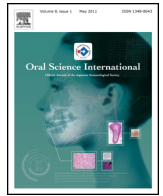




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Case Report

A case of papilloma associated with topical tacrolimus ointment for tongue ulcers

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ABSTRACT

We report a case of tongue papilloma that developed after the topical administration of tacrolimus. A 68-year-old man was admitted to our hospital with pain in his mouth. The diagnosis was ulcerative stomatitis. Although corticosteroids were ineffective, marked improvements were noted with the use of tacrolimus ointment. During follow-up observations, papillomas were observed on the tongue at the site of ointment application. The recurrence of papillary lesions was noted, but the lesions disappeared following the oral administration of a 5-fluorouracil formulation after pancreatic cancer surgery. In this case, tacrolimus ointment may have been associated with the formation of papilloma on the tongue.

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1. Introduction

Tacrolimus ointment is an immunosuppressant that has been approved as a topical medicine for atopic dermatitis and is widely used as a corticosteroid ointment [1]. Topical tacrolimus is effective for oral lichen planus (OLP) and other erosive and ulcerative diseases including chronic graft versus host disease (GVHD), mucous membrane pemphigoid, pemphigus vulgaris, and exfoliative cheilitis [2–6]. However, some reports have referred to adverse effects such as malignant transformation of original diseases of the long-term use of tacrolimus ointment on the oral mucosa [7,8]. Herein, we report a case of refractory chronic oral ulcer, which was successfully treated by the long-term use of tacrolimus ointment and followed by secondary papilloma probably induced by tacrolimus.

2. Case report

A 68-year-old man was admitted to our department with oral pain in November 1998. The symptom appeared 12 years before admission and subsequently continued in cycles of amelioration and exacerbation. In 1990, OLP and ulcers were diagnosed at another hospital. Furthermore, metal allergy was suspected by the dermatology department. However, pain did not improve even when metal prostheses were removed at a local dentist's office. He received treatments for diabetes mellitus and hepatitis C as

reported in his medical history. Hepatitis C virus (HCV) infection in this patient was first confirmed in 1995, and a negative result against the HCV RNA test was obtained after interferon treatment in 2004.

No abnormalities were detected on the skin. In the oral cavity, there were multiple mucosal lesions consisting of erosions/ulcers and reddish changes in the tongue, palate, and the gingival and buccal mucosa. Hill-shaped protuberances were observed on the dorsal surface of the tongue (Fig. 1A). A histological examination of the tongue lesion revealed a nonspecific ulcer, where fibrin precipitation and inflamed granulation tissue formation were noted in the area lacking surface epithelium (Fig. 1B and C). Therefore, a diagnosis of ulcerative stomatitis was reached. Corticosteroid ointment was applied as a treatment. The oral administration of corticosteroids was performed at a dose of 2 mg/day for 4 days and 1 mg/day for 3 days for 7 consecutive days but was discontinued because of the lack of noticeable improvements. In September 2003, we decided to treat oral lesions with tacrolimus ointment one to two times per day. This treatment was performed after the approval of the Ethics Review Committee of this institute. After starting the application of 0.1% tacrolimus ointment, pain at the lesions on the tongue, palate, and the gingival and buccal mucosa improved within approximately 2 weeks, and lesions were limited to the tongue after 4 months (Table 1).

In 2006, 3 years after the start of the application of tacrolimus ointment, white spots appeared and spread widely on the dorsal surface of the tongue (Fig. 2A). In a histological examination of a white lesion, the epithelium showed parakeratosis, with thickening and slight downward proliferation, which was accompanied by the infiltration of inflammatory cells in the subepithelial layer (Fig. 2B and C). No cellular atypia was noted. The diagnosis was epithelial

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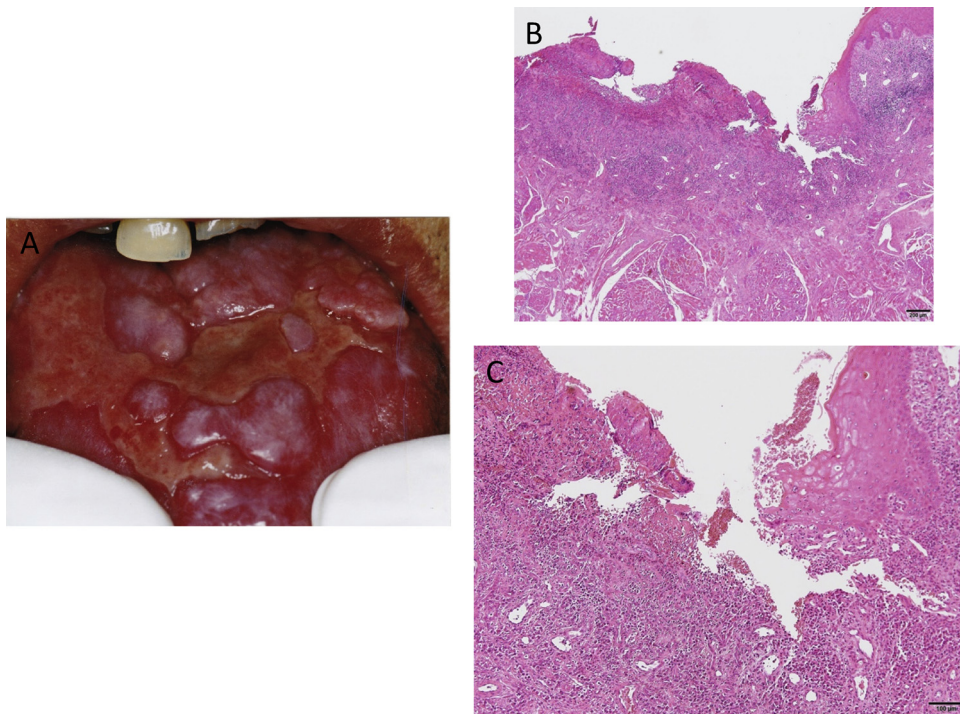


Fig. 1. Clinical appearance and histology of oral lesions in the first visit. (A) Erosive and ulcerative lesions were observed on the dorsal surface of the tongue. Furthermore, hill-shaped protuberances were detected. (B) A histological examination of the tongue lesion revealed a nonspecific ulcer, where fibrin precipitation and inflamed granulation tissue formation were noted in the area lacking surface epithelium (H-E stain; bar, 200 μ m). (C) High magnification of histology of the tongue lesion. (H-E stain; bar, 100 μ m).

Table 1
Medical history.

| Year | Medical institution (Department) | Clinical findings/diagnosis | Histology | Treatment |
|------|----------------------------------|--------------------------------|------------------------|--|
| 1987 | Dental clinic | Onset of pain | | Topical CS |
| 1990 | Hospital (Oral Surgery) | OLP | | Topical CS |
| | Hospital (Dermatology) | OLP, ulcer | | |
| | Dental clinic | Metal allergy | | |
| 1998 | Hospital (Oral Surgery) | Ulcerative stomatitis | Ulcer | Removal of metal prostheses Topical CS, systemic CS |
| 2003 | | Healing of ulcers | | Topical tacrolimus |
| 2006 | | White lesion on the tongue | Epithelial hyperplasia | |
| 2010 | | Mass formation on the tongue | Papilloma | |
| 2012 | | Mass formation on the tongue | Papilloma | Limitation of tacrolimus use |
| 2014 | Hospital (Surgery) | Pancreatic cancer | | Surgery for pancreatic cancer, S-1 treatment |
| | | Disappearance of tongue tumors | | |

OLP, oral lichen planus; CS, corticosteroid.

hyperplasia. Owing to the potential involvement of tacrolimus in epithelial hyperplasia, the use of tacrolimus ointment was limited when subjective symptoms appeared.

In 2010, 7 years after the start of the tacrolimus treatment, papillary tumors formed on the dorsal surface of the tongue grew slowly (Fig. 3A, B, and C). Excisional biopsy of the tumor revealed papilloma. Although the use of tacrolimus was limited from 2012, papillary lesions recurred on the dorsal surface of the tongue 6 months later and follow-up observation of the tumors did not show marked size increases.

In 2014, the patient underwent partial pancreatectomy for pancreatic cancer at another hospital. His postoperative course was good, and he received 100 mg/day S-1, an oral 5-fluorouracil (5-FU) formulation, as adjuvant therapy after surgery. At the time of re-examination 3 months after the initiation of S-1, tumors on the dorsal surface of the tongue disappeared without any other therapeutic modality (Fig. 4).

3. Discussion

Tacrolimus forms a complex with the intracellular FK506-binding protein (FKBP); inhibits the dephosphorylation of the nuclear factor of activated T cells (NFAT), which is a substrate of calcineurin; and suppresses the production of IL-2, INF- γ , IL-3, IL-4, IL-5, TNF- α , IL-1 β , and IL-6. It also suppresses antigen presentation on Langerhans cells, histamine release from mast cells and basophils, and the degranulation of eosinophils [9,10]. Corticosteroids have potent immunosuppressive and anti-inflammatory effects, but unlike tacrolimus, their actions are not specific for T cells.

Although tacrolimus ointment has been used in the treatment of atopic dermatitis, its application range is now expanding [6]. Erosive OLP is treated with tacrolimus if corticosteroid ointment is not effective. Hodgson et al. [3] reported that 47 of 50 (94%) patients with OLP responded to this treatment, and the same effec-

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