

## Actinic Cheilitis: Analysis of Clinical Subtypes, Risk Factors and Associated Signs of Actinic Damage

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Actinic cheilitis (AC) is a common condition that mainly involves the lower lip, which is associated with chronic exposure to ultraviolet (UV) radiation. AC is considered a precursor of malignancy (1), but the rate of progression from AC to invasive squamous cell carcinoma (SCC) has not yet been established. An epidemiological study previously described the prevalence of AC and its associated variables in the Galicia region (north-western Spain); the prevalence of AC in a population aged 45 years and over was 31.3%, and multivariate analysis showed that significant and independent risk factors for AC were age  $\geq 60$  years, Fitzpatrick skin phototypes I and II, working outdoors for more than 25 years, and a history of non-melanoma skin cancer (NMSC) (2). We report here a subanalysis of the clinical manifestations of AC and the associations of AC with other markers of actinic damage.

### METHODS

A cross-sectional multicentre study was conducted in Galicia (the total population in 2016 was 2,718,525, data from Galician Statistics Institute; <http://www.ige.eu>), a region located in north-western Spain. Eight dermatology departments participated in the study, and patient data were collected prospectively from 12 January 2016 to 31 January 2017. Consecutive patients aged  $\geq 45$  years that attended a general dermatology outpatient clinic were recruited once a week. A physical examination of each patient was performed visually with or without a magnifying glass (2). Clinical characteristics of AC were precisely specified in a previous meeting attended by all the investigators to minimize inter-observer bias; characteristics were classified as follows: persistent desquamation, persistent erythema, a mottled appearance (erythema and white patches), and a plaque (solid, raised, flat lesion  $>1$  cm) and/or an erosion/ulceration that could not be attributed to other dermatological disorders (modified from Ribeiro et al.) (3). Patients with uncertain eroded/ulcerated lesions underwent a biopsy to exclude SCC. A binary regression logistic analysis was performed to determine the significant associations with each clinical form of AC. Univariate and multivariate analyses of the different variables related to other markers of actinic damage (lentigines and actinic keratosis (AK)) in patients with AC were also analysed.

The study protocol was approved by the Research Ethics Committee of Pontevedra-Vigo-Ourense, Spain (protocol number 2015/582).

All statistical analyses were performed using SPSS 22.0 statistical software for Windows.

### RESULTS

A total of 1,250 patients were selected for the study. Eleven patients declined to participate in the study or were not willing to sign the consent form; therefore, a total of 1,239 patients completed the screening form. Of these, 410 were diagnosed with AC, and complete data were available for 408 patients. The prevalence of AC in the study population was 31.3% (95% confidence interval (95% CI) 28.7–33.8).

Regarding AC clinical manifestations, 47.3% (193) of patients had only one clinical manifestation of AC, 40.2% ( $n=164$ ) of patients had 2 manifestations, 12.3% ( $n=50$ ) of patients had 3 manifestations, and 0.2% ( $n=1$ ) of patients presented with 4 AC clinical manifestations. The most frequent presentation was a mottled appearance (73.8%), followed by desquamation (53.7%), erythema (30.1%), plaque (4.2%) and erosion-ulceration (3.7%). A history of NMSC was significantly associated with the presence of a mottled appearance (odds ratio (OR) 1.931,  $p=0.049$ ). The presence of desquamation was associated with high alcohol intake (OR 2.077,  $p=0.037$ ) and working outdoors for more than 25 years (OR 1.744,  $p=0.017$ ), while male sex was a protective factor (OR 0.586,  $p=0.048$ ). Erythema was associated with high alcohol intake (OR 2.172,  $p=0.026$ ) and working outdoors for more than 25 years (OR 2.364,  $p=0.003$ ), and being a smoker or former smoker was considered a protective factor for this clinical manifestation (OR 0.582,  $p=0.041$ ). No statistically significant associations were found with the less prevalent clinical manifestations (plaque and erosion-ulceration).

The presence of other actinic damage indicators, such as AK and/or lentigines, was detected in 73.5% of patients with AC. Lentigines had a higher prevalence, at 32.1%, followed by AK, at 21.8%, and 19.6% of patients with AC presented with both types of lesions. Statistically significant associations with lentigines were Fitzpatrick skin phototypes I and II (OR 1.81,  $p=0.041$ ) and age  $>65$  years (OR 2.65,  $p=0.001$ ). The variables associated with the presence of AK were Fitzpatrick skin phototypes I and II (OR 2.74,  $p=0.0003$ ), age  $>65$  years (OR 5.86,  $p=0.000$ ) and a history of NMSC (OR 3.86,  $p=0.003$ ).

## DISCUSSION

To our knowledge, the possible associations between the different clinical AC manifestations and AC risk factors have not been reported previously. Both desquamation and erythema were associated with working outdoors for more than 25 years and high alcohol intake. Male sex was a protective factor for desquamation, indicating that women had a higher tendency of this manifestation. Smoking or former smoking was shown to be a protective factor for erythema, meaning that tobacco consumers are more prone to present any of the other clinical AC presentations. A mottled appearance was the only clinical manifestation of AC that had a significant association with a past history of NMSC; this finding is very interesting, as it may be a simple clinical sign that could possibly indicate an increased chance of NMSC, although this association should be confirmed in future studies.

UV radiation has been considered the main risk factor for the development of AK and lentiginos (4–6), but to our knowledge, risk factors associated with AK and lentigo development in patients with AC have never been reported. Both Fitzpatrick skin types I and II and age > 65 years were associated with the presence of AK and lentiginos in patients with AC, as expected. A past history of NMSC was related only to AK, but not lentiginos, confirming the known correlation between NMSC, especially SCC, and AK, which is, in fact, considered an *in situ* SCC.

Regarding the limitations of the study, the inclusion of patients aged 45 years and older may exclude younger patients with AC, even though it is accepted that most AC occurs in people aged over 50 years (3, 7–9). Furthermore, even though a precise definition of AC and its different subtypes was established before the start of the study and all investigators were dermatologists with broad experience, inter-observer bias cannot be completely ruled out.

A description of the different clinical manifestations of AC and their associated risk factors, as well as the analysis of actinic damage markers in a population with AC, is presented here. Interestingly, different clinical manifestations were related to different risk factors, and these associations have never been reported previously.

The significant correlation between a mottled appearance and a past history of NMSC may have practical clinical implications, both in terms of early diagnosis and follow-up. Notably, the presence of other markers of chronic sun exposure, such as AK and/or lentiginos, was detected in 73.5% of patients with AC, stressing that a clinical examination of the lip should be performed on all patients with actinic damage, and lip photoprotection should be emphasized.

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