Case Report

Combining aminolaevulinic acid photodynamic therapy with carbon dioxide laser therapy to treat adult-onset laryngeal papillomatosis: case reports and a literature review

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Abstract: This paper describes 3 cases in which 5-aminolevulinic acid photodynamic therapy (ALA-PDT) was combined with carbon dioxide (CO_2) laser therapy to treat patients with adult-onset laryngeal papillomatosis (ALP). Laryngeal papilloma is the most common benign laryngeal tumor, and is usually caused by human papillomavirus (HPV) types 6 and 11. It has the characteristics of rapid growth and frequent recurrence, and has a tendency of malignant transformation. Moreover, it can spread to the lower respiratory tract, which might lead to a rise in mortality risk. Laryngeal papilloma lesions are frequently found on the vocal cords or in the laryngeal cavity, and the characteristic koilocytosis is dispensable in pathological diagnosis of papilloma. Common symptoms include various degrees of hoarseness and wheezing. In the cases reported herein, all 3 patients suffered a recurrence of ALP following treatment. After the removal of the laryngeal papilloma using a combination of ALA-PDT and CO_2 laser therapy, the patients were cured; there was no recurrence, and no further malignant transformation was found in the 6–12 months postoperative follow-up period. Our experiences show that ALA-PDT combined with CO_2 laser therapy is feasible and effective in the treatment of ALP, and produces no obvious adverse reactions. However, further clinical trials need to be undertaken to confirm the efficacy of this treatment.

Keywords: Aminolevulinic acid photodynamic therapy (ALA-PDT); CO_2 laser therapy; laryngeal papillomatosis; case report

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Introduction

Adult-onset laryngeal papilloma (ALP) is the most common laryngeal benign tumor and is usually caused by human papillomavirus (HPV) types 6 and 11 (1). The overall prevalence of ALP is 1.8 per 100,000 people, and the predilection age is 20–40 years (1,2). ALP characteristically manifests with rapid growth and frequent recurrence, and has a tendency of malignant transformation (3). It can spread to the lower respiratory tract, which might lead to a rise in mortality risk (4). Despite the availability of many methods, such as traditional surgery, carbon dioxide (CO_2) laser therapy (3), micro- dehybridization (5), bevacizumab, cidofovir (6), interferon alpha (IFN-α), and newly introduced vaccines, there is no satisfactory and effective treatment for HPV at present (7). However, the application of aminolevulinic acid photodynamic therapy (ALA-PDT) has produced some promising results in the treatment of condyloma acuminatum and non-melanoma skin cancers (8,9). Additionally, a few recent reports have provided some novel insights into the use of 5-ALA-PDT in the treatment of laryngeal papilloma (8,10,11). In this paper, we present 3 case studies in which patients with ALP were treated with a combination of 5-ALA-PDT and CO_2 laser therapy. Our observations show that this combination is effective in

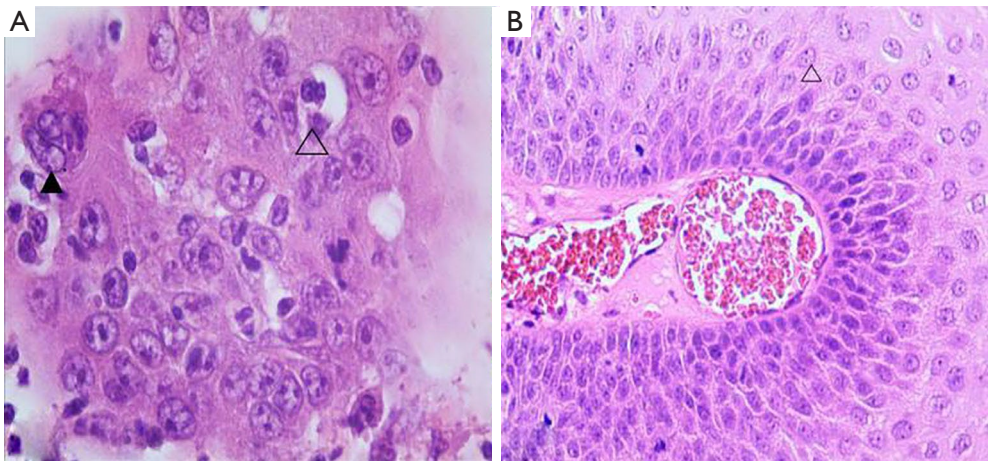

Figure 1 HE ×400 Histopathologic examination: enlarged hyperchromatic nuclei with mitotic figure (A, ▲) and characteristic koilocytosis in papilloma (A, B, △).

the treatment of ALP and can even eliminate proliferating cancer cells in patients with ALP. We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2985).

