

Traditional Chinese Medicine for Treatment of Laryngeal Papillomatosis

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Abstract

Objective: The objective of this study was to assess the clinical effectiveness of Traditional Chinese Medicine (TCM) as an adjuvant therapy for recurrent respiratory papillomatosis.

Design: The design of this study was a case series.

Location and subjects: Fifty-one (51) patients with laryngeal papillomatosis who were treated at Keio University Hospital between May 1981 and April 2008 were incorporated in this study.

Interventions: Individually formulated TCM was orally administered postsurgically to 20 patients with aggressive laryngeal papillomatosis requiring multiple laser ablations (at least biannually) because of frequent recurrence. Eight (8) patients were excluded because of discontinued visits or medication (6 patients), or malignant transformation of the lesion (2 patients). The remaining 12 patients were enrolled in this study.

Outcome measures: Retrospective chart review and review of the patients' recorded laryngeal images were performed. Clinical response to TCM was measured by the surgical necessity and Derkay's severity score for each patient, followed by statistical analyses.

Results: Surgeries were required statistically less often ($p = 0.0029$) after TCM administration compared with the pre-TCM period. Furthermore, Derkay's severity score was significantly lower ($p = 0.022$) at the patients' last visit compared with the score before TCM administration.

Conclusions: TCM may be a useful adjuvant therapy to treat aggressive laryngeal papillomatosis. Further studies are necessary to clarify the pharmacological mechanism of TCM in the treatment of laryngeal papillomatosis.

Introduction

PAPILLOMATOSIS IS A DISEASE of the respiratory tract caused by human papilloma virus (HPV, predominantly types 6 and 11). It sometimes requires multiple surgeries and involves multiple lesions in the larynx, trachea, and lungs (i.e., recurrent respiratory papillomatosis [RRP]). Uncontrolled disease may lead to severely impaired voice and ultimately airway obstruction. Hoarseness is the most frequent symptom, and stridor, dyspnea, and chronic cough are observed in some cases. The disease is often difficult to treat because of its potential for multiple recurrences. Although surgical excision and CO₂ laser ablation of the tumor is the mainstay of treatment, no single therapy has been decisively effective in erad-

icating RRP. Various adjuvant treatments such as interferon,¹ indole-3-carbinole (I3C),² cidofovir,³ and photodynamic therapy with dihematoporphyrin ether⁴ have been reported to be effective in some cases. These therapies work through any of the following pharmacological mechanisms: immunological, hormonal, antiviral, or chemotherapeutic effect.

Traditional Chinese Medicine (TCM) has been used in the Orient for thousands of years to treat or prevent various diseases such as cancer, infectious disease, and allergy. The herbs used in TCM have pharmacological mechanisms such as augmentation of nonspecific immunological function including the upregulation of antiviral interferon. TCM has also been reported to protect adrenocortical function in patients to exert antitumor activity.⁵ In this study, we assessed

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Part of this study was presented at the annual meeting of the American Academy of Otolaryngology–Head and Neck Surgery Foundation, Denver, CO, September 9–12, 2001.

the clinical efficacy of TCM against RRP according to the impact of the drug on the frequency of surgery and Derkay's severity score of the patients.

Patients and Methods

Fifty-one (51) patients with laryngeal papillomatosis were treated at Keio University Hospital between May 1981 and April 2008. We started TCM administration as an adjuvant therapy to treat papilloma in 1989. Thirty-one (31) patients were administered TCM; 20 of them suffered aggressive papilloma requiring multiple surgeries every year. These severe cases were enrolled in this study.

TCM was individually formulated by experienced physicians based on East Asian natural philosophical principles. Several kinds of herbs were utilized for formulation and the patients boiled raw herbs in water just before taking TCM 3 times a day. The basic combination was *Astragali radix*, *Platycodi radix*, *Angelicae radix*, *Ostreae testa*, *Coicis semen*, *Carthami flos*, *Ligustrum lucidum*, licorice, *Fritillariae bulbus*, *Persicae semen*, and the amount of each ingredient and additional herbs were decided individually.

Derkay's staging format⁶ is a system to quantify the severity of RRP based on the implicated site and subsites. In previous reports, Derkay's severity score after the treatment was utilized to evaluate the clinical effect of the medication on the treatment of RRP.³ On the other hand, severe RRP cases require multiple surgeries over a short time period, and the frequency of the required surgeries should reflect the clinical severity of RRP. In this study, impact of TCM on the treatment of RRP was evaluated based on both Derkay's severity score and the frequency of required surgeries. Surgical indications included (1) severe hoarseness induced by the tumor to interrupt the patient's verbal communication, or (2) airway obstruction by the tumor to induce stridor or dyspnea. Surgeries were performed by experienced surgeons (H.F. or A.S.) in a consistent manner throughout this study.

The length of time from the onset of the lesion to TCM administration (pre-TCM period) was calculated. Subsequently, the number of surgeries performed on each patient during the pre-TCM period was divided by the length of this period to obtain the pre-TCM surgical necessity score (pre-TCM surgical score, times per year [times/year]). The length of time from the start of TCM administration to the last patient visit at our hospital was also calculated (post-TCM period). The number of surgeries during the post-TCM period of each patient was divided by the length of this period to obtain the post-TCM surgical necessity score (post-TCM surgical score, times/year).

Retrospective chart review and review of video tape recorder (VTR) recorded laryngeal images were conducted to obtain Derkay's severity score of each patient.⁶ The scores of their last visit at our hospital were utilized as the final Derkay's severity scores. Surgical scores were compared between the pre-TCM and post-TCM periods. Pre-TCM Derkay's severity scores and final Derkay's severity scores were also compared with each other. Informed consent was obtained from all the patients incorporated in this study.

Comparison of surgical score and Derkay's severity score between the pre-TCM and post-TCM periods was performed with Wilcoxon signed-ranks test. The significance level was set at $p < 0.03$.

Results

Twenty (20) patients were enrolled to evaluate the efficacy of TCM in the treatment of RRP. Two (2) of these patients were excluded because of malignant transformation (to squamous cell carcinoma) of their papilloma. Another 6 patients decided to quit their medications or visits by their own judgments and were therefore excluded. Finally, 12 patients were available for long-term follow-up and further studies.

The final sample included 8 men and 4 women, with the mean age of onset of the papilloma being 13.6 years (age range = 0–50 years). Nine patients had juvenile-onset RRP and three patients had adult-onset RRP. The mean post-TCM follow-up period was 7.8 years (range = 2–17 years). Administration of TCM was started at a mean age of 27.3 years and was administered for a mean duration of 43.3 months (range = 8–91 months). No remarkable adverse effects related to TCM were observed in this study.

Mean surgical score was 2.46 times/year (range = 0.20–6.00 times/year) and mean Derkay's severity score was 12.8 (range = 7–20) before TCM administration. Statistically significant improvement was observed in both surgical score (mean = 0.39 times/year; range = 0–2.48 times/year; $p = 0.0029$) and Derkay's score (mean = 2.3; range = 0–8; $p = 0.022$ after TCM administration (Table 1, Fig. 1). Mean interval between last surgery and the measurement of Derkay's severity score was 87.3 months (range = 5–269 months).

Two (2) cases showed TCM administration to be remarkably effective, and these representative cases are described in the following.

Patient 1: 1-Year-Old Boy

This patient had hoarseness from birth. Gradual appearance of inspiratory stridor was observed and he was brought to our hospital in November 1987 at age 1 year. Fiberscopic examination showed a laryngeal papilloma involving the right vocal fold, bilateral false vocal folds and subglottis on his first visit. Severe growth of the tumor was observed, and CO₂ laser ablation of the laryngotracheal papilloma was performed 9 times by December 1993. However, severe recurrence of the tumor was observed soon after repeated surgeries (Fig. 2A), and emergency tracheotomy was required because of airway obstruction in January 1994. Subsequently, oral administration of TCM was started. Although two extra surgeries were required for tumor ablation, no further surgery was necessary. The last surgery was performed in August 1995 and TCM was administered for 62 months until February 1999. No recurrence of the papilloma was observed for 12 years and Derkay's severity score was 1 at his last endoscopy in September 2007 (Fig. 2B and 2C).

