Successful treatment of an early invasive oral squamous cell carcinoma with topical 5-aminolevulinic acid-mediated photodynamic therapy

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Our previous studies showed successful treatment of a series of 36 oral verrucous hyperplasia lesions and an extensive oral verrucous carcinoma with a topical 5-aminolevulinic acid (ALA)-mediated photodynamic therapy (topical ALA-PDT) protocol (with a fluence rate of 100 mW/cm² and a light exposure dose of 100 J/cm²) using a 635-nm light-emitting diode (LED) light source. In this case report, we tested whether an enhanced topical ALA-PDT protocol (with a fluence rate of 200 mW/cm² and a light exposure dose of 200 J/cm²) could be used to treat an early invasive oral squamous cell carcinoma (OSCC) with a verrucous appearance of the left lower posterior edentulous alveolar mucosa of a 67-year-old male former areca-quid chewer and ex-smoker. The main verrucous lesion showed complete regression after eight treatments with PDT. However, 10 extra treatments were needed to eradicate the multiple residual leukoplakia lesions on the edentulous alveolar mucosa. Moderate to severe post-PDT pain was noted during the initial eight treatments, and the patient needed analgesics (codeine phosphate, 30 mg three times daily) to control the pain. No recurrence of the OSCC lesion was found after a follow-up period of 4 years. We suggest that our enhanced topical ALA-PDT protocol may have good potential to be used as a treatment of choice for a superficially invasive OSCC without regional or distant metastasis before the commencement of other effective therapies.

Introduction

Oral cancer is the fifth most common cancer in the world.1 In Taiwan, oral cancers ranked as the sixth most prevalent cancer in both sexes and was the fourth most common cancer in males in 2006.2 The main etiologies of oral squamous cell carcinoma (OSCC) in Taiwan are areca quid (AQ) (betel nut,
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Areca catechu) chewing, cigarette smoking, and alcohol consumption. There are 2 million people who habitually chew AQ, and approximately 80% of all oral cancer deaths are associated with this habit. In Taiwan, oral cancers are usually treated with radical surgical excision, chemotherapy, and radiotherapy, separately or in combination. Although various treatment modalities are used, the survival rate for oral cancer patients in Taiwan remains low. The respective 5-year survival rates are 72%, 39%, 27%, and 12% for those with stage I, II, III, and IV oral cancers. The low 5-year survival rate in patients with advanced oral cancers suggests the importance of early detection and treatment of oral cancers. In addition, one of the best strategies to prevent oral cancers is to identify the oral cancers at their precancerous stages or at as early a stage as possible and eliminate them to prevent their further transformation into oral cancers.

Oral verrucous carcinoma (OVC) is a low-grade but usually extensive tumor of the oral mucosa. An OVC may develop into an invasive OSCC during its late carcinogenic stage. Traditional treatment for OVC is total surgical excision that always leads to scar formation. Photodynamic therapy (PDT) is another effective treatment option for human premalignant and malignant lesions because it is noninvasive, is well tolerated by patients, can be used repeatedly without cumulative side effects, and results in little scar formation. 5-Aminolevulinic acid (ALA) itself is not a photosensitizer but serves as the biological precursor of the photosensitizer, protoporphyrin IX (PpIX), in the heme biosynthesis pathway. PDT with topically applied ALA (topical ALA-PDT) is used for treatment of human oral premalignant lesions with relatively good clinical outcomes. Our previous studies showed successful treatment of 36 oral verrucous hyperplasia (OVH) lesions and an extensive OVC with a topical ALA-PDT protocol (with a fluence rate of 200 mW/cm² and a light exposure dose of 200 J/cm²) using a 635-nm light-emitting diode (LED) light source. In this case report, we tested the efficacy of an enhanced topical ALA-PDT protocol (with a fluence rate of 100 mW/cm² and a light exposure dose of 100 J/cm²) using a 635-nm light-emitting diode (LED) light source.

