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CASE REPORT

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Recurrent Respiratory Papillomatosis: A Report of two cases and review of literature

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Abstract *Background:* Recurrent Respiratory Papillomatosis (RRP) is a non-cancerous tumour of the upper airway caused by the human papilloma virus, presenting as "wart-like" growth, which could be anywhere from the nose to the lungs commonly in the larynx.
Design and Setting: Review of two cases at the National Hospital Abuja (NHA).
Objectives: To highlight the challenges in the management of RRP.
Subjects: Two patients diagnosed with RRP were referred to the paediatric respiratory clinic between 2009 and 2012. Case one is a four year old female who presented with persistent hoarseness of voice, breathing difficulty and noisy breathing of one year duration. She was born at term by spontaneous vertex delivery to a mother who had vaginal warty lesion excised during pregnancy. A neck X-ray showed opacities around the laryngeal region with total obliteration of air column with histological confirmation of squamous papilloma. She had eight excision surgeries within a two years period with treatment with oral acyclovir, interferon, and methotrexate and tracheotomy tube in situ. Case two, a six year old female presented with persistent hoarseness of voice that progressed to loss of voice, noisy and difficulty in breathing, snoring and frequent arousal from sleep of 1½ years. Histology was diagnostic of laryngeal Papillomatosis and she had two excisions surgeries and treatment with oral acyclovir and tracheotomy tube in place.
Conclusion: RRP though a slow growing tumour, presently has no definitive cure. Excision surgeries provide temporal relief and antiviral agents adjuvant therapies. Prevention with vaccination is desirable.

Keyword: Recurrent respiratory Papillomatosis, Human papilloma virus.

Introduction

Recurrent respiratory Papillomatosis (RRP) is caused by a viral agent –the Human papilloma virus (HPV) of which serotype six and 11 are the most common types.[1] RRP is characterized by exophytic wart–like growth that could be found anywhere from the nose to the lungs, with the larynx as most common site of occurrence.[2] Although the condition is a common benign neoplasm of the larynx among children and a frequent cause of childhood hoarseness, the course is variable in expression with some patients experiencing spontaneous regression and others suffering aggressive papilloma growth requiring multiple surgical procedure and medication for relief.[2] The morbidity and mortality of RRP are attributable to the tendency of the tumour growth to recur and spread throughout the respiratory tract causing airway obstruction.[2, 3] It is associated with a less than one percent risk of malignant transformation.[2, 3, 4]

RRP is categorized into juvenile onset RRP (JORRP) and adult onset RRP (AORRP) depending on the presentation before and after the age of 12 years, respectively.[2, 4, 5] The prevalence of the disease is variable depending on the age of presentation, country and socioeconomic status of the population being studied, but generally accepted to be between one and four per 100 000.[2] A prevalence 2.59/100 000 and 1.6/100 000 was found among paediatric population in two United States cities (Atlanta and Seattle) respectively. [6] Mgbor NC et al from Enugu, Nigeria reviewed 54 cases of laryngeal Papillomatosis, over an eleven year period (1988 – 98) of which 64% were children (≤15 years), with most presenting as upper airway emergency that necessitated emergency tracheotomies.[7] The children required multiple surgeries than the adult group.[7] Despite the low prevalence of RRP, it has been shown to have significant economic and emotional burden on the patients as they go through the cycle of recurrence and surgeries.[1]

This report therefore aims to highlight the challenges in management of RRP in a resource poor setting.

Case 1

Miss TJ, is a four years old female resident with her parent in Nyanya, Nasarawa state (a border town to Abuja- Nigeria). She was first seen in the paediatric respiratory clinic in July 2009 on referral from the ENT clinic. Her complaints were that of persistent hoarseness of voice, noisy and difficulty in breathing of one year duration. Her hoarseness of voice has been progressive since first noticed by the parents. She had no history to suggestive voice abuse, foreign body inhalation, cough or catarrh. She had worsening difficulty in breathing with fast breathing, but no cyanosis, orthopnea or leg swelling.

She was born at term, by spontaneous vertex delivery. Mother had vaginal warty lesions which were excised during pregnancy. Her immunization was routine NPI vaccines and she's had a normal developmental history.
Her father is a 42 years old Taxi driver with tertiary level education, and her mother is a 38 years old housewife with secondary level education. She is the youngest child in the family with two elder sisters and a brother, all doing well.

