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Case Report

Topical Imiquimod 5% as a Treatment Option in Solitary Facial Keratoacanthoma

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Abstract

BACKGROUND: Keratoacanthoma (KA) is a rapidly growing epithelial tumour with histopathologic and clinical features similar to squamous cell carcinoma (SCC) and a certain tendency toward spontaneous regression.

CASE PRESENTATION: This article presents a unique and rare case of keratoacanthoma arising from the upper lip of a young male patient. These two features are in contrast to most of the reported cases in elder male individuals and on the lower lip. Relevant management protocol of the case has also been discussed.

CONCLUSION: The article emphasises the significance of discerning such lesions from squamous cell carcinoma thus carrying diagnostic and therapeutic implications. However, in case of the dilemma it is prudent to assume that the lesion is SCC unless proved otherwise clinically and histologically.

Introduction

Keratoacanthoma (KA) is a rapidly growing epithelial tumour with histopathologic and clinical features similar to squamous cell carcinoma (SCC) and a certain tendency toward spontaneous regression.

The etiologic factors involved in the development of keratoacanthoma are multiple. The role of UV radiation, chemical carcinogens, radiation therapy, genetic factors and various forms of antecedent trauma, including surgery, grafting, thermal burns, laser resurfacing, and vaccination have been documented [1] [2].

The lesion has a predilection for sun-exposed areas of face, neck, forearms. Lower lip location is six times more prevalent in comparison to upper lip [3].

The incidence increases with age, and it is more common after the age of 40 years with a slight predominance in males. The youngest reported is a 15-year-old patient with traumatically induced keratoacanthoma [1]. It is also more common in light-skinned persons.

The short history relative to the size of the lesion and its typical clinical course carries diagnostic importance. It begins as a rapidly enlarging nodule over a period of 4 - 5 weeks, followed by a period of stability for another 4 - 8 weeks before undergoing spontaneous involution and complete resolution over a period of 6 months to 2 years with the expulsion of keratin leaving a depressed scar [4] [5].

Keratoacanthomas show a tendency to a spontaneous resolution, and, in typical cases, some practitioners adopt the so-called watchful waiting approach, particularly in the cosmetically relevant

areas. However, KA can be easily misdiagnosed as SCC; therefore in most cases, surgical excision is considered the treatment of choice.

Case Report

A 31 – year - old Caucasian male was referred to our Maxillofacial surgery department for evaluation of a rapidly growing asymptomatic solitary nodule located on the mucocutaneous upper lip, present for the last 4 weeks.

Clinical examination revealed a well-demarcated, firm, dome-shaped nodule 1.5 cm in diameter with a small central keratinous plug (Figure 1). The patient reported that the growth developed in the site of a previous scar result of a shaving accident two years ago.

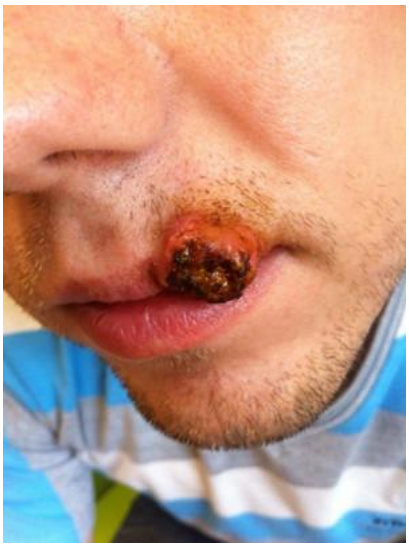

Figure 1: Patient presenting with KA of upper lip at the initial visit

Working clinical diagnosis of solitary KA was made based on the history of short duration, rapid enlargement and morphology. Neck palpation did not reveal any suspicious lymph nodes. Past medical history was positive for vitiligo for which he was not interested in evaluation or therapy. The patient did not practice photoprotection.

Subsequently, incision biopsy was performed under local anaesthesia. The histopathological evaluation confirmed the diagnosis of KA. We treated him with topical application of imiquimod cream 4 times a week. The inflammatory reaction appeared in less than 2 weeks of application. The size of the tumour had decreased considerably, and central core expulsion was noted which left central depression surrounded by epithelial tags (Figure 2).

