Erosive-ulcerative lesions on the lower lip with malignant potential: efficacy of incisional biopsy followed by topical hyaluronic acid and systemic selenium-vitamin combination

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ABSTRACT

Objective: Ulcerative lesions on lower lip are common. Aggressive forms lead to lip distortion and affect function and esthetic. Suggested treatment strategies are still facing controversy. This study aimed to evaluate the potential therapeutic efficacy of a combination of topical hyaluronic acid (HA) and systemic selenium plus vitamin A, C and E (ACE).

Methods: Nine patients affected with symptomatic lesions on lower lip of erosive-ulcerative areas with moderate severity were enrolled. Age range: 47—67 years. They were diagnosed clinically and histopathologically by incisional biopsy. A topical HA gel was applied undiluted with a cotton bud four times daily. Selenium-ACE was prescribed systemically once daily. Treatments were applied for a 6-week period and lesions’ areas were followed for six months for any recurrence. Pain and severity of lesions were scored. Results: All patients had sun exposure, six were heavy smokers whereas two had sometimes alcohol consumption. In general, six patients were diagnosed as benign lesions that healed uneventfully with complete resolution. Four of them were inflammatory lesions, whereas two were oral lichen planus. On contrary, three patients were malignant (SCC), did not heal completely and referred to surgical resection with safety margin. No significant improvements occurred within malignant patients, neither for lesion healing nor pain alleviation, except only 2 vs 6 weeks that showed no improvement. On contrary, no significant improvements occurred within malignant patients, neither for lesion healing nor pain alleviation, except only 2 vs 6 weeks that showed alleviation of symptoms. Conclusion: Topical HA gel combined with selenium-ACE may be a useful additional treatment option for erosive ulcerative lesions of the lower lip.

KEY WORDS: Antioxidant vitamins, hyaluronic acid, lower lip, selenium, ulcerative-erosive lesion

INTRODUCTION

Generally, lips have an important key role in speech, eating as well as in the different facial expressions. The lip affection with a variety of ulcerative lesions is common. Such lesions especially aggressive forms may lead finally to lip distortion that may affect function and or esthetic appearance. Therefore, finding suitable treatment lines are mandatory for such kind of ulcerative lesions. However, some similarity in the clinical appearance of most of the ulcerative lesions on the lower lip may be found. This may lead to the occurrence of some possible confusion among the different diseased forms, for example: inflammatory, autoimmune, precancerous or even cancerous lesions. Thus, some ulcerative lesions are discovered as benign whereas others as malignant cases.

Malignant lesions affecting the lip constitute nearly a percentage of 23.6 to 30% of the malignant tumors of the oral cavity [1-5]. Squamous cell carcinoma (SCC) is considered as the most frequent malignant tumor in relation to lip malignancy, whereas adenocarcinoma and melanoma rarely occur [3, 4]. SCC is an invasive carcinoma with cells characterized by a high keratinization degree than not lesioned tissues. Thus, it has a strong invasive and recurrent character and also sometimes a local-regional metastasis may occur which differentiate such lesions from basal cell carcinoma [6,7].

The possible explanation of the exact pathogenic pathway still remains controversy. Among the most common predisposing factors are the exposure to sun rays, smoking and alcohol consumption. The lower lip has a greater frequency of the pathologic changes than the upper lip, since the latter is less exposed to sun rays [8]. The lower lip affection reaches a frequency of more than 90% of the involved cases [2, 9]. However, the suggested etiologic factors of lip malignancy are multifactorial also include tobacco, genetic tendency, immunodeficiency and/or immunosuppression [8, 10].

Hyaluronic acid (HA) is a linear polymer of glucuronic acid and N-acetylgalactosamine disaccharide. The main function of HA is to enhance tissue healing through the promotion of cell proliferation, migration and angiogenesis. It also promotes re-epithelialization via proliferation of basal keratinocytes [11]. HA is used for the treatment of traumatic ulcers, recurrent and generalized oral aphthous ulcers, as well as ulcers associated with drug reactions, orthodontic brackets and wires, ill-fitting dentures, diseases such as lichen planus, or Behcet’s disease, radiotherapy and/or chemotherapy [12-14]. It is also indicated for the treatment of oral mucositis, xerostomia, Sjogren’s syndrome and post-vaporization of oral lesions with carbon dioxide laser [15-19]. HA 0.2% gel offers advantages over topical steroids in that it is safe to be used in all grades of oral ulceration [15, 16] and the only contraindication known is the presence of history of allergy.
or hypersensitivity to HA or any of the ingredients.