Examination revealed a well nourished young child with a functional tracheostomy tube in situ. She had no respiratory distress. Further evaluation by indirect laryngoscopy showed a wart- like lesion on the vocal cord, while a neck X-ray showed opacities around the laryngeal region with total obliteration of air column. Histology report grossly was of multiple pieces of whitish soft tissue aggregating 2.1 x 1.5 cm in the glottis and epiglottis; while microscopy was hyperplastic stratified squamous epithelium overlying a loose fibrovascular stroma; the epidermis tends to have finger-like projections into the core, with several cell of superficial epidermis of koilocytic atypia. Retroviral screening was nonreactive. Diagnosis was recurrent laryngeal Papillomatosis.

She's had eight excision surgeries ranging from two months to eight months interval from recurrence. Drug treatments given were oral acyclovir for two year, interferon and lately methotrexate. Her tracheostomy tube has been in place for over two years.

Case 2

Miss AF, a six years female was first seen at the ENT department and referred to the paediatric respiratory clinic of the hospital. Her complaints started 1½ yrs earlier when she developed persistent hoarseness of voice that progressed to loss of voice. There was associated noisy and difficult breathing, snoring while asleep and frequent arousal from sleep. Later in the course of the illness she developed cough that was productive of yellowish sputum. She had no history of sore throat, dysphagia, and odynophagia or globus sensation. She has no hearing loss or otalgia, no fever, no night sweats, but with some weight loss. Other systemic review was essentially normal. She had a course of antibiotics to relief the cough.

Her pregnancy was not adversely eventful and was delivered by spontaneous vertex with an uneventful neonatal period. She is the first child in a monogamous family setting with two other females and a male sibling, all alive and well. Her father is 48 years civil servant with tertiary level education, while the mother a 36 years old housewife also with tertiary level education. No history of warty lesion was reported in either of the parents.
On examination she was an underweight child with a tracheostomy tube in insitu. She had an inaudible voice and was not in respiratory distress. Other examination findings were essentially normal. Histology report grossly showed greyish white tissue aggregating 3x2x1cm; and microscopy was hyperplastic and papillomatos stratified epithelium overlying a fibrovascular tissue, with the epithelium koilocytic atypia. Diagnosis was recurrent laryngeal Papillomatosis. She has had two excisions surgeries for laryngeal polyps within a one year period and was commenced on oral acyclovir.

Discussion

RRP was first described by Sir Morrell Mackenzie in 1800s; he recognized it as a distinct lesion of the larynx in children. It was with modern genetic technology in 1990s that HPV was confirmed as the causative agent.[2, 4] Over a 100 serotype of HPV have been identified, with serotypes sometimes classified by anatomical sites; namely anogenital, non- genital cutaneous and non-genital mucosal. The HPV six and 11 can cause both genital warts and laryngeal Papillomatosis.[5] Some are also classified as 'high risk' type when it is associated with malignant transformation or 'low risk' type manifestig as warts (Condylomatosis), with low risk for malignancy. [5] The low risk serotypes six and 11 are the most common types found to be involved as causative agent of RRP. [2, 5, 8] The aetiology of JORRP is generally agreed to be vertical transmission either in pregnancy or at child delivery, especially when a mother has frank condylomatosis or is actively shedding disease from a recent HPV infection.[3,5] The two patients, had symptoms before age five, which is common presentation in the juvenile form of the disease, mostly transmitted vertically during gestation or delivery.[5,9] The mother of case number one had a history of anogenital wart which was excised in pregnancy, a risk for JORRP especially when its present at time of delivery.[3, 5] Some reports have showed that about 30- 60 percent of mothers with genital papilloma had their children affected with JORRP.[9, 10] Three major risk factors that have been identified for development of JORRP include; teenage mother, vaginal delivery and first born.[3, 9, 10] The two mothers of the cases in this series were well over twenty, while the second case was the first child of the