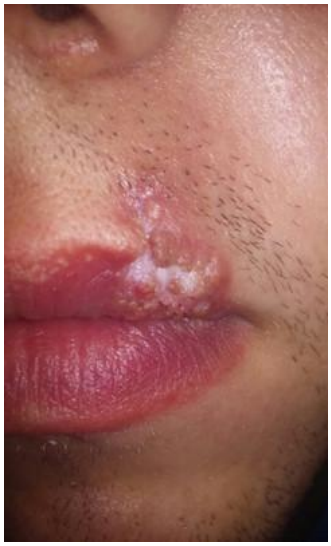

Figure 2: The same patient after 2 weeks of treatment with topical Imiquimod 5%

After 8 weeks, the mass was markedly flattened. At week 10 of therapy further improvement was recorded. The lesion had healed with a hypopigmented scar and remaining epithelial tags. The treatment was discontinued at this point. During the follow-up visit at week 12 further improvements were noted mainly in the smaller epithelial tags (Figure 3). During the subsequent follow up visits the improvement remained stable. We performed shave biopsy of the epithelial tags. Histopathology revealed no residual tumor elements.

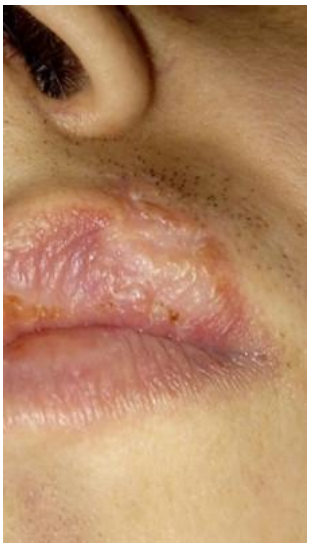

Figure 3: The same patient at week 12 (2 weeks after completion of treatment with topical Imiquimod 5%

The lesion was photographed sequentially and documented until complete resolution.There was no recurrence after 12 months follow - up.The patient was also advised of the importance of photoprotection and referred for a dermatological evaluation.

Discussion

KA is an epithelial neoplasm which is clinically indistinguishable from SCC and has a strong histological similarity to well differentiated SCC [5][3][6].

Some authors are of the opinion that solitary KA represents an extremely low-grade SCC [7] [6].

KA of the lip may arise from the skin rather than labial mucosa, which could well have been the case in the present patient [4] [6].

Some authors consider KA as a self-limiting and benign tumour which undergoes spontaneous resolution in contrast to SCC which is considered a biologically malignant neoplasm with a potential to metastasise and local tissue destruction [4].

Difficulties in differentiating between these two lesions are of huge importance since it carries therapeutic implications. Solitary large keratoacanthomas (KAs) of the head and neck present a management dilemma, due to the unpredictable clinical course. Therapeutic options proposed in the literature include complete excision, topical agents as podophyllin, 5 - fluorouracil and imiquimod [8], intralesional injection of bismuth, bleomycin, interferon Alfa - 2a, methotrexate [9] and triamcinolone (corticosteroids) [10], oral retinoids and photodynamic therapy, cryotherapy and radiotherapy with various outcomes [11].

Continued growth or significant pain despite the therapy, may suggest an underlying SCC in clinically classic KA. In these cases, surgery is recommended [12].

Complete surgical excision is the treatment of choice, but complete excision can be too destructive and cosmetically or functionally unacceptable for tumours on cosmetically important sites. Despite this, the recommended treatment in literature for solitary KA of the lip is surgical excision because of the concern that the lesion may be a squamous cell carcinoma and clinical as well as histological differentiation of the two lesions is difficult [13].

The advantages of surgical excision include rapid treatment and availability of a complete specimen for histologic examination.

Laser and cryotherapy as treatment modalities have some limitations as they can lead to substantial defects with functional or cosmetic morbidity, and do not allow for the histopathologic confirmation of the clinical diagnosis. Radiotherapy is an effective treatment of KA and offers the potential for a cure without requiring surgery or the need for reconstruction and has also been used as an adjunctive treatment following surgery, but it may not be advisable for younger patients, and it may pose an inconvenience due to the need for multiple hospital visits.

Systemic retinoids, such as isotretinoin, can be considered for patients with multiple lesions for which surgery is not adequate treatment modality.

Intralesional methotrexate (MTX), 5 - fluorouracil, bleomycin, and steroids have all been used with success in patients who are either poor surgical candidates or have lesions not amenable to surgery because of size or location [10]. A 2007 review of the use of intralesional injection of MTX on 38 patients, showed a 92% clinical "resolution" rate. However, patients needed an average 2.1 injections to achieve it [9].

Intralesional methotrexate and 5 - FU have also been recommended for extensive lesions or lesions in more cosmetically sensitive areas, with advantages of intralesional methotrexate over 5 - FU including decreased number of injections decreased pain and lower cost.

