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CASE REPORT

Solitary keratoacanthoma of the lip vermilion: case report and comprehensive review of literature

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Abstract:

Solitary keratoacanthoma (S-KA) is a benign epithelial proliferation that affects the sun-exposed skin of elderly. It presents rapid growth often followed by spontaneous remission. S-KA clinical and microscopic features are very similar to the squamous cell carcinoma's (SCC) and differentiating them can be a challenge. S-KA involving the lip is rare and frequently is managed as SCC, leading to overtreatment. Despite of few investigations aiming at differentiate S-KA and SCC are available, there is no compilation of case reports of lip S-KA. Thus, our aim was to conduct a comprehensive review of the literature and report a case of lip S-KA. The review was conducted until 2016 and only 21 cases were found. Lip S-KA was more common in elder man, lower lip, and most of them were asymptomatic. The lesions measured 16.7mm on average with duration of approximately 12 weeks. The most performed treatment was excisional biopsy of lesion despite of the self-healing potential of the lesion.

Keywords: Keratoacanthoma; Carcinoma, Squamous Cell; Lip; Neoplasm Regression, Spontaneous

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INTRODUCTION

Keratoacanthoma (KA) is a benign epithelial proliferative lesion of the skin. It is frequently observed in light-skinned elderly, affecting mainly the sunlight exposed areas. Besides ultraviolet radiation, immunosuppression seems to be an additional risk factor. Data regarding the epidemiology of KA affecting the lips are still scarce once most of the cases are published as single case[1-14] or grouped in small series[15-17].

Keratoacanthoma may be solitary as well as multiple[18], being the first one the most common. The solitary KA (S-KA) usually presents as a pink or flesh-coloured and dome-shaped ulcer with a central keratin plug and measures between 1 to 2cm in diameter[18]. When its size exceeds 3cm in diameter, it is called giant keratoacanthoma[18]. Multiple KAs are less common and can be classified into Grzybowski type, Ferguson Smith type, and Witten and Zak type[18]. In this paper, we focused on the lip S-KA type because this is the one that most affects the lips and, as a consequence, is the most relevant type for dental professionals.

KA manifests as a fast growing ulcer which center is filled with keratin and possesses the curious potential of self-involution within 4-8 weeks[18, 19]. Microscopically, S-KA typically exhibits hyperplastic squamous epithelium with a central keratin plug, in a lip-shaped form. Mild mitotic activity and absence of epithelial dysplasia[18, 19] are also found. Three different stages are determined by the histological examination during the evolution of KA: proliferative phase, resting fully developed mature stage, and regression[3].

Due to the clinical and microscopic resemblance of S-KA with squamous cell carcinoma, much effort has been invested in differentiate both diseases[19-23]. However, there is a remarkable lack of studies investigating the clinical and microscopic aspects of KA affecting the lips. Therefore our purpose was to provide a comprehensive review of the literature regarding lip S-KA together with a case report.

CASE REPORT

A white 66-year-old man was referred for evaluation of a lesion in the inferior lip. The patient had smoked straw cigarette for the last 45 years, related alcohol consumption ten years ago, and had been worked exposed to the sunlight for a long period. He noticed the lesion 4 months before the consultation and did not refer pain. Clinically, it was observed a crusted ulcer with elevated and indurated borders, white surface, and 1.2cm diameter located in the left inferior lip vermilion (Figure 1-A). Incisional biopsy was performed with differential diagnosis of squamous cell carcinoma, paracoccidioidomycosis, leishmaniasis, and keratoacanthoma. Microscopic analysis showed hyperplastic stratified squamous epithelium with long finger-like projections, keratin pearls, and few typical mitoses. In one border, cup-shaped epithelium was observed (Figure 2-A). In the underlying connective tissue, it was seen an intense mononuclear inflammatory infiltrate and congested blood vessels (Figure 2-B). The final diagnosis was keratoacanthoma. In the one-week post-operatory visit, the lesion showed signals of involution (Figure 1-B). The patient was advised about solar exposure role in the development of the lesion and five months later, the ulcer regressed spontaneously leaving a scar (Figure 3).

