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Case report

Intralesional cidofovir as adjuvant for the successful management of aggressive respiratory papillomatosis in an infant

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ABSTRACT

Recurrent respiratory papillomatosis (RRP) in young children is frequently characterized by a recalcitrant course and need for multiple surgeries. Periodic surgical debulking and ablation is the mainstay of therapy as a cure for RRP rarely occurs. Benefits of adjuvant treatment with local injection of cidofovir in aggressive cases of RRP have been reported in both children and adults. However, a consensus on initiation, dosage, or scheduling of this drug has not been established in the very young patient. Literature on successful remission in children less than 1 year of age is not available. One such case of an infant with aggressive RRP treated with local adjuvant cidofovir is described herein.

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1. Introduction

Recurrent respiratory papillomatosis (RRP) is a condition caused by human papilloma virus (HPV) that commonly affects the larynx and trachea. Characterized by clusters of benign proliferative pedunculated and sessile exophytic projections over affected sites, RRP typically presents with hoarseness, stridor or life threatening airway obstruction.

RRP can present at any age. However a bimodal distribution of onset has been described. There is a juvenile form present in children and adult onset RRP. Usually the juvenile form is more aggressive and progressive, especially when discovered at a young age. The patients who are younger than 3 years are more likely to require more than 4 surgical procedures a year, have two or more affected anatomical subsites, and develop distal airway spread [1]. Greater morbidity, mortality, and higher likelihood of tracheostomy are reported in neonates presenting with RRP [2].

Standard treatment for RRP consists of periodic endoscopic debulking or vaporization of papillomata by cold steel techniques, microdebrider or CO_2 laser techniques. Unfortunately these treatments alone rarely result in cure with patients returning frequently to the operating room for management. Further the disease course may be unpredictable with remissions and exacerbations. Adjuvant therapy may be indicated for aggressive RRP requiring more than 4 surgical procedures annually, with rapid recurrence, airway compromise and lower airway spread. Several adjuvant therapies have been described in the literature including interferon [3], indole 3-carbinol and viral vaccines like mumps vaccine [4]. Although these have shown promise, none of the supplementary adjuvant therapies have consistently resulted in long term RRP resolution.

Cidofovir is an antiviral agent that has been successfully used as supplementary adjuvant in the management of RRP. Successful use of intralesional cidofovir in children [5] and adults [6] with beneficial outcomes has been described. There are few reports in literature on management of RRP in infants with use of intralesional cidofovir [7] and inhaled cidofovir [8], however none reporting complete and sustained remission in children less than 1 year of age. One such case is presented here where the management of aggressive RRP in an infant with local adjuvant cidofovir is described.

2. Case report

A six month old Caucasian female presented to the clinic with persistent noisy breathing since shortly after birth. She developed progressive increase work of breathing, inspiratory stridor, and retractions during the week prior to presentation. A hoarse and weak cry had been present since birth. There were no other aerodigestive tract complaints except increased work of breathing

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with feeding. Her birth history included full term normal vaginal delivery. She had no other significant medical history and her immunizations were up to date. There was no history of warts in the mother.

On examination she was an alert, well developed child with biphasic stridor and chest wall retractions. Oxygen saturations were measured and in the low 90's. Office based flexible laryngoscopy was performed and revealed papillomata on both vocal folds and extending across into the ventricular folds. The true vocal folds were difficult to visualize completely due to vibrating papillomata obstructing the glottis. Progressive work of breathing and fatigue occurred during clinic necessitating an urgent microlaryngoscopy and bronchoscopy (MLB) with excision of vocal fold lesions.

Intraoperative findings included bilateral extensive and ball-valving protruberant papillomatous masses on the true and false vocal folds (Fig. 1A). Extensive anterior commissure involvement was noted. The nature of the true vocal cords could not fully assessed as their view was blocked by the obstructing lesions.

A biopsy of the lesion and surgical debulking using micro-debrider, was performed of all areas. The anterior commissure was preserved. No lesions were identified in the remaining tracheo-bronchial tree. CO_2 laser was not performed due to the protuberant nature of the disease. She was discharged after overnight observation with dramatic improvement in breathing and feeding. Biopsy revealed squamous papilloma with no evidence of dysplasia. Viral typing was not performed.

Repeat intraoperative endoscopy was performed at 4 weeks after the first procedure, due to airway obstruction and revealed RRP matching that seen at the first procedure. The vocal folds, adjoining ventricle and the ventricular folds were involved. Papillomata were excised with the laryngeal microdebrider while exercising extreme caution trying to preserve the anterior commissure and true vocal folds, where CO_2 laser was used to ablate sessile lesions on the anterior commissure and true cords.

Three endoscopic procedures were required at 4 week intervals. The disease remained aggressive and persistent in the original sites. Subcordal involvement was then noted bilaterally (Fig. 1B). Recurrent papillomata continued to cause airway compromise. No distal disease was present. At this stage discussions were held with the family members regarding the aggressive nature of RRP. Adjuvant therapy was introduced as a means of addressing the disease. In particular, the pros and cons of injectable cidofovir were discussed including its benefit in aggressive disease, lack of FDA approval for its use in RRP, possibility of nephrotoxicity and malignant potential. Family elected to proceed with adjuvant cidofovir therapy.

In the following two procedures, performed 4 weeks apart, microdebrider excision and CO2 laser ablation was followed by submucosal injection of 0.8–1 mL of cidofovir (5 mg/mL) in the affected areas under microscopic guidance using a 25 gauge laryngeal injector.

The following MLB, 4 weeks later, revealed no evidence of papillomas at the previously involved sites (Fig. 1C). A subsequent follow up MLB, 8 weeks later, showed no evidence of disease. Another three endoscopies were performed at 6–8 week intervals up to 18 months of age (Fig. 1D). The patient remains symptom and disease free. The false and true vocal folds appeared remarkably normal, with no evidence of residual disease or interventional sequelae.

She is being followed up as an outpatient with symptomatic assessment and examination and reports no signs and symptoms of disease recurrence.

3. Discussion

HPV is an epitheliotropic DNA virus. Different subtypes of HPV exist although type 6 and type 11 are most commonly associated with RRP and are believed to have a low malignant potential. Cidofovir is a cytosine nucleotide analog that has a broad spectrum

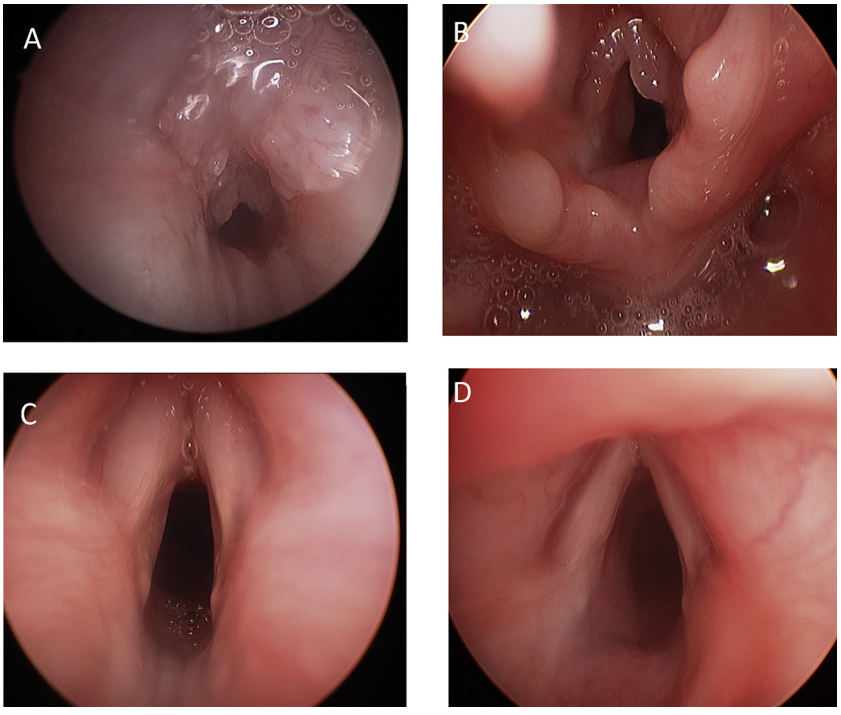

Fig. 1. Microlaryngoscopic images of larynx at various stages of treatment. (A) First microlaryngobronchoscopy. Age of the patient – 6 months. (B) Third microlaryngobronchoscopy showing subcordal involvement. Age of the patient – 9 months. (C) Microlaryngobronchosopy four weeks after last injection of cidofovir. Age of the patient – 12 months. (D) Microlaryngobronchoscopy six months after cidofovir. Age of the patient – 18 months.