Photodynamic Therapy With Topical 5-Aminolevulinic Acid as a Post-Operative Adjuvant Therapy for an Incompletely Resected Primary Nasopharyngeal Papillary Adenocarcinoma: A Case Report

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Background and Objectives: Surgical excision of primary nasopharyngeal papillary adenocarcinoma is sometimes incomplete with remaining microscopic disease. Post-operative radiotherapy only has limited efficacy but may cause many complications.

Study Design/Materials and Methods: Photodynamic therapy (PDT) was used as a post-operative adjuvant therapy for an incompletely resected primary nasopharyngeal papillary adenocarcinoma. A special form of 20% topical 5-aminolevulinic acid (5-ALA), which was originally a liquid form and became a gel form after applied on the nasopharynx, was used as the photosensitizer. A 2-mm optic fiber delivered the light (633 nm wavelength) to the lesion with a fluence rate of 100 mW/cm^2 generated by a diode laser under 5 mm 0° endoscope assistance. The total energy delivered was 150 joules/cm^2.

Results: No significant acute side effect was noted and the nasopharyngeal wound healed rapidly. The patient is alive without locoregional recurrence or distant metastasis for 5 years. Articulation, salivation, and swallowing functions are all well preserved.

Conclusion: Post-operative adjuvant PDT can successfully cure an otherwise difficult to treat disease with preservation of good life quality of the patient. Potential complications of PDT (e.g., photosensitivity) can be prevented by a special formulation of topical 5-ALA preparation. Lasers Surg. Med. 38:435–438, 2006.

Key words: chemoradiation; nasopharyngeal cancer; photosensitizer

INTRODUCTION

Malignant tumors arising from the nasopharynx include nasopharyngeal carcinoma (NPC), malignant lymphoma, and various types of minor salivary gland malignancies such as mucoepidermoid carcinoma or adenoid cystic carcinoma. Among them, NPC comprises most of nasopharyngeal cancers whereas other tumors are relatively rare. The incidence of primary nasopharyngeal papillary adenocarcinoma is extremely rare, even in endemic areas of NPC such as in Hong Kong or in Taiwan [1,2]. Since Wenig et al. identified this specific disease entity in 1988, there were no more than 30 cases reported in the English literature [1–3]. In general, primary nasopharyngeal papillary adenocarcinoma is thought to be a low-grade malignancy compared with other types of nasopharyngeal cancers. The prognosis is good after complete surgical resection of the tumors [1,3]. However, because of anatomical limitations, it is sometimes difficult to completely remove the nasopharyngeal tumor with adequate safety margin, especially in cases of large infiltrative tumors. Thus adjuvant treatment modalities are sometimes needed in such tumors [3]. Unfortunately, there is no effective adjuvant treatment modality so far for incompletely removed tumors because the response of papillary adenocarcinoma to conventional radiotherapy or chemotherapy is relatively poor [4].

Photodynamic therapy (PDT) is a new treatment modality for head and neck cancers with satisfactory treatment responses and minimal complications [5–8]. The basic concept of PDT is to deliver light of a specific wavelength to activate photosensitizers for site-specific tumor destruction [9]. Although the location of nasopharynx is situated deeply beneath the skull base, laser fiber can be easily delivered to

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the nasopharynx under endoscope assistance to conduct PDT. In some pilot studies, PDT has been successfully used in the treatment of locally recurrent NPC [10,11]. Because papillary adenocarcinoma is usually limited in the nasopharyngeal region with very low incidence of lymph node metastasis [1,3], this type of cancer seems to be a good candidate for PDT. In this paper, the authors report the first experience of successful treatment of nasopharyngeal papillary adenocarcinoma by nasopharyngectomy plus post-operative adjuvant PDT with topical 5-aminolevulinic acid (5-ALA) as the photosensitizer.

MATERIALS AND METHODS

Preparation of ALA Liquid

The formulation of ALA was prepared using Pluronic F127 (BASF, Mount Olive, NJ) and Carbopol 971P, which was kindly provided by BF Goodrich. Double concentrated gels of Pluronic F127 and Carbopol 971P in water were separately prepared prior to mixing. The "cold method" was adopted for preparing the Pluronic F127 gel [12]. After refrigerating at 4°C overnight, clear solution form of Pluronic F127 was mixed with equal volume of the Carbopol gel, and the mixture was stored at 4°C. Prior to use, 200 mg of ALA was mixed with 800 mg of the gel and packed into a 1-cc syringe. The formulation was used within 3 hours.

Photodynamic Therapy

The procedure was performed with the consent of the patient and was approved by the Investigating Review Board of National Taiwan University Hospital (No. 91-00006821). At the day of treatment, the patient was asked to lie on the bed with a pillow on the head in a clear consciousness. The pledgets rinsed with a solution of 1% lidocaine and adrenaline (1:100,000) were packed in the bilateral nasal cavities for 10 minutes. After adequate topical anesthesia and shrinkage of the inferior turbinates, 20% 5-ALA solution was topically applied on the surface of the nasopharynx under the 5 mm 0° endoscope guide. All of the nasal and nasopharyngeal secretion was suctioned out before and during the initial 10 minutes after topical application of 5-ALA. PDT was performed 3 hours after the 5-ALA application. Before light treatment, the nasopharyngeal area was irrigated with cold saline to remove the residual ALA on the lesion. The light source consists of a diode laser with a 633 nm wavelength emission of red light (CeramOptec GmbH, Bonn Germany). The fluence rate of device at the lesion surface was 100 mW/cm^2 with a spot size of 1 cm^2 at a distance of 1.5 cm. The light was delivered onto the surface of the nasopharynx via an optical fiber (2 mm in diameter). The fiber passed through the inferior meatus of the nasal cavity under the guidance of a 5 mm 0° endoscope. The light treatment was performed in a way that the first 50 J/cm^2, 3-minute break; another 50 J/cm^2, 3-minute break, and the last 50 J/cm^2 with a total delivered dose of 150 joules/cm^2. Each illumination took 500 seconds and there were 31 minutes totally, including three PDT illuminations and two breaks. The doctor performing the treatment held the optic fiber during the whole treatment period. Analgesics were prescribed to the patients to control the post-PDT pain. The patient was then followed up once a week in the first month and once a month thereafter.

CASE REPORT

A 35-year-old woman presented with a 3-month history of right epistaxis and blood-stained sputum in the morning. There was no aural fullness, headache, facial numbness, or diplopia. Physical examination revealed a protruding mass at the right side of nasopharynx. Biopsy was performed and the report showed papillary adenocarcinoma. Pre-operative computed tomography revealed a tumor at the right nasopharynx, extending into the sphenoid sinus with some bony destruction (Fig. 1). There was no parapharyngeal space involvement or cervical lymphadenopathy. Wide excision of the tumor was performed via transpalatal approach. The pathology revealed an adenocarcinoma with papillary structure and focal glandular formation. The papillae were linked by a layer of cuboidal to low columnar cells, with irregularly distributed vesicular nuclei (Fig. 2). The cancer cells were non-immunoreactive to both thyroglobulin and thyroid transcription factor-1 protein (TTF-1), which excluded metastatic cancer. Because surgical margin was involved by cancer cells, the patient received PDT at 4 week after the operation. The patient received only one PDT treatment and did not receive radiotherapy or chemotherapy. One year later, elective random nasopharyngeal biopsies were performed and the pathology showed no cancer cells. The magnetic resonance image 3 years post-operation revealed normal appearance of the nasopharynx without evidence of recurrence (Fig. 3). The patient is alive without any locoregional recurrence or distant metastasis till now for 5 years.

