International Journal of Pediatric Otorhinolaryngology 93 (2017) 103–106

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: http://www.ijporlonline.com/

Case Report

Therapeutic use of the HPV vaccine in Recurrent Respiratory Papillomatosis: A case report

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ARTICLE INFO

Article history:
Received 9 September 2016
Received in revised form
22 December 2016
Accepted 24 December 2016
Available online 27 December 2016

Keywords:
HPV
Vaccine
Papillomatosis
Laryngeal
Recurrent

ABSTRACT

Recurrent Respiratory Papillomatosis (RRP) is a condition characterized by recurring squamous papillomas in the aerodigestive tract due to Human Papilloma Virus (HPV) infection. Treatment includes surgical debridement of the lesions often with adjuvant therapy. A newer adjuvant agent being tested is the HPV vaccine. The case report includes a child with RRP who underwent 10 surgeries in a year with an average inter-surgical interval (ISI) of 46 days. The patient then received the scheduled regimen of 3 doses of 9 valent HPV vaccine. Since beginning the vaccination, her average ISI increased to 113 days and as of writing of this paper only 1 surgery in the last 340 days. It is theorized that the increase in humoral response to the virus can slow the course of the disease, lengthen the ISI, and decrease morbidity. The results of this case report lends evidence to the use of the HPV vaccine as a therapeutic adjuvant therapy for RRP.

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1. Introduction

Recurrent Respiratory Papillomatosis (RRP) is a condition more commonly observed in the pediatric population than in adults and results in the growth of squamous papillomas in the aerodigestive tract [1]. It most commonly affects the larynx and often recurs by spreading through the aerodigestive tract [2]. These growths can cause airway compromise, leading to dysphonia, respiratory distress, and complete occlusion. This condition is generally caused by Human Papilloma Virus (HPV) infection, with the vast majority caused by HPV serotypes 6 and 11 [3]. While the mode of transmission isn't fully understood, it is theorized that vertical transmission of HPV from mother to baby occurs by ascending infection due to exposure to HPV+ papillomas in the genital tract by the newborn or intrauterine transplacental infection. Sexual intercourse, self-inoculation, and horizontal transmission through saliva have also been described and more commonly affect older children and adults. This disease has an incidence of 4.3 cases in 100,000 in children, and 1.8 cases in 100,000 in adults [2]. The treatment of these cases results in over $150 million a year [1]. In children who were born to women with active condyloma there was a 231-times increased risk of RRP, and a 2-fold risk for children born from extended labor [4]. While the strong association between the presence of maternal condyloma with extended labor indicates perinatal exposure to HPV in the genital tract during the birth process as a major risk factor, C-section is not indicated as intrauterine transplacental infection may also play a role in transmission of the virus and only 1 in 400 children with perinatal exposure to HPV condyloma went on to develop RRP [5].

The majority of cases involve frequent and recurrent treatments. The mainstay of treatment involves surgical removal of the papillomas to maintain the patency of the airway. Surgery is done using cold microsurgery, laser microsurgery, or removal using a microdebrider. These surgeries rarely prevent recurrence of the papillomas and these patients frequently require multiple surgeries [6]. On average, a child with RRP will require 4.9 debridement surgeries per year. The number of procedures per year significantly increases if the child was diagnosed with RRP under the age of 2 years old [7]. These surgical procedures do not completely eliminate the HPV, so the use of adjuvant therapy can help reduce the recurrence of papillomas. Adjuvant therapies commonly used include cidofovir and bevacizumab, but many other treatments have been tried including methotrexate, interferon, cimetidine, mumps vaccine, ribavirin, acyclovir, photodynamic therapy, and indole-3-carbinol [6,8,9]. Some adjuvant therapies, especially cidofovir, have provided good response against RRP. However, significant side effects

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http://dx.doi.org/10.1016/j.ijporl.2016.12.035
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of these adjuvant therapies most significantly including nephrotoxicity with cidofovir alongside uncertain long term effectiveness of many adjuvant therapies drives the development of newer therapies. One new adjuvant therapy that has been used more recently as a treatment is the HPV vaccine. There are several case studies that show good results from and a case series showing no benefit from the HPV vaccine, however there are no randomized clinical trials outlining its efficacy [10–16]. The purpose of this paper is to discuss an individual case of pediatric RRP treated with the HPV vaccine and review the current literature in regards to its treatment role.

