CASE REPORT

An unusual case of juvenile-onset recurrent respiratory papillomatosis with lower airway involvement in a 15-month-old boy

Dafni **Moriki** [1], Konstantinos **Douros** [1], Savvas **Kaklis** [2], Periklis **Foukas** [3], Vassiliki **Papaevangelou** [1], Kostas N. **Priftis** [1, 4, *]

[*] **Correspondence to:**
kpriftis@otenet.gr. ORCID: https://orcid.org/0000-0002-8368-0237

ABSTRACT

Recurrent respiratory papillomatosis (RRP) is a rare disease caused by human papillomavirus (HPV) infection, especially with types 6 and 11. It is characterised by the presence of multiple airway papillomas located mainly in the larynx; involvement of the distal airways and lungs may also occur. There are two clinical forms of the disease depending on the age of onset, juvenile-onset RRP (JoRRP) and adult-onset RRP (AoRRP). JoRRP is the most common clinical form and usually affects children younger than 5 years of age. It is generally more aggressive with a high recurrence rate and is acquired by vertical transmission during vaginal delivery of infected mothers. There is currently no effective treatment for RRP and surgery remains the main treatment option. However, systemic treatment with bevacizumab, a recombinant humanized monoclonal antibody that binds to vascular endothelial growth factor-A (anti-VEGF-A) and prevents angiogenesis, has been proposed as adjuvant therapy in advanced RRP cases. We present an unusual and aggressive case of JoRRP with distal airway involvement in a 15-month-old boy who showed a complete response to systemic bevacizumab.

IMPACT STATEMENT: Bevacizumab is a promising adjuvant therapy for recurrent respiratory papillomatosis, particularly in cases involving the distal airways that are difficult to treat with standard surgical procedures.

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a rare disease characterized by the recurrent growth of papillomas in the airways. Papillomas are benign epithelial tumors usually located in the larynx. However, occasionally, they may become more aggressive and spread distally to the lower airways and, rarely, to the lung parenchyma (1). Despite their benign nature, papillomas can grow rapidly and thus pose a potential risk for airway obstruction. In addition, they tend to relapse and show an increased risk of malignant transformation. More than 90% of all RRP cases are caused by infection with human papillomavirus (HPV) types 6 and 11. Other HPV subtypes, such as 16 and 18 have also been detected, but are much less common (2). Based on their association with malignant transformation HPV subtypes can be divided into low- and high-risk. In particular, HPV

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[1] Third Department of Pediatrics, School of Medicine, National and Kapodistrian University of Athens, Attikon General University Hospital, Athens, Greece
[2] Department of Anesthesiology, Pediatric Center of Athens, Marousi, Athens, Greece
[3] Second Department of Pathology, School of Medicine, Attikon General University Hospital, National and Kapodistrian University of Athens, Athens, Greece
[4] Pediatric Center of Athens, Marousi, Athens, Greece

ABBREVIATIONS

AoRRP: Adult-onset RRP
HPV: Human Papillomavirus
JoRRP: Juvenile-onset RRP
RRP: Recurrent Respiratory Papillomatosis

KEY WORDS

Recurrent respiratory papillomatosis; human papilloma virus; bevacizumab; adjuvant therapy; papillomas.

types 6 and 11 are considered low-risk, while types 16 and 18 are considered high-risk (3).

RRP has a bimodal age distribution with young children and young adults being most affected. There are two clinical forms of the disease depending on the age of onset, with the age limit usually set at 18 years (4). Juvenile-onset RRP (JoRRP) is the most common clinical form with an estimated incidence of 4.3 per 100,000 (5). However, recent data show a significant reduction after the implementation of HPV vaccination (6). In children with JoRRP, HPV infection is usually acquired by vertical transmission during vaginal delivery of infected mothers. It occurs most often in children under 5 years of age with the mean age of onset ranging from 2.8 to 4.6 years in different studies (7). Adult-onset RRP (AoRRP), on the other hand, has an incidence of 1.8 per 100,000 (5). In this case, HPV infection is sexually transmitted and is therefore more common in young adults between 20-40 years of age (8).

The clinical presentation of RRP is variable and depends on the location and size of papillomas. HPV infection usually affects the larynx and thus progressive hoarseness of voice and stridor are the most common manifestations. Patients with RRP may less frequently present with dysphagia, chronic cough, recurrent pneumonia, or respiratory distress (9). The differential diagnosis of JoRRP includes acute laryngitis, congenital airway abnormalities (*e.g.*, laryngomalacia, laryngeal cysts, *etc.*), vocal cord paralysis, airway hemangiomas, vascular malformations, and asthma in case of lower airway involvement (10, 11). The clinical course of the disease is unpredictable. Some patients develop an aggressive disease that requires frequent surgical interventions to maintain airway patency, while others achieve progressive and spontaneous remission (2). JoRRP is generally considered more aggressive than AoRRP and has a high recurrence rate (12).

Management of patients with RRP is difficult and there is currently no effective treatment. Surgical excision of the papillomas with lasers or microdebriders remains the mainstay of treatment. Estimated lifetime surgical procedures at JoRRP range from 6 to 13 (7, 13). The aim is to relieve symptoms and prevent airway obstruction. However, approximately 20% of patients require some type of adjuvant therapy due to the aggressive nature of the disease and its tendency to relapse (14). Adjuvant therapy is considered in cases with a frequent need for surgery (more than 4 to 6 per year) or in cases where papillomas are spread beyond the larynx (15). It includes interferon, antiviral agents (*e.g.*, cidofovir), inhibitors of cyclooxygenase-2 (*e.g.*, celecoxib), monoclonal antibodies (*e.g.*, bevacizumab, pembrolizumab), and HPV vaccine.

Herein we describe an aggressive case of a 15-month-old boy with primary diffuse papillomatosis of the trachea and main bronchi who showed a complete response to systemic treatment with bevacizumab.

CASE REPORT

This is the case of a boy who is now 4 years old and was diagnosed with JoRRP at the age of 15 months. He is the only child in the family and was born at term by cesarean section for non-medical reasons. The perinatal history was unremarkable. His mother had no evidence of HPV infection and had a recent PAP test that was negative. He was breastfed until 12 months of age and his growth was normal. He had no previous medical history and was fully vaccinated. He first presented to our department at 15 months of age with recurrent and progressively worsening episodes of inspiratory stridor over two months. The patient had been treated by his primary care physician with repeated courses of oral dexamethasone but had shown only a partial and transient response. Due to the aggressive and unusual presentation of the disease, the patient was also evaluated for cellular immune deficiency, but no abnormal findings were detected. Therefore, he was referred to a pediatric pulmonology clinic.

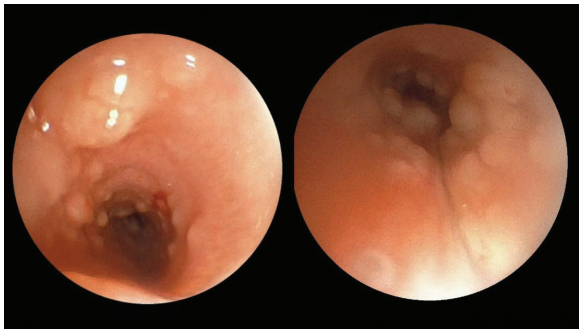

***Figure 1**. Diffuse papillomatosis of the trachea causing significant obstruction.*

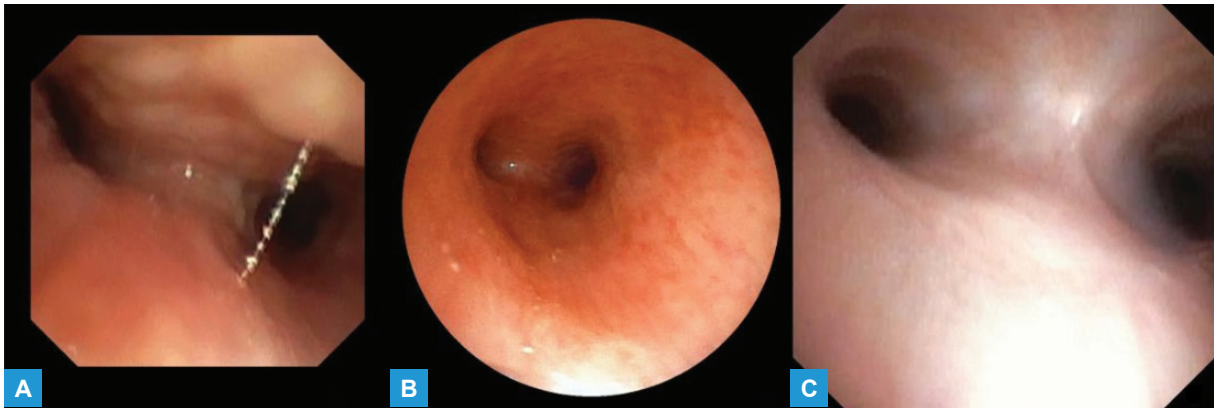

***Figure 2**. (**A**) Diffuse papillomatous lesions in the trachea and main bronchi. (**B**) dramatic regression of papillomas after administration of the third dose of bevacizumab; (**C**) complete response to bevacizumab.*

