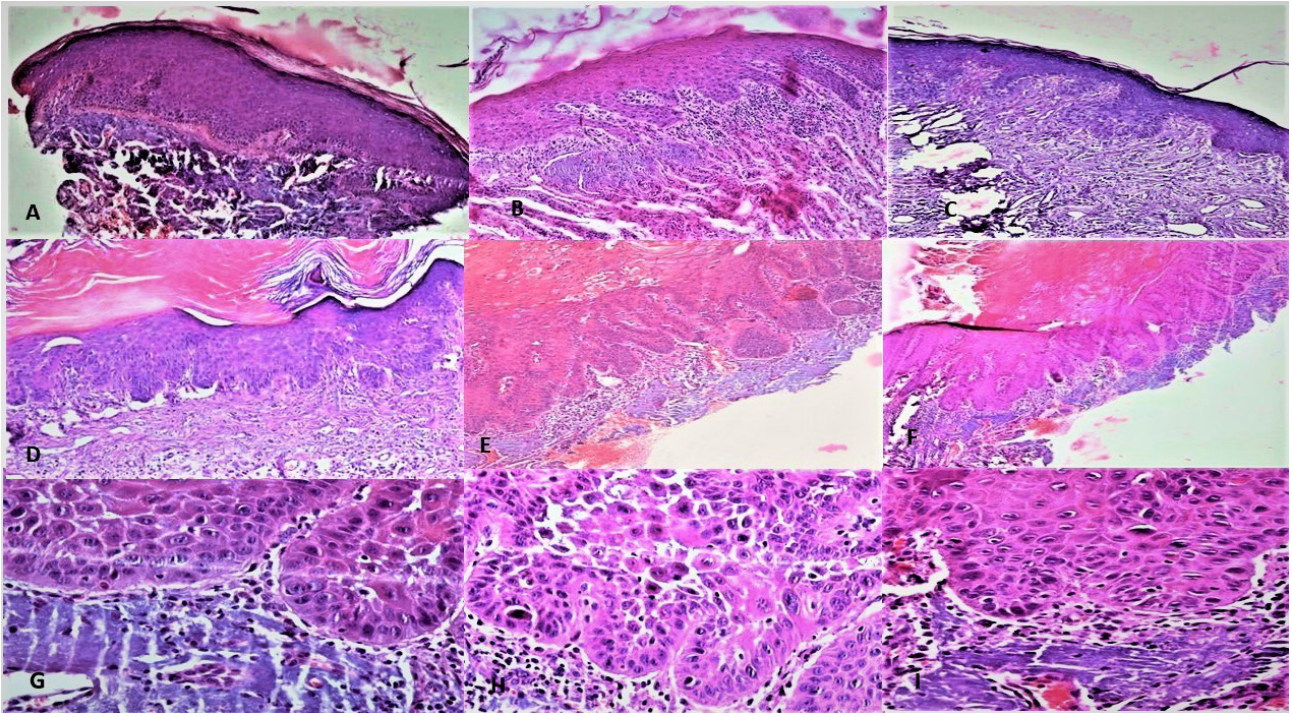

Figure 1. Histopathological Images Showing Biopsies From Actinic Cheilitis Lesions: **(A)** Without Dysplasia (X100), **(B)** Mild Dysplasia and Epithelial Hyperplasia (X100), **(C)** Mild Dysplasia and Epithelial Atrophy (X100), **(D)** Moderate Dysplasia and Hyperkeratosis (X100), **(E)** Severe Dysplasia (X250), **(F)** Severe Dysplasia (X100), **(G)** Cellular Atypia (X400), **(H)** Dyskeratosis and Loss of Epithelial Cell Cohesion (X400), and **(I)** Cells With Hyperchromatic and Pleomorphic Nuclei (X400). *Note*. Notice solar elastosis in images

angiogenesis, promotion of cell migration and invasion, and proliferation of cancer cells (21,22).

Given the substantial propensity of AC to progress into invasive SCC, the early identification of AC significantly enhances the prospects of successful intervention. Notably, reported rates of malignant transformation in AC range from 10% to 30%. Remarkably, a striking 95% of SCC cases affecting the lower lip stem from preexisting AC. Moreover, SCC originating in the lower lip exhibits heightened aggressiveness and an elevated risk of metastasis in contrast to SCC arising on the skin (23,24). Over the past few decades, diverse therapeutic modalities have been explored to manage AC. These encompass procedures such as vermilionectomy, cryotherapy, and topical applications such as imiquimod and 5-fluorouracil (4). In recent times, photodynamic therapy has emerged as a promising avenue for AC treatment. Encouragingly, a comprehensive clinical response has been documented in 68.9% of cases subjected to photodynamic therapy (4,24).

Conclusion

The clinicopathologic profile observed in this study series of patients with AC confirmed that patients were more frequently males aged ≤ 62 years. Erythematous and atrophic lesions were predominant clinical features. However, in cases with dysplasia, ulceration has emerged as the most frequent clinical finding. This suggests a potential role of inflammation in malignant transformation. The results underscore the necessity of educational intervention strategies aimed at raising awareness about the etiology of AC. Nonetheless, this study has certain limitations, particularly the absence of a comprehensive history of smoking in medical records. Accordingly, further research with larger sample sizes is imperative to explore the potential role of smoking and other environmental factors in the development of AC and its potential malignant transformation.

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Authors' Contribution

Conceptualization: Soussan Irani.
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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

This study received ethical approval from the Ethics Committee of Hamadan University of Medical Sciences (approval No. IR.UMSHA.REC.1398.043).

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