

Microinvasive oral squamous cell carcinoma preceded by erythroplakia in a young adult

CASE REPORT






Carcinoma de células escamosas oral microinvasivo precedido por eritroplasia en un adulto joven

Carcinoma de células escamosas oral microinvasivo precedido por eritroplasia em adulto jovem

Abstract

A significant increase has been observed in cases of oral squamous cell carcinoma (OSCC) in young adults without a history of tobacco use, alcohol consumption, or infection with high-risk human papillomavirus (HPV). This article presents the case of a 39-year-old woman with no history of smoking or alcohol use. She presented with a red plaque featuring ulcerated areas on the left lateral border of the tongue, measuring 3 cm at its greatest diameter, with an 8-year history marked by periods of exacerbation and remission, accompanied by a burning sensation in the affected area. Based on a clinical hypothesis of oral erythroplakia (OE), an incisional biopsy was performed. Histopathological analysis revealed severe epithelial dysplasia, disruption of the basement membrane, and small epithelial islands on the surface of the adjacent connective tissue, which tested positive for pancytokeratin in immunohistochemical analysis. A diagnosis of microinvasive OSCC was established. The patient underwent surgical treatment, with the diagnosis confirmed in the surgical specimen, and she is currently disease-free. This case highlights the importance of early diagnosis and histopathological evaluation of OE to prevent progression to OSCC—an entity increasingly observed in young adults without identifiable risk factors. We emphasize the need for further research, including genetic studies, to help clarify and explain cases of OSCC and potentially malignant lesions in young adults, such as the one described here.

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Resumen

Se ha observado un aumento significativo en los casos de carcinoma de células escamosas oral (CCEO) en adultos jóvenes, sin relación con el tabaquismo, el consumo de alcohol o el virus papiloma humano (VPH) de alto riesgo. Este artículo presenta el caso de una mujer de 39 años que negó hábitos como el tabaquismo y el consumo de alcohol. Presentaba una placa roja con áreas ulceradas, localizada en el borde izquierdo de la lengua, con un tamaño de 3 cm en su mayor diámetro y una evolución de 8 años, caracterizada por períodos de exacerbación y remisión, acompañados de una sensación de ardor en la zona. Bajo la hipótesis de eritroplasia oral (EO), se realizó una biopsia incisional y el análisis histopatológico reveló displasia epitelial severa, ruptura de la membrana basal y pequeñas islas epiteliales en la superficie del tejido conectivo adyacente, que resultaron positivas para pancitoqueratina en el análisis inmunohistoquímico. El diagnóstico fue de CCEO microinvasivo, y la paciente fue tratada quirúrgicamente, con confirmación del diagnóstico en la pieza quirúrgica, y actualmente está libre de la enfermedad. Se destaca la importancia del diagnóstico y estudio histopatológico precoz en EO para evitar la progresión a CCEO, entidad cada vez más presente en adultos jóvenes sin factores de riesgo asociados. Reiteramos que se necesitan más estudios, incluidos estudios genéticos, para esclarecer y explicar casos de CCEO y lesiones potencialmente malignas en adultos jóvenes, como el reportado en este caso.

Palabras clave: Carcinoma de Células Escamosas de Cabeza y Cuello, Adultos Jóvenes, Medicina Oral, Leucoplasia Oral, Reporte de Caso.

Introduction

Squamous cell carcinoma (SCC) is the most common malignant neoplasm of the oral cavity.⁽¹⁾ Factors such as tobacco use and alcohol consumption are associated with the pathogenesis of SCC in this location,⁽²⁾ and it is more frequently observed in men around 60 years of age.⁽³⁾ However, in recent years, there has been a rise in cases of oral squamous cell carcinoma (OSCC) in young adults under the age of 40.^(4,5) In this group, risk factors such as tobacco use, alcohol consumption,^(2,4) and high-risk human papillomavirus (HPV) are not associated. Although HPV plays a role in oropharyngeal SCC, it has not yet been linked to cases of OSCC in this age group, whose pathogenesis remains unclear.^(6,7)