DISCUSSION

Primary papillary adenocarcinoma of the nasopharynx is extremely rare [1–3]. Thus it is necessary to exclude the

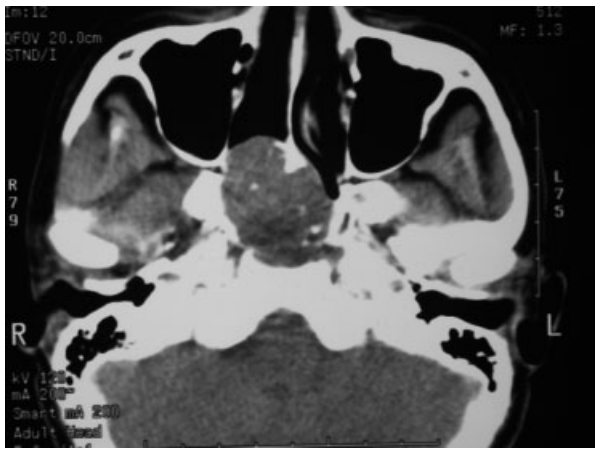

Fig. 1. The axial view of the CT scan shows a protruding tumor in the nasopharynx with occlusion of the posterior nasal choanae and adjacent bone destruction.

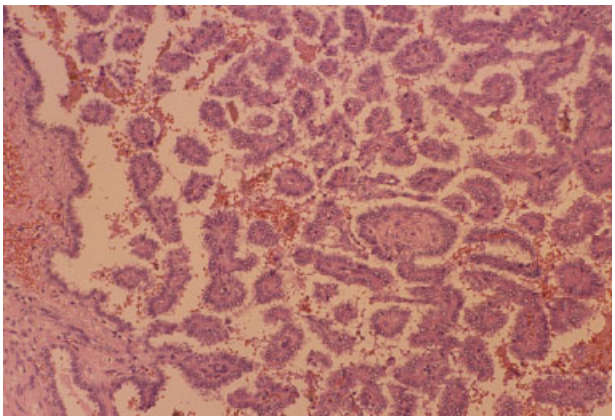

Fig. 2. The tumor shows the typical growth pattern of papillary carcinoma. The papillae are complex and branching and contain a central fibrovascular core. (H&E, 33× original magnification). [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]

possibility of nasopharyngeal metastasis from other sites of the body before the treatment is started. Papillary adenocarcinoma of the thyroid gland is the first that needs to be ruled out because histologically both nasopharyngeal and thyroid papillary adenocarcinomas show similar papillary and glandular growth patterns, vesicular nuclei, and focal psammoma body formation [13]. Besides, occult thyroid papillary adenocarcinoma with obvious metastases are not uncommon and images studies do not exclude very small cancer focus in the thyroid gland [14–17]. Fortunately, immunohistochemical studies with thyroglobulin and TTF-1 antibodies are helpful to distinguish these two diseases. Primary nasopharyngeal papillary adenocarcinoma lacks thyroglobulin and TTF-1 expression whereas thyroid papillary adenocarcinoma often highly expresses them [18]. Immunohistochemical staining in this case confirmed the diagnosis of primary nasopharyngeal papillary adenocarcinoma.

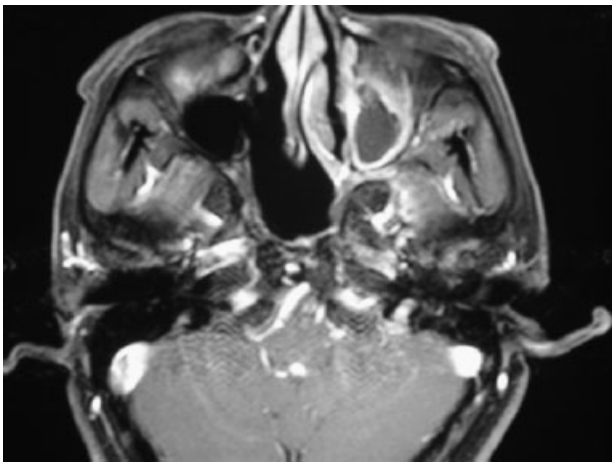

Fig. 3. The axial view of the T1-weighted MRI with Gadolinium enhancement done 3 years after treatment shows no abnormal tumor lesion in the nasopharynx.

Primary nasopharyngeal papillary adenocarcinoma usually grows as a papillomatous protruding tumor in the nasopharynx without deeply infiltrating into the adjacent structure, such as to the parapharyngeal space or the intracranial region; or metastazing to cervical lymph nodes [1,3]. Therefore, most of the reported cases were successfully treated by surgical excision [1,3]. However, because the nasopharynx is located in the center of the head with many vital structures nearby such as the internal carotid artery, surgical excision with oncologically sound safety margin is sometimes impossible especially in large infiltrative tumors [19]. Therefore, an effective adjuvant treatment modality is necessary to eradicate the residual disease after surgery. For most of the head and neck cancers, that is, squamous cell carcinoma or undifferentiated carcinoma, chemoradiation is commonly used as primary or adjuvant therapy. However, papillary adenocarcinoma belongs to a well-differentiated adenocarcinoma group, which is not thought to be sensitive to conventional chemoradiation [4]. Furthermore, chemoradiation may cause many acute or late complications. Because of low benefit and high cost, chemoradiation is not considered as an ideal adjuvant therapy for this tumor.

PDT is a new developing site-specific cancer treatment involving the administration of a photosensitizer followed by focal activation in the presence of oxygen using light of a wavelength matched to an absorption peak of the photosensitizer [9]. In the past decades, effective treatment of various human malignancies, either squamous cell carcinomas such as skin, cervical, esophageal or head and neck cancers or adenocarcinomas such as gastric, breast or colorectal cancers, by PDT has been reported [9]. More importantly, PDT has good anatomical and functional preservations of adjacent normal tissues and can be repeatedly applied safely [5,9]. Therefore, PDT may be a more suitable alternative method than conventional chemoradiation for adjuvant treatment of nasopharyngeal papillary adenocarcinoma. Although it is difficult to verify this point because of few case numbers, we have successfully treated a case and bring up the potential of implementing PDT as an adjuvant treatment for incompletely excised low-grade adenocarcinomas.

5-ALA-mediated PDT (5-ALA-PDT) is a well-tolerated and effective treatment for various malignancies and is suitable to treat the mucosal malignancy of the nasopharynx because of its adequate penetration depth [9,20,21]. For minimizing systemic unwanted photochemical skin reaction, a special formulation of topical 5-ALA preparation, which has been proved to be effective in superficial less-invasive malignant lesions of the mucosa [21–23] was used as a photosensitizer to treat this patient. This topical 5-ALA preparation contains a thermoresponsive sol–gel transition of the vehicle [21–23]. So the liquid form, which is easily applied on the nasopharynx, of 5-ALA solution at room temperature, becomes a gel form at body temperature upon contacting the diseased mucosa. The gel form of 5-ALA preparation is then adhesive to the mucosa and

partially resistant to the dilution of the secretion so that cancer cells have enough incubation time to uptake the 5-ALA [21–23]. This special 5-ALA delivery formulation may greatly increase the intra-lesional drug concentration and reduce the unwanted absorption of the drug by normal tissues and can be easily applied through the endoscopic guidance. Using this formulation and a small-caliber optic fiber to deliver the light, we would be able to treat lesions anywhere over the aerodigestive tract as long as the endoscope can reach. Treatment efficacy could be improved while systemic photosensitivity could be prevented.

CONCLUSION

Surgery is the mainstay of treatment for primary nasopharyngeal papillary adenocarcinoma. If the tumor is not completely removed, PDT may be an effective modality of the post-operative adjuvant therapy to eradicate the residual disease. Good treatment outcome is achieved without compromising the patient's life quality.

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