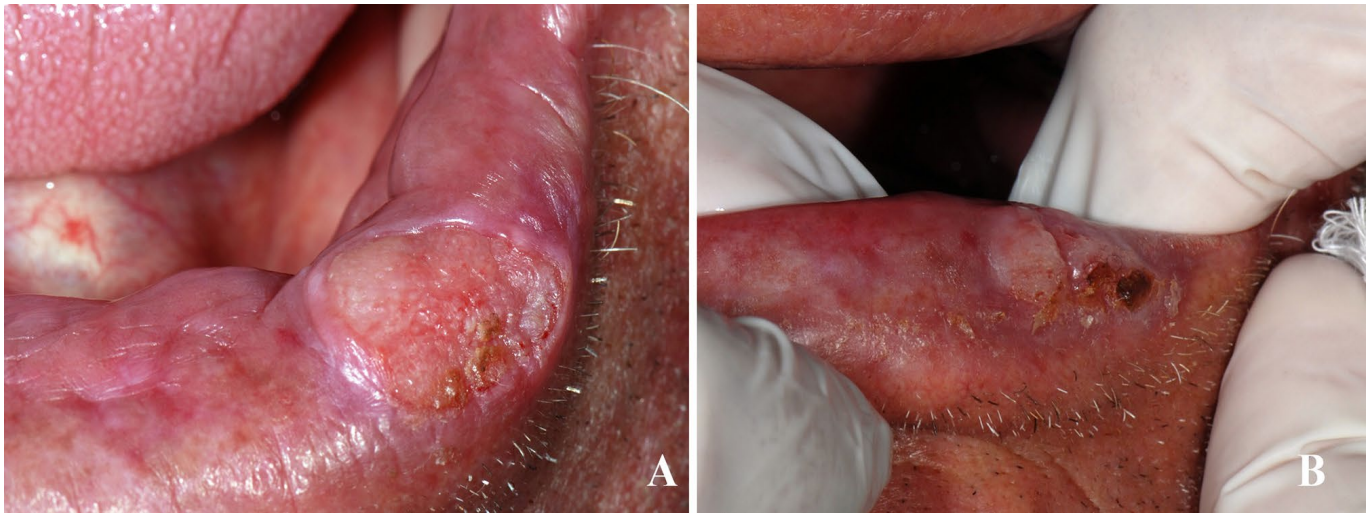

Figure 1 - A: Initial aspect of the lesion. Crusted ulcer with elevated and indurated borders, white surface, 1.2cm diameter in the left lower lip vermilion; B: Partial remission of the lesion 1 week after performing the incisional biopsy.