Resumo

Há um aumento significativo nos casos de carcinoma de células escamosas oral (CCEO) em adultos jovens, sem relação com tabagismo, consumo de álcool ou com o vírus do papiloma humano (HPV) de alto risco. Este artigo apresenta o caso de uma mulher de 39 anos que negou hábitos como tabagismo e consumo de álcool. Ela apresentava uma placa avermelhada com áreas ulceradas, localizada na borda esquerda da língua, medindo 3 cm em seu maior diâmetro, com uma evolução de 8 anos, caracterizada por períodos de exacerbção e remissão, acompanhados de sensação de queimação na região. Sob a hipótese de eritroplasia oral (EO), foi realizada uma biópsia incisional, e a análise histopatológica revelou displasia epitelial grave, rompimento da membrana basal e discretas ilhas epiteliais na superfície do tecido conjuntivo adjacente, que foram positivas para pancitoqueratina na análise imunohistoquímica. O diagnóstico foi de CCEO microinvasivo, e a paciente foi tratada cirurgicamente, tendo o diagnóstico confirmado na peça cirúrgica, e atualmente está livre da doença. Ressalta-se a importância do diagnóstico precoce e do estudo histopatológico na EO para prevenir a progressão para o CCEO, entidade cada vez mais presente em adultos jovens sem fatores de risco associados. Reiteramos que novos estudos, como estudos genéticos, podem esclarecer e explicar casos de CCEO e lesões potencialmente malignas em adultos jovens, como o relatado aqui.

Palavras-chave: Carcinoma Espinocelular de Cabeça e Pescoço, Adultos Jovens, Medicina Oral, Leucoplasia Oral, Relato de Caso.

OSCC may be preceded by oral potentially malignant disorders (OPMDs), such as oral leukoplakia (OL) and oral erythroplakia (OE).⁽⁸⁾ Malignant transformation rates of up to 34% have been reported in OL and up to 50% in OE.⁽⁸⁻¹⁰⁾ Notably, proliferative verrucous leukoplakia (PVL), a non-homogeneous variant of OL, also shows high transformation rates.^(11,12) Although numerous studies have focused on the chemopreventive treatment of OL,⁽¹³⁾ surgical excision is currently considered the gold standard.⁽¹²⁾ Like OSCC, OPMDs have also been observed in young patients. A literature review reported that out of 1,246 patients with OPMDs, 115 (9.2%) were under 40 years of age, had no associated risk fac-

tors, and some progressed to SCC.⁽¹⁴⁾ The etiology of OSCC and OL in this population remains unknown.⁽¹⁴⁾ Therefore, early detection and accurate diagnosis of OPMDs are essential to prevent OSCC.

This report presents a case of microinvasive OSCC preceded by an undiagnosed OPMD in a young patient without associated risk factors. The objective is to illustrate the clinical and histopathological presentation of this rare case and to discuss future directions for research on similar cases.

Case report

Informed consent was obtained from the patient for the publication of this case report, and she authorized its dissemination. This case report complies with the recommendations and guidelines of the Declaration of Helsinki.

A 39-year-old female patient, allergic to metals and a vegetarian supplemented with vitamin B12, denied

both smoking and alcohol consumption. She presented to the Oral Medicine Clinic at the University of Chile with a complaint of a lesion on the left lateral border of the tongue, with an 8-year evolution. She described periods of exacerbation and remission accompanied by burning sensations and reported having previously been diagnosed and treated by another professional for recurrent aphthous stomatitis, without achieving clinical resolution.

Extraoral physical examination revealed no abnormalities. Intraoral examination showed a red plaque with ulcerated areas located on the left lateral border of the tongue. The lesion was oval-shaped, with diffuse margins, reddish coloration, and measured 3 cm at its greatest diameter (**Figure 1**). An incisional biopsy was performed under the clinical suspicion of OE and was sent to the Pathology Department of the Faculty of Dentistry (SAP-FO).



Figure 1 Initial clinical presentation of the lesion. Red plaque with mottled appearance on the left lateral border of the tongue.

