CASE REPORT

Glottic neurofibroma in a background of juvenile onset respiratory papillomatosis and obstructive sleep apnoea: A baffling discovery

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SUMMARY

Laryngeal neurofibromatosis and papillomatosis are relatively uncommon, the former being extremely rare cause for an obstructed paