Size-reductive Neoadjuvant Immunotherapy using Imiquimod in Squamous Cell Carcinoma of the Lower Lip

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Cutaneous squamous cell carcinoma (SCC) is the second most common skin cancer. In particular, invasive SCC has a high risk of metastasis and sometimes, this can be fatal. At present, the treatment of choice for invasive SCC is complete excision with a proper surgical margin, but most cases of SCC develop on cosmetically-sensitive areas, so sometimes significant scarring or deformities can lead to an unhappy result. An 80 year-old female presented with a 4 × 1.5 cm sized SCC on her lower lip. Although surgery was the first line therapy for this invasive SCC, a cosmetically poor outcome was expected. Thus the patient did not want to undergo a surgical operation, so we had to explore other treatment options. Recently there have been many reports that show imiquimod 5% cream is effective in the treatment of invasive SCC. Therefore we started topical therapy with imiquimod 5% cream five times a week. After 6 months, the lesion size was reduced to 2 × 1.5 cm and we could remove the remnant tumor by wedge resection with cosmetically acceptable result. We suggest this neo-adjuvant immunotherapy can be an alternative for the treatment of cosmetically-critical SCC and present this case as a good example that has shown successful size-reductive neoadjuvant immunotherapy using imiquimod in invasive SCC.
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Key Words: Imiquimod, Immunotherapy, Lip, Neoadjuvant treatment, Squamous cell carcinoma

INTRODUCTION

Cutaneous squamous cell carcinoma (SCC) is the second most common skin cancer. It usually occurs in the sun exposed areas of elderly people who have a light skin color tone. The important risk factors are UV irradiation, chronic inflammation, chemical carcinogens and human papilloma virus[1,2]. It is considered a key etiology of SCC that UV irradiation induces mutation of genes which are in charge of chromosomal repair and cell apoptosis[3]. The SCC usually arises from precancerous lesions like Bowen' disease or actinic keratosis in the photo-damaged skin which may then progress to invasive SCC in 3-26% of untreated cases[4]. The treatment of choice for invasive SCC is radical surgery. However, cancers in the cosmetically-sensitive areas may leave unwanted scarring after surgical treatment, and this could be as distressful to the patients as the cancer itself. The goal of the treatment for skin cancer should be complete eradication of the disease with minimal morbidity. Topical imiquimod has shown antiviral and anti-tumor effects in animal experiments by potentiating both the innate immune response and the acquired immune response which is mainly Th1 cell mediated[5,6]. Many case reports and studies have revealed the effectiveness of topical imiquimod in the treatment of condyloma accuminata, molluscum contagiosum, actinic keratosis,

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Bowen′ disease, basal cell carcinoma, squamous cell carcinoma, mycosis fungoides, Paget′ disease, extramammary Paget′ disease and malignant melanoma[5-7]. We used imiquimod 5% cream on invasive SCC of the lower lip, before resorting to surgical eradication and we obtained both good cosmetic result and disease cure. We report this case as a good example which has shown successful size-reductive, neo-adjuvant immunotherapy using imiquimod in invasive SCC.

CASE REPORT

An 80 year-old woman presented with a hyperkeratotic plaque on her lower lip (Fig. 1A). The lesion had appeared several years before and had slowly increased in size. The patient had suffered from slight pain and the occasional bleeding.

The lesion was a well-demarcated, 4 × 1.5 cm sized, irregular-shaped, brown, hyperkeratotic, hard-surfaced plaque. No abnormalities were found besides the solitary skin lesion upon general physical examination. Furthermore, no palpable lymph node enlargement was perceived. Previously she was healthy. There was no remarkable medical history in her family. Routine laboratory studies including CBC, LFT, a renal function test and urinalysis were all within normal limits.

At first, actinic cheilitis and cutaneous squamous cell carcinoma were suspected, and therefore a punch biopsy was performed on the middle area of her lower lip. The histopathologic diagnosis was well-differentiated squamous cell carcinoma, which showed nests of atypical squamous cells imposing on the dermis (Fig. 2). Radical removal was considered as the first line therapy. However, the resultant defect after removal of the tumor would be more than two thirds of the lip length. The defect would then have to be repaired with orbicularis oris flaps