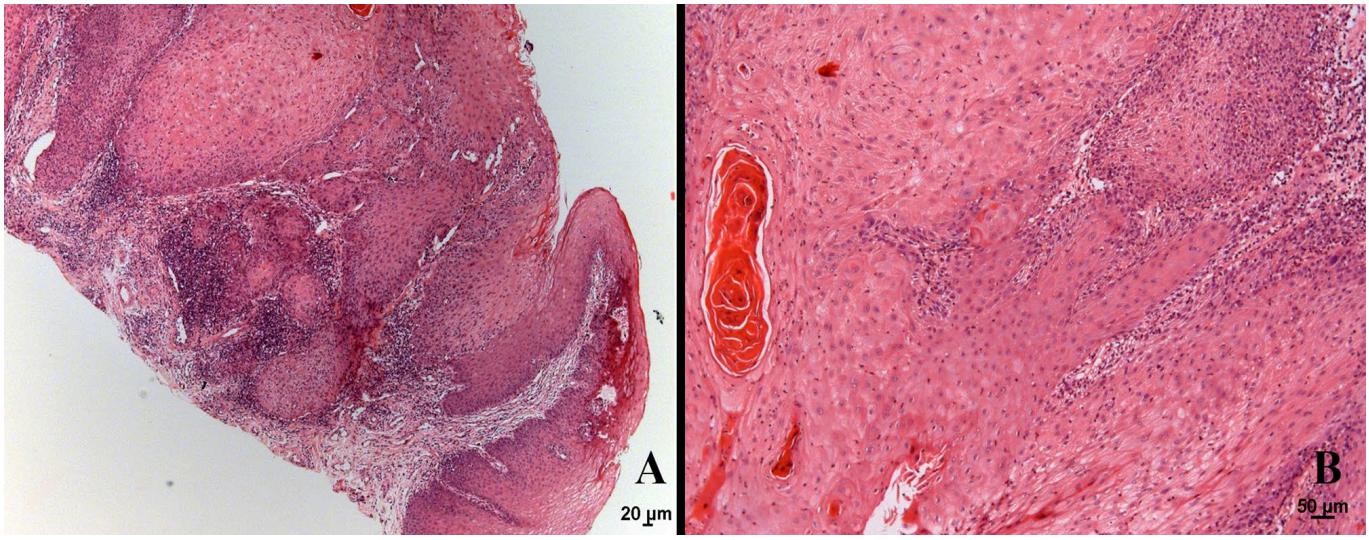

Figure 2 - A: Hyperplastic, stratified and cup-shaped squamous epithelium. In the underlying connective tissue, it is observed an intense chronic inflammatory infiltrate (H&E). B: Keratin pearl, absence of cellular dysplasia, and few typical mitoses (H&E).

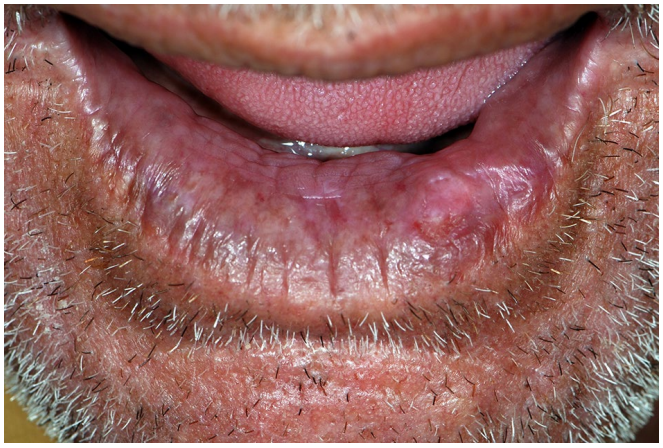

Figure 3 - Regression of the lesion after follow-up of 5 months.

REVIEW OF THE LITERATURE AND DISCUSSION

The literature review was conducted, without restriction on date, in the PubMed/Medline database until April 2016. The used term was: "keratoacanthoma" accompanied by the descriptive term "lip". The inclusion criteria were 1. Case reports or case series of solitary keratoacanthoma containing complete information regarding the demographic, clinical, and microscopical aspects of the(s) case(s) or case reports that showed involution of the lesion after treatment and 2. Cases affecting the vermilion border of the upper or lower lip. The exclusion criteria were 1. Animal studies and literature reviews, 2. Cases involving exclusively the skin portion of the lip, 3. Cases in which the biopsy was not performed or when the microscopical image was not available, and 4. Papers in other language than English. A manual search was also conducted analyzing the references of the selected papers.

The review resulted in a total of 123 titles/abstracts and 17 fulfilled the inclusion criteria (16 from the Pubmed/Medline database and 1 from the manual search). A total of 20 case reports was obtained. Information were compiled in a spreadsheet by one reviewer and checked by a second one. The relevant data regarding the already published S-KA and the one reported here (total of 21 cases) are summarized in the Table 1.

There were sixteen males and five females (male:female ratio was 3.2), suggesting a predilection of S-KA for man while skin lesions do not see to have a preponderance of any gender[24]. The mean age at clinical presentation was 51.8 years (range 14–79 years). Only two patients were below 30 years old. The first one was 14 years old and also had discoid lupus erythematous. Thus his immunological imbalance added to a reported sunlight chronic exposure might have had role in the S-KA development[10]. The second individual, 20 years old, was a "goza" (also called narghile, hookah, shisha, and water-pipe) user[15] which mutagenic potential may have a role in the development of S-KA[24]. Disregarding those two patients, the main age at clinical presentation rose to 53 years old and 17/21[1, 3-9, 11, 13, 14, 16, 17] patients were above 45 years old.

Almost all patients (20/21) had the lower lip affected by the S-KA. The only case presented in the upper lip[7] was sited in the middle portion. The location of the inferior S-KA in the lower lip were homogeneously distributed: eight in right side of the lip vermilion, eight in left side, and five in middle portion of the lip vermilion.

Table 1. Clinical features of the reported cases of lip keratoacanthoma (1957–2016).