Patient 2: Nine-Year-Old Girl

Microlaryngeal surgeries were repeated 8 times over a 3-year period since the patient was 6 years. She visited our hospital in February 1989 (Fig. 3A); the papilloma involved the epiglottis, arytenoids, vocal folds, false vocal folds, subglottis, and upper level of trachea on that visit. Supraglottic stenosis caused by multiple surgeries was also observed. Severe growth of the tumor was observed soon after her first visit and emergency tracheotomy was necessary because of

TABLE 1. PATIENT CHARACTERISTICS

| Patient no. | JORRP/AORRP | Gender | Age at onset of RRP (yr) | Pre-TCM administration | | | TCM administration | | | Post-TCM administration | | | Pre-TCM Derkay's Severity Score | Post-TCM Derkay's Severity Score |
|-------------|-------------|--------|--------------------------|------------------------|--------------------|-----------------------------|-----------------------------|-------------------|--------------------|-----------------------------|-------------------|--------------------|---------------------------------|----------------------------------|
| | | | | Surgeries (times) | Follow-up (months) | Surgical score (times/year) | TCM administration (months) | Surgeries (times) | Follow-up (months) | Surgical score (times/year) | Surgeries (times) | Follow-up (months) | | |
| 1 | JORRP | M | 1 | 9 | 73 | 1.5 | 62 | 2 | 164 | 0.1 | 20 | 1 | | |
| 2 | JORRP | F | 6 | 16 | 37 | 8.1 | 50 | 0 | 204 | 0.0 | 15 | 1 | | |
| 3 | JORRP | M | 9 | 3 | 12 | 3.0 | 39 | 2 | 120 | 0.2 | 18 | 1 | | |
| 4 | AORRP | M | 35 | 2 | 10 | 6.0 | 8 | 1 | 24 | 0.3 | 18 | 0 | | |
| 5 | JORRP | F | 0 | 6 | 61 | 1.2 | 66 | 4 | 112 | 0.4 | 12 | 3 | | |
| 6 | JORRP | M | 1 | 5 | 10 | 6.0 | 8 | 6 | 29 | 2.5 | 9 | 0 | | |
| 7 | JORRP | F | 0 | 10 | 489 | 0.2 | 68 | 0 | 115 | 0.0 | 8 | 4 | | |
| 8 | JORRP | F | 11 | 6 | 283 | 7.2 | 24 | 1 | 125 | 0.0 | 8 | 1 | | |
| 9 | JORRP | M | 8 | 6 | 486 | 0.3 | 91 | 0 | 91 | 0.1 | 14 | 8 | | |
| 10 | AORRP | M | 41 | 5 | 10 | 2.4 | 36 | 1 | 42 | 0.5 | 7 | 0 | | |
| 11 | JORRP | M | 1 | 52 | 180 | 3.5 | 51 | 1 | 51 | 0.2 | 13 | 8 | | |
| 12 | AORRP | M | 50 | 3 | 178 | 0.2 | 17 | 1 | 41 | 0.3 | 12 | 1 | | |
| Mean | | | 13.6 | 10.3 | 152.4 | 3.3 | 43.3 | 1.6 | 93.2 | 0.4 | 12.8 | 2.3 | | |

JORRP, juvenile-onset recurrent respiratory papillomatosis; AORRP, adult-onset recurrent respiratory papillomatosis; RRP, recurrent respiratory papillomatosis; M, male; F, female; yr, years old; TCM, Traditional Chinese Medicine.

airway obstruction in March 1989. Subsequently, laser ablation of the laryngotracheal papilloma was performed under the laryngofissure approach. Microlaryngeal surgeries were repeated 8 times afterward until December 1989, after which she started oral administration of TCM and the antitumor effect of TCM was remarkable in this patient. TCM was administered for 50 months until February 1994 and no recurrence of the papilloma was observed for 11 years until her last visit. Derkay's severity score was 1 on her last endoscopy in November 2007 (Fig. 3B and 3C).