Case presentation

The cases include 3 patients with ALP (2 males and 1 female). The patients were diagnosed with ALP between the ages of 31–73, and the disease lasted for 23–36 months from their presentation. Genotyping analysis detected a low risk of HPV 6 and 11, and a high risk of HPV 18. There was no relevant family medical history for any of the patients. All 3 patients had suffered from a recurrence of ALP after previous treatment. The first patient, aged 73, reported progressive hoarseness at the consultation. The patient's laryngeal papilloma had resurfaced 3 months after 5 surgical resections. In preoperative examinations, moderate to severe atypical hyperplasia and focal cancerization were observed in his histologic sections via electronic laryngoscopy (*Figure 1A*). The second patient had a relapse of ALP 4 months after 3 microdebrider treatments. The third patient experienced a recurrence of ALP months after CO_2 laser therapy. The common symptoms included various degrees of hoarseness and wheezing. Physical examinations revealed that the ALP lesions were located on the vocal cords or in the laryngeal cavity. The pathological diagnoses were made preoperatively. All 3 patients presented with characteristic koilocytosis in the papilloma, and the second and third patients showed signs of cancerization (*Figure 1B*).

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients.

Methods

The operations were performed under general anesthesia. During the CO_2 laser therapy, double-sac reinforced tracheal intubation and the maintenance of pulmonary ventilation at a low concentration of oxygen (<30%) were necessary. Visible papilloma lesions were removed with a CO_2 laser after a pedestal laryngoscope and a laryngeal endoscope (*Figure 2A,B*).

Five-aminolevulinic acid (ALA) powder (118 mg/bottle, Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co., Ltd.) was dissolved in normal saline to create a 20% concentration solution in the dark. A sterile cotton gauze soaked in ALA solution was placed in the entire laryngeal cavity, including the infraglottic, glottic, and supra-glottic portions. The surgical excision area was covered by the ALA-soaked cotton gauze, with care taken to ensure irregular cavity gaps were not neglected (*Figure 2C*). The ALA cotton gauze was replaced with fresh gauze every 30 minutes. After a total administration time of 3 hours, the ALA cotton gauze was removed from the laryngeal cavity, and then the surgical excision areas were irradiated at a wavelength of 635 nm using 100–120 J/cm^2 power for 20 minutes through a columnar optical fiber of a photodynamic therapy instrument (Wuhan Linyun Photoelectronic System Co, Ltd., Wuhan, China)