2. Case report

In this case we present a child with recurrent respiratory papillomatosis. The patient was born at 34 weeks to a HPV positive mother, but with no major medical issues at the time. She was initially evaluated at 12 months of age in June 2014 after recent admission to the pediatric intensive care unit for stridor and respiratory distress resulting in intubation. After systemic steroid therapy and successful extubation the patient underwent flexible fiberoptic nasopharyngolaryngoscopy showing evidence of obstructive laryngeal papilloma. Subsequent examination in the operating room under direct laryngoscopy revealed an anterior papilloma with near complete obstruction of the airway with involvement of both vocal cords and vestibular folds. Fig. 1 shows visualization of the papilloma from the most recent visit. Between June 2014 and December 2016, she underwent direct laryngoscopy with bronchoscopy and ablation of papilloma using the Diego microdebrider 14 times secondary to recurrence of the disease. Pathology report indicated HPV 6/11+ infection by in situ hybridization analysis, no immunogenicity tests were performed on the patient. On September 18th, 2015, she was started on an HPV vaccine regimen, with subsequent vaccinations on December 4th and April 8th, 2016. Prior to the vaccine series, her intersurgical interval averaged around 46 days. Subsequent to the second vaccination, her ISI significantly increased to 113 days with an associated decrease in morbidity. The graph of her intersurgical intervals can be found in Fig. 2. She has improved clinically as she no longer has stridor at rest and a hoarse voice which she had at her first visit and her Derkay scores improved throughout treatment. At initial presentation her clinical score was 7, anatomical score 10, for a total of 17. Immediately prior to vaccination her clinical score was 1, anatomical 9, for a total of 10. As of last visit her clinical score was 0, anatomical 5, for a total of 5. The patient continues to be followed in our clinic for symptom exacerbation and possible future interventions.

3. Discussion

Recurrent Respiratory Papillomatosis is a rare, but potentially debilitating disease. While some patients may have mild symptoms and the papillomas can spontaneously resolve, for many patients they do not. Our patient had a severe course of disease, having to undergo 13 surgeries under the age of 3. Her shortened ISI necessitated aggressive treatment, and adjuvant therapies were considered to compliment her surgical interventions. The HPV vaccine was considered to be a safe option that other case reports had shown to be effective in treatment, so it was decided to treat with the vaccine [10–16]. The 9-valent vaccine was chosen as this was the vaccine used in affiliated clinic and while the papilloma was shown by hybridization to show serotypes 6/11, the 9 valent vaccine covers additional cancer causing serotypes which can account for 15% of cervical cancers. Other adjuvant therapies such as cidofovir and bevacizumab have shown success, however we proceeded to the HPV vaccine due to its excellent safety profile and recommendations for the HPV vaccine [17]. Analysis of the Derkay scores show improved clinical scores associated with the debridement procedures, however the anatomical scores were lowered substantially after administration of the vaccine.

While the HPV vaccine has been shown to prevent HPV infection and papillomas, it has not been proven as a treatment modality. The HPV creates several proteins, including the core proteins E1, E2, E4, E5, E6, E7 and the capsid proteins L1 and L2. The E5, E6, and E7 proteins promote cell proliferation and are considered the oncoproteins responsible for the development of the papillomas [18]. The 9-valent vaccine uses inactivated viral capsid protein L1 to induce immunogenicity against the HPV serotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58 [18]. This stimulates T-cell immunity and causes an increase in anti-HPV antibody titers [19]. The antibodies then

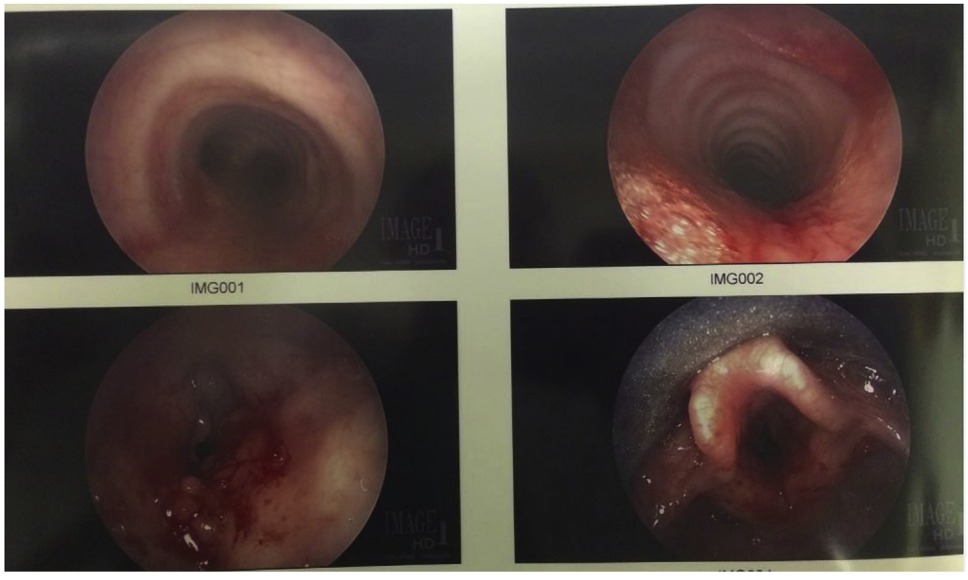

Fig. 1. Demonstrates visualization of the papilloma under direct laryngoscopy and bronchoscopy.

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