Recently, there are a few reports of successful treatment of solitary KA by applying 5% imiquimod cream a member of the imidazoquinoline family of drugs, commercially available as Aldara, as a topical immunomodulator in the group of toll-like receptor 7 and 8 agonists. Imiquimod has a therapeutic role as an antiviral and antitumour drug.

Most patients applied the cream 3 times a week for 5 to 7 months. Four to 11 weeks of application were required for the treatment, and sometimes adverse effects which depended on the inflammation resulting from the immunological reaction, such as burning sensation, itching, bleeding, stinging sensation, pain, erythema and erosions occurred. Other side effects include upper respiratory tract infection, sinusitis, and headache. Pregnant women should use imiquimod only if the potential benefits outweigh the risks. Clinicians should also be aware of pigmentation changes in patients [14].

The severity of side-effect is dose-dependent. In spite of these inconveniences, KA can be successfully treated with topical imiquimod, because of lower invasiveness and non-inferiority in the functional or cosmetic outcome.

In previously reported cases of keratoacanthoma treated with imiquimod cream, the average duration to obvious improvement was 5.0 ± 1.8 weeks, and that to complete remission was 7.4 ± 2.2 weeks [8].

In a report of two cases of KA-treated with imiquimod 5% cream in which the cream was applied daily for the first 6 or 7 days, and then reduced to alternate days according to the tolerance and erythema severity of the patient, the results show that frequent application of imiquimod at the initial treatment induces a prompt regression of KA and in both patients, the tumours fully regressed after five weeks of treatment [15].

However, the analysis of previously reported cases showed no statistically significant difference in the duration to remission between cases applied once per day (median: 6.5 weeks; range of 5 to 8 weeks) and less than once per day (median: 6 weeks; range of 4 to 11 weeks). Similarly, the duration to complete remission was not related to age, size and the duration of KA.

In a previously reported analysis of 18 cases the medians of the duration to complete remission was 6 weeks in 14 previously reported cases (range of 4 to 11 weeks), and 10 weeks in another 4 cases (range of 9 to 11 weeks) [8].

Mature KA undergoes regression in 6 weeks, and topical imiquimod can promote the regression of KAs [16].

In 18 - year retrospective study on the outcomes of keratoacanthomas with different treatment modalities the median duration to resolution was 6 months for intralesional, oral or topical medications [17].

Also suggests that lesions treated with imiquimod cream should be considered for biopsy to judge histopathological remission after 5 to 8 weeks of application to shorten the duration of the treatment [8].

In cases of solitary KAs after rapid proliferation, a mature KA undergoes regression in 4 to 6 weeks, leaving an atrophic and hypopigmented scar. This process from proliferation to regression usually takes about 4 to 9 months, but there are some persistent cases which take more than one year [8] [4].

Claims that spontaneously resolved keratoacanthomas leave poor quality scars that may need surgical revision were not confirmed in the illustrated series of 19 patients with solitary KAs which is the largest published to date [13].

There are contrasting opinions on cosmetic outcomes with spontaneous resolution of the KA versus therapeutic intervention. Treatment minimises scarring which helps better cosmetic results. Therefore, treatment is recommended in most cases. Some authors advocate surgical excision to result in a superior cosmetic outcome in comparison to lesions observed for spontaneous regression [4].

Failure of treatment with any of these medications is indicated by a further progression of the lesion associated with pain. This may signal an underlying aggressive SCC in clinically classic large KAs.In these cases, complete surgical excision of the lesion with histologic evaluation is recommended.

In conclusion, the results from our case report demonstrate that topical imiquimod can be an effective treatment option for solitary KAs when present in cosmetically sensitive areas. During treatment, the patient experienced only mild stinging sensation at the site of application.

The choice of imiquimod as a therapeutic modality was based on patient's age, lesion size and location, medication availability and the patient's reluctance to receive intralesional injections.

In our case, the outcome of the topical treatment with imiquimod was cosmetically and functionally superior to complete surgical excision.

Treatment of keratoacanthoma (KA) is primarily surgical. Medical treatment should be reserved for exceptional cases where surgical intervention is either not feasible or desirable. For example, medical intervention may be appropriate in patients with multiple lesions, in lesions not amenable to surgery because of size or location, and in patients with comorbidities that dissuade surgical procedure.

Most of the literature concerning medical intervention for keratoacanthoma is limited to case reports or case series. Be cautious when deciding to pursue medicine instead of surgical intervention and perform appropriate follow-up.

Failure to treat keratoacanthoma appropriately may result in local destruction, unacceptably high levels of recurrence and metastasis, or in other cases, may result in an unfavourable risk-to-benefit ratio.

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