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CASE REPORT

Juvenile laryngeal papillomatosis: a rare cause of upper airway obstruction with possible dysplasia

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ABSTRACT

Laryngeal papillomatosis is a rare and potentially severe cause of recurrent laryngeal dyspnea resistant to the usual treatments. It results from human papilloma virus (HPV) infection, transmitted during the perinatal period, and is mainly observed during the childhood. Upper airway obstruction is due to the growth of benign tumor, with rare malignant transformation. However, genetic mutation in association with viral integration can lead to the development and clonal expansion of malignant lesions. We report one pediatric case of recurrent upper airway obstruction due to severe laryngeal papillomatosis with histological dysplasia. Through this case, the Authors emphasize the importance of early detection, close follow up, and appropriate treatment. They also call for increased HPV immunization coverage in low-income countries where medical resources are limited.

IMPACT STATEMENT: Juvenile laryngeal papillomatosis is a rare but serious recurrent respiratory emergency with possible malignant transformation. Its management is challenging in low-income countries, and the HPV immunization is a promising measure.

INTRODUCTION

Upper airway obstruction (UAO) consists of a blockage of any part of the airway located above the thoracic inlet. It is a pediatric emergency, and its management is based on a proper clinical approach, followed by an appropriate investigation in doubtful cases (1). Laryngeal dyspnea is one of its main causes, mostly due, in children aged 2 and more, to viral infections or the presence of a foreign body. Laryngeal papillomatosis is a rare but a serious etiology of laryngeal dyspnea, caused by human papillomavirus infection (90% from subtypes HPV-6 and HPV-11), acquired at birth from maternal genital warts, and due to benign tumors increasing gradually (2-5). It is the most common benign laryngeal neoplasm in children and remains the second most common cause of childhood hoarseness (3-8). It is generally described as juvenile because starting mainly in early childhood, and the worst outcome is observed in the youngest ages. This condition should be known as a cause of laryn-

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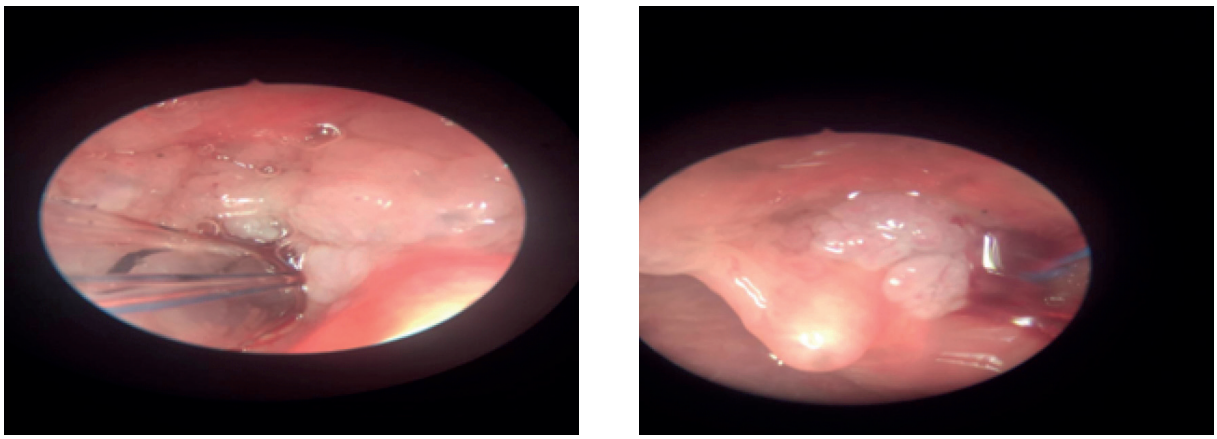
KEY WORDS
Dysphonia; Human Papilloma Virus (HPV); Recurrent Respiratory Papillomatosis (RRP); dysplasia; vaccine.

geal dyspnea, requiring early intervention and proper management (2-4). The treatment mainly consists in surgical removal of papillomas to clear the airway, and in some cases, adjuvant therapy is used concurrently. In particularly aggressive cases, tracheotomy may be required (2-4). The difficulty of its management lies in the high recurrence of papilloma growth after surgical removal and in rare cases the possible malignant transformation. In developing countries, diagnosis and treatment are challenging because of the lack of diagnostic and therapeutic means. Thus, prophylactic vaccination is essential to prevent this condition (2, 3, 9). However, this immunization coverage remains low in most developing countries. We report a case of recurrent respiratory papillomatosis (RRP) in a very young child, hospitalized in a severe condition, and during several days before diagnosis establishment. This case illustrates the difficulties of management in the context of limited resources, and thereby highlights the importance of the prevention by HPV vaccination.

CASE REPORT

We report the case of a 3-year-old girl, with no known personal or familial past medical history, who was brought to the emergency room and then directly admitted for respiratory distress. Her parents reported a hoarseness of voice for several months, with the addition of a more recent moderate cough, as well as a gradually worsening dyspnea for the last 2 to 3 days. No choking episode and/or ingestion of a foreign body was reported. No fever was noted. Upon examination, the patient had dysphonia, tachypnea at 64 respirations per minutes, moderate stridor, and suprasternal retractions with a few bilateral rales. Nebulized epinephrine and then salbutamol were administered, associated with oxygen supplementation to reach a normal SpO2. These measures resulted only in partial and temporary improvement. Laboratory tests including blood cells' count, C-reactive protein and procalcitonin were unremarkable. Chest x-ray appeared normal. In the absence of significant improvement, IV steroids and several antibiotics protocols were initiated the days following admission: azithromycin, then IV amoxicillin with clavulanic acid, then IV ceftriaxone with gentamycin. Chest CT did not identify any foreign body. Bronchoscopy was requested but as not available at our center, making it required a private appointment. It should also be noted that the family needed some time to raise the necessary funds for this diagnostic test at a private facility. Direct microlaryngoscopy with bronchoscopy was finally performed for our patient one week later under general anesthesia. It revealed papillomatous growth occluding the glottis extending to the trachea (**Figures 1**, **2**). The exploration showed multiple laryngeal and tracheal other papillomas, which were excised and sent for histopathology study. No other localizations of exophytic lesions were reported. The patient recovered almost fully, with only persisting hoarseness of voice, and was discharged from the hospital three days after the intervention in excellent condition.



Figures 1, 2. *Aggressive laryngeal and tracheal papillomas on laryngoscopy, nearly obstructing the airway, with difficile intubation, that was possible only with a small endotracheal tube.*

The pathological study of our patient's specimen showed benign exophytic proliferative lesions in the mucosa of the airways with a few mitoses (**Figure 3**). The conclusion was a respiratory papillomatosis with low-grade dysplasia, requiring a regular histological control. Viral and genetic studies were not performed on the histological sample due to the unavailability of these tests at our facility. When asked, the mother reported recurrent genital infections that she was following up with her gynecologist but did not wish to provide more information. Details on the child's condition were given to her, and a letter with child's medical report was sent to her gynecologist. Antiviral treatment was considered but remains pending as it is not available at our structure. Six weeks after the first intervention, the child developed similar symptoms with the same poor response to medical treatment and required another microlaryngoscopy with removal of a new growth of papillomas. Several comparable episodes occurred over the subsequent months at closer and closer intervals. Vaccination by HPV vaccine was discussed but dropped due to the child's young age. The child is currently stable at time of writing this report, and the family decided to stay in the capital city of the country as it is the only place where access to bronchoscopy and microlaryngoscopy is available for children, with an ENT team experienced in pediatric bronchoscopy.

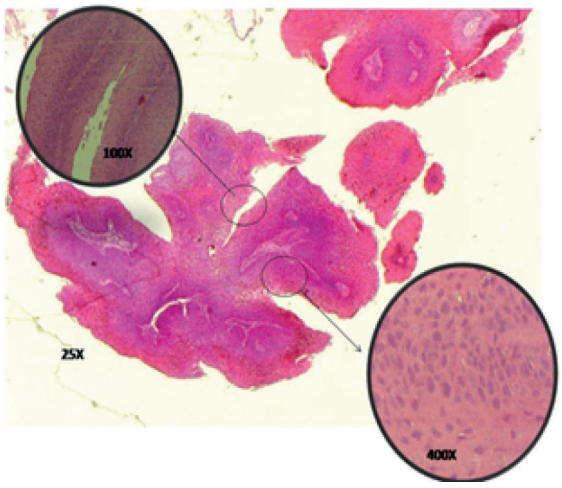


***Figure 3**. Histological study showing laryngeal papillomatosis (25K and 100K) with low-grade dysplasia (400K).*

DISCUSSION

RRP is a rare but serious condition mainly affecting children and characterized by recurrent UAO. It is primarily caused by vertically transmitted HPV types 6 and 11. The causative lesions are recurrent exophytic proliferative lesions in the mucosa of the respiratory tract known as papillomas. While the lesions are most commonly located in the larynx, as illustrated by our case, they can also spread distally into the trachea, large bronchi, and even to the lung parenchyma (5). Our patient, diagnosed at age 3 years, was born vaginally, to a mother followed for recurrent genital infections. The child's age falls in the interval of ages at diagnosis of several studies on juvenile RRP, from 2.8 to 4.6 years (10). In a Sudanese study, 90% of the overall cases were younger than 20 years old (7). Clinical manifestations typically begin in infancy and include biphasic stridor and hoarse voice/cry, followed by progressive persisting dysphonia, stridor and respiratory distress. Our patient presented most of these symptoms starting by the persisting dysphonia, highly indicative of RRP, as demonstrated by Seedahmed's study that found change in voice to be the first symptom in all the cases (7). Laryngeal papillomatosis should be recognized as a potential cause of laryngeal dyspnea resistant to the usual treatments. Diagnosis is established by respiratory endoscopy, and confirmed by histopathology study after resection, coupled, when possible, with viral and genetic analysis. In developing countries, RRP is often prone to misdiagnosis and mismanagement due to clinician's lack of familiarity with the disease and to the lack of resources, as shown by Fasunla's study in Nigeria, where only 2 out of 38 cases were correctly diagnosed by the referring clinicians. In the same study, diagnosis was delayed for 5 weeks to 3 months (9). For our patient, laryngoscopy was performed after approximately one week after admission due to the non availability of this test at our hospital. Additionally, viral, and genetic studies could not be performed as not feasible in our facilities. This reflects the difficulties encountered in low-income countries (9). Management options, which are limited and rarely curative, consists of repeated endoscopic procedures to remove the papillomas, and include laser therapy and interferon (2, 5). Recent studies have described