HA is commercially available as sodium hyaluronate combined with polyvinylpyrrolidone (PVP) and glycyrrhetinic acid [15]. Sodium hyaluronate coats the oral mucosa, thus enhances tissue hydration and accelerates healing. PVP is a hydrophilic polymer with muco-adherent and film-forming properties, which also enhances tissue hydration. Glycyrrhetinic acid is a breakdown product of glycyrrhizin, the active component of licorice, which has anti-inflammatory properties aid in ulcer healing. It is also used as a flavoring agent.

The increased level of reactive oxygen species that is called oxidative stress may be related to certain diseased conditions. These reactive species may lead to protein denaturation, DNA destruction, and lipid peroxidation with eventually cell membrane damage and impairment of function [20]. Antioxidants are sometimes prescribed for the treatment and prevention of some serious diseases [21]. The combination of selenium with vitamins A, C and E (selenium-ACE) acts as an important antioxidant and may have a supporting role for the immune system through the enrollment in the eradication of toxic free radicals. Vitamin A and E inhibit lipid peroxidation, whereas vitamin C stabilizes collagen structure [22].

In this research work, we are presenting a certain line of treatment in managing such kinds of ulcerative lesions on the lower lip at first examination. Accordingly, a combination of a topical application of HA and a systemic administration of selenium-ACE has been used in a trial to achieve a complete healing in order to regain function and esthetics comfortably.

SUBJECTS AND METHODS

Selection criteria

Patients with the following criteria were included to the study:

- lesions were located on the lower lip with moderate severity degree regarding lesion size (grade 2) and pain sensation (score 2), as followed in methods of clinical evaluation thereafter;
- mostly had a recent affection without any previous definitive diagnosis;
- had symptomatic forms of erosive-ulcerative areas, with moderate severity, that interfere with function and esthetics;
- no underlying systemic diseases known;
- not received any medication yet, such as non-steroidal anti-inflammatory drugs, vitamins, topical nor systemic steroids and immunosuppressive medications;
- no pregnancy and no lactation for female patients;
- willing to participate and continue in the study.

Study design

A total of 9 patients (3 females and 6 males) were enrolled in this study and collected from the Oral Medicine Clinic of the Department of Oral Medicine, Periodontology, Oral Diagnosis and Radiology, Faculty of Dentistry, Fayoum University, Al-Fayoum, Egypt. The age of the patients ranged from 47 to 67 years. The period of patient’s recruitment lasts for approx. 9 months. All patients were affected with symptomatic lesions in the form of erosive-ulcerative areas with moderate severity. The patients were diagnosed clinically and then histopathologically. The lesions were located on the lower lip border. A consent form was obtained from each patient after explaining the situation completely. As a general rule, a questionnaire about the name, sex, habitation area, date of onset, date of diagnosis, location of the lesions was fulfilled for all patients. Therefore, the patient charts were planned with the following information: age, sex, smoking habits, sun exposure, clinical stage, macroscopic features of the primary lesions, type of planned treatment modality, follow-up and outcome.

Treatment modality and intervention

Because the patients came to our clinic with symptomatic forms of erosive-ulcerative areas at moderate severity that interfere with function and esthetics, a prompt suitable treatment modality would be planned to be applied without delay. There was no definite date of onset determined by most of the patients. Thus, the decision of taking an incisional biopsy was planned with the purpose of histopathologic examination to confirm the diagnosis.