family. No other members of the family manifested the warty- lesions in the second case. Both of the patients were delivered vaginally. The relative risk of developing RRP after vaginal delivery ranges from two to seven in 1000, corresponding to odd ratio of 231 to 400 compared with children born vaginally without condylomata showing a low risk of transmission. [1, 8] The HPV DNA has been identified in the upper airways of as many as 25% of normal unaffected children.[8] This has fuelled debate on the benefit of offering caesarean section routinely to mothers with anogenital condylomata. [8] JORRP occur in one of 109 children delivered via caesarean section to mother with HPV infection of the anogenital region. This suggests other modes of transmission, among which is the haematogenous spread of HPV to the fetus while in- utero as HPV have been demonstrated in cord blood. [11] Postnatal contact with infected mother is also a possible mode of transmission.[11] In contrast, the risk for AORRP has been associated with sexual transmission especially in persons with multiple sexual partners and frequent oral sex. [10, 11]

JORRP affects male and females in equal proportions, [10] although the two cases presented were females, while the males are mostly involved AORRP. [10] The age of occurrence reported ranges from one day to 84 years; however a bimodal distribution is seen with the peak age range of juvenile form at two to four years and that of the adult at 20 to 40 years.[11] The two cases in this review had onset of the disease within the peak age for the juvenile form. RRP most often involves the larynx but can be seen in any part of the aero digestive tract. [2, 11] Extra- laryngeal spread of RRP occurs in 30% of children and 16% of adult, [11] which is an indication of progressive disease common with the JORRP type. The two patients in this report had progressive hoarseness, stridor and respiratory distress. Most reviews show that hoarseness of voice is the principal presenting symptoms among paediatric patients.[10, 11] Stridor which is the second common symptom begins as inspiratory, and then progress to biphasic.[11] Other symptoms identified includes, chronic cough, paroxysms of choking, recurrent pneumonia, failure to thrive, dyspnoea, dysphasia and acute life threatening event which are demonstrated in the two cases. At time of presentation it is important to identify respiratory distress for immediate transfer of patient to emergency room or operating room to ensure that a safe airway is established. A laryngoscopic examination should be performed on stable patient. This is challenging in children and requires examination under anaesthesia in operating room.

The natural history of RRP is highly variable; patient may experience a lifelong remission after initial disease whereas some will require periodic surgeries ranging from days to weeks in addition to adjuvant medical therapies.[1, 2, 4] The clinical features of RRP are often mistaken as asthma, croup, allergy, laryngitis, vocal nodules, bronchitis, foreign body aspiration, gastroesophaeal reflux disease, and malingering. Stridor present since birth may be diagnosed as laryngomalacia, subglottis stenosis, or a vascular ring, but RRP is still a possibility. [10, 11]
Patients with asthma, bronchiolitis or allergies tend to have recurrent coughs and wheezes and a possible family history atopy. Most RRP are diagnosed via laryngoscope or bronchoscopy as a cauliflower-like warty growth. It is necessary that viral typing is done to determine the prognosis where the facility is available. Chest and neck radiograph may reveal intratracheal densities. Other findings in chest radiograph include segmental or lobar atelectesis and post obstructive pneumonia.
CT scan of the upper airway may be helpful to reveal tumor-like papillomatous growth. Histological findings in biopsied lesion show growth of keratinized squamous epithelium overlying a fibrovascular core. Koliocyte, vacuolated cells with clear cytoplasmic inclusion are seen, with variable degrees of dysplasia and metaplasia.[10]

Several staging methods have been put forwarded for RRP, but none is uniformly accepted. Attempts are to standardize the evaluation of RRP patients, based on area of involvement, severity of involvement, and observation data such as the patient voice quality and extent of respiratory distress. [11,13]

At present, there is no cure for RRP and no single treatment has consistently been shown to be 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 CO_2, Nd: YAG laser, pulse dye laser and most recently the Shaver technology.[1-3, 9-11] Surgical techniques aim to remove papillomatous lesion, maintain safe airway and normal airway anatomy.[3] Despite successful removal, recurrence after surgery is common with complications like dysphonia, excessive airway scarring and stenosis.[11] The case one in this report has had eight surgeries with intervals from two months to eight months, which is a great burden for the family. Serotype 11 has being shown to be more likely associated with development of aggressive disease requiring frequent surgical procedure, adjuvant medical therapies and sometimes tracheostomy to keep airway patent. [1]