Discussion

Adjuvant therapy against RRP

Reportedly, as many as 10% of the patients with laryngeal papillomatosis require some form of adjuvant therapy⁷ because of the aggressive nature of the disease that requires multiple surgeries. Of the variety of adjuvant therapies available for RRP, the current popular adjuvant therapies include α -interferon, I3C, and cidofovir.

The most popular adjuvant therapy is interferon α -2A. Interferon is a family of nonspecific regulatory proteins associated with a variety of antiviral, antiproliferative, and immunomodulating activities.⁸ Interferon has the potential to activate macrophages⁹ and augment NK activity.¹⁰ Interferon reportedly exhibits the antitumor activity against papillomas through the inhibition of viral replication, inhibition of cell growth, alteration of cell surface antigen expression, and effects on various aspects of immune reactivity, such as the level of cytotoxic effector cells and/or antibody production. Leventhal et al.¹ reported that subcutaneous injections of interferon α -2A are effective in slowing the growth of RRP: of the 60 patients studied, 22 had complete remissions (37%) and 25 had partial remissions (42%) in their long-term (4 years) results. Adverse effects of interferon comprise transient fever, fatigue, nausea, elevated liver transaminase levels, and febrile seizures.

I3C is classified as a dietary supplement by the Food and Drug Administration (FDA). I3C affects metabolism of estrogen. Newfield et al.¹¹ have demonstrated that laryngeal tissue is very sensitive to I3C-induced changes in estrogen metabolism. I3C was found to abrogate the proliferative effects of estradiol on laryngeal cells *in vitro* and reduced the development of papilloma in HPV-infected human laryngeal tissue xenografts using a murine model *in vivo*.¹² Rosen et al.² reported a case series of 18 children with RRP orally administered I3C. Of these, disappearance of papilloma was observed in 6 patients (33%), reduced volume of papilloma was observed in 6 patients (33%), and no clinical response was observed in the remaining 6 patients (33%). In the long-term follow-up study (mean = 4.8 years), they reported that 11 of 33 patients (33%) experienced remission of papilloma requiring no further surgery and 10 patients (30%) required less frequent surgery after I3C administration while no clinical response to I3C was observed in 12 patients (36%).² No adverse effect have been reported so far concerning I3C administration to treat RRP.

Cidofovir is an antiviral drug initially approved by the FDA for intravenous treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome and has recently been adapted for use in patients with RRP. The efficacy of adjuvant intralesional injection of cidofovir to

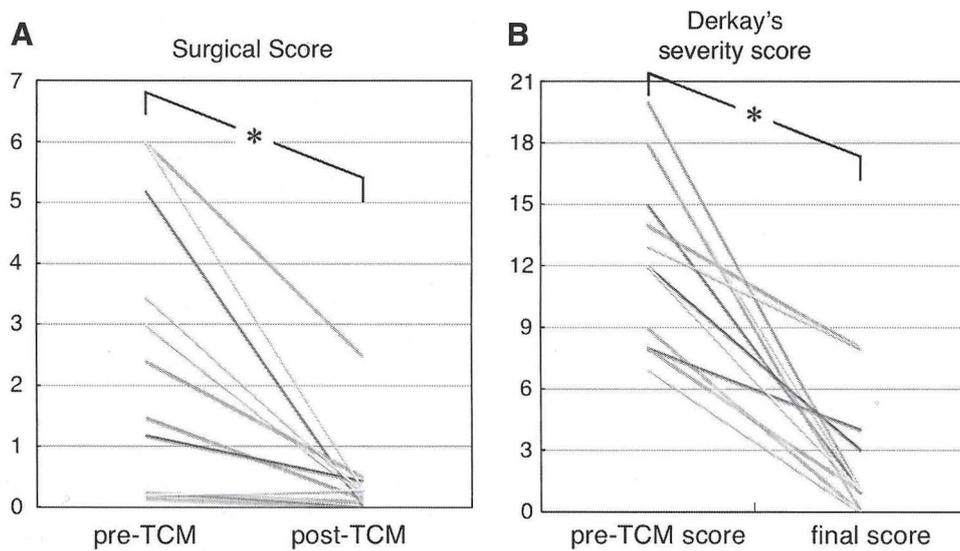


FIG. 1. Clinical effect of Traditional Chinese Medicine (TCM) on recurrent respiratory papillomatosis. Impact of TCM on the surgical score (A) and Derkay's score (B) is shown. Significant improvement in both surgical score and Derkay's score was observed after TCM administration. * $p < 0.03$ (Wilcoxon signed-ranks test).