Then, the prescribed treatment involved the application of a topical HA 0.2 % in a gel form (Gengigel®, Ricerfarma, Milano, Italy). The gel was applied undiluted with a cotton bud and prescribed as 4 times daily, every 6 h. It was advised not to eat or drink for at least 1 h following use. In addition, it was recommended to the patients taking selenium-ACE medication (Selenium-ACE; Wassen International, Wakefield, UK) on an empty stomach in the early morning as once daily systemically. Each tablet of Selenium-ACE contains: vitamin A (beta-carotene and retinol, 1500 IU); vitamin E (natural source, 30 mg); vitamin C (90 mg) and selenium (100 µg). The treatments were applied for a total period of 6 weeks. The lesions’ areas were followed for 6 months after the end of the above treatment to exclude any possible changes and/or recurrence.

Clinical evaluation

Evaluation is based upon previous instructions of a recent study by Belal [23] to go through certain steps for evaluating clinical response as follows:

Lesion size: grading of size was defined as; 0 = normal mucosa, 1 = lesion size is > 0 up to 1.5 cm, 2 = lesion size is > 1.5 up to 3 cm, 3 = lesion size is > 3 cm.

Pain sensation: Pain sensation was assessed and marked by the patients as points from 0 (no pain) to 10 (extreme pain), representing their pain perception as follows: 0 = no pain, 1 = mild pain (> 0 & ≤ 3.5), 2 = moderate pain (> 3.5 & ≤ 7), 3 = severe pain (> 7 up to 10).

Clinical response (improvement of lesions and symptoms): the clinical improvement and patient satisfaction were assessed every 2 weeks and graded as the following scores; 0 = no
resolution of lesions (i.e. no change), 1 = partial resolution with mild degrees of improvement in signs and symptoms and also in patient satisfaction (patients still have grade 2 of lesion size and score 2 of pain sensation but minimized and improved), 2 = moderate resolution with reasonable and/or notable degrees of improvement in signs and symptoms and a moderate patient satisfaction (patients are changed into grade 1 of lesion size and score 1 of pain sensation, but in the upper half of these grades), 3 = marked resolution with evident degrees of improvement in signs and symptoms and a remarkable patient satisfaction (patients still located in grade 1 of lesion size and score 1 of pain sensation, but minimized and improved to be more nearer to complete healing and normal mucosa), 4 = complete resolution with frank improvement in signs and symptoms and a complete patient satisfaction (patients become in grade 0 of lesion size and pain sensation, i.e. almost reached to normal mucosa without lesion and no pain).

Statistical analysis
The statistical analyses were performed using mean and standard deviation (SD) values. The comparison between the different follow-up periods (2 vs 4 & 6 weeks, 4 vs 6 weeks) was done within both benign and malignant patients by using paired t-test (Table 1). Statistical differences were considered significant at P ≤ 0.05. All of the statistical analyses were performed using SPSS (version 21; SPSS Inc, Chicago, IL, USA).

RESULTS
All of the involved patients showed an exposure to sunlight due to the nature of their occupation. Five patients were acting as farmers (the 3 female and 2 of the male patients). In addition, all of the 6 male patients were heavy smokers: they were outdoor workers; 2 were farmers, 2 were car drivers who were travelling in the desert areas for long periods of time as they have stated, and the last 2 were workers in industrial factories also under day sunlight. Furthermore, the two car drivers reported also to take alcohol from time to time.

In general, 6 of the 9 patients were diagnosed as benign lesions on the lower lip and healed uneventfully without any adverse effects. A complete resolution of the lesion areas was achieved in these patients. They were 3 male patients (2 farmers and 1 industrial worker) and the 3 female patients. A number of four of these 6 patients were diagnosed as inflammatory lesions (Figure 1), whereas the last two (1 male farmer and 1 industrial worker) were diagnosed as oral lichen planus.

On the other hand, 3 of the 9 patients were diagnosed as having malignant lesions (Figures 2 and 3) on the lower lip (SCC). The lesion areas did not heal completely and the patients were referred to do surgical resection with safety margin. These cases were then managed by radiotherapy and/or chemotherapy according to the case. The 3 patients were males as follows: 2 car drivers and 1 industrial factory worker.

