International Journal of Otorhinolaryngology and Head and Neck Surgery
Sharma N et al. Int J Otorhinolaryngol Head Neck Surg. 2023 Aug;9(8):685-689
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937

DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20232231

Case Report

Thuja as an adjuvant medical management of juvenile recurrent laryngeal papillomatosis: our experience

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Received: 13 June 2023
Revised: 14 July 2023
Accepted: 19 July 2023

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ABSTRACT

A subgroup of recurrent respiratory papillomatosis, which is a larger clinical entity, is laryngeal papillomatosis. The vocal folds produce recurrent papillomata, which is a hallmark of the condition. The two most prevalent strains of human papillomavirus have been linked to the development of laryngeal papillomas, types 6 and 11. Distinctive presence of warty lesion on endoscopy is basis for clinical diagnosis. Surgery is the foremost treatment possibility, combined with adjuvant therapy such antiviral medications and immunomodulators. Thuja occidentalis, a tree whose leaves and leaf oil have anti-oxidant,antiviral,anti tumoral,anti inflammatory, antibacterial and antifungal properties. It has been extensively utilized to treat warts and condylomatous skin lesions. In this article, we go through the results of using Thuja as an adjuvant therapy for laryngeal papillomatosis in a 16-year-old female.

Keywords: Laryngeal papillomatosis, Thuja, Human papilloma virus

INTRODUCTION

Laryngeal papillomatosis, also known as recurrent respiratory papillomatosis or glottal papillomatosis, is a rare medical condition in which benign tumors (papilloma) form along the aerodigestive tract. There are two variants based on the age of onset: juvenile and adult laryngeal papillomatosis.The tumors are caused by HPV infection of the throat. HPV is a small deoxyribonucleic acid (DNA) nonenveloped capsid virus of the Papovaviridae family, which has a predilection of infecting epithelial cell.[1]The tumors may lead to narrowing of the airway, which may cause vocal changes or airway obstruction.Two subtypes of HPV are associated with recurrent respiratory papillomatosis-HPV 6 and 11 which are also responsible for causing congenital condyloma, anogenital warts. HPV infects the keratinocytes within the basal layer of larynx and activates EFGR pathway and inactivates tumour suppressor proteins (p53 and pRB) which leads to cellular proliferation and diffective epithelial differentiation, thus interfering with cell growth control and progressing to malignant transformation. The mode of transmission in juvenile-onset has been closely associated with vertical transmission during childbirth. However, the exact mode of transmission is still unknown. Risk factors are prima-gravid women, firstborn child, and recently acquired genital warts. A mother's first birth usually has a longer stage of labor, leading to a longer time of exposure to the neonate. In addition, recently acquired genital warts have a higher virulence. In adult-onset LP, the mode of transmission is speculated to be oral sex. Yet, research has demonstrated that other factors have to be implemented in the infection since the presence of HPV alone on the mucosa does not necessarily cause the condition.[2]

Laryngeal papillomatosis is initially diagnosed through laryngoscopy examination upon observation of growth on

the larynx and can be confirmed through a biopsy. Treatment for laryngeal papillomatosis aims to remove the papillomas and limit their recurrence. Due to the recurrent nature of the virus, repeated treatments usually are needed. The ideal therapies aim to maintain airway patency, improve voice quality, and avoid the complications.

Surgery, with classic cold knife microsurgery, laser (CO_2, argon, and Nd-YAG), microdebrider and coblator is the preferred mode of treatment but does not prevent lesions from recurring.[3] Recent studies suggest beneficial role in the prevention of laryngeal papillomatosis in peadiatric age population through HPV vaccine-bivalent/ quarivalent to females of reproductive age group.[4,5] The evolution of laryngeal papillomatosis is highly variable. Though total recovery may be observed, it is often persistent despite treatment.