At the time of referral, the patient was afebrile. He had inspiratory stridor and signs of moderate respiratory distress with normal oxygen saturation levels. Lung auscultation was normal. No choking episode or ingestion of a foreign body was reported by his parents. Blood tests including blood cell count, biochemistry and C-reactive protein were unremarkable. Chest x-ray was also normal. He underwent flexible bronchoscopy, which revealed multiple papillomatous lesions in the trachea and the main bronchi (**Figures 1, 2A)**. These lesions caused significant obstruction, particularly in the middle third of the trachea. No lesions were found in the larynx **(Figure 3)**. Endobronchial biopsies were obtained for histopathological analyses. During flexible bronchoscopy, the patient developed persistent oxygen desaturation and was intubated. Therefore, he was admitted to the intensive care unit for a few days. Histopathological analyses confirmed the diagnosis of benign squamous cell papillomas, and polymerase chain reaction detected HPV type 16. Chest computed tomography (CT) showed no spread of HPV infection to the lung parenchyma.

Surgical excision of the papillomas was not feasible due to multiple lesions and involvement of the distal airways. Adjuvant therapy was necessary and, after discussion with the parents, systemic treatment with bevacizumab, an anti-vascular endothelial growth factor-A (anti-VEGF-A) was initiated. Specifically, he was started on intravenous bevacizumab at a dose of 10 mg/kg every 2 weeks. In addition, he received the 9-valent HPV vaccine (Gardasil 9). A significant clinical improvement was observed immediately after the first dose of bevacizumab. Flexible bronchoscopy was repeated after the administration of the third dose and showed dramatic regression of the papillomas **(Figure 2B)**. After 6 doses, the treatment interval was gradually extended to every 2 months for almost a year. During this period, the patient was closely monitored for relapse symptoms and side effects associated with bevacizumab such as hypertension, epistaxis, and proteinuria. No relapse symptoms or side effects were observed. Follow-up bronchoscopies showed no recurrence of papillomas and HPV DNA was no longer detected in endobronchial biopsies **(Figure 2C)**.

The patient is now 51 months old and has been treated with bevacizumab for 3 years. He has been receiving bevacizumab at 6-month intervals for the past 18 months and remains free of symptoms.