Histological sections revealed severe epithelial dysplasia, characterized by cellular and nuclear pleomorphism, hyperchromatism, mitotic figures, and dyskeratosis. There was also apparent discontinuity of the basement membrane and detachment of epithelial cells, which occasionally invaded the adjacent connective tissue (**Figure 2**).

Immunohistochemical staining with pancytokeratin confirmed microinvasion; however, there was no evidence of infiltration into muscle tissue, blood vessels, or nerve tissue (**Figure 3**, A and B). The final diagnosis was microinvasive OSCC.

Figure 2 Histological sections of the incisional biopsy showing dysplastic epithelium with hyperplastic and acanthotic areas, chronic inflammatory infiltrate, basement membrane discontinuity, and epithelial cells occasionally invading superficially into the adjacent connective tissue within the lamina propria (Staining: hematoxylin and eosin).

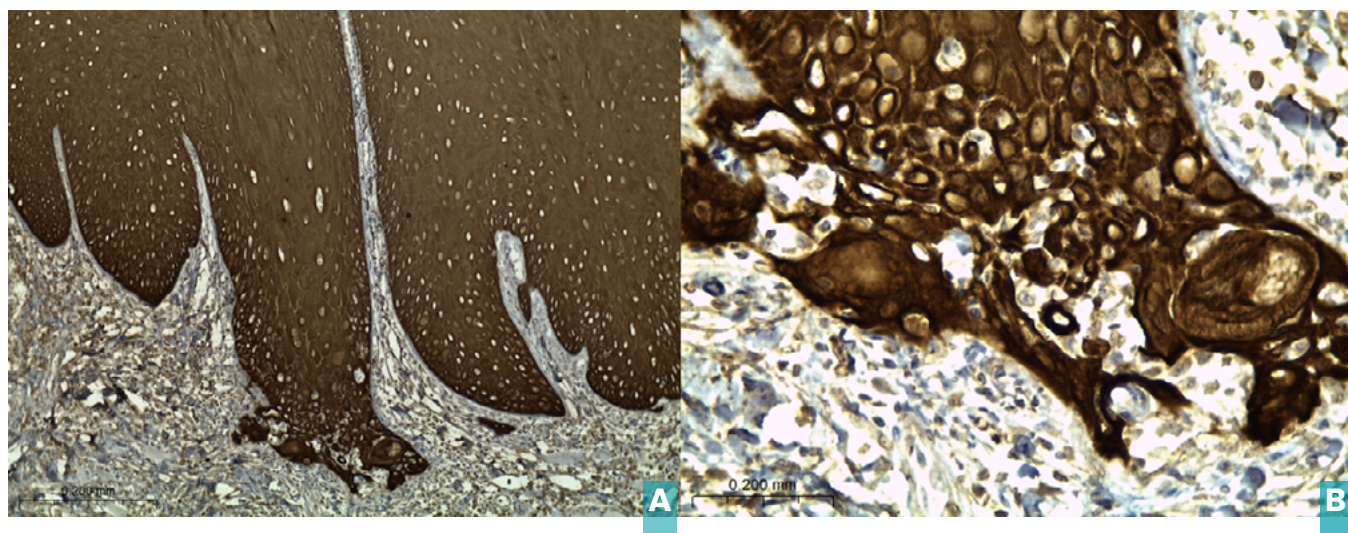
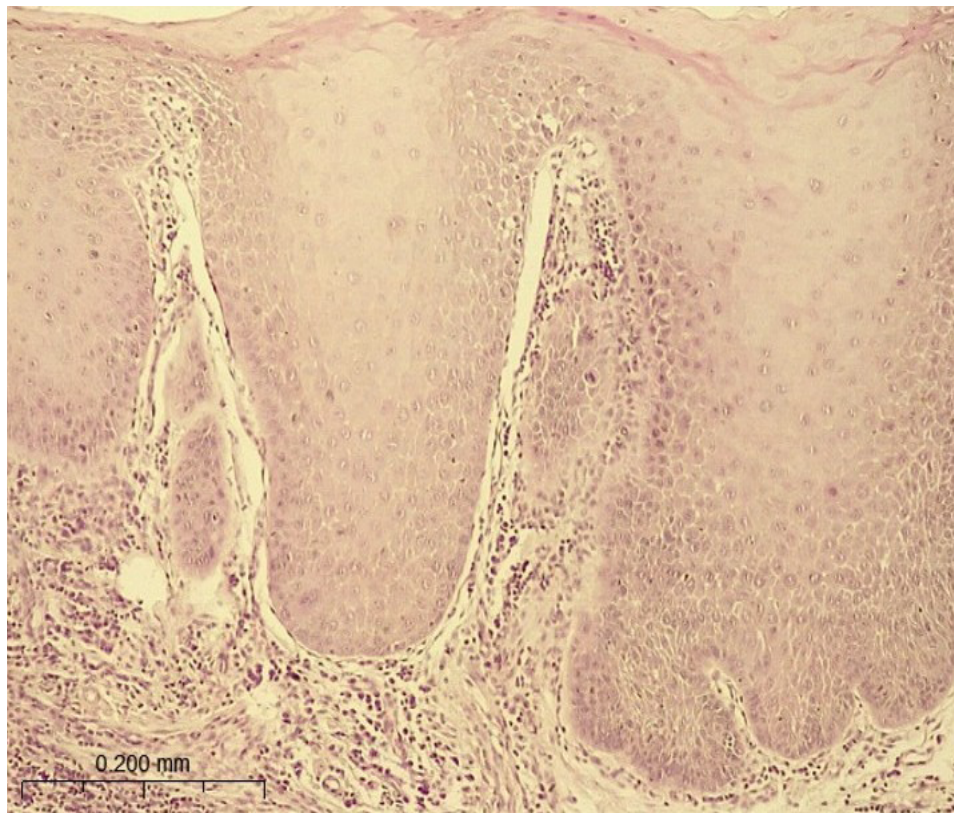