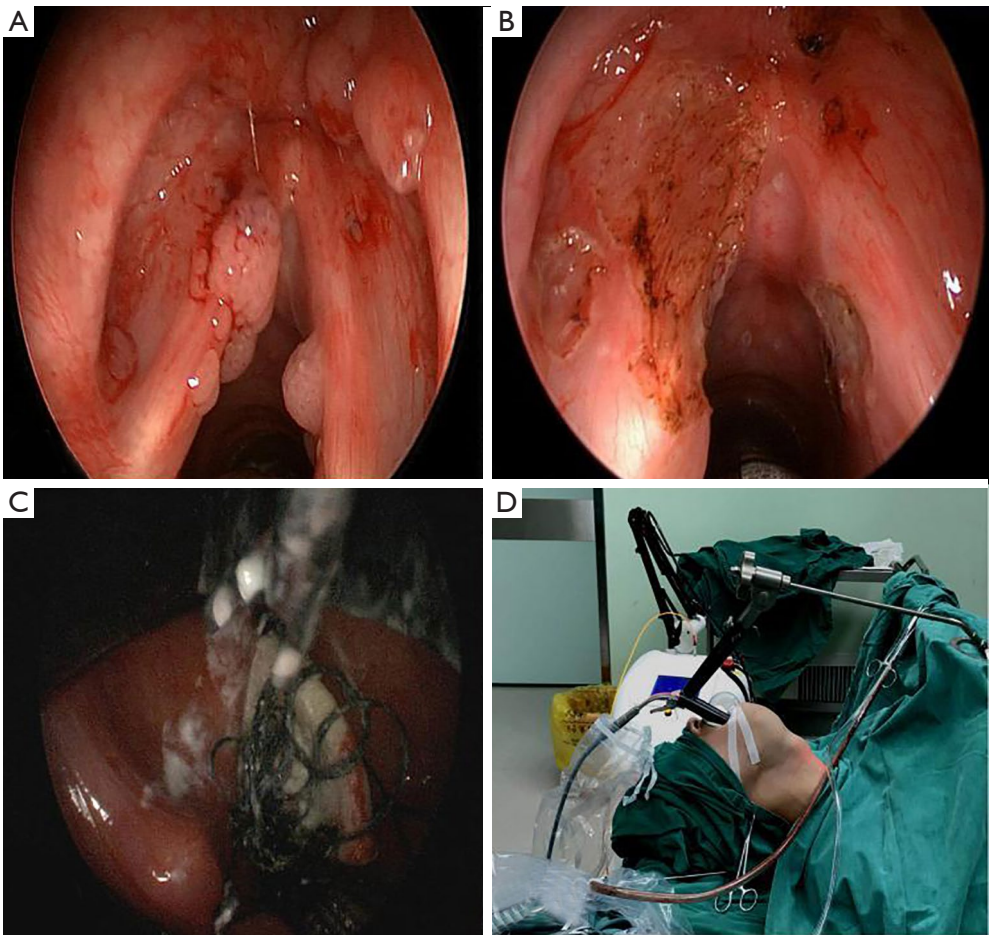

Figure 2 Visible papilloma lesions were removed using a CO_2 laser after pedestal laryngoscope and laryngeal endoscope (A,B). After a total administration time of 3 hours, the ALA cotton gauze was removed from the laryngeal cavity, and the surgical excision areas were irradiated using PDT via a columnar optical fiber (C,D).

(*Figure 2D*). A follow-up appointment was conducted 3 weeks after the first cycle of treatment. If visible papilloma lesions were absent, 2 extra cycles of PDT irradiation were carried out. If papilloma lesions were present, they were removed using a CO_2 laser, and the irradiation was performed again. After the first cycle of PDT, an inflammatory fibro-polypus was found in case 1 who had been diagnosed with focal cancerization preoperatively. A pathological examination of the lesion revealed the presence of common inflammatory hyperplasia with characteristic koilocytosis, but no further malignant transformation was observed (*Figure 3A,B*). A follow-up appointment was arranged 6–12 months later, followed by a final cycle of PDT irradiation for all 3 patients. No recurrence was found, and interestingly, the oldest patient showed no sign of neoplasia.

Discussion

The etiology of laryngeal papillomatosis was first described by Ullmann in 1923, and was later confirmed using electron microscopy and polymerase chain reaction techniques (12). ALP is the most common benign laryngeal tumor, with an incidence of approximately 1.8 cases per 100,000 people (2). The condition is caused by HPV infection, including the high-risk types of HPV6/11 and the low-risk types of HPV16/18 (12). HPV can distribute throughout the whole respiratory tract, especially in the larynx, and generate exophytic papillomas, which can lead to symptoms of hoarseness, wheezing, dyspnea, or asphyxia. Clinically, the prognosis is often unsatisfactory, and this condition is often resistant to therapy and recurs frequently. The deregulated expression of viral early genes in basal