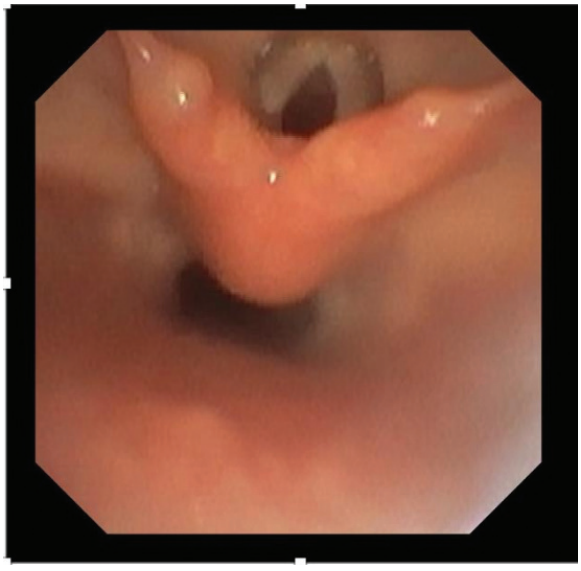

***Figure 3**. No papillomatous lesions were observed in the larynx.*

DISCUSSION

RRP is a relatively rare disease characterized by the development of papillomas in the respiratory tract. It affects both children and adults and is caused by a local infection with HPV. Although there are more than 200 subtypes, HPV types 6 and 11 account for more than 90% of all RRP cases. Other HPV subtypes, such as 16, 18, 31 and 33, can also be detected but at a lower rate (2). There are two clinical forms of the disease depending on the age of onset. JoRRP is the most common and usually occurs before the age of 5 years (8). In this clinical form, HPV infection is usually transmitted at birth, during passage through the birth canals of infected mothers. However, in about 12% of cases, vertical transmission can occur before birth through the placenta (2). Therefore, cesarean section does not eliminate the possibility of vertical transmission of HPV infection to the newborn. Firstborns and children of young mothers are most likely to be infected (7, 16), possibly due to a longer delivery time which implies a prolonged time of exposure to the virus (17). It has also been suggested that newly acquired HPV infections are more likely to be transmitted than chronic infections (18). Notably, our patient was born by cesarean section and although there was no evidence of maternal infection, HPV was probably transmitted through the placenta during pregnancy.

Clinical presentation of the disease is variable and depends on the location and size of papillomas. The larynx, and particularly the vocal cords and surrounding tissues, are the most common sites of infection. Therefore, progressive hoarseness of voice and stridor are the main presenting symptoms. Severe respiratory distress due to airway obstruction may also occur (1). It is estimated that approximately 14% of patients require a tracheostomy to prevent life-threatening airway obstruction (5). Due to its non-specific clinical presentation, JoRRP must be differentiated from other clinical entities such as acute laryngitis, vocal cord paralysis, subglottic stenosis, laryngeal cysts, vascular malformations, laryngomalacia, tracheomalacia, and airway hemangiomas (10, 11). More rarely, papillomas can spread distally to the lower airways and lung parenchyma. In these cases, JoRRP may present with dyspnea, wheezing, chronic cough and recurrent pneumonia, and thus asthma and chronic bronchitis must be excluded (2, 10). Distal airway involvement occurs in 2-5% of patients with laryngeal papillomatosis, while the pulmonary parenchyma is affected in only 1% of cases (1). Involvement of the distal airways in the absence of papillomatous lesions in the larynx, as in the case of our patient, is extremely rare and only a few case reports have been described (19, 20).

Laryngoscopy and/or flexible bronchoscopy are the most reliable methods for the diagnosis of RRP. Endoscopy enables direct visualization of the central airways and collection of biopsy specimens for histopathological analysis. Papillomas usually appear as single or multiple exophytic, pedunculated nodules. Histopathological confirmation and detection of HPV DNA are essential for the diagnosis of RRP (1). The role of chest computed tomography (CT) is complementary and should be considered in patients with a clinical presentation suggestive of pulmonary involvement (21). The typical CT pattern of pulmonary papillomatosis includes multiple multilobular nodular lesions of various sizes, which are often cavitated and distributed throughout the lungs (1). Other less common findings include consolidation, atelectasis, bronchiectasis, air trapping, and pleural effusion (22). The clinical course of the disease is unpredictable. Some patients develop an aggressive disease with distal spread and high recurrence rate, while others achieve progressive and spontaneous remission (2). The severity and aggressiveness of the disease is determined by the number of annual and/or lifetime surgical procedures, distal spread, or a combination of the three (7). Available data suggest that age of onset and HPV subtype may influence the clinical course and severity of the disease. Specifically, age at diagnosis younger than 5 years and infection with HPV type 11 have been associated with more aggressive disease and extralaryngeal spread (7, 23, 24).

Despite the benign nature of papillomas, malignant transformation may occur in 3-5% of RRP cases (25). It mainly affects adults with additional risk factors, such as smoke and radiation exposure, but also children with persistent, advanced disease with distal spread (26). HPV subtype also plays an important role. Infections with HPV types 16 and 18 are considered high-risk and are associated with the potential for malignant

transformation, particularly in squamous cell carcinoma. Within the low-risk types, HPV type 11 has a higher malignant potential compared to HPV type 6 (2). Our patient was diagnosed at a very young age with an unusual and aggressive clinical presentation. Moreover, endobronchial biopsies detected HPV type 16. Therefore, he is a high-risk patient for both papilloma recurrence and malignant transformation.