N	YEAR	AUTHORS	SEX	AGE	SIDE	SITE	SIZE (mm)	TYPE	DURATION (wks)	SYMPTOM	TREATMENT	FOLLOW-UP (mo)
1	1957	Whittle	M	48	Right	Lower	10	Typical	6	N/A	Hidrocortisone + Antibiotic + Biopsy 6 weeks after	12
2	1958	Karnauchow	M	45	Left	Lower	10	Typical	8	N/A	Excisional biopsy	N/A
3	1972	Kohn	M	60	Right	Lower	N/A	N/A	7	No	N/A	84
4	1972	Kohn	M	51	Left	Lower	10	Typical	4	No	Incisional biopsy	4
5	1974	Azaz	F	46	Right	Lower	10	Typical	2	Yes	Excisional biopsy	50
6	1996	Visscher	M	46	Middle	Lower	30	Giant	8	Yes	Incisional biopsy + follow-up	10
7	1999	El-Hakim	M	20	Middle	Lower	N/A	N/A	N/A	N/A	Shaving excision	18
8	2000	Spieth	F	79	Right	Lower	20	Giant	4	Yes	Incisional biopsy + MTX	N/A
9	2002	Visscher	M	68	Right	Lower	35	Giant	6	N/A	Incisional biopsy + MTX	48
10	2004	Oh										
M	70	Left	Lower	16	Typical	3	N/A	Incisional byopsy + Inteferon alfa- 2b	19			
11	2004	Oh										
M	70	Right	Lower	18	Typical	8	N/A	Incisional byopsy + Inteferon alfa- 2b	27			
12	2007	Minicucci	M	14	Left	Lower	15	Typical	N/A	N/A	Excisional biopsy	8
13	2009	Ramos	F	40	Left	Lower	15	Typical	28	No	Incisional biopsy + follow-up	24
14	2011	Chauhan	M	50	Left	Lower	20	Giant	6	No	Excisional biopsy	3
15	2011	Pinto-Almeida	M	45	Middle	Lower	30	Giant	48	No	Excisional biopsy	24
16	2013	Chaiben	M	42	Left	Lower	N/A	N/A	12	No	Excisional biopsy	6
17	2014	Zargaran	M	54	Right	Lower	8	Typical	8	Yes	Excisional biopsy	N/A
18	2014	Zargaran	F	60	Right	Lower	13	Typical	48	No	Excisional biopsy	N/A
19	2015	Gulati	M	51	Middle	Upper	10	Typical	2	N/A	Excisional biopsy	6
20	2016	Guimarães	F	62	Middle	Lower	20	Giant	8	N/A	Incisional biopsy + Excisional biopsy	17
21	2017	Moraes-da-Silva	M	66	Left	Lower	12	Typical	16	No	Incisional biopsy + follow-up	5

The locations of the lesions, middle upper lip and whole lower lip, are the anatomically most prominent parts of the lips and, as a consequence, the most ones exposed to sunlight, supporting the role of the UV radiation in the onset of S-KA[19].

Eight patients, including ours, did not refer any symptom[2, 3, 9, 11, 12, 17] related to the S-KA, three reported pain[4, 13, 17] and one, a xeroderma pigmentosum patient, referred burning sensation with onset after a long and acute exposure to sunlight and duration of 2 weeks, until the lesion appeared[1]. Nine case reports did not mention this aspect[5–8, 10, 14–16]. The length of symptoms of the S-KA was approximately 12 weeks (range 2-48 weeks), similar to our patient, with an evolution period of 16 weeks. Two cases did not report the length of symptoms of the lesions[10, 15].

The most cited clinical features of the S-KA were exophytic, sessile, erythematous, and done-shaped ulcer with a central crust and indurated border. The S-KAs measured 16.7mm on average (range 8-35mm) in the greatest dimension; 12 lesions were smaller than 20mm and classified as typical S-KA while 6 were larger than 20mm and fitted in the giant S-KA category (Table 1). Pinto-Almeida *et al*[11] reported an atypical case of a giant S-KA emerging from the lower lip and forming a bifurcated horny projection with 30mm in height each, resembling a bird's beak.