CASE REPORT

A sixteen year old female presented to outpatient department with complaints of hoarse, strained, breathy voice since two and half years with accompanying breathing difficulty especially during moderate to heavy work and exercise since nine month associated with chronic dry cough since two months. Wheezing episodes started two weeks earlier, with gradually worsening hoarseness, mild rhinorrhea and cough. Her breathing was noisy. There was no report of fever or choking episodes. Child was a term delieverd by vaginal delivery, first born child. No history of ICU admission or airway intervention. No relevant history in family or siblings were found. No history of warts in other parts of body. Examinaton of the nose, oral cavity, oropharynx and the neck revealed no abnormality.

Investigation

Laryngoscopic evaluation

Fibre optic laryngoscopic examination shows pedunculated warty growth on laryngeal surface of epiglottis,B/L aryepiglottic folds, medial surface of both false vocal cords and free border of B/L true vocal cords occupying whole supraglottic region arising from anterior part of larynx and proximal subglottis region. Pink to deep red in colour, warty and papillary surface varying in size.

Routine blood investigations were within normal limits. Chest X-ray suggestive of B/L normal lung fields. Challenges like getting pre anesthetic fitness in juvenile patient, finding of malignant focus, complete removal of papilloma, difficult intubation due to narrow laryngeal passage, risk of intra-operative asphyxia were kept in mind. Pre operative steroids inj. dexamethasone two cc IV bd with inj. hydrocortisone 100 mg IV bd given for two days to relieve airway inflammation (Figure 1).

Figure 1: Laryngoscopic view of pedunculated papillomatous growth involving supraglottis and glottis.

Intra operative

Excision of papilloma under general anesthesia using microscopic laryngeal guidance was planned for the patient.Emergency tracheostomy was kept on stand by in view of narrow laryngeal passage due to risk of intra-operative asphyxia and in case of difficult intubation condition. General anaesthesia administered through inhalational agents after prior tracheostomy stoma creation in midline at level of 2-3 tracheal ring region and tracheostomy tube insertion with standard 7 mm cuffed tracheostomy tube. General anaesthesia maintained through i.v. route. Microscopic setup done. On direct laryngoscopy multiple greyish-brown to greyish-white soft papillimatous growth were present over supraglottic, glottic and subglottic region involving B/L aryepiglottic folds extending upto true vocal cords and anterior and posterior comissures. Hypopharynx and distal subglottis-trachea region were spared of disease. Laryngeal inlet was partially visible. Papillomatous growth were excised out as much as possible using laryngeal microdebrider and laryngeal coblator under microscopic guidance. Post-op recovery uneventful. strict PPE equipments were used by personnal during debridement and ablation of warty laryngeal growth to prevent in contact of mucous membrane of toxic inhalational fumes containing heavy HPV viral load during operative procedure.[6]

Figure 2: Intraop laryngoscopic view of papilloma over B/L true and false vocal cords.

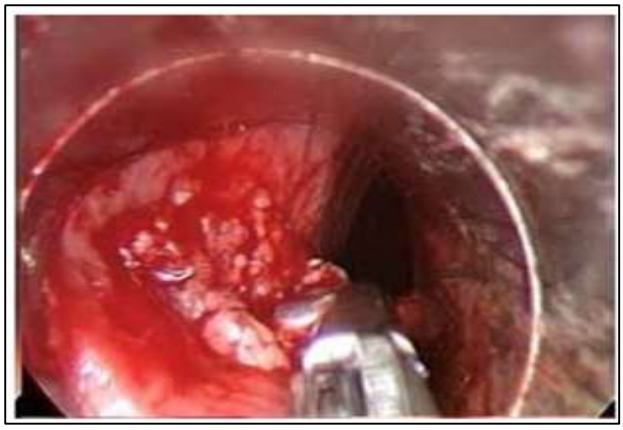

Figure 3: Intraoperative laryngoscopic excision of papilloma.

Post operative

Outcome and follow-up

Excised papillomatous tissue was sent for histopathological examination which was suggestive of marked proliferation of stratified squamous epithelium over bilateral vocal cords with underlying tissue shows chronic infllamatory infiltrate.