Long-term management of the disease is challenging due to the frequent relapse of papillomas. Persistence of the viral genome in residual tissue is thought to be the main cause for such relapse (27). Current standard treatment of RRP involves repeated local surgical interventions with lasers or microdebriders, which are associated with a significant risk of complications and chronic morbidity. Therefore, a number of adjuvant therapies have been proposed to enhance surgical outcomes by increasing intervals between procedures or preventing the recurrence of papillomas. It is estimated that adjuvant therapy is required in 20% of patients and is considered in cases with frequent need for surgery (more than 4 to 6 per year) or in cases with lower airway involvement (15). The majority of adjuvant therapies act through immunomodulation, inhibition of HPV replication, control of inflammation, and prevention of angiogenesis. Interferon is one of the first systemic adjuvant therapies used for the management of RRP. Despite some positive evidence, its efficacy remains controversial and is now rarely used due to frequent side effects and the emergence of other adjuvant therapies (14). Such therapies include antiviral agents (*e.g.*, cidofovir), anti-inflammatory drugs such as inhibitors of cyclooxygenase-2 (*e.g.*, celecoxib) and monoclonal antibodies (*e.g.*, bevacizumab, pembrolizumab) (14). These drugs can be administered either systematically or intralesionally. HPV vaccine has also been proposed as adjuvant therapy. There is evidence that HPV vaccination increases the interval between papilloma recurrences and, consequently, the mean duration between surgeries (28). Unfortunately, the majority of these treatments have only been evaluated in small cohorts or case studies, and therefore, more powerful randomized controlled trials are needed to adequately assess their efficacy in the management of RRP.

Our patient presented with primary diffuse papillomatosis of the trachea and main bronchi and, thus, surgical treatment was not appropriate. Systemic adjuvant therapy was required as initial treatment and, after discussion with the parents, intravenous bevacizumab was initiated. The choice of bevacizumab was based on its better safety and efficacy profile compared to other available systemic therapies (14). Bevacizumab is a humanized monoclonal antibody that binds to circulating VEGF-A and prevents receptor activation and subsequent angiogenesis. *In vitro* studies have shown significant expression of VEGF-A in papilloma epithelium and expression of the messenger RNAs of vascular endothelial growth factor receptor 1 and 2 (VEGFR-1 and VEGFR-2) in underlying vascular endothelial cells, suggesting that VEGF activity plays a role in papillomas formation (29). Bevacizumab can be administered either intralesionally or systematically. Recently, a systematic review based on case reports, concluded that systemic bevacizumab is well tolerated and effective in reducing airway and lung lesions and should therefore be considered as adjuvant therapy for severe JoRRP (30). However, clinical trials are lacking and it remains an off-label indication. Based on the available data, the use of systemic bevacizumab is now recommended in cases of progressive and/or severe disease burden and in cases with disease in sites that are difficult to treat with standard surgical procedures (31). To date there is no standard protocol for the dosage regimen and duration of treatment. Bevacizumab is usually administered at a dose of 5-10 mg/kg intravenously at initial mean intervals of 3 weeks (range 2-5 weeks) until maximum response to treatment is achieved. Subsequently, the intervals of maintenance doses are gradually extended to 2-4 months (30). Current data indicate that treatment with systemic bevacizumab is well tolerated in children. Some side effects such as hypertension, proteinuria, epistaxis, joint pain and fatigue have been reported but are mild and usually reversible after discontinuation of treatment (32, 33). A major drawback is that long-term treatment is required for sustained improvement. Indeed, long-term follow-up of patients who received systemic bevacizumab showed that papillomas recurred on average 5.4 months after discontinuation of treatment (34). Our patient showed a complete response to systemic bevacizumab. He has been treated for 3 years and no relapse symptoms or side effects have been reported.

CONCLUSIONS

RRP is a rare disease of the respiratory tract caused by HPV infection. The clinical presentation and course of the disease is variable and depends on several factors including age of onset, HPV subtype and site of infection. Although rare, JoRRP may initially present with multifocal lesions in the distal airways, even in the absence of laryngeal involvement. These cases are difficult to treat with standard surgical procedures and adjuvant therapy is required. Bevacizumab is a promising adjuvant therapy, however, further research is needed to better define its role in the treatment of advanced RRP.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Author contributions

DM collected the data and wrote the manuscript. KD and KNP supervised the management of the case, carefully reviewed and co-authored the manuscript. SK and VP participated actively to the management of the case. PF performed histopathological analyses. All Authors have read and agreed to the published version of the manuscript.

Ethical approval

Human studies and subjects

The Authors confirm that the patient's parents have given their consent for the anonymous publication of the clinical information.

Animal studies

N/A.

Data sharing and data accessibility

Data are available upon motivated request to the Corresponding Author.

Publication ethics

Plagiarism

The contents of the article are original and any overlaps with other articles are by the Authors themselves and appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

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