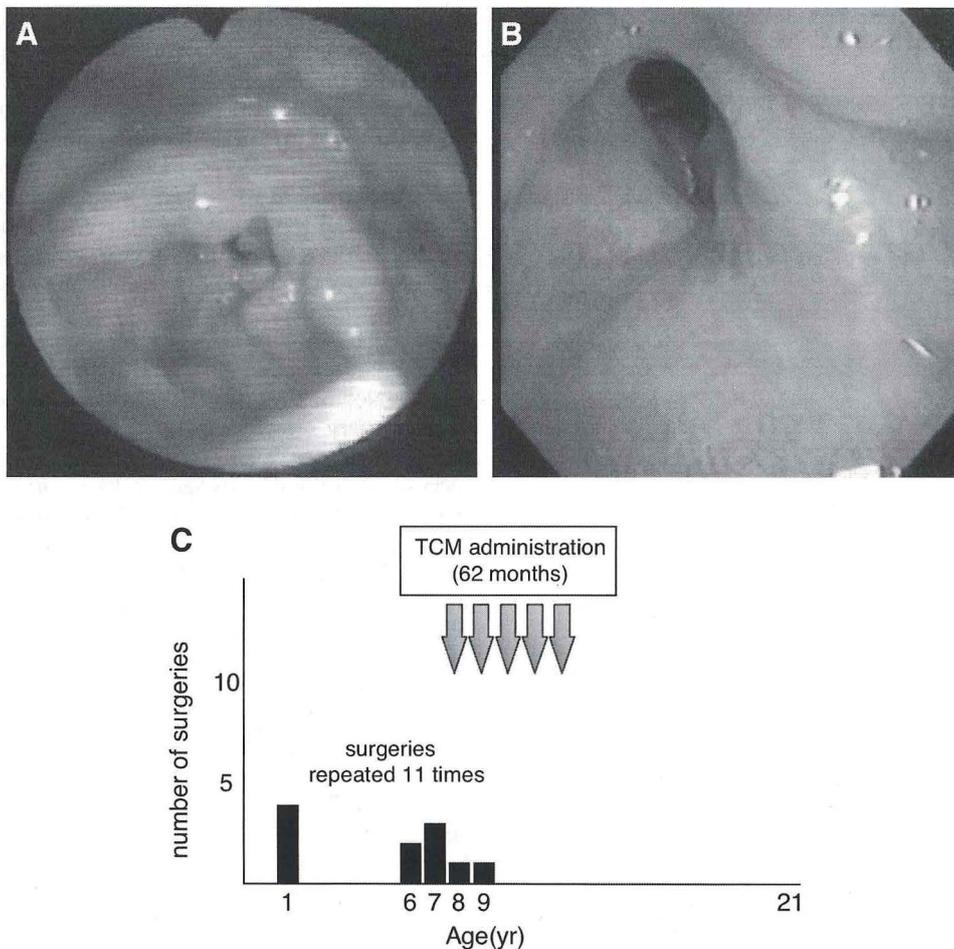


FIG. 2. Clinical course in patient 1. Laryngeal images before Traditional Chinese Medicine (TCM) administration (A, November 1993) and on the latest visit (B, September 2007) are shown. (C) The time course of this patient, showing number of surgeries and period of TCM administration.

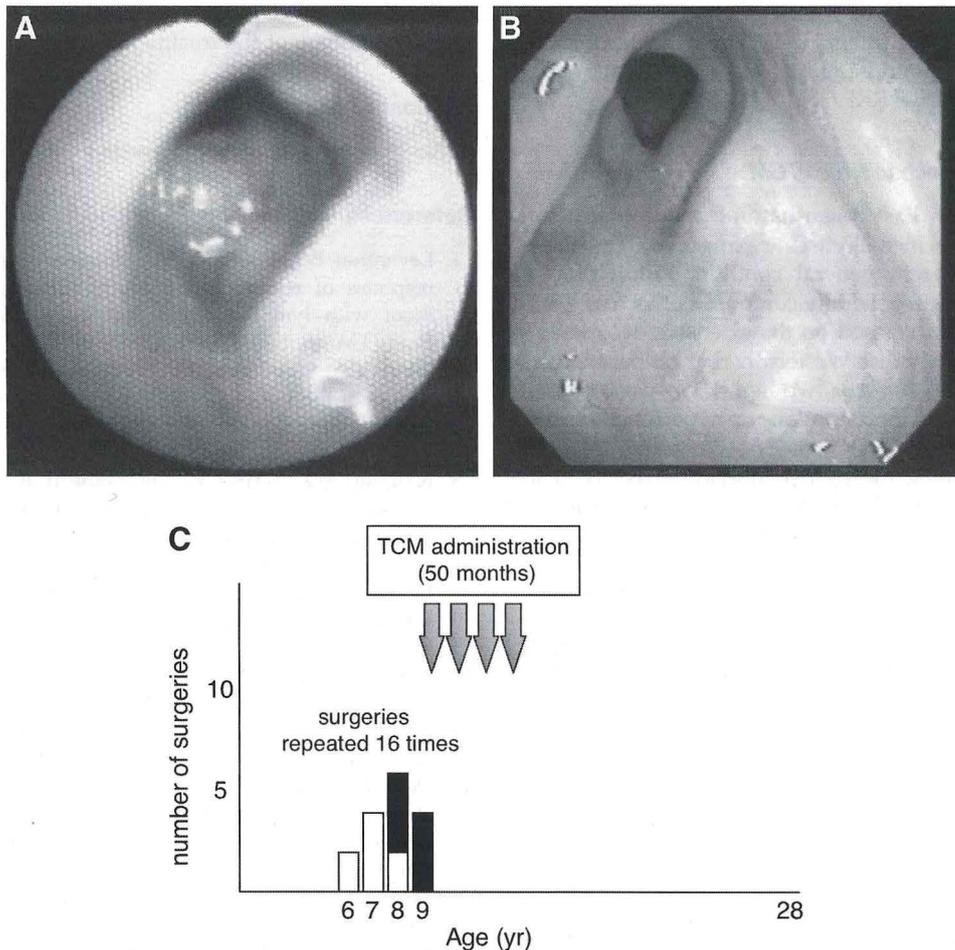


FIG. 3. Clinical course in patient 2. Laryngeal images on the first visit (A, February 1989) and latest visit (B, November 2007) are shown. (C) The time course of this patient, showing number of surgeries (open bars: eight total in previous institutions; filled bars: eight total in our institution) and period of Traditional Chinese Medicine (TCM) administration.

treat RRP has been reported recently in several facilities.^{3,13} It has been reported that cidofovir administration was significantly effective against papilloma in 60% of the patients, based on the 13 articles identified between 1998 and 2006¹³; a partial response to cidofovir was observed in 29% of the patients. However, a recent randomized, blinded, placebo-controlled trial showed no significant difference in remission between the cidofovir group and the placebo group.¹⁴ Therefore, the clinical effect of cidofovir in the treatment of RRP still remains controversial. Although repeated intralesional injections of cidofovir under general anesthesia were utilized in previous studies, a standardized protocol has not been achieved yet. Furthermore, attention to the potential carcinogenicity of cidofovir may be necessary for clinical use.¹⁵

In this study, statistically significant improvement in the surgical score and Derkay's severity score was observed after TCM administration through the long-term follow-up period in the patients with aggressive RRP. Although multiple surgeries were required in these patients before TCM administration (mean = 2.46 times/year; range = 0.15–6.00 times/year), much fewer surgeries were necessary after TCM administration (mean = 0.39 times/year; range = 0–2.48 times/year; $p = 0.0029$). Furthermore, the mean Derkay's severity

score was 12.8 (range = 7–20) before TCM administration, following which the mean score decreased to 2.3 (range = 0–8; $p = 0.022$). In patient 6, surgeries were repeated six times even after TCM administration; however, his final Derkay's severity score was 0 and a satisfactory result was obtained. Although improvement in Derkay's severity score was observed in all the patients, the final Derkay's severity score of patients 9 and 11 was 8, which is relatively high compared with the other patients (mean = 1.2; range = 0–4), indicating that TCM was not clearly effective to eliminate RRP in these patients. These 2 patients still had severe RRP, although only one additional surgery was required post-TCM administration on patient 11. Despite the statistically significant improvement in surgical score and Derkay's score after TCM administration, we consider this therapy effective in 10 of the 12 cases (83%) because of the relatively high final Derkay's score of patients 9 and 11. Although the possibility of natural remission of RRP cannot be completely ruled out, our results demonstrate that TCM may be one of the useful treatment options against aggressive RRP. Although the possibility of natural remission of RRP cannot be completely ruled out especially in juvenile-onset RRP cases, TCM was dramatically effective even in adult-onset RRP cases in our study to result

in very low post-TCM surgical score (range, 0.3–0.5) and Derkay's severity score (range, 0–1). Thus, our results demonstrate that TCM could be one of the useful treatment options against aggressive RRP.

Pharmacological mechanism of TCM

TCM is based on East Asian natural philosophical principles according to which illnesses are considered imbalances in the body's inherent general condition. Individualized TCM formulations are generally composed of as many as 10 or more herbs and are based on the extensive experience of expert physicians, whereas Western herbal preparations are typically composed of one or two herbs. *Yin-yang* representing the patient's constitution, hypo- or hyperfunction of the body, and the Heat–Cold character of disease are important factors in determining the proper individualized TCM formulation in Asian natural philosophical principles. The main ingredients of TCM for laryngeal papillomatosis are *Astragali radix*, *Platycodi radix*, *Angelicae radix*, *Ostreae testa*, *Coicis semen*, *Carthami flos*, *Ligustrum lucidum*, licorice, *Fritillariae bulbus*, and *Persicae semen*.

Astragali radix is a common TCM plant widely used as a tonic to enhance the body's natural defense mechanism¹⁶ and has been shown to be capable of restoring impaired T-cell function in patients with cancer.¹⁷ *Platycodi radix* shows marked antiulcer, anti-inflammatory, and expectorant action, and also provides moderate analgesic, antipyretic, antitussive, and anticholinergic activity. *Angelicae radix* reportedly improves mitogenic activity of murine B lymphocytes and human splenic lymphocytes. Furthermore, this ingredient is known to upregulate the activity of polyclonal B lymphocytes and adjuvant activity of immunoglobulin M antibody production against sheep erythrocytes.¹⁸ It has also been reported that this ingredient upregulates the antitumor immunity against Ehrlich ascites cells.¹⁸ *Ostreae testa*, *Coicis semen*, and *Carthami flos* are expected to upregulate antitumor immunity. *Ligustrum lucidum* is a nourishing herb used in many cases because of its antitumor, antidiabetic, and hepatoprotective properties. Licorice is an herbal drug used as a demulcent and elixir in TCM.¹⁹ One of the main active components of licorice extract is glycyrrhizin, and antiviral effects of glycyrrhizin have been reported in 1979.²⁰ Furthermore, the interferon-inducing ability of glycyrrhizin was reported in a murine model.¹⁹ Licorice extract is also useful as an antitussive. *Fritillariae bulbus* has been utilized for lung diseases as an expectorant or antitussive. *Persicae semen* has been investigated as antimutagenic substance.

Individual formulations of these herbs were utilized in this study. A complex of multiple herbs could offer a much wider array of active ingredients than single-herb modalities and possibly induce a synergistic effect against papillomas. Although a tumoricidal effect through enhancement of antitumor immunity is expected, the concept of treatment using TCM is based on empiricism and the detailed pharmacological mechanism of TCM remains to be further studied.

Conclusions

TCM can be a safe and clinically effective treatment as an adjuvant therapy to treat RRP. Further studies are needed to

clarify the detailed pharmacological mechanism and determine the essence of the treatment.

Disclosure Statement

No competing financial interests exist.

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