Adjuvant medical therapy is indicated as surgery does not eradicate the disease.[4] Several adjuvant therapies have been employed; unfortunately, most of these methods have not been rigorously tested.[8] The criteria for commencement of adjuvant therapy are the necessity for more than four surgical procedures annually, rapid regrowth of papillomata with airway compromise and remote multisite spread of the disease.[3] The list of adjuvant medical therapy include; antiviral agents (acyclovir, ribavarin, cidofovir); interferon, retinoid (oral metabolite or analogue of vitamin A), photodynamic therapy, zinc, antireflux medication, cyclooxygease -2- inhibitor, methotrexate, preventive vaccine (mumps, MMR, quadrivalent HPV, heat shock protein E7) and gene therapy.[2-4,9-12] These treatment focus on several mechanisms like immunomodulation, disruption of molecular signalling cascade or HPV replication resulting in apoptosis,

inhibition of proliferation, growth arrest and/or promotion of normal differentiation in HPV infected cells. [3] In both of the cases, acyclovir was employed as first line adjuvant medication. This is for reason of availability and documented evidence of usage for treatment of RRP. Activity of acyclovir is dependent on the presence of virally encoded thymidine kinase, an enzyme that is not known to be encoded by HPV. Acyclovir, however have been found effective in some cases when a concurrent viral infection or viral co- infection with herpes simplex virus, cytomegalovirus and Epstein - Barr virus occur. Patient with co-infection appear to have more aggressive clinical course. [1] Interferon has been extensively investigated for treatment of RRP. They are class of protein that are manufactured by cells in response to a variety of stimuli including viral infection. The exact mechanism of action is unknown; however, they modulate immune system and epithelial development by increasing production of protein kinase and endonucleases which inhibit viral protein synthesis. Interferon has shown to reduce severity of growth of papilloma.[1] Common interferon side effect includes acute reactions (fever, generalized flu-like symptoms, chills, headache, myalgia and nausea) and chronic reactions (reduced growth, increased liver transaminase level, lecopenia, diplegia, febrile convulsion, rash, thrombocytopenia, alopecia, dry skin, generalized pruritis and fatigue).[1] For children, the dosage for treatment of RRP is 5MU/m^2 subcutaneous daily dose for 28 days; then three days per week for six month. With good response the dosage is reduced to 3MU/m^2 3 days per week followed by slow weaning.[1] If no clinical response is seen at 6 month, it is advised to discontinue with the treatment as in the first patient, with Methotrexate employed as alternate medication. It is an antimetabolite that inhibits DNA synthesis and repair by affecting folate metabolism.[9] There are reports of cases where the uses have demonstrated a marked improvement in both severity of the disease and surgical interval. [9, 12] Both cases in this report have had adjuvant therapies with interferon and acyclovir in addition to surgeries.

The economic and medical burden of RRP makes prevention of paramount importance. There are two HPV vaccines available for usage. These are Gardasil^R from Merck, and Cervirix^R from GlaxoSmithKline (GSK).[5] Both vaccines were developed with virus-like particle (VLP) that stimulates the surface of HPV. The Cervirix contains VLP to stimulate response to serotype 16 and 18, while Gardasil is a quadrivalent vaccine with VLP for serotypes 6, 11, 16 and 18. Successful stage II trials have been conducted with these two vaccines. [5] Although the usage is targeted at young age group before commencement of sexual activities for the prevention of cervical cancers, with a future hope for the decline of RRP also.

Conclusion

RRP is a chronic disease caused by HPV characterized by cauliflower-like warty growth in the aerodigestive tract. The lesion is commonly found in the larynx. Hoarseness of voice is the commonest symptom and patient can present with acute life threatening airway obstruction. Surgery is mainstay of treatment but does not provide cure. Several adjuvant medical treatments are required for frequent relapse, lesions with rapid regrowth causing airway obstruction and those in remote site. RRP cause substantial emotional and economic burden in patient and the family as well as create management challenge to the medical practitioner. The greatest promise for future prevention rest with the development of an HPV vaccine, and hence reduced management challenges for HPV- associated diseases.

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