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Recurrent Respiratory Papillomatosis: Case Report of an Aggressive Course with Dysplastic Lesions in a Saudi Infant

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Abstract

Background: Recurrent respiratory papillomatosis is a disease that is caused by Human papilloma virus that occurs in both children and adults. Recurrent respiratory papillomatosis tends to take a more aggressive clinical course in children than in adults. Recurrent respiratory papillomatosis can be fatal because of it is tendency to recur and spread throughout the respiratory tract. Mortality comes from more than one source: malignant transformation and respiratory tract obstruction.

Case presentation: Our patient is, a female gender infant, had symptoms at a very young age and required frequent surgical debulking by micro laryngoscopy and bronchoscopy, every three to four weeks to maintain her airway.

Conclusions: We present this case as first reported Saudi infant with sever extra laryngeal spread of respiratory papilloma, to highlight the challenges in the management of recurrent respiratory papillomatosis with extra laryngeal spread of respiratory papillomas and introduction of Human papilloma virus vaccine may have a positive impact on this disease.

Keywords: recurrent respiratory papillomatosis, human papilloma virus

Introduction

RRP is a disease that is caused by human papilloma virus (HPV), which occurs in both children and adults. The vocal fold is usually the first and predominant site of papilloma lesions, and hoarseness is the principal presenting symptom. Stridor is often the second clinical symptom to develop, initially inspiratory, then becoming biphasic. Less common presentations include chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, and acute respiratory distress [1].

RRP is classified as juvenile onset RRP (JORRP) or adult onset RRP (AORRP), depending on the presentation before and after the age of 12 years. The true incidence and prevalence of RRP are uncertain. It is estimated that between 80 and 1,500 new cases of JORRP occur in the United States each year [1]. The prevalence of RRP varies and depends on the age of presentation, country and socioeconomic status of the population being studied. However, it is generally accepted that it is between one and four per 100,000 [2]. The JORRP usually occurs between the ages of two and four, whereas AORRP usually occurs between 20 and 40 years of age.

In the 1990s, HPV was confirmed as the causative agent of RRP. With the advent of molecular probes, HPV DNA has been identified in virtually every papilloma lesion that has been studied. The most common types that have been identified in the airway are HPV 6 and HPV 11. These are the same types that are responsible for more than 90% of genital condylomata. Specific viral subtypes may be correlated to the severity of the disease and the clinical course. Children who are infected with HPV 11 appear to be at a higher risk of obstructive airway disease and have a greater likelihood of needing a tracheotomy to maintain a safe airway [3]. Extra laryngeal spread of respiratory papillomas has been identified in 13% to 30% of children and in 16% of adults. The most common sites, in decreasing order of frequency, are the oral cavity, the trachea, the bronchi and the esophagus [1]. Lung involvement in RRP is thought to be rare, and 1% to 5% of patients show pulmonary spread [4]. When the disease has progressed to the lung, however, it is believed to be almost invariably fatal within 10 years [5].

The mainstay of RRP treatment has been the primary resection of lesions. However, the reported use of adjuvant treatments in paediatric patients is increasing. Surgeons typically consider adjuvant therapy in patients getting surgery more than 3–4 times per year, but actual indications are not well defined [6]

Use of adjuvant medical therapy in RRP treatments focus on several mechanisms, such as immunomodulation, disruption of molecular signaling cascade or HPV replication resulting in apoptosis inhibition of proliferation, growth arrest and/or promotion of normal differentiation in HPV infected cells [7]

We present this case as first reported Saudi infant with sever extra laryngeal spread of respiratory papilloma, to highlight the challenges in the management of recurrent respiratory papillomatosis with extra laryngeal spread of respiratory papillomas and introduction of HPV vaccine may have a

positive impact on this disease.

Case Presentation

Our patient is a female gender infant, who presented to our hospital at age of 10 months, the product of a full-term gestation and normal spontaneous vertex vaginal delivery, with a birth weight of 3Kg. Her mother was a 23yo G1P0 with a history of genital warts that were noted in the 3rd trimester and resolved without medical treatment. The baby was discharged with the mother post-delivery in good condition and was doing well for the first few months of life.

At the age of six months, the baby began to have frequent attacks of shortness of breath that were associated with noisy breathing. These were labeled as a case of hyperactive airway disease and the baby was started on salbutamol and fluticasone MDI with fair response. At the age of eight months, the baby was admitted to a local hospital with the same complaint and again was managed as a case of hyperactive airway exacerbation.

At 10 months of age, the baby was brought to our hospital with severe shortness of breath associated with stridor with poor response to nebulized salbutamol and racemic epinephrine. Just prior to being brought to the hospital, the baby developed facial cyanosis for about one minute and became more tachypneic and distressed. The baby was seen by pulmonary and otorhinolaryngology ENT teams. Flexible pharyngolaryngoscopy was conducted and showed papillomas on the palate, supraglottic and glottic areas.

