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Chronic hyperplastic candidosis: a pilot study of the efficacy of 0.18% isotretinoin

Giuseppe A. Scardina, Alessia Ruggieri and Pietro Messina

Department of Oral Sciences, University of Palermo, Palermo, Italy

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Abstract: Management of oral candidiasis depends on an accurate diagnosis, identification and elimination of predisposing factors, and, often, use of antifungal agents. Chronic hyperplastic candidosis (CHC) is considered a premalignant lesion of the oral mucosa, occurring as speckled or homogeneous white lesions. If the lesions are untreated, a minor proportion may become dysplastic and progress to carcinoma. The traditional treatment of this lesion is based on the use of antifungal agents. The aim of this study was to examine the efficacy of 0.18% isotretinoin for treatment of nystatin-resistant candidiasis. Isotretinoin was administered topically twice a day for one month to six patients affected by nystatin-resistant CHC. In all six patients, daily antimycotic topical therapy with nystatin for 30 days had failed to resolve the candidal stomatitis. After one month of isotretinoin treatment, five of the six patients were negative for *Candida*, whereas in untreated control patients the situation was unchanged. Only one patient with suspected sicca syndrome was found to have oral *Candida* 15 days after the last administration of isotretinoin. None of the patients had any complaints about the medication. These findings suggest that 0.18% isotretinoin applied twice a day for one month is able to suppress nystatin-resistant candidiasis. (J Oral Sci 51, 407-410, 2009)

Keywords: chronic hyperplastic candidosis; candidal leukoplakia; retinol; isotretinoin; vitamin A.

Correspondence to Dr. Giuseppe Alessandro Scardina, Department of Oral Sciences, University of Palermo, Via Del Vespro, 129-90127 Palermo, Italy
Tel: +39-916552244
Fax: +39-916552212
E-mail: scardina@odonto.unipa.it

Introduction

Chronic hyperplastic candidosis (CHC) presenting as leukoplakia appears as well demarcated, palpable, raised lesions that may vary from small, translucent whitish areas to large opaque plaques that cannot be rubbed off. The most common site for these lesions is the buccal mucosa, especially the commissural areas. The palate and tongue may also be involved, although less frequently, with the former being affected relatively more often. Not uncommonly, the commissural lesions of CHC tend to be associated with angular cheilitis.

For normal healthy patients, the treatment of oral candidiasis is relatively simple and effective. Topical medications are usually adequate. An anti-fungal agent that is commonly prescribed, nystatin oral suspension, usually resolves most infections. However, topical medications must be in contact with the organism to eliminate it. Periodically, patients will have multiple recurrences of oral candidiasis infection (1,2). Vitamin A and its derivative, isotretinoin, have very important biological functions. *In vitro*, vitamin A inhibits the malignant transformation caused by chemical carcinogenetic agents, ionizing radiations and viruses by interfering with the first phase of epithelial transformation. Such a preventive effect has proven useful even for oral mucosa cells (3-5). Both topical and systemic retinoids have been found to suppress head and neck and lung carcinogenesis in animal models and to inhibit carcinogenesis in individuals with premalignant lesions and a high risk of developing cancers of the digestive tract (6-9). In the light of these studies, the aim of the present pilot study was to evaluate the utility of 0.18% isotretinoin for treatment of nystatin-resistant candidiasis.

Materials and Methods

We enrolled six patients (mean age ± SD = 62 ± 4.6 y;

M/F = 1/5) who were affected by nystatin-resistant CHC. We had conducted many microbiological analyses to establish the presence of mycosis. Oral swabs for fungal microbiological culture were obtained, and the tests revealed *Candida* infection. Clinical and histological examinations confirmed the diagnosis of CHC. Histologically, hyperkeratosis and epidermal hyperplasia were evident. Treatment with traditional topical drugs (nystatin oral suspension) had been ineffective, and the infection had proved intractable. After a one-month washout period, we started administration of topical isotretinoin at a concentration of 0.18%. This concentration is the most effective and acceptable to patients; a higher concentration could have undesirable effects, such as soreness, which would make completion of the therapy cycle by the patients extremely difficult. Only transitory soreness was observed, and this disappeared in the first 30 min after application. In our opinion, therefore, the variable effectiveness of vitamin A synthetic derivates for CHC therapy is mainly attributable to these two aspects (10). The clinical study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics review board.

The drug was administered topically twice a day for one month, and then suspended. The patients were advised to apply the drug to a gauze and then apply this to the lesion site. The use of a gauze permits application for an adequate period, reducing salivary interference. The patients were advised to keep the gauze in place for at least 10 min. The application was carried out twice a day, in the morning after breakfast and in the evening after dinner, and after accurate oral care. During the month of treatment, the patients were observed every 7 days to evaluate the clinical progress of the lesions and to check for drug application compliance. At the end of the therapy, we carried out routine hematological examinations and did not observe any alterations of hematological and serological parameters. The patients were evaluated both clinically and histologically for any changes in the lesions, then observed for six months after interruption of isotretinoin administration.