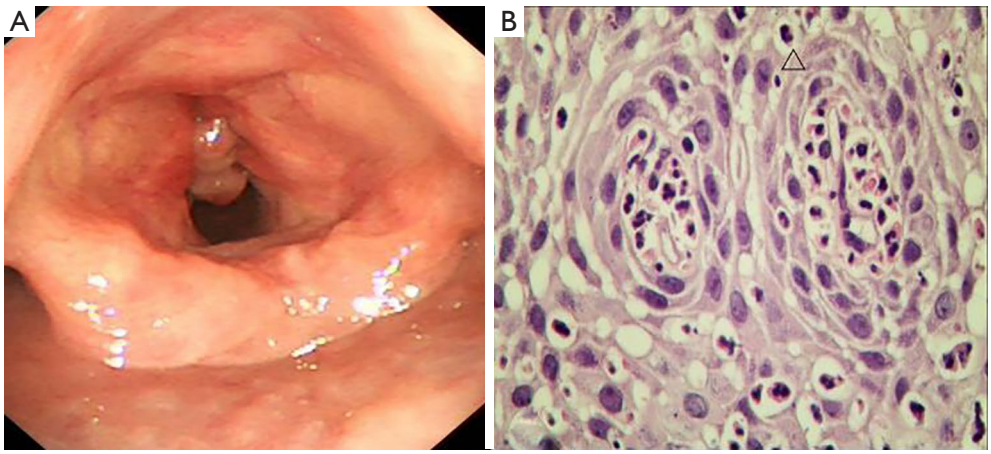

Figure 3 An inflammatory fibropolypus (A, laryngeal endoscope) with koilocytosis (B, HE ×400, △) was found in the patient with preoperative focal cancerization after the first cycle of PDT, but no further malignant transformation was observed in the pathological examination (B, HE ×400).

epithelial cells and genomic instability, causing secondary host genomic imbalances, are considered key events in the progression of HPV-promoted lesions (12). Notably, malignant transformation has been reported (13,14), and did occur in 1 of our patients. Despite the availability of numerous treatments, such as traditional surgery, CO_2 laser therapy (3), micro-debridization (5), bevacizumab, cidofovir (6), IFN-α, and newly introduced vaccines, there is currently no satisfactory and effective treatment for HPV (7).

In this paper, we examined 3 cases in which patients suffered a recurrence of APL after receiving treatments including surgery, micro-debridization, and CO_2 laser therapy. These patients were subsequently treated with a combination of ALA-PDT and CO_2 laser therapy. This treatment proved to be extremely efficacious; all of the patients were cured, and there was no second recurrence. However, further clinical trials should be conducted to verify the efficacy of this treatment.

In recent years, PDT has been approved to treat lung cancer, esophageal cancer, and Barrett's esophagus (15,16). The application of ALA-PDT in the treatment of condyloma acuminatum, HPV infection, and non-melanoma skin cancers has produced some promising results (8,9). ALA-PDT can effectively eliminate latent or subclinical HPV infections, and thus can reduce the recurrence of condyloma acuminatum (17). PDT induces the death of HPV-infected cells by apoptosis or necrosis after the laser excitation of the photosensitizer (18). The photosensitizer is activated by light and interacts with molecular oxygen to produce reactive singlet oxygen, resulting in the destruction of proliferating cancer cells (15). In 2014, Zhou *et al.* first successfully used PDT to treat juvenile laryngeal papillomatosis (19). Zhang later showed that ALA-PDT with a self-retaining laryngoscope combined with CO_2 laser therapy is safe and effective for clearing juvenile and adult laryngeal papilloma (11). Similarly, topical ALA-PDT can significantly reduce the recurrence of ALP and improve its cure rate (10).

In the present study, we used ALA-PDT to treat 3 patients with ALP, who were all cured. The patients all underwent self-retaining laryngoscopy combined with CO_2 laser therapy previously. According to Liang *et al.* (10), ALP relapses at a rate of 15.4% after ALA-PDT combined with CO_2 laser therapy. After treatment, the focal cancerization in the oldest patient transformed into common inflammatory hyperplasia, and no further malignant transformation was found. ALA-PDT can selectively eliminate abnormally proliferating cells without damaging healthy tissue (15). Further, synechia formation of the anterior commissure after CO_2 laser therapy can be avoided to some degree (20). No glottic synechia was observed following treatment in our cases. In addition to the above-described mechanism of action, ALA-PDT increases CD4+, CD4+/CD8+ and IFN-γ, and reduces CD8+, IL-4, and IL-10 in HPV-infected cells, which may also contribute to the curing of intractable laryngeal papillomatosis (21).

The main adverse reactions of PDT include inflammatory reactions, local edema, liver toxicity, pain, and phototoxicity (22). Most of these reactions are mild, and

patients recover quickly (8,23). Notably, no complications were recorded in our patients. Due to the high risk of malignant transformation in ALP (24), we are of the view that histological examinations should be undertaken before the removal of lesions during each cycle of ALA-PDT.

In conclusion, ALA-PDT combined with CO_2 laser therapy is feasible and effective for the treatment of ALP, and can obtain a good curative effect. However, further clinical trials need to be undertaken to determine whether ALA-PDT alters the course of laryngeal papillomatosis or adds any benefits to the surgical treatment of laryngeal papillomatosis.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2985). The authors have no conflicts of interest to declare.

Ethical Statement: Both authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients.

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