Despite of the similar features of the S-KA and SCC, there are scant studies focusing on differentiate both entities clinically. The distinction between KA and SCC is a challenge because both have clinical and morphological similarities. However, features of true malignancy are not observed in S-KA microscopically such as severe cellular pleomorphism and prominent atypical mitoses. The most reported features of KA were dome-shaped and hyperplastic squamous epithelium with a central craterlike depression extended to the connective tissue and containing a thick layer of keratin plugging. Intense chronic inflammatory infiltrate was also found. Two cases[1, 6] presented cellular epithelial dysplasia and another two[17] exhibited slight cellular pleomorphism. Eight cases[1, 2, 6, 7, 12, 17], including ours, presented high mitotic activity and two cases[8, 10], occasional proliferative cells. No study reported atypical mitosis. Despite of few reports of metastatic and aggressive KAs were published, it is likely it was the result of an inaccuracy in diagnosis of SCC. Three different stages are determined by histological examination during evolution of KA: a proliferative phase, the resting fully developed mature stage, and regression. Thus, the pathologist may have different pictures of KA depending on the phase it was biopsied and it is essential the professional is aware about this difference.

All the S-KA characteristics cited above show its similarity to squamous cell carcinoma and, indeed, the majority of the S-KA had as presumptive diagnosis SCC[3, 8, 10, 12,] SCC and S-KA[2, 6, 17], or SCC, S-KA, and other diseases[7]. The other twelve case reports suppressed this information. In our case, we also suspected of SCC besides infectious diseases, and S-KA but our clinical diagnosis was SCC due to the SCC-typical clinical features found added to the risk factors the patient presented (elder, male, ex-smoker, ex-alcoholic, and worked under chronic exposure to sunlight). Out of the five cases with suspicion of S-KA, only one[6] and ours were not surgically excised immediately despite of S-KA being remarkably described as a self-healing lesion. Guimarães *et al.*[6] performed an incisional biopsy that confirmed the diagnosis of S-KA but still opted for the excision of the lesion, maybe because the giant lesions are less prone to regress. This fact reinforces the resemblance of S-KA with oral cancer and the rarity of the first one, which was not even suspected in most of the cases.

Interestingly, all the eight S-KA managed conservatively presented total regression of the lesions (5 were typical and 3 were giant S-KAs). Four cases, including the one reported here, were solely followed-up after incisional biopsy[4, 9, 12], two cases were managed with adjuvant intralesional methotrexate (MTX) injection[5, 13], and two, with intralesional applications of the interferon alfa-2b[16]. The average time of regression of the lesions managed by the "watch and wait" approach was 22.6 weeks (range 8-40 weeks) while the T-SA managed with the adjuvant drugs took 6.8 (range 5-8 weeks) to disappear. The intralesional injection of keratoacanthomas with MTX[25, 26] and interferon alfa-2b[27] has been shown success in cutaneous lesions and it seems to be also effective for lip lesions. As those drugs have an improved action in proliferating cells, it is believed that their efficacy may be higher in the proliferative phase, shortening the natural course of the S-KA. Thus, in cases in which incisional biopsy is conclusive for S-KA, the follow-up with or without adjuvant agents seems to be a smart strategy once the topographic location of the lip favors a nonsurgical approach[13] to avoid reconstructive surgeries. On the other hand, as Spieth, Gille, and Kaufmann[13] point, the S-KA typically shows signals of involution after one or two weeks following the beginning of the treatment or after its proliferative phase; thus the close observation of the lesion is highly recommended to detect non-responsive lesions or even to reconsider the diagnosis due to the noteworthy similarity of KA and SCC.

The average time of the follow-up of the S-KA was 21 months (range 3-84 months); four cases did not mention this aspect[8, 13, 17]. No recurrences were observed in any case. From the seven non-surgically removed lesions, all completely regressed, as mentioned above, but 5/7 left a discrete scar in the site of the lesion[6, 13, 15, 16], including the presented case. One can hypothesize it is a consequence of an incisional biopsy in an injured tissue, which is not able to heal adequately.

In summary, solitary keratacanthoma is a benign lesion of the skin that rarely affects the lips, with only 21 cases reported so far. Our review of the literature showed that S-KA predominantly affected males older than 45 years old and it was more frequent in light-skinned individuals. All patients but one presented S-KA in the lower lip vermilion. These lesions were fast growing (average of 12 weeks), with mean diameter of 16.7mm, and often asymptomatic. Microscopically, S-KA presented some features similar of the SCC. Older publications have suggested malignant potential for S-KA, however there are no complete reports in the literature proving that and it was likely the SCC was misdiagnosed due to the resemblance of both diseases. S-KA managed conservatively exhibited self-involution, reinforcing the benign nature of this lesion.

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