Figure 3 Immunohistochemical staining using AE1/AE3 antibody. A and B. Neoplastic epithelial cells superficially invading the lamina propria.

The patient was referred to the Head and Neck Surgery Department of a regional referral hospital, where she underwent surgical treatment, including a partial glossectomy and excisional biopsy of the cervical sentinel lymph node, also on the left side. Histopathological analysis of the surgical specimen confirmed the diagnosis from the incisional biopsy and showed that the margins

were free of dysplastic and/or neoplastic tissue. The sentinel lymph node showed no evidence of neoplastic involvement.

The patient has been under clinical follow-up through routine consultations for two years following treatment, with no signs of lesion recurrence (**Figure 4**).



Figure 4 Clinical appearance of the site following surgical treatment with partial glossectomy. No signs of recurrence after two years of clinical follow-up.

Discussion

OPMDs of the oral cavity present with a variety of clinical manifestations. OL is described as a white plaque with uncertain malignant potential, and its diagnosis can only be confirmed after ruling out other specific conditions.^(9,10,14,15) OE, another OPMD, is similarly defined as a bright red plaque that cannot be clinically or pathologically characterized as another disease.⁽¹⁵⁾

Clinically, OE appears as a red plaque that may have a granular surface, while histopathologically it may exhibit epithelial dysplasia or even frankly invasive SCC.⁽¹⁶⁾ In this case, the symptoms, clinical features, and histopathological findings suggest that although the final diagnosis was microinvasive SCC, it was preceded by a misdiagnosed OE. Thus, errors or omissions in clinical diagnosis and professional management can enable the development of malignant neoplasms at the site,⁽¹⁷⁾ negatively affecting the patient's prognosis.

A systematic review of the literature aimed to characterize OL and OE in young patients.⁽¹⁴⁾ It analyzed case series of patients diagnosed with OL and OE, identifying 115 individuals under the age of 40 with OPMDs, all of them presenting with OL. This finding highlights that OE is a OPMD rarely reported in young adults. However, this case demonstrates that individuals in this age group can develop OE and, subsequently, OSCC. Therefore, OE

should be included in the clinical differential diagnosis regardless of age and confirmed by incisional biopsy when suspected.