Evaluation of clinical response
The paired t-test was used to analyze and compare the obtained results between the different follow-up periods (2 vs both 4 and 6 weeks as well as 4 vs 6 weeks) within
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Table 1. Clinical improvement, lesion size and pain sensation of lower lip lesions at different follow-up periods

<table>
<thead>
<tr>
<th></th>
<th>2 weeks Mean ± SD</th>
<th>4 weeks Mean ± SD</th>
<th>6 weeks Mean ± SD</th>
<th>2 vs 4 weeks Paired t-test (t / P)</th>
<th>2 vs 6 weeks Paired t-test (t / P)</th>
<th>4 vs 6 weeks Paired t-test (t / P)</th>
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<tr>
<td><strong>Lesion Size</strong></td>
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<tr>
<td>Benign</td>
<td>1.5 ± 1.04</td>
<td>3.7 ± 0.52</td>
<td>-3.79 / 0.013*</td>
<td>-7.05 / 0.001*</td>
<td>-3.87 / 0.012*</td>
<td></td>
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<tr>
<td>Malignant</td>
<td>1.0 ± 0.0</td>
<td>1.6 ± 0.58</td>
<td>-1 / 0.423</td>
<td>-2 / 0.184</td>
<td>-1 / 0.423</td>
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<td><strong>Pain Sensation</strong></td>
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<tr>
<td>Benign</td>
<td>0.67 ± 0.58</td>
<td>2.5 ± 1.04</td>
<td>-7.05 / 0.001*</td>
<td>-3.79 / 0.013*</td>
<td></td>
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<tr>
<td>Malignant</td>
<td>1.8 ± 1.17</td>
<td>3.7 ± 0.52</td>
<td>-2 / 0.102</td>
<td>-5.96 / 0.002*</td>
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*Statistically significant

the benign and malignant patients (Table 1). In general, pain sensation and lesion size were significantly improved and/or reduced in the benign patients upon using the intended treatment therapies, since statistically significant differences were noticed between the whole intervals except only when comparing 2 vs 4 week periods of pain sensation that showed no improvement.

On the contrary, there were no significant improvements occurred in the malignant patients neither for healing of lesion size nor for alleviation of pain sensation (Table 1), since no significant differences observed between the whole intervals except only the period of 2 vs 6 week for pain sensation that showed alleviation of symptoms.

In general, there was no allergy or hypersensitivity to HA or any of its ingredients reported in any patient. In similarity, the administration of selenium-ACE systemically did not show any allergic reactions in the treated patients.

DISCUSSION

The purpose of the present study was to try to find a possible curative treatment for the evident presented symptomatic lesions in the form of erosive-ulcerative areas affecting lower lip and interfering with function and esthetics with a moderate severity. The findings of the present study indicated that such kinds of lesions are not always benign and considered sometimes as malignant. Thus, these lesions are sometimes characterized by a high keratinization degree and considered a malignancy that needs a careful urgent intervention as well as a thorough follow-up.

Because early detection and treatment may lead to decreased morbidity and mortality and the role of dentist is important for early diagnosis of such suspected lesions, incisional biopsies were done in the present study for all cases to make a diagnosis. The application of a topical HA (4 times daily) and the administration of systemic selenium-ACE (once daily) were then immediately started for a period of 6 weeks. The lesions’ areas were followed for another 6 months after the end of the above treatment to exclude any possible changes and/or recurrences. Furthermore, the unhealed lesions that were confirmed by the histopathologic analysis as malignancy (3 of 9 patients) were referred without delay to a surgical resection in the form of an excisional biopsy with a safety margin, as a mandatory therapy.

Since there was no definite date of onset determined by most of the patients, the suggested treatment modalities were intended to be applied immediately without delay to save time as much as we could. The present study involved a number of 9 patients as three females and 6 males. The female patients were farmers indicating exposure to sun rays for long periods of time during their life. The lesion areas in these female patients were completely resolved with the intended treatment therapies and healed uneventfully. This excellent outcome is also encountered in other 3 patients of the male category (2 farmers and 1 industrial worker). From a significant etiological viewpoint, the present study noticed that all of the 6 male patients were outdoor workers suggesting their exposure to the same sun rays similar to the female patients, but in addition they were also heavy smokers. Furthermore, 2 of these male patients who work as car drivers were reported as sometimes undertaken alcohol consumption.