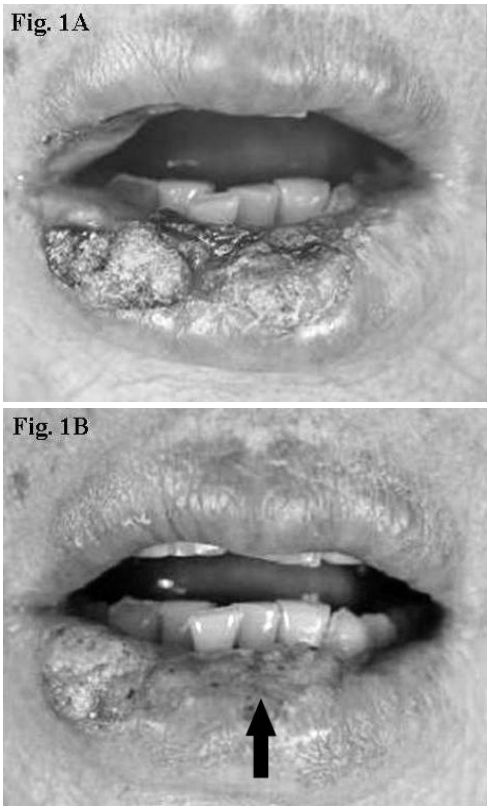


Fig. 1. Hyperkeratotic plaque on the lower lip at the first visit (A) and after the removal of the crust (B). A punch biopsy was performed on the middle area of her lower lip (arrow).

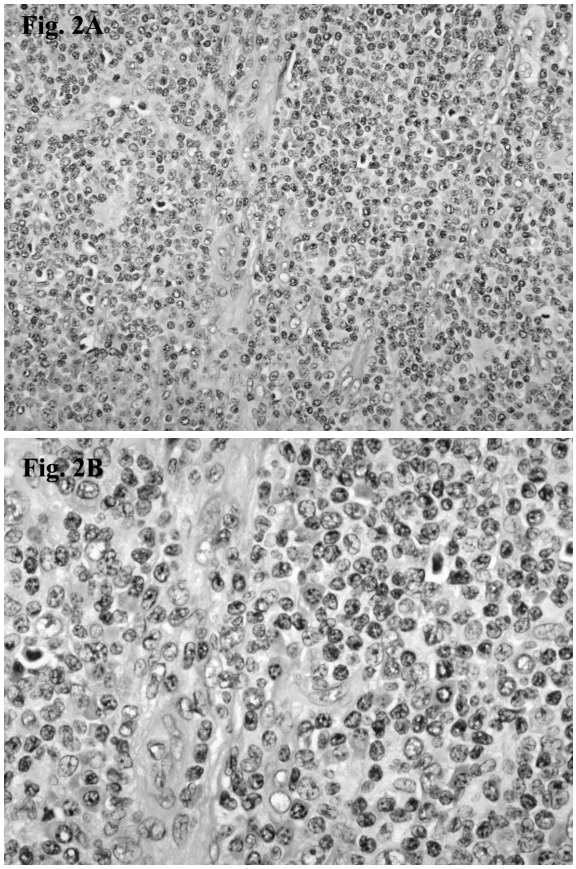


Fig. 2. The clusters of atypical squamous cells imposing in the dermis (A, B: H & E, ×)0).

or depressor anguli oris flaps. Even after this surgical treatment, the expected cosmetic outcome was poor, the degree of this dependant on the surgeon′ skill. The patient was extremely concerned about morbidity after the operation, so she refused surgical treatment. Hence we explored other treatment options. We started with topical therapy using imiquimod 5% cream on the skin lesion as previous reports and studies had shown the effectiveness of topical imiquimod for skin cancer. For efficient absorption of the cream, we first detached the crusts of the lesion (Fig. 1B). The imiquimod cream was applied five times a week. During the treatment, the patient complained of irritation to the application site, but this was tolerable so the treatment was continued for 6 months. After 6 months, the lesion size was greatly reduced to 2 × 1.5 cm, and was smaller than one third of the lip length. The remnant tumor was removed by wedge resection and repaired by primary closure without flaps and this was performed successfully (Fig. 3). The depth of tumor cell invasion was 0.6cm in the excised tumor mass and resection margins were histopathologically clear (Fig. 4). The tumor was excised completely and the lower lip where the lesion had been located was left functionally and cosmetically acceptable (Fig. 5). Up to 10 months after the operation, no sign of recurrence was seen at the treatment site. The patient also found no discomfort when speaking or eating.

DISCUSSION

The first line treatment of invasive SCC is radical surgical excision of the tumor with histopathologic examination of the surgical margins. Topical immune modulatory agents such as imiquimod can be used as another choice of treatment. Imiquimod enhances the innate immune response and the adaptive immune response via interaction with toll like receptor 7 on the various immune cells. It also induces apoptosis of tumor cells via binding of the Fas receptor to the Fas ligand[5,8]. Imiquimod has shown efficacy against many skin cancers such as superficial SCC, basal cell carcinoma, Bowen′ disease, cervical intraepithelial neoplasia, and keratoacanthoma[5-7]. Imiquimod has been reported to be effective in several cases of invasive SCC. In the reported cases, the frequency of imiquimod application varied from three times a week to once per day, the mean duration of treatment was 9.4 weeks

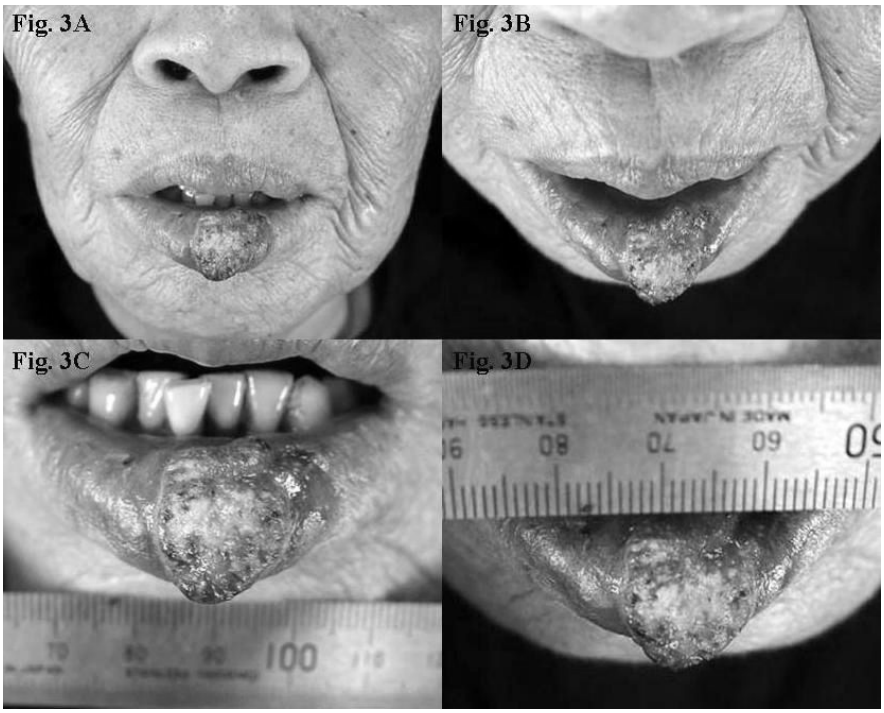
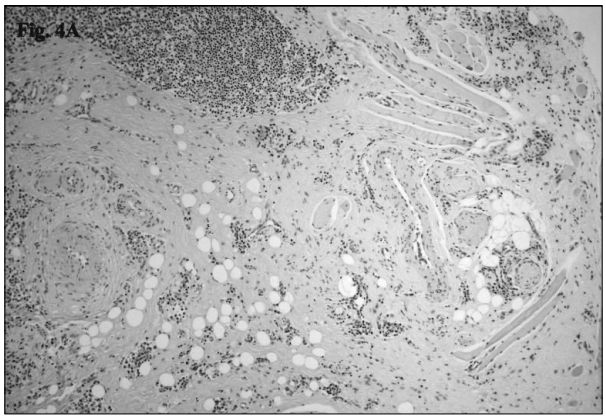
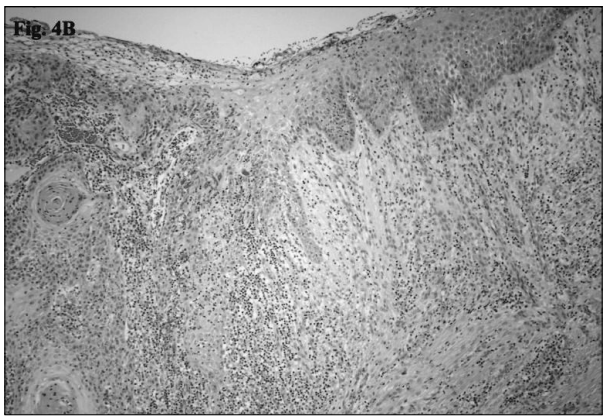


Fig. 3. Size-reduced lesion on the lower lip after 6 months of topical imiquimod therapy.





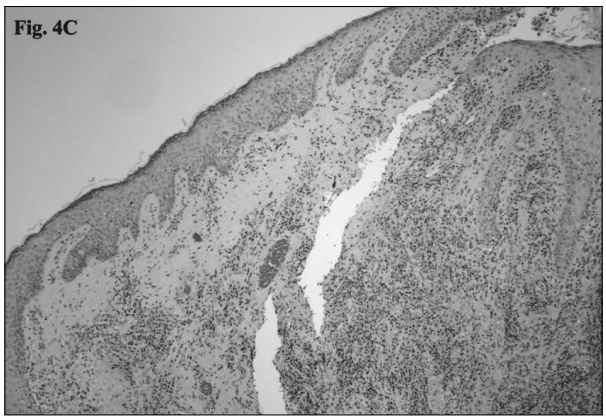
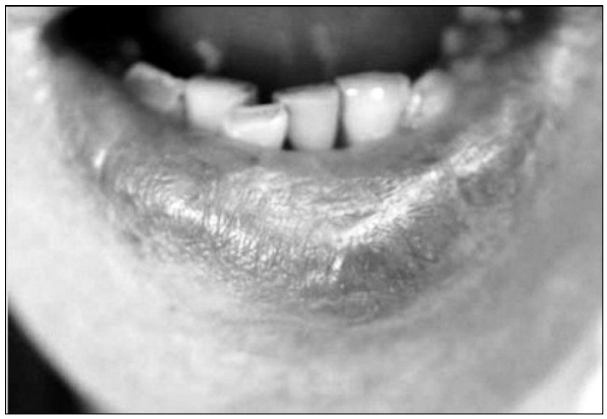


Fig. 4. The histopathology of the free resection margins after tumor excision.
(A: deep resection margin, H & E, × 100. B, C: lateral resection margin, H & E, ×)0)

and the longest recurrence-free follow up was 4 years[9-14]. The regime of imiquimod therapy for our case was similar with the previous reports. However six months was the longest duration of treatment of all the cases, and this could have been enough time for the cancer to metastasize. We did not intend six months treatment time, but it took time



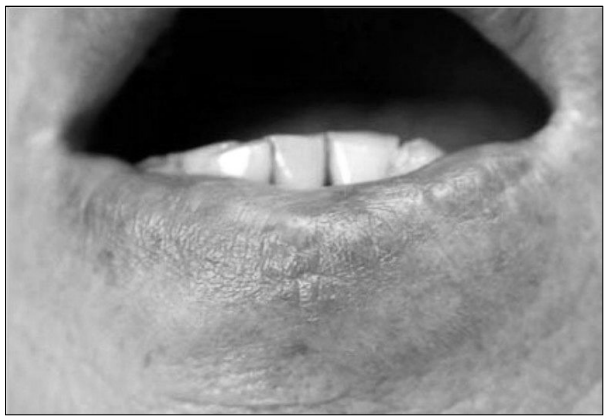


Fig. 5. Well-healed lip 2 months after surgical removal of the tumor.

to persuade the patient to have surgery,

Treatment with topical imiquimod has several weak points in comparison with surgical excision. The topical imiquimod can cause local skin irritation, which may decrease treatment compliance. Patients apply the imiquimod at home by themselves, so treatment compliance is an extremely important factor for cure. Our patient also experienced mild local skin irritation. We encouraged her to continue the topical application by saying that mild skin irritation is commonly experienced. Encouragement or temporary reduction of the application frequency are good ways to address the weak points of imiquimod.

And in contrast with surgical excision, the topical imiquimod needs a longer treatment duration time. Invasive SCC can metastasize easily and spread via the lymphatic system. An increased treatment period will therefore increase the chance of tumor cells metastasizing and spreading. The prognosis of SCC on the lower lip is not good because of the high

risk of metastasis about 16%, with about 50% mortality in metastatic cases[15]. Considering this, our patient should have been treated promptly but she refused surgery at first. Hence, we had no choice but to apply imiquimod to the lesion during this time. The alternative treatment, topical imiquimod therapy, was very successful and greatly reduced the tumor size, plus there was no evidence of metastasis. We think that she experienced a fortunate outcome, but six months is not recommended for the duration of neoadjuvant therapy. Although disease eradication was not achieved, tumor size reduction was extremely beneficial to the patient. The operation method depends on the mass size, and the chance of complication and morbidity decreases with the simplicity of the operation. Small defects up to 33% of the lower lip can be repaired via direct approximation and primary closure. Cosmetic and functional disturbances after primary repair are acceptable. However, large defects over 33% of the lower lip should be repaired by a flap technique such as a Karapandzic flap or Abbe flap[16]. The problem with these flaps are the significant microstomia and vermilion deficiency which can result[17]. At first, we planned treatment by radical tumor excision then lip reconstruction with orbicularis oris flaps. However, after topical imiquimod therapy, the tumor could be totally removed leaving a small defect which could be repaired without using flaps. She suffered from no cosmetic or functional disturbances after the treatment for invasive SCC.

Additional treatment given before the main treatment is called neoadjuvant therapy. Various therapies can be used as neoadjuvant therapy besides topical imiquimod therapy. Topical imiquimod is not usually effective in immunocompromised patients with low CD4 counts[18]. In contrast to this, cryotherapy is effective in patients with low CD4 counts. However, cryotherapy destroys tissue and this makes histological examination difficult[19]. Photodynamic therapy is also a useful method to treat skin cancer, although it is less efficacious in hyperpigmented and hyperkeratotic lesions[20].

Topical imiquimod therapy has many weak points and limitations for it to be a main treatment of invasive SCC, however it is a good optional choice that makes the following surgery conservative. We recommend that this neoadjuvant immunotherapy can be an alternative for the treatment of cosmetically-critical SCC.

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