various adjuvant therapies used for RRP, including cidofovir (10). Only repeated removal of papillomas has been performed to our patient, as other measures were not available in our facilities. This procedure is the only therapeutic method used in developing countries where the adjuvant medical treatment is not yet a routine practice in RRP, as shown in most low-income countries' studies (2, 3, 7, 9). By convention, RRP's severity or aggressiveness has been based on the number of annual and/or lifetime surgeries, distal spread, or a composite of the 3 (10). The difficulty of management is related to the often-delayed diagnosis and the high recurrence of papilloma growth after surgical removal. This makes RRP unique not only in its high rate of multisite recurrence, but also in its high burden on patient quality of life, and in its high associated healthcare costs (11). Furthermore, tracheostomy may be required to ensure an adequate airway, but should be avoided, when possible, because reports suggest a related seeding of the distal airways with tumor. The poor availability and accessibility of appropriate healthcare services in developing countries are barriers to early diagnosis and to appropriate management, requiring many patients to undergo a tracheostomy, whose management is difficult in insufficiently developed settings with limited means and skills (2, 9). About 90% of Fasunla's group of patients required as such emergency tracheotomy (9). Scarring secondary of repeated surgical treatment for RRP is common and should be identified and prevented whenever possible (12). Additionally, malignant transformation of juvenile-onset RRP has been observed in young adults and in rare cases in children, causing a worse outcome (13, 14). As with our patient, dysplasia can be identified in up to 50% of RRP cases, requiring a regular histological control, as envisaged in our case. Malignant transformation occurs in about 1-2% of cases in adult series (15). Determination of HPV strain is not routinely performed in the standard of care for RRP patients. HPV genotyping is however interesting as biomarker for disease severity and progression (16). Since HPV infection is the cause of this severe condition, and as vaccination has shown a good efficiency in reducing prevalence of this infection, the prevention of this disease is possible in the HPV vaccine era. Australia was the first country to show a decline in juvenile RRP incidence, following the implementation of a national HPV vaccination program that achieved rapid and high vaccination coverage in target and catch-up age groups (17). A greater effort should be made on HPV-immunization coverage, especially in developing countries where resources remain limited (2, 6, 8, 18). This immunization is even more acritical as some observational studies suggest longer inter-surgical intervals and occasional remissions after vaccination (10, 19). Therefore, some physicians offer HPV vaccination to children with RRP before the routinely recommended age (10, 18). This measure is discussed for our patient but remains pending due to the low age. It should be noted that limited data exist on the safety of vaccinating children aged under 9 years. However, in a randomized controlled trial of 2-dose bivaalent (Cervarix) vaccination in girls aged 4-6 years, the vaccine had an acceptable safety profile as well as producing a high and sustained immunological response during 30 months of follow-up (20). A study conducted in USA concluded in very high direct costs of treating new cases of juvenile RRP and suggested to consider its results in HPV vaccination promotion investment decisions (21). The 2020, the world health organization (WHO) Global Strategy recommends that HPV vaccines should be included in all national immunization programs and should reach 90% of all girls by age 15 by 2030 (22). In Mauritania, HPV immunization was introduced in the public health program recently in 2021, and the vaccine coverage remains very low, similar to that of most developing countries (23). These elements demonstrate the immediate need for implementing vaccination in all regions of the world, and promoting a better HPV immunization coverage, as it is one of the most effective preventive measures.

CONCLUSIONS

Patients with RRP are still suffering from delayed and insufficient management in most low-income countries. Laryngeal papillomatosis should be early considered as a differential diagnosis in children with persisting laryngeal symptoms. It is etiologically linked with the HPV infection. Endoscopic resection remains the main treatment but has a limited success. The use

of adjuvant medical treatment in developing countries is not a routine practice. Malignant transformation is possible requiring sustained vigilance. Therefore, HPV vaccination should be encouraged as an important preventive measure, and possibly as an adjuvant therapy for RRP.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Author contributions

MS supervised the management of the case, researched and organized data, and she wrote and edited the manuscript. MSL, CAML participated actively to the surgical management of the case and to the collection of data. AEHMV provided pathological data and participated to the scientific discussion of the case. MT, SN, and HM participated actively to the management of the case. KF, FA and AB participated in reviewing the mother's obstetrical data and reviewed the recommendations of the future center concerning the risk of HPV transmission.

Ethical approval

Human studies and subjects

The Authors declare that the study protocol was approved by the competent Ethics Committee of the National Center of Oncology in Mauritania, in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

Animal studies

N/A.

Data sharing and data accessibility

The data underlying this article can be shared just before a reasonable 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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