Figure 4: Patient in immediate post operative period showing tracheostomy tube *in-situ*. Tracheostomy tube was sucessfully decannulated after 2 weeks post op.

Patient was given oral steroid in tapering doses and oral proton pump inhibitors post operatively for 6 months and was instructed for regular follow up.Decannulation of tracheostomy tube was achieved 2 weeks post operatively. Homeopathic medicine Tab. THUJA (Thuja occidentalis) 1 M (1000 potency) monthly dose taken by orally was prescribed postoperatively for 3 consecutive months followed by monthly dose of 10 M (10000 potency) for next 3 months.[7] Patient was followed up every week for 24 weeks for recurrence of papilloma by fiber-optic laryngoscopy examination during each post-op visit. On each follow up visit patient was undergone fibre-optic laryngoscopic examination under Local Anaesthesia for devlopment of recurrent lesions in laryngeal tract and close monitoring was done for recurrance of symptoms during entire survilleance period. Patient was advised for post operative HPV vaccination-nonavalent gardasil 9 with doses scheduled for 0, 1 and 6 months. Patient was encouraged for intake of sprouts,brocolli, cabbage in daily diet for regular supplimentation of indole-3-carbinol. Post operatively patient restored her voice with speech therapy. No evidence of recurrence of disease noted in post operative period and after completion of medical management.

Figure 5: Postoperative laryngoscopic view showing recovery from papillomatous disease after Thuja administration during subsequent follow ups 6th, 12th and 24th week.

Table 1: Difference between juvenilelaryngeal papilloma and adult laryngeal papilloma.

Juvenile laryngeal papilloma	Adult laryngeal papilloma
Children and adolescents	Adults
Usually multiple	Male >female
Arising on true vocal cords	Usually solitary
Spreads to false vocal cords, supra glottic and sub glottic area	Less tendency to spread
Recurs more frequently after removal	Reccurs less frequently
Infection transmitted through infected birth canal	Infection transmitted through adult exposure

Goals of conservative treatment of laryngeal papillomatosis

Immunomodulation, disruption of HPV replication, control of inflammation and prevention of angiogenesis

Neo-adjuvant therapies for laryngeal papillomatosis

Bevacizumab, celecoxib, proton pump inhibitors, cidofovir, other anti-virals-ribavirin, acyclovir, cis-retinoic acid, interferon-pegylated-IFN-alpha -2a, HPV vaccine-nonavalent gardasil 9, mumps vaccine, Hspe 7, PD 1 inhibitor- pembrolizumab, cimetidine, photodynamic therapy and indole-3-carbinol-sprouts, brocolli, cabbage.

DISCUSSION

Juvenile laryngeal papillomatosis also known as juvenile respiratory papillomatosis or recurrent respiratory papillomatosis is a common accquired respiratory disorder of viral origin causing respiratory distress and stridor in young adolescents and school going age group children particulary prevalant in low socio-economic groups. It is usually characterized by wart-like exophytic lesions that have a predilection for the larynx. The estimated incidence is 4.3 cases per million in children and 1.8 cases per million in adults annually. The first line of treatment is surgery to remove papillomas. Typically performed using a laryngeal endoscopy, surgery can protect intact tissues and the individual's voice, as well as ensure that the airway remains unobstructed by the disease. However, surgery does not prevent recurrences, and can lead to a number of serious complications.

The tracheostomies use breathing tubes to reroute air around the affected area, thereby restoring the person's breathing function. CO_2, Argon, and Nd-YAG laser surgery in particular, has been more frequently for the removal of papillomas; and has been associated with a higher occurrence of respiratory tract burns, stenosis, severe laryngeal scarring, and tracheoesophagyeal fistulae. HPV DNA has been found in laser fumes and current CDC recommendation is wearing N-95,N-100 masks, appropriately ventilated room using standard precautions, local exhaust ventilation (e.g. smoke evacuator).

Microdebriders are gradually replacing laser technology as the treatment of choice for laryngeal papillomatosis, due to their ability to selectively suction papillomas while relatively sparing unaffected tissue; is reportedly less expensive, less time-consuming, and more likely to give the person a better voice quality than the traditional laser surgery approaches. Lasers and microdebriders does not prevent lesions from recurring. Laryngeal coblators are used as powered instruments to achieve hemostasis during operative period and removal of papilloma near vocal fold comissures. However coblator have to be used cautiously as it may causes charring of tissues and may generate toxic inhalational fumes containing HPV particles which may cause production of papilloma on raw mucosal surfaces after contact. Therefore strict PPE protocal has to be applied in operative room to prevent contact with toxic inhalational fumes.

Nonsurgical neo-adjuvant treatment given for prevention of recurrence are supplemental to surgery; include interferon IFα, antiviral drugs (cidofovir, ribavirin and acyclovir), and photodynamic therapy. The monoclonal antibody against vascular endothelial growth factor (VEGF): Bevacizumab has shown promising result as an neo-adjuvant therapy in the management of recurrent respiratory papillomatosis.

Role of Thuja occidentalis L. (Arbor vitae or white ceda) in laryngeal papilloma: Thuja's antiviral action and immunopharmacological potential, such as stimulatory and co-stimulatory effects on cytokine (TNFα, IL-1, IL-6) and antibody production and activation of macrophages and other immunocompetent cells. Its acts as immunomodulator agent and is active against warts and HPV infection, thus reducing recurrence. T. koraiensis oil is a known remedy with topical application in the treatment of the HPV, as well as for genital or common warts treatment, as an antioxidant, and for antibacterial properties. Thuja occidentalis L. presents a varied range of pharmacological activities, such as antioxidant activity anti-inflammatory antitumoral antiviral, immunostimulent.[8-19]

Role of HPV vaccine in prevention: currently available prophylactic recombinant HPV vaccines (L1 capsid antigens) quadrivalent HPV (6, 11, 16, 18) vaccine (Gardasil) and bivalent HPV (16, 18) vaccine (Cervarix) is highly effective in preventing laryngeal papillomatosis and also used in prevention of cervical cancer. The combined efficacy against persistent infection with HPV types 6, 11, 16, and 18 was 90% thirty months after vaccination, it has been used as adjuvant therapy to downregulate the disease in patients with Laryngeal papillomatosis.[20]

Advantage of Thuja occidentalis

Cost effective, traditionally accepted, provides non-specific immunity, builds up natural resistance and antioxidant activity

CONCLUSION

Mainstay of treatment of laryngeal papillomatosis are surgical excision with better aggressive surgical instrument modality like microdebriders, lasers, coblators followed with neo-adjuvant medical management to reduce recurrence.Due to higher prevalance of HPV papillomatosis in lower socio-economic population lack of availability of neo-adjuvant medical management produces a significant burden of disease on community. Tab. THUJA produce immunomodulation, viral

elimination and recurrence prevention without causing significant systemic side effects. Thuja occidentalis was found to effectively reduce the incidence of recurrence of papilloma post-operatively with minimal adverse effects like non-significant dyspepsia or nausea which are effectively overcome with the uasge of proton-pump inhibitors in daily doses. In this present paper we recommend that 1 M (1000 Potency) monthly dose for 3 months followed by 10 M (10000 potency) for next 3 months post-operatively in resolution of residual papilloma and prevention of recurrance. Finally, patient education and counseling regarding the recurrent nature of disease is paramount as patient is required to be kept in regular follow-up to prevent disease exacerbation and airway obstruction.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Sharma N, Mishra A. Thuja as an adjuvant medical management of juvenile recurrent laryngeal papillomatosis: our experience. Int J Otorhinolaryngol Head Neck Surg 2023;9:xxx-685-9.