A shift in the epidemiology of OSCC has been observed. While the number of new cases in patients over 40 years of age has declined in recent years, there has been a 106% increase in OSCC diagnoses among young adults under 40,⁽¹⁸⁾ as exemplified by this case. In this age group, risk factors such as tobacco use, alcohol consumption,⁽²⁾ and HPV infection⁽⁶⁾ do not appear to play a significant role. However, genetic alterations are suspected to be associated with the rising incidence of OSCC in this population,^(19,20) which frequently presents at advanced clinical stages at the time of diagnosis, suggesting greater biological aggressiveness.⁽²¹⁾ Although this report describes a case of microinvasive OSCC, it is understood that it was preceded by OE, which remained misdiagnosed for eight years.

For this specific case, p16 immunohistochemical analysis was not performed. Based on the patient's medical history, along with clinical, histological, and immunohistochemical findings, it was concluded that the SCC originated from a prior OE, thereby ruling out a possible association with HPV. Identifying potential factors linked to the development of certain SCC cases

remains a challenge. One study reported that germline alterations in DNA repair genes are associated with an increased risk of developing head and neck cancer at an early age, specifically in patients under 49 years old.⁽²²⁾ Similar findings emerged from our recent systematic review of the literature on germline genetic variations in patients with SCC.⁽²³⁾ These insights could guide future research and help clarify the occurrence of SCC and OPMDs in young adults without identifiable risk factors, as illustrated by this case.

Microinvasive SCC is described as an early stage of squamous cell carcinoma.⁽²⁴⁾ A literature review noted that it is commonly located on the tongue and may present clinically as spots, plaques, or ulcers⁽²⁵⁾. In line with this, microinvasive OSCC may manifest as OL or OE, as observed in this case, highlighting the importance of incisional biopsy for accurate diagnosis.

Histopathologically, microinvasive SCC is defined as being confined to the superficial stroma or lamina propria.⁽²⁶⁾ In this case, basement membrane discontinuity was observed, along with the detachment of epithelial

cells that remained superficial within the connective tissue. However, the presence of inflammatory infiltrate at the site can hinder visualization of the basement membrane's integrity or obscure microinvasion, potentially leading to diagnostic uncertainty.⁽²⁷⁾ In such scenarios, immunohistochemical staining with epithelial markers, such as pancytokeratin, can assist in detecting microinvasion, as demonstrated here.

Studies and case reports on microinvasive SCC are scarce, and no standardized epidemiological, clinical, histopathological, treatment, or follow-up parameters have been established.⁽²⁵⁾ However, a multicenter study by Ferreira and Costa et al.⁽²⁸⁾ on SCC in patients under 40 years of age reported multiple cases exhibiting microinvasion into connective tissue. It remains unclear whether this pattern is specific to this age group or reflects earlier diagnoses in younger individuals. Nevertheless, surgical excision has been the treatment of choice in such cases,⁽²⁵⁾ as was done in the case presented here.

Conclusion

Delay in the diagnosis of OPMDs may compromise lesion progression and negatively affect the patient's prognosis when SCC develops—whose incidence has risen in young adults without associated risk factors. Microinvasive SCC presents both clinical and histopathological challenges due to its potential for very superficial invasion or the possibility of being obscured by inflammation. Therefore, we suggest that immunohistochemical staining with pancytokeratin may serve as a valuable tool in the histopathological diagnosis, enabling confirmation of invasion or its absence in the connective tissue.

In addition, we underscore the importance of further studies on SCC and OPMDs in young adults to identify currently unknown contributing factors, including genetic investigations in this population. This emerging area of research could improve the diagnosis, prognosis, and treatment of cases like the one reported here.

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Data availability

All data supporting the findings of this study are included within the article.

Conflict of interest statement

The authors declare no conflict of interest.

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Marcela Hernández Ríos			X		X	X	X						X	X
Juan Pablo Aitken-Saavedra			X		X	X	X						X	X
Daniela Adorno-Farias	X		X	X	X	X	X	X		X		X	X	X

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