Results

After one month, five of the six patients were negative for *Candida*, whereas the situation was unchanged in the untreated controls. Only one patient with suspected sicca syndrome had oral *Candida* at 15 days after the last administration of isotretinoin. None of the patients had any complaints about the medication. At the beginning of the treatment, all the patients had a white patch at the commissural site. After application of isotretinoin, we observed evident improvement of the lesions (Figs. 1 and

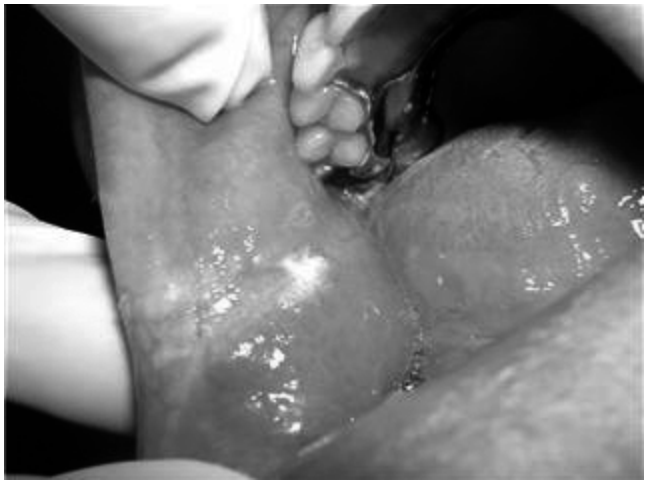

Fig. 1 Clinical appearance of the disease before treatment.

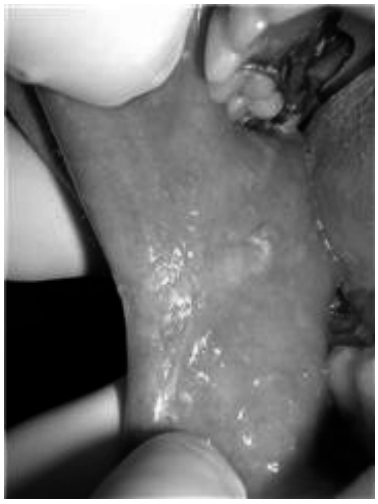

Fig. 2 Clinical appearance of the disease after topical application of isotretinoin at 0.18%.

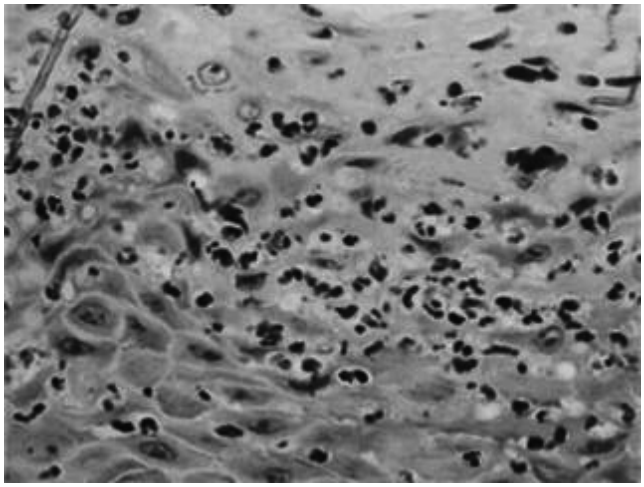

Fig. 3 Histological examination confirms the diagnosis of CHC.

2). Histological findings after treatment included reduction of hyperkeratosis and epidermal hyperplasia (Fig. 3). Only transitory soreness was observed, and this was resolved within 30 min after application. In the follow-up period, we did not observe any recurrence of the oral lesions.

Discussion

Despite the availability of a number of effective antimycotics for the management of oral candidosis, therapeutic failure is not uncommon. Furthermore, the presence of many clinical variants of oral candidosis, both new and old, may confound the unwary clinician and complicate the management of the condition. These problems were partly overcome by the introduction of the triazole group of antimycotics, which initially appeared to be highly effective. However, an alarming increase in organisms resistant to triazoles has been reported recently (2). As suggested in recent reviews, the overall database on the etiology, pathogenesis, and management of CHC is still in its infancy, but most importantly the eventual role of *Candida* in the progression of oral epithelial malignancy is still highly questionable.

A number of treatment modalities for CHC have been used, with variable results. These include medical management in the form of antifungal therapy or topical application of retinoids, bleomycin, beta carotene or mixed tea, and surgical methods (11). The surgical methods have included cold-knife surgery, laser therapy, and cryosurgery. The lesion is usually excised, and if the wound is small it is primarily closed. However, extensive lesions may require a split-skin graft. This may or may not be combined with carbon dioxide laser therapy or cryotherapy. Many clinicians prefer to treat the lesions for a while with topical and/or systemic antifungal agents prior to surgical management. There has been a paucity of information or indeed any controlled clinical trials with regard to these management methods, and there is no overall clinical consensus as to the best approach. If the lesions are untreated, a minor proportion may become dysplastic and progress to carcinoma (12-15).

The present pilot study investigated the use of 0.18% isotretinoin for nystatin-resistant CHC. CHC is a variant of oral candidosis that usually appears as a white patch on the labial commissures of the oral mucosa. Epithelial changes in the oral mucosa, such as hyperplasia and dysplasia, may compromise the mucosal barrier and facilitate candidal invasion. From this viewpoint, the utilization of vitamin A or isotretinoin could be useful for the regulation of epithelial differentiation. Isotretinoin acts on the immune system and also on the mechanisms of inflammation, and is considered to exert a chemo-preventive effect against apoptosis and angiogenesis (16-19). The oral cavity is a wet environment where it is not easy to apply a drug that can remain in contact with lesions for an extended time (20). The use of a gauze reduces the cleaning effect of saliva, and also makes drug application fairly simple, as was reported by our patients. The isotretinoin concentration of 0.18% we employed is the most effective and acceptable to patients. A higher concentration could have undesirable effects, such as soreness, which would make therapy compliance extremely difficult (21). Only transitory soreness was observed, and this disappeared within 30 minutes after application. We used local topical administration for a limited time to avoid any side effects of systemic therapy. Topical administration virtually eliminates the risk of teratogenesis, which is a common feature of therapy with Vitamin A derivatives (22). In conclusion, the present pilot study has demonstrated that topically applied 0.18% isotretinoin is an effective treatment for nystatin-resistant CHC.

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