

Recurrent Respiratory Papilloma in Saudi patients

By

Haya T. Al-Subaie, MD

Ahmed Y. Al-Ammar, MD, FKSU

* From the department of Otolaryngology Head and Neck Surgery
King Abdulaziz university hospital.
Riyadh, Saudi Arabia

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Abstract

Objective:

Is to review our cases of recurrent respiratory papillomatosis (RRP), and to compare our data to that available in the international literature.

Method:

A retrospective analysis of the data available in the charts of 9 patients with the diagnosis of RRP at King Abdulaziz University Hospital (KAUH), Riyadh, Kingdom of Saudi Arabia (KSA), was performed. All of the patients were managed between July 1997 and June 2007. Patient's files were evaluated for demographic data, presenting symptom, Intervention types, frequency of intervention, follow up duration and outcomes.

Result:

All of the patients presented with hoarseness of the voice, and upper airway obstruction was also presenting feature. Approximately 88% of the patients underwent their first endoscopic technique in our institution. Microdebrider was used more frequent than CO2 laser (29 vs. 6 times) to resect laryngeal papilloma. Adjuvant therapy was used in to 2 of the patients in the form of Cidofovir local injection.

Conclusion:

In conclusion RRP is considered to be the most common benign neoplasm in the larynx and the second most common cause of hoarseness in the pediatric population. According to our data

diagnosis of RRP at an age of 3 years or less is associated with frequent recurrences. Surgical debulking utilizing microdebrider is safe, less time consuming and does not associate with significant bleeding. Human papilloma virus (HPV) vaccine is having a promising role in the management of RRP.

Introduction

Recurrent Respiratory Papillomatosis (RRP) is an enigmatic disease which can be devastating to those whom it affects. This disease is viral in its origin caused by Human papilloma viruses (HPV), most common subtypes are 6 and 11, also subtypes 16 and 18 have been identified in RRP and are thought to pose a risk for malignant transformation .¹ The infectious nature of RRP was first demonstrated in 1923, when Ulman developed warts after inoculating himself with laryngeal tissue from an infected 6 years old boy.²

Clinically RRP is classified into juvenile onset (JORRP) and the less frequent adult onset (AORRP). The etiology of JORRP is generally agreed to be due to transmission of virus during gestation or through exposure to the virus during transit through the birth canal at the time of delivery. The risk is thought to be highest in women with frank condylomas or actively shedding disease from a recent HPV infection at the time of delivery though a third or more of these women have no visible lesions.³ The risk of transmitting the disease is estimated as 200–400-fold increase compared to a child delivered to a woman without condyloma.³ The adult form typically occurs when patients are in the third decade of life and infection is thought to represent either a reactivation of a latent infection or as a newly acquired sexually transmitted disease.³

RRP is considered to be the most common benign neoplasm in the larynx and the second most common cause of hoarseness among pediatric population .^{4,5} The most common presentation is hoarseness of voice, other presenting symptoms such as stridor and respiratory distress may occur and may initially be misdiagnosed with asthma or croup .⁶

Although the true incidence of RRP is unknown, most likely because of the lag between the onset of hoarseness or voice change

and definitive diagnosis,⁷ it was estimated in the United States to be 4.3 per 100.000 .⁸ Sex distribution differs among the different age groups; in patients younger than 12 years old , it is equally distributed , while in the adult onset , it has a slight male predilection .⁹ Generally, the diagnosis of RRP is based on clinical findings, mainly on the physical appearance of the airway lesion , and is confirmed by histopathologic study. Histologically, RRP lesion is composed of multiple finger -like projections of non keratinized stratified squamous epithelium overlying a vascularized core of connective tissue stroma .¹⁰ On the other hand, there are no simple *in vitro* culture methods available for identifying HPV infection. Unfortunately, serologic testing is insensitive, too. Techniques for identifying the virus are based on nucleic acid detection, either via direct hybridization or after PCR amplification.

Reviewing the literature regarding this devastating laryngeal lesion, many studies were found in different areas of the world, this was encouraging to do this retrospective study to shed some light on RRP in Saudi Arabia and compare our data to that in the international literature.

Methods

This is a retrospective study, involving the review of charts of 9 consecutive patients with diagnosis of RRP. All the patients were diagnosed and treated at King Abdulaziz University Hospital (KAUH), Riyadh, Saudi Arabia, between July 1997 and June 2007. Diagnosis was based on clinical examination at the outpatient clinic utilizing fiberoptic scope as well as intraoperatively by microlaryngoscopy and bronchoscopy. Confirmation was made by histopathological study of biopsies taken during direct laryngoscopy. All of the patients underwent laryngobronchoscopy for resection of the papilloma utilizing CO₂ laser or microdebrider.