**Case presentation**

This 67-year-old male patient was referred to our outpatient dental clinic for treatment of a verrucous lesion measuring about 3 × 1.5 cm on the buccal gingiva of tooth 33 and the edentulous alveolar mucosa of the teeth 34–36 region (Fig. 1A). The patient had hypertension (systolic pressure of 140 mmHg and diastolic pressure of 90 mmHg on average) that was under drug control. The patient denied having any other major systemic diseases. The patient had chewed AQ (40–50 quids/day) for 30 years and had smoked (20 cigarettes/day) for 40 years. He had quit chewing AQ 10 years previously, but had only quit smoking 4 months previously. He began to notice a verrucous tumor on the left lower posterior edentulous alveolar mucosal area 4 months previously. Although he had quit smoking 4 months previously, the tumor continued to grow to the present form and size. During the past 4 months, the patient had received no treatment. Based on the size and appearance of the lesion, the tentative clinical diagnosis was an OVC. However, an incisional biopsy taken from the tumor portion of the edentulous alveolar mucosa of the tooth 34 area showed an early invasive OSCC (Figs. 1B and 1C). Magnetic resonance imaging revealed no metastatic lymph nodes in the bilateral submandibular, carotid or posterior cervical region. In addition, a whole-body bone scan revealed no bone metastasis. The patient refused to undergo wide surgical excision of the tumor. After discussion with the patient, we decided to use an enhanced topical ALA-PDT protocol (with a fluence rate of 200 mW/cm² and a light exposure dose of 200 J/cm²) to treat him after he provided informed consent.

The treatment course for this patient was the same as that for our previous OVH or OVC patients as described previously, except that a twofold higher light exposure dose was given to the patient in this case. In brief, at the first visit, an oral examination and incisional biopsy were performed. At the second appointment, we did a kinetics study with topical ALA using ALA-induced PpIX fluorescence spectroscopy and found that the PpIX reached its maximum level in the lesional epithelial cells 1.5 hours after local ALA application. Therefore, the subsequent light treatments were set at 1.5 hours after topical application of ALA to the lesion. The topical ALA-PDT was performed once a week beginning from the patient’s third appointment. On the day of treatment, 0.8 mL of 20% ALA was applied to the entire tumor upon the patient’s arrival. The light treatment was composed of multiple 3-minute sessions of irradiation with an LED red light at 635 ± 5 nm separated with several 3-minute rest periods for a total of 1000 seconds (with a fluence rate of 200 mW/cm² and a light exposure dose of 200 J/cm²) which was delivered 1.5 hours after topical ALA application. Light treatments were carried out under local anesthesia using 2% lidocaine with the patient fully conscious. The tip of the LED light device was kept as close to the surface of the lesion as possible. The verrucous lesion showed nearly
Fig. 1 Clinical photographs and histologic microphotographs of an early invasive squamous cell carcinoma (SCC) lesion. (A) An initial oral verrucous carcinoma-like lesion at the buccal gingiva of tooth 33 and the edentulous alveolar mucosa of the teeth 34–36 region before treatment. (B, C) Incisional biopsy of the tumor portion at the edentulous alveolar mucosa of the tooth 34 area showing a verrucous carcinoma with early invasion of SCC tumor nests into the underlying connective tissue (hematoxylin and eosin stain; B: original magnification ×5, C: original magnification ×25). Clinical photographs of the early invasive SCC lesion showing a partial response of the main verrucous lesion after (D) three and (E) six treatments of the enhanced topical ALA-PDT, nearly complete regression of the main verrucous lesion after (F) eight PDT treatments, multiple residual leukoplakic lesions at the edentulous alveolar mucosa after (F) eight and (G) 14 PDT treatments, and complete regression of the lesion after (H) 18 PDT treatments. (H) A white lesion of oral submucous fibrosis is still evident at the left buccal mucosa.
complete regression after eight treatments of the enhanced topical ALA-PDT (Figs. 1D−F). However, the multiple residual leukoplakia lesions needed 10 extra treatments to achieve complete regression (Figs. 1G and 1H). Because of the severe post-PDT pain, codeine phosphate (30 mg/tablet, 1 tablet 3 times/day) was prescribed for the patient for the former eight treatments and acetaminophen (500 mg/tablet, 1 tablet 4 times/day) was given to the patient for the latter 10 treatments after PDT. After completion of the entire treatment course, the patient was followed up once every 2 weeks in the 1st month, once every 2 months in the following 6 months, and once every 3 months thereafter. No recurrence of the lesion was found after a follow-up period of 4 years.

Discussion

In this case report, we describe treatment of an early invasive OSCC on the buccal gingiva of tooth 33 and the edentulous alveolar mucosa of the teeth 34−36 region of a 67-year-old male former AQ chewer and ex-smoker by a new enhanced topical ALA-PDT protocol. The early invasive OSCC lesion showed complete regression after a total of 18 treatments of topical ALA-PDT. In our previous studies, a topical ALA-PDT protocol was successfully used to treat 36 OVH lesions, an extensive OVC lesion, and an extensive OVH lesion.10−16 The results of the present report confirmed that our new enhanced topical ALA-PDT protocol also has good potential as an effective treatment modality for superficially invasive OSCC lesions.