On the other hand, malignant changes have been noticed in lesions of 3 male patients: the 2 car drivers (who reported alcohol consumption in addition to heavy smoking and sunlight) and 1 of the industrial factory workers. The lesions were diagnosed histologically as SCC of the lower lip indicating the possible role of the cumulative etiologic factors such as sunlight, smoking and alcohol consumption. However, there were no lymph nodes noticed, no signs of metastasis and no neck affection. The lesion areas did not heal completely and the patients were referred for making surgical resection with safety margin. There were no significant improvements occurred within malignant patients neither for healing of lesion areas nor for alleviation of pain sensation, since no significant differences observed by comparing the whole intervals except only the period of 2 vs 6 weeks that showed alleviation of pain symptoms (Table 1).

In this context, some previous reports [24, 25] stated the association of the presence of high numbers of the etiologic agents with different risk rates in developing a carcinoma with squamous cells of the head and neck region. Thus, such etiologic agents may play a complex interaction to act as
necessary items for producing a certain type of malignancy. Other researches stated that alcohol and tobacco may play a role in the gastric cancer’s genesis, and the sulfocyanate in the tobacco smoke is a strong catalyst of the nitrosation reaction [26-29]. Also, Xia and Talley [30] reported that the usage of ethanol as well as tobacco increased the risk of head and neck cancer hundred times, influencing patient survival rates. In addition, some investigators [31-34] denoted that SCC ranks as the second in the frequency rates among skin cancers, appears often on the exposed areas to sun and may arise either de-novo or precancerous lesions (such as actinic keratoses or even erosive lichen planus). Clayman et al [35] and Veness et al [36] noticed that 80% of the SCC cases are located on the semi-mucosal lining of the lower lip and most of the mucosal forms have an ulcerous aspect from the start.

From statistical viewpoint, the findings of the present study denoted significant differences when comparison was done between the whole follow-up intervals within benign patients regarding lesion size and pain sensation. This means an improvement in clinical response in the form of good healing of lesion areas as well as alleviation of pain symptoms. The only exception hereby was the comparison between 2 vs 4 week periods of pain sensation, since no significant effect observed (Table 1).

In accordance to the results of the present study some previous reports suggested a beneficial use of HA in the treatment of oral ulcerations. Nolan et al [12] evaluated the efficacy of a topical HA preparation (0.2%) in the management of recurrent aphthous lesions in 120 patients in a randomized, placebo-controlled, double-blind trial. They recorded few ulcers on day 5 of the investigation compared to those treated with placebo, and also the occurrence of new ulcers was lower in the HA-treated group on day 4. Lee et al [13] tested the efficacy of topical 0.2% HA gel (twice daily for 2 weeks) in 33 patients with recurrent aphthous ulceration or Behcet’s disease. After 2 weeks, a subjective reduction in the number of ulcers and a decrease in the ulcer healing period were observed in 72.7% of the patients, whereas 75.8% experienced improvement in pain sensation. Nolan et al [14] studied the efficacy of topical HA (0.2%) in the management of erosive oral lichen planus and reported some benefit and stated also that the frequent applications should be considered to obtain a more significant clinical benefit. Furthermore, some previous studies indicated that HA exhibits beneficial anti-inflammatory and antibacterial activity in the treatment of gingivitis and periodontitis [37, 38].

In addition, other previous studies suggested an efficient role of selenium-ACE since they postulated that selenium acts as cofactor of glutathione peroxidase enzyme to protect the body from reactive oxygen species. The glutathione peroxidase is found with lower levels in patients having diseases [39], and the decreased activity of this enzyme denotes an inefficient removal of hydrogen peroxide [40]. In addition, some previous animal studies on experimentally induced arthritides have demonstrated an anti-inflammatory role of some antioxidants [21, 41].

Thus, we can conclude finally that topical HA gel when used in combination with selenium-ACE may be a useful addition to the treatment options of the erosive ulcerative lesions of the lower lip.

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