All of the endoscopic procedures were performed under general anesthesia utilizing insufflation technique without use of endotracheal intubation for most of the cases. Intubation was performed for only distressed patients for a brief period of time to facilitate relieving the airway obstruction.

Files of all of the patients were evaluated for demographic data, presenting symptoms, type of intervention, frequency of intervention, use of adjunctive treatment, duration of follow up, outcome and complications.

Result

Five (56%) of our patients were female and 4(44%) were male. Age at presentation was ranging between 1.5 year and 44 years (mean of 13 year). All of our patients were children except for 2 (22 %) adults. All of our patients presented with hoarseness of a voice, other presenting symptoms are shown in the table. All of the cases had papilloma involving the larynx (mainly vocal cords), except for one of the cases who had an island of papilloma involving the upper trachea.

Seven (88%) of these patients underwent the first airway procedure at our institution, while two patients were referred to our institution after having their first surgical intervention.

In our institution, 6(66%) of the patients underwent carbon dioxide (CO₂) laser as the first endoscopic intervention, while resection of the papilloma was performed by microdebrider as the

first intervention in the other 3 (33%) patients. After August 2004, all the following endoscopic procedures were performed utilizing microdebrider (table). We used CO2 laser only 6 times, while microdebrider was used 29 times (table). The frequency of the surgical intervention was ranging between 1-10 times.

Adjunctive therapy in the form of intralesional Cidofovir injection was used in two of our patients; the first one received 4 doses (maximum intralesional injection of 10 mg each time) one month apart, while the second patient received only one dose (table). None of the patients who received Cidofovir had remission of RRP.

We followed up our patients for a period ranging between 18 months and 5 years.

We achieved clinical remission in 6 of our patients (67%), 4 of them were children and 2 were adults.

Discussion

Recurrent respiratory papillomatosis is a relatively uncommon disease characterized by warty exophytic growths preferentially affecting the larynx.¹

Although benign, the disease can be difficult to manage due to its recurrent nature and its ability to spread throughout the aerodigestive tract. RRP may affect patients of any age, but is commonly diagnosed in children between 2 and 4 years of age. Age at the diagnosis is the most important determinant of the disease severity, with patient younger than 3 years old requiring more surgical interventions.^{4,11}

In our study, three (33%) of our patients were diagnosed to have RRP at the age of 3 years or less, subsequently underwent more frequent endoscopic surgeries than the others, except for one patient who was diagnosed at the age of 6 years who underwent 10 endoscopic operations. The rest of our patients who were diagnosed at an older age had less frequent surgical interventions.

Death related to RRP may be as high as 1–2% while spread outside of the larynx into the trachea occurs in up to 25% and into the lung parenchyma in 2–5%.¹² Once spread of these lesions occurs below

the larynx, they become very difficult to manage and may lead to complete airway obstruction. One of our cases (11%) had upper tracheal involvement, this child was having frequent recurrences despite the use of intralesional cidofovir, and he was demanding frequent endoscopic interventions.

Current treatment of RRP aims at maintaining a patent airway and acceptable voice, while preventing complications such as laryngeal scarring or stenosis. Surgical intervention remains the principal modality of treatment, with patients requiring a mean of 4.4 procedures during the first year of diagnosis.^{4,13}

Treatment of the disease is focused on removal of the obstructing papilloma, in a hope of preventing regrowth.⁷ There are many different surgical modalities to achieve this goal. Since the popularization of CO₂ laser for laryngeal surgery in 1970, laser ablation of RRP lesions was the mainstay of therapy.

In our study 6 (66%) of our patients had their first surgical intervention utilizing CO₂ laser ablation, all of them were managed before August 2004, after this date we started to use microdebrider for resection of laryngeal papilloma (table).

Although some of the investigators have limited success with laser at keeping the lesion controlled through repeated surgeries, now it is generally acceptable that laser treatment is not a curative technique.^{7,14}

In 1999 Myer et al,¹⁵ reported the first experience with the laryngeal microdebrider for treatment of RRP. In our hands, use of microdebrider was safe, less time consuming, was not associated with extensive bleeding and did not result in an increased complications.

In a retrospective review of 18 patients who were younger than 18 years of age who were treated at two institutions with CO₂ laser and microdebrider techniques, Patel et al,¹⁶ reported a significantly shorter operative time for microdebrider.

In the last 30 years, more attention has been directed towards adjuvant treatment.⁷ Numerous agents including interferon α -2a,

Indole-3- carbinol, ribavirin , acyclovir , methotrexate and isotretention have been tried .¹ Unfortunately, none of these agents gained widespread acceptance as a useful adjunct in the management of RRP. Furthermore questions related to toxicity and appropriate dosing schedules persist for most of these agents .⁹ Although the clinical guidelines for instituting adjunct therapy have not been developed, however, the most common indications in the literature are; the need for more than four surgical procedures per year, spread of the disease to multiple distal sites or rapid regrowth of lesion with airway compromise.^{7,8,12}

The most extensively investigated adjuvant therapy is systemic interferon α -2a, which is a naturally occurring polypeptide that is capable of inducing intracellular enzymes to control viral replication of DNA and RNA .^{6,12} Recently interest was focused on the intralesional cidofovir. Cidofovir { (s)-1- (3 hydroxy-2-phosphonyl-1-methoxypropyl) cytosine } is an antiviral agent that is approved by the US food and drug administration for intravenous use to treat cytomegalovirus retinitis in patient who have AIDS.¹ In 1995, Van Cutsem et al,¹⁷ were the first to report the successful use of intralesional cidofovir in an adult with squamous papilloma in the esophagus and hypopharynx. Three years later, in 1998, Snoeck et al,¹⁸ reported the successful treatment of 16 of 17 patients who had severe laryngeal papilloma by intralesional injection of cidofovir in various volumes of 2.5 mg /ml at 2 weeks intervals.

We used cidofovir to our most aggressive patients, who had the highest frequency of recurrences. The use of this drug for our patients was not associated with inducing remissions despite the observation that they had slower recurrences and reduction of frequency of interventions. This observation was more obvious especially in the case who received 4 doses of cidofovir.

Currently there are two human papilloma virus vaccines in development. These are Gardasil from Merck, and Cervarix from GlaxoSmithKline (GSK) .¹⁹ Merck has recently received FDA

approval for their vaccine. The GSK vaccine contains virus-like particles (VLPs) to stimulate response to HPV 16 and 18. The Merck product is a quadravalent vaccine with VLPs for not only HPV 16 and 18 but for HPV 6 and 11 as well. The response to the vaccine has been very good with 99.7% of those vaccinated developing an antibody response.¹² These vaccines have been developed to stimulate immunity to the most common subtypes that cause cervical cancer but also include those responsible for RRP. With the possibility this could drastically reduce the incidence of RRP, the otolaryngology community should advocate for implementation of these vaccines.

Few studies have addressed factors that may predict remission, however, "remission" itself is not defined.

Ruparelia et al, defined remission in a study of 165 cases of RRP as no surgical procedures needed for at least 1 year.²⁰ In our study, we considered remission if the patient is being free of the papilloma for 6 months. So in our study we achieved remission in 6 of our patients, 2 of them were adults while the other 4 were children.

In conclusion RRP is considered to be the most common benign neoplasm in the larynx and the second most common cause of hoarseness in the pediatric population. According to our data diagnosis of RRP at an age 3 years or less is associated with frequent recurrences. Surgical debulking utilizing microdebrider is safe, less time consuming and does not associate with significant bleeding. Human papilloma virus (HPV) vaccine is having a promising role in the management of RRP.

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Patients	Age at diagnosis /gender	Presentation	Type and frequency of surgical intervention		Use of cidofovir	outcome	Follow up duration
			CO2 Laser	Microdebrider			
1	11 y / F	Hoarseness of voice.	1			Remission	3 y ,2 m
2	28 y / M	Hoarseness of voice	1			Remission	4 y
3	44 y / M	Hoarseness of voice	1	1		Remission	5 y ,4 m
4	1 y, 1m, / F	Hoarseness of voice. Stridor. Frequent respiratory distress.	1	9	4 doses	Recurrence	3 y ,2 m
5	4 y / F	Hoarseness of voice. Stridor	1	1		Remission	3 y, 1 m
6	6 y, 1 m / M	Hoarseness of voice Stridor. Frequent respiratory distress.	1	9	1 dose	Recurrence	2 y ,7m
7	15 y / F	Hoarseness of voice		2		Remission	1 y ,10 m
8	3 y / M	Hoarseness of voice. Stridor		5		Recurrence	1 y ,6 m
9	2 y, 6 m / F	Hoarseness of voice Stridor		2		Remission	1 y , 5 m

Table; showing the order of the patients according to the date of presentation, age at

presentation & gender, the clinical presentation, type and frequency of intervention, use of cidofovir, outcome and the duration of follow up