The clinical appearance and treatment course of this superficially invasive OSCC lesion were comparable to those of our previously reported extensive OVH lesion.16 Both lesions had a verrucous appearance and showed complete regression after 18 treatments with enhanced topical ALA-PDT. The incubation period (the time needed for the transformation of ALA into PpIX) was 1.5 hours, and the total light exposure dose per treatment was 200 J/cm² for both lesions. In addition, both lesions demonstrated nearly complete regression after eight treatments of the enhanced topical ALA-PDT. This suggests that doubling the light dose may slightly shorten the treatment course compared with that for our previously reported extensive OVH case. However, more-severe post-PDT pain was experienced by this early invasive OSCC patient than by our previous OVC patient. Therefore, stronger analgesics were needed for this patient to control the post-PDT pain than for the previous OVC patient.

PDT with topically applied ALA is used to treat oral precancerous lesions like oral leukoplakia (OL) and OVH and cancerous lesions like OVC with promising clinical outcomes.7−16 Kubler et al.7 treated 12 OL lesions with PDT after local application of 20% ALA cream and found a complete response (CR) in five, a partial response (PR) in four, and no response (NR) in three. Sieron et al.8,9 treated 17 OL lesions with PDT after topical application of 10% ALA ointment or emulsion in two separate studies. A CR was observed in 14 of 17 OL lesions. Our previous studies showed that complete regression of 36 OVH lesions was achieved with fewer than seven treatments of topical ALA-PDT once a week.14 However, for an extensive OVC or OVH lesion, more treatments are needed.15,16 Our previous studies revealed that topical ALA-PDT is not very effective for OL lesion. The 65 OL lesions treated with topical ALA-PDT once a week showed a CR in five, a PR in 33, and NR in 27. The 32 OL lesions treated with the same topical ALA-PDT twice a week demonstrated a CR in 11 and a PR in 21. The twice-a-week treatment modality had a better clinical outcome for OL lesions than the once-a-week modality.13 The need for 10 treatments of PDT to eradicate the multiple residual OL lesions in this patients also indicates the relative difficulty of obtaining a CR with topical ALA-PDT with medium- and small-sized OVH lesions.14 However, the results of the above-mentioned investigations suggest that PDT with topical ALA may be an effective treatment modality for OVH and OVC lesions and may have a good potential to be used as a treatment of choice for OVC and superficially invasive OSCC lesions without regional or distant metastasis. Further studies are needed to assess whether the new enhanced topical ALA-PDT is more effective than the previously used topical ALA-PDT for treating OL lesions.

The successful clinical outcome for this early invasive OSCC lesion treated by the new enhanced topical ALA-PDT may have been due to the ALA preparation, the specific topical ALA-PDT protocol used, and the characteristic clinical, histologic and biologic features of the lesion itself. The reasons why our specific ALA preparation and the topical ALA-PDT protocol used resulted in a successful clinical outcome for OVH lesions were previously described.11−14,16 Similar reasons could be used to explain the successful clinical outcome for this case as well. The verrucous appearance of the present lesion provided a large area for good retention of ALA on the surface, and the less keratotic epithelium of this lesion than OL lesions also provided a more permeable surface layer for good absorption of ALA into the oral epithelial cells. Furthermore, malignant epithelial cells may retain more ALA than hyperplastic epithelial cells, and the thinner surface keratin layer may only have a minimal effect on reducing the light intensity. In addition, there are more epithelial cells in the cell division cycle in cancerous than in hyperplastic oral
lesions. Malignant epithelial cells in the cell division cycle are more susceptible to destruction by PDT-generated singlet oxygen molecules and free radicals than those epithelial cells not in the cell division cycle. The sufficient photosensitizer and light dose ultimately resulted in a good clinical outcome for this early invasive OSCC lesion.

In this case report, we succeeded in treating a superficially invasive OSCC with an enhanced protocol of topical ALA-PDT. Although further studies are needed to verify the true efficacy of this enhanced treatment protocol, we suggest that our enhanced topical ALA-PDT protocol has good potential to be used as a treatment of choice for an early invasive OSCC without regional or distant metastasis before the commencement of other effective therapies.

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References