From the age of 10 to 20 months, the baby presented to the hospital on 12 occasions with moderate to severe respiratory distress, shortness of breath and cyanosis secondary to airway obstruction. She required surgical debulking in all admissions, using microdebriders or CO2 laser. A trial of five sessions of intralesional cidofovir injection did not decrease the severity of the disease. A trial of propranolol was held because of the side effects, which included difficulty with breathing and bradycardia. The baby underwent a tracheostomy due to progression of the disease and recurrent aspiration pneumonia (Figure 1).

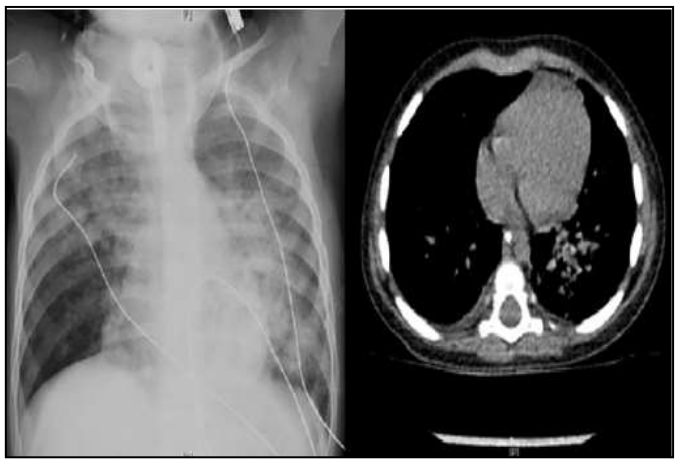

Fig 1: CXR showing consolidation in left perihelia areas and reticulations. The CT scan of the chest shows consolidation in the left lower lobe.

The last laryngobrochoscopy showed an aggressive disease of papillomatosis involving the lingual and laryngeal surface of epiglottis, both false vocal cords bilaterally, subglottic area, the upper and middle third of the trachea and right main bronchus (Figure 2). Histopathological study of tissue specimen showed the presence of mitosis, which was suggestive of mild to moderate dysplasia.

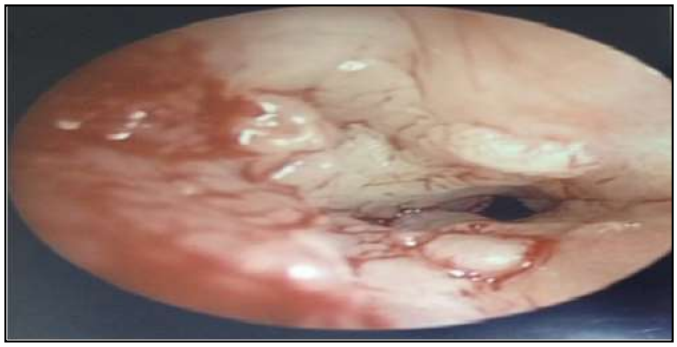

Fig 2: Bronchoscopic picture showing severe progression of the papillomas.

Unfortunately, the baby died at 22 months of age due to severe respiratory distress and cardiopulmonary arrest.

Discussion

RRP is characterized by recurrent formation of non-keratinized, squamous papillomata within the epithelium of the upper aerodigestive tract. DNA studies have identified human papilloma virus (mostly types 6 & 11) as a causative pathogen in RRP [1] Malignant transformation has been reported solely for HPV11-associated RRP in 2–4% of all RRP-cases, but not for HPV6. Treatments for RRP are aimed at removing symptomatic tumor bulk, while preserving as much anatomy and function as possible. Surgery itself may not be curative, but is thought to contain the disease and treat symptoms, whilst natural host immunity to the causative pathogen develops. Our patient required micro laryngoscopy and bronchoscopy with debulking every three to four weeks to maintain her airway.

Most cases of RRP are diagnosed at two to four years of age with an average delay in diagnosis from the time of onset of the symptom of about one year [1] Childhood onset is more common and aggressive than adult onset. Children who are diagnosed before three years of age were found to be 3.6 times more likely to require more than four surgical procedures per year and 2 times more likely to have the involvement of two or more anatomic sites [1] Our patient had symptoms at a very young age and required frequent surgical debulking. The disease is likely transmitted vertically during gestation or delivery [7] This is consistent with our case, as the mother of the patient had a history of genital warts during pregnancy, which is the classic risk factor for RRP [8] Fifty to 70% of patients who had JORRP are born to mothers who had genital warts during pregnancy or while giving birth. In addition, 72% of the affected patients are the first-born child, delivered vaginally and born to a teenage mother [9] The risk of a child contracting the disease from a mother, who has an active genital condyloma lesion during vaginal delivery, is 1 in 231 to 400 [1].

Imaging studies may raise the suspicion of a soft tissue lesion

prior to endoscopy in patients who have obstructive respiratory symptoms. Chest and neck radiograph may reveal intratracheal densities, segmental or lobar atelactesis and post obstructive pneumonia. Computed tomography scan of the upper airway may help to reveal tumor-like papillomatous growth. In our patient, soft-tissue lateral neck x-ray did not show the airway very well. The CXR findings were not very specific. The CT scan of the chest was more helpful in delineation the extension of the disease and showed scattered patchy areas of consolidation with areas of air bronchogram.

Most RRPs are diagnosed by means of laryngoscopy or bronchoscopy. Typical finding is cauliflower-like warty growth. This finding was consistent with our patient. The first flexible pharyngolaryngoscopy of our patient showed papillomas on the palate, supraglottic and glottic areas.

Histological findings of RRP classically show growth of keratinized squamous epithelium overlying a fibrovascular core; this was also found in specimens taken from our patient. Koilocytes, vacuolated cells with clear cytoplasmic inclusion, are often seen, with variable degrees of dysplasia and metaplasia [10]. Our case specimen microscopy suggested mild to moderate dysplasia, no carcinoma in situ (CIS) seen and no evidence of malignancy.

At present, there is no cure for RRP and no single treatment has been shown to be consistently effective in eradicating RRP [1]. Surgery is the mainstay of treatment [2]. With several surgical methods that include direct resection with operating microscopes, endoscopic debulking with microdebriders, laser ablative surgery using CO2, Nd: YAG laser and pulse dye laser. The main objective of the surgical approach is to remove papillomatous lesion, maintain airway patency and normal airway anatomy [11]. Although papillomas in the upper airways, the trachea, and the bronchi are amenable to excision through endoscopic surgery, those that invade the lung parenchyma are not. Resection of affected areas is possible only if the disease is localized. The typical picture of lung papillomatosis is that of numerous nodules scattered throughout the lungs, with some evolving to cavitation, and the associated risk of chronic infection. In our case we used microdebrider and CO2 laser for debulking with temporary relief of symptoms allowing the patient to go home in good condition. However this relief lasted for only three to four weeks with frequent recurrence.

Despite their successful removal, recurrence after surgery is common with complications like dysphonia, excessive airway scarring and stenosis [11]. From the age of 10 to 20 months, our patient presented to hospital on 12 occasions with moderate to severe respiratory distress, shortness of breath and cyanosis secondary to airway obstruction, requiring surgical debulking in all admissions. This was a great burden for the family.

Adjuvant medical therapy may be indicated when surgery does not eradicate the disease. Several adjuvant therapies have been employed. Unfortunately, most of these methods have not been rigorously tested [12]. A trial consisting of five sessions of intralesional cidofovir injection did not decrease the severity of the disease in our case. A trial of propranolol was held because of side effects that included difficulty with breathing and bradycardia. Surgeons typically consider adjuvant therapy in patients getting surgery more than 3-4 times per year, but actual indications are not well defined.[6]. Adjuvant treatments that have been used in the treatment of RRP include interferon, cidofovir, acyclovir, propranolol, COX-2 inhibitors, HPV Vaccine, Bevacizumab and others [1].

Identifying the serotype is helpful, as it may be an indication of disease progression or a prognostic factor. Serotype 11 has been shown to be more likely to be associated with development of aggressive disease requiring frequent surgical procedure, adjuvant medical therapies and, sometimes, tracheostomy to keep the airway patent [1] In addition, knowledge of the serotype would be helpful in understanding the possible impact of the HPV vaccine. The current HPV vaccine that includes serotypes 6 and 11, if given in adolescence, may be the best way to prevent the vertical transmission of this difficult-to-treat condition [13]. It would be interesting to see the impact of the vaccine on the incidence of RPR in the future.

Conclusion

In conclusion, RRP onset at a very young age is often aggressive and requires frequent surgical debulking with widespread involvement of the airway leading to significant morbidity. Management is complex and multimodal. The introduction of HPV vaccine may have a positive impact on this disease and may be the best way to reduce the incidence of this disease.

Declarations

This case accepted to be reported by department of Paediatrics and department of Otorhinolaryngology in National Guard Hospital, King Abdul-Aziz Medical City, King Abdullah Specialist Children Hospital, and Riyadh, Saudi Arabia.

Members of departments and committee's:

Department Otorhinolaryngology

Dr. Khalid A. Al-Mazrou, ENT consultant and head of department.

Department of Pediatrics

Dr. Suliaman Alola, Pediatric ID Senior consultant.

Patient family agree to report this case and their informed consent taken for case reporting with chest X–Ray and endoscopy finding pictures.

The authors declare that they have no competing interests.

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