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CLINICAL REPORT

Management of Adult Recurrent Respiratory Papillomatosis with Oral Acyclovir Following Micro Laryngeal Surgery: A Case Series

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Abstract To demonstrate the role of oral acyclovir in monthly regimes after microdebrider assisted excision in 3 patients with adult recurrent respiratory papillomatosis (ARRP). Three patients with ARRP who presented to a tertiary referral hospital in stridor were initially treated with a tracheostomy in order to secure airway. On further evaluation by videolaryngoscopy extensive bilateral laryngeal papillomatosis was noted with history of similar conditions in the past for which they were repeatedly operated. They were admitted and underwent Microlaryngeal surgery and laryngeal microdebrider assisted surgery under general anesthesia. Post operatively a course of oral acyclovir at 800 mg/5 times/day for 5 days was administered. On repeat assessment with videolaryngoscopy at monthly intervals a complete remission of the disease was noted with no residual disease at the end of 1 year in 2 cases. One case had a recurrence. Renal parameters were monitored periodically. It may be concluded that the action of anti viral drugs at regular intervals in addition to a short course of oral steroids lead to rapid recovery and prevented latent virus activation within the laryngo tracheal system hence maintaining long term improvement. This can avoid multiple laryngeal surgeries, repeated respiratory emergencies and risk for malignant transformation in the future thereby reducing morbidity and effect on quality of life.

Keywords Adult recurrent respiratory papillomatosis (ARRP) · Papillomatosis · Acyclovir · Human papilloma virus (HPV)

Introduction

Recurrent respiratory papillomatosis (also known as laryngotracheal papillomatosis) is a rare disease characterized by multiple papillomas seen in upper airways, usually on the vocal cords [1, 2]. They have been divided into juvenile and adult types, because of their distinct clinical courses and different incidence of malignant transformation, according to the age at onset and the presence or absence of laryngeal involvement [3]. Multiple papillomas are associated with Human papilloma virus (HPV) infection and it has been reported that low-risk (i.e., low malignant potential) HPV types 6 and 11 cause about 90% of cases of recurrent respiratory papillomatosis [1, 4]. The primary therapeutic method is endoscopic surgery, and approximately one-tenth of patients are cured after the first surgical intervention. Spontaneous remissions are also seen, but in the majority of patients the disease is recurrent and thereby demands other treatment methods [5]. Role of Interferon (IFN)-Alpha has been well documented in the treatment for laryngeal papillomatosis. [6] Anti-viral drugs such as cidofovir, acyclovir and ribavirin have also been tried, but their role in controlling this disease is still doubtful [7]. We present a series of 3 cases diagnosed with Adult Recurrent Respiratory Papillomatosis (ARRP) and discuss their post operative management with oral acyclovir and steroids after a review of relevant literature.

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Cases

Case 1

A 65 year old lady, a known case of ARRP, presented to the Emergency Room (ER) of a tertiary referral hospital with a history of stridor since 48 h which was preceded by hoarseness of voice since 6 months. She had a history of multiple Micro Laryngeal Surgeries (MLS) performed on her in the past for similar complaints, the last MLS done 1 year ago. She was a known Diabetic and Hypertensive. An Emergency Tracheotomy was carried out in order to secure airway following which a 90° Video Laryngoscopy (VLS) was performed. It revealed extensive laryngeal papillomatosis involving bilateral vocal cords (Fig. 1a). She underwent Microlaryngeal surgery with excision of the papillomatous lesion using a laryngeal microdebrider. Tissue was sent for a histopathological evaluation which was later reported to be consistent with ARRP. A repeat 90° VLS in the 1st post operative day confirmed no residual papillomatous tissue (Fig. 1b). She was treated with oral Acyclovir 800 mg 5 times/day for 5 days along with oral prednisolone 1 mg/kg body weight for 3 days. Repeat 90° VLS at 3 weeks showed formation of minimal web like tissue at the anterior commisure along with edema of the vocal cords (Fig. 1c) A course of Oral acyclovir (mentioned earlier) was administered monthly for 1 year. Renal parameters were monitored. The laryngeal web and edema subsided within a month with no recurrence even after 1 year (Fig. 1d) She was decanulated successfully from her tracheostomy with no complications at the stomal site. She is currently on follow up and maintaining improvement.

Case 2

A 25 year old male presented to the outpatient department of Otolaryngology and head and neck surgery at a tertiary referral hospital in Bangalore with a history of voice fatigue, hoarseness of voice and worsening breathing difficulty since 1 year. A 90° VLS revealed papillomatous lesion over bilateral true vocal cords (Fig. 2a) He underwent a direct laryngoscopy and biopsy under general anesthesia followed by MLS and stripping of the left vocal cord (Fig. 2b, c). The papillomatous lesion on the left vocal cord was not addressed as the plan was to treat it in a second sitting a month later in order to avoid chances of adhesion formation between raw surfaces of the vocal cords. The Histopathology was consistent with Laryngeal papillomatosis. A post operative re-assessment showed no residual papillomatous lesion in the left vocal cord (Fig. 2d). A month later a 90° VLS prior to second procedure showed extensive recurrence of the disease for which he was re-operated. He was treated

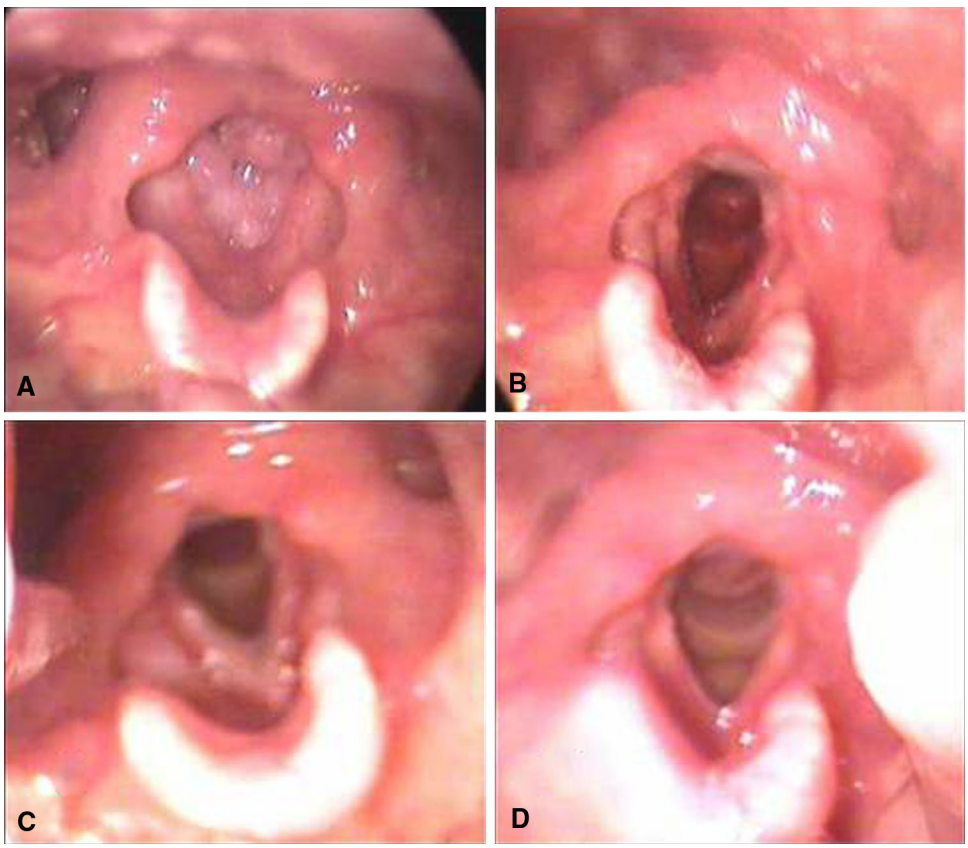

Fig. 1 Case 1 **a** Extensive laryngeal papillomatosis involving bilateral vocal cords. **b** A repeat 90° VLS in the 1st post operative day confirming no residual papillomatous tissue. **c** Repeat 90° VLS at 3 weeks showed formation of minimal web like tissue at the anterior commissure along with edema of the vocal cords. **d** The laryngeal web and edema subsided within a month with no recurrence even after 1 year

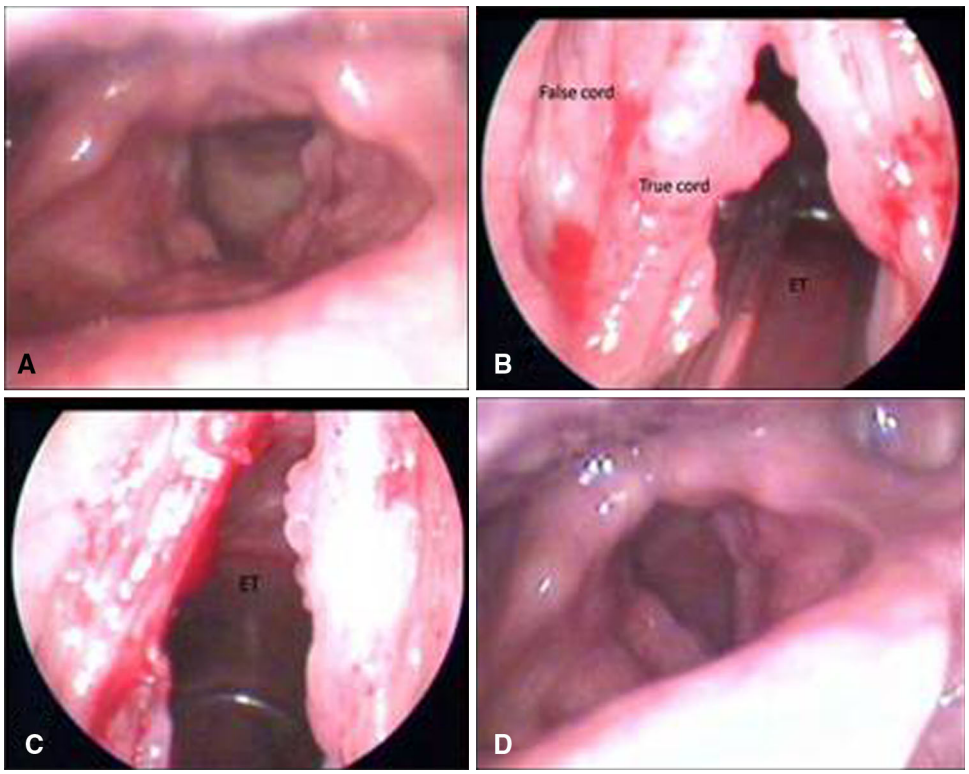

Fig. 2 Case 2 **a** 90° VLS revealed papillomatous lesion over bilateral true vocal cords. **b**, **c** MLS and stripping of the left vocal cord. **d** A post operative re-assessment showed no residual papillomatous lesion in the left vocal cord

with oral Acyclovir 800 mg 5 times/day for 5 days along with oral prednisolone 1 mg/kg body weight for 3 days followed by monthly administration of a course of oral acyclovir for 1 year. However patient did not respond successfully and developed recurrence.

Case 3

A 27 year old lady, known case of ARRP on a metallic tracheotomy tube presented to the outpatient department of Otolaryngology at a tertiary referral hospital in Bangalore with a history of hoarseness of voice since 7 years. She was operated (MLS) for similar complaints twice within the last 7 years during which 3 years ago she required a tracheotomy for compromised airway. A 90° VLS revealed extensive bilateral laryngeal papillomatosis (Fig. 3a) She underwent Micro laryngeal surgery and laryngeal microdebridement of the lesion under general anesthesia. Excised tissue was sent for a histopathological evaluation which was later reported to be consistent with laryngeal papillomatosis. A repeat 90° VLS revealed no residual laryngeal papillomatosis however a small mucosal web was

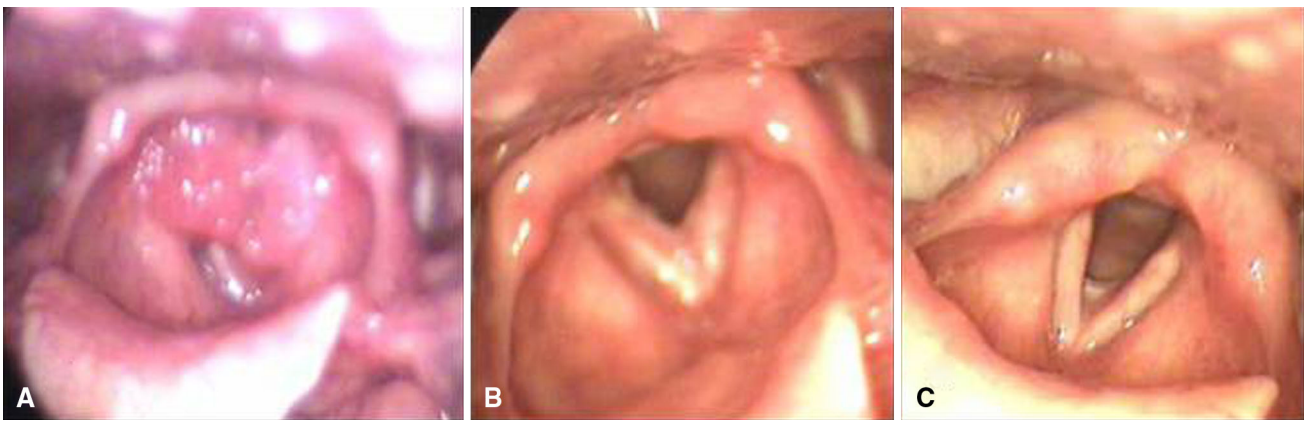

Fig. 3 Case 3 **a** 90° VLS revealed extensive bilateral laryngeal papillomatosis. **b** A repeat 90° VLS revealed no residual laryngeal papillomatosis however a small mucosal web was noted at the anterior commisure. **c** A repeat 90° VLS showed no recurrence of disease after 12 months of follow up

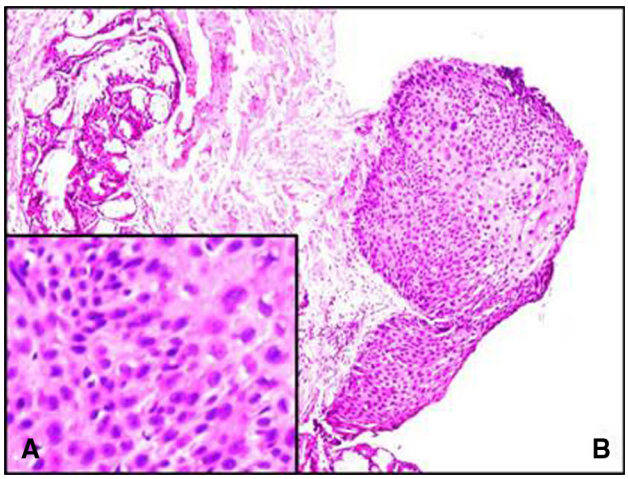

Fig. 4 **a** *Inset* Hematoxylin and eosin stain: original magnification ×400 showing Koilocytes (vacuolated cells with clear cytoplasmic inclusions that signal presence of viral infection) are observed. **b** Hematoxylin and eosin stain: original magnification ×200 showing papillary fronds of multilayered benign squamous epithelium that contain fibrovascular cores. No surface keratinization is observed

noted at the anterior commissure (Fig. 3b) She was treated with oral Acyclovir 800 mg 5 times/day for 5 days along with oral prednisolone 1 mg/kg body weight for 3 days followed by monthly administration of a course of oral acyclovir for 1 year. A repeat 90° VLS showed no recurrence of disease after 12 months of follow up (Fig. 3c).

None of the patients developed renal complications. Monitoring of renal parameters was achieved by monthly testing of serum creatinine and blood urea. All biopsies were subjected to histopathological evaluation with findings suggestive of Laryngeal papilomatosis demonstrating fingerlike projection of nonkeratinized stratified squamous epithelium and vascularized connective tissue stroma (Fig. 4a, b).

Discussion

Tracheobronchial papillomas have three distinct clinical presentations: multiple papillomas, inflammatory polyps, or solitary papillomas [8]. Multiple papillomas originate primarily in the larynx, with a tracheal incidence of about 2% [9] and lung involvement of <1% [2]. They have been divided into juvenile and adult types, because they present distinct clinical courses and different incidence of malignant transformation, according to the age at onset and the presence or absence of laryngeal involvement [3]. The symptoms of this uncommon disease may vary from hoarseness to severe obstruction of the airway.

Papillomatosis is associated with HPV, a deoxyribonucleic acid papovavirus with a specific affinity for squamous epithelial cells. The virus has several antigenic subtypes. It has been reported that low-risk (i.e., low malignant potential) HPV types 6 and 11 cause about 90% of cases of recurrent respiratory papillomatosis [1, 4]. Their existence as latent infections in morphologically normal tissue of the airway and are believed to be the source of recurrent disease [10, 11]. The association between the virus and the characteristic lesions of this disease was proven with electron microscopic studies and DNA analysis. Microbiologic studies revealed antigenic similarity to genital papillomavirus, suggesting that the infection is transmitted during labor (vertical transmission) [17]. HPV type 11 is found to cause more severe disease. Longstanding disease may cause dysplasia, leading to malignant transformation to squamous cell cancer. Rarely the subtypes 16 and 18 are identified.

The primary therapeutic method is endoscopic surgery, and approximately one-tenth of patients are cured after the first surgical intervention. Spontaneous remissions are also seen, but in the majority of patients the disease is recurrent and thereby demands other treatment methods [5]. To achieve cure, therapy must either eliminate latent infection or prevent its activation. The HPV is a commensal organism in humans, with widespread latent infection usually suppressed by the host immune system [12]. Results of recent studies [13, 14] suggest that the immune response to HPV proteins is altered in patients with RRP. The use of Photo Dynamic Therapy (PDT) with Meso-Tetra (Hydroxyphenyl) Chlorin (m-THPC) showed significant efficacy in the treatment of RRP, probably reflecting improvement in the immune response by indirectly immunizing the patient to HPV proteins. However, the effects were not permanent, possibly owing to a relatively short-term immune improvement [15].

Role of IFN-Alpha has been well documented in the treatment for laryngeal papillomatosis [6]. Anti-viral drugs such as cidofovir, acyclovir and ribavirin have also been tried, but their role in controlling this disease is still doubtful [7].A few side-effects of cidofovir have been reported there is some concern about the potential carcinogenicity of cidofovir. There have also been some reports of dysplasia in humans after the use of intralesional cidofovir [16]. However, spontaneous malignant degeneration of RRP is possible. The reported incidence of this malignant degeneration is 2–5% [16].

In our case series we would like to highlight the presence of Recurrent Respiratory papillomatosis in an adult age group along with the severity of clinical symptoms at presentation, which are uncommon in recurrent respiratory papilomatosis. The remarkable improvement in the post operative period and maintenance of improvement up to an year with monthly courses of oral acyclovir remains the hallmark of this report. This indicates the effectiveness of multiple administration of anti viral agents in order to prevent recurrence of residual disease. The fact that there

was recurrence even after treatment with acyclovir in case 2 only supports residual viral activity when disease is not addressed completely. A two staged procedure may be at a higher risk of recurrence as part of the disease is left behind on the opposite vocal cord. Such regimes with oral acyclovir at monthly intervals have not been documented in literature in the past and further studies with larger number of cases are required to establish the use of this regimen in treatment of this disease in the future.

Conclusion

It may be concluded that the action of anti viral drugs at regular intervals in addition to a short course of oral steroids may lead to rapid recovery and prevented latent virus activation within the laryngo tracheal system hence maintaining long term improvement. This can avoid multiple laryngeal surgeries, repeated respiratory emergencies and risk for malignant transformation in the future thereby reducing morbidity and effect on quality of life. However larger number of cases in the series would be necessary to support this conclusion strongly.

Summary

- Three adult individuals diagnosed to have recurrent respiratory papillomatosis were admitted at a tertiary referral hospital.
- All patients underwent MLS and laryngeal microdebrider assisted surgery under general anesthesia.
- For one patient lesions on either vocal cords were addressed individually after an interval of 3 months. This patient later had a recurrence.
- All patients were administered oral acyclovir at 800 mg, 5 times a day for 5 days post operatively and continued monthly for 1 year.
- No recurrence of residual disease was noted at the end of 1 year in two patients.
- Oral acyclovir as a single regime might not be effective in treating the disease however its monthly oral administration can prevent recurrence of disease. None of the patients developed renal complications.

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