

Recalcitrant lip verrucous carcinoma successfully treated with acitretin after carbon dioxide laser ablation



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Key words: acitretin; carbon dioxide laser; imiquimod; photodynamic therapy; verrucous carcinoma.

INTRODUCTION

Verrucous carcinoma is a rare variant of well-differentiated squamous cell carcinoma with locally aggressive and minimal metastatic potential.¹ Oral verrucous carcinoma (OVC) is the most common type of verrucous carcinoma in the head and neck regions and accounts for 55.9% of 2350 such cases.¹ The overall 5-year survival rate for OVC is approximately 50% in a retrospective cohort study.² The risk factors for OVC include chronic inflammation induced by chemical carcinogenesis associated with betel quid chewing, smoking, human papillomavirus infection, and immunosuppression.^{1,2} The treatment of OVC remains in debate and is challenging. Many options, including surgery, radiation, chemotherapy, cryosurgery, laser ablation, photodynamic therapy (PDT), systemic retinoid, and recombinant α -interferon, either in combinations or alone, are reported with varied success rates. Radiotherapy is controversial because anaplastic transformation after irradiation has been reported, whereas other reports show OVC to be radiosensitive.³ Surgical excision with adequate margins seems to have the lowest recurrence rate.^{1,2} However, tumor removal usually leads to disfigurement or loss of function of the oral cavity. Our report concerns a patient with OVC of the lips who, refusing wide excision after failed nonsurgical treatments, was successfully treated with systemic acitretin after tumor debulking with a carbon dioxide (CO₂) laser.

Abbreviations used:

CO₂: carbon dioxide
OVC: oral verrucous carcinoma
PDT: photodynamic therapy

REPORT OF A CASE

A 54-year-old Taiwanese man visited the department of otolaryngology of our hospital in 2012 for a growing mass on his lower lip for 11 months (Fig 1, A). He was a heavy smoker and chewed betel quid frequently with unremarkable medical history. The tumor progressed from verrucous hyperplasia into verrucous carcinoma at 9-month follow-up after he refused surgical intervention. He was referred to another hospital for intra-arterial chemotherapy. Computed tomography scan showed metastasis to the regional lymph nodes on the same side as the primary tumor (clinical staging IVa, T1, N2b, M0). He received intra-arterial methotrexate infusion continuously for 7 days (50 mg/d) followed by a weekly bolus of methotrexate (25 mg) for 12 weeks.⁴ The tumor responded initially and enlarged again 1 year after treatment. He was then treated with topical aminolevulinic acid-mediated PDT every 3 to 4 weeks with 200 J/cm² at 100 mW/cm² for around 10 months (total, 2000 J/cm²). Unfortunately, the tumors continued to grow and spread to the buccal

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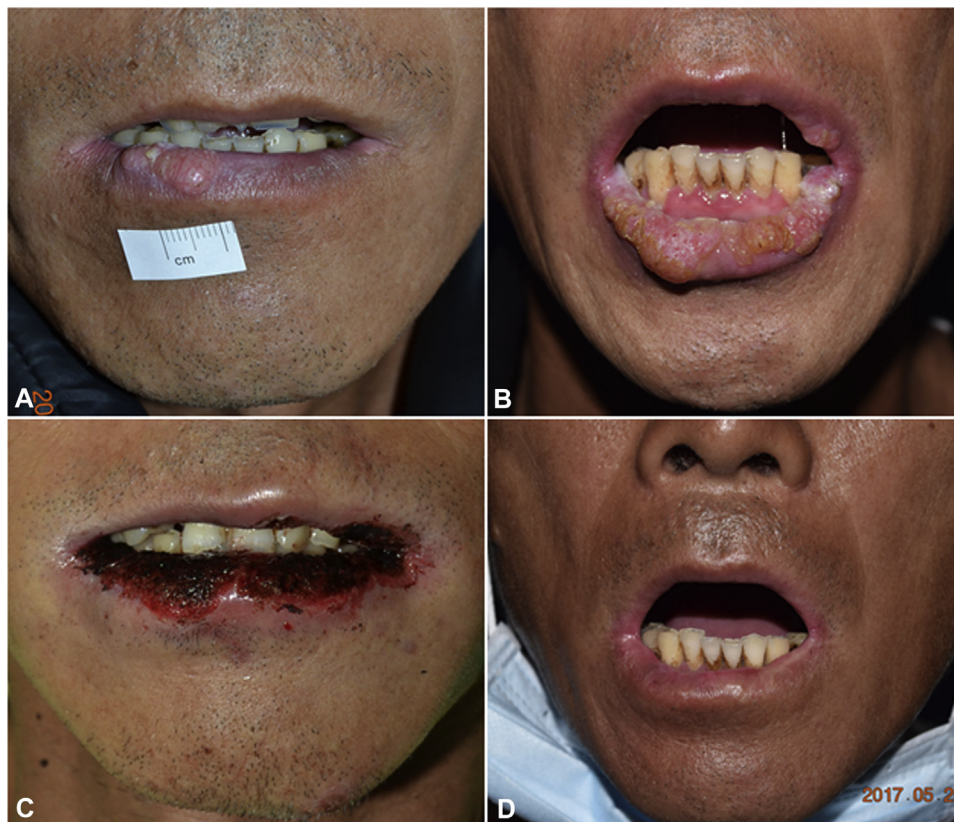


Fig 1. **A**, Rapidly enlarging, exophytic tumors on the lower lip of a middle-aged man. **B**, Tumors recurred and grew into multiple verrucous tumors that occupied almost the entire lower lip with extension to the left upper lip and anterior aspect of buccal mucosa after 3 months of intra-arterial methotrexate chemotherapy followed by 10 months of topical aminolevulinic acid–mediated photodynamic therapy and 5 weeks of cryoimmunotherapy. **C**, Picture taken immediately after CO₂ laser ablation. A 5-mm free margin was vaporized to destroy the potential lateral extension of the tumor. **D**, No tumor was detected at 15-month follow-up after acitretin 30 mg/d postoperation.

mucosa. In 2015 he visited our outpatient clinic. On physical examination, multiple verrucous tumors occupied almost his entire lower lip and parts of the left upper lip with extension to the anterior aspect of buccal mucosa. No lymph node was palpated on the neck. Verrucous carcinoma was reconfirmed by histopathology. He was treated with weekly cryoimmunotherapy, which consisted of liquid nitrogen sprayed on parts of the tumors (around 1 × 0.5 cm, with 2 cycles of 30-second freezing and left for spontaneous thaw) after topical anesthesia with lidocaine spray followed by daily topical application of imiquimod. The purpose was to minimize pain sensation and hopefully to generate tumor antigens after tumor destruction. After 5 weeks of cryoimmunotherapy, the treated areas showed partial responses, whereas untreated tumors continued to grow (Fig 1, B). We decided to minimize the tumor burden with CO₂ laser ablation.

After tumescent anesthesia with lidocaine 0.2% and adrenaline 1:1000000, CO₂ laser (model LX-20; Luxar Corp, Bothell, WA) ablation was performed with focused mode at a power level of 6W with the hand piece held 1 to 2 cm from the surgical plane to excise the main tumors. The hand piece was held 10 cm from the skin surface in a defocused mode for vaporizing the remaining tumors and for coagulation. A 5-mm free margin was vaporized to destroy the potential lateral extension of the tumor (Fig 1, C). Acitretin, 20 mg/d (0.3 mg/kg), and once-daily topical imiquimod were started on the day after the laser treatment. Imiquimod had to be discontinued because of severe pain 2 days later. The side effects of acitretin, including dry mouth and dry eyes, were well tolerated. The dose was titrated to 30 mg/d (0.5 mg/kg) on week 2. A small suspicious regrowth of the tumor on the left lower lip was detected on week 7 and was removed with the CO₂

laser. No tumor was detected at 15-month follow-up (Fig 1, D). The patient was satisfied with the outcome. He is still taking the same dose of acitretin.

DISCUSSION

Mohs micrographic surgery is recommended for OVC because it provides microscopic control of margins with less chance of recurrence.² However, traditional wide excision or Mohs micrographic surgery would have led to unacceptable disfigurement in our patient. Intra-arterial chemotherapy has theoretical advantages over intravenous chemotherapy because it delivers a higher accumulation of drug to the tumor with minimal systemic toxicity.⁴ Unfortunately, the tumor was resistant to methotrexate after 1 year of treatment. PDT may be effective in selected OVC patients. However, the procedure is very painful to areas with abundant nerve endings, such as fingers, genitalia and lips.⁵

It is well documented that tumor cells often induce an immunosuppressive microenvironment.⁶ Removal of the tumor was found to restore lymphocyte function in a murine model.⁷ We hypothesized that reduction of the tumor volume may have played a critical role in the success in this patient. The CO₂ laser offers precise excision of oral carcinoma, a better visualization of the operational field, and minimal blood loss. The healing process is usually excellent with limited contraction and scarring.⁸ Although the CO₂ laser is widely used in treating premalignant lesions in the oral cavity, only limited cases of its use in OVC are reported. Two patients with OVC on the lips were successfully treated with topical imiquimod after tumor debulking.² Unfortunately, the imiquimod treatments did not help our patient. Azevedo et al⁹ reported the beneficial effects of topical retinoic acid in orabase as chemoprevention of OVC recurrence in 2 patients with tumors on the tongue after CO₂ laser ablation. One patient had excellent and persistent effect for 3 years after 2 months of retinoic acid treatment, whereas the other patient had a persistent white plaque on the tongue after a 4-month topical treatment, but the plaque did not develop into OVC at 4-year follow-up.⁹ The results support the beneficial effect of retinoic acid in treating OVC after tumor debulking.

Acitretin is believed to induce normalization of differentiation and proliferation of keratinizing epithelia, induction of apoptosis, and modification of inflammatory responses.¹⁰ In one instance, multiple verrucous carcinomas in a patient disappeared within 6 months after treatment with daily 50-mg acitretin.¹¹ In our case, the tumors were expected to be more recalcitrant to treatments after other therapies failed. We believe that removal of the unfavorable immunosuppressive microenvironment by CO₂ laser is one of the key elements of success in our patient. Further cases are needed to confirm the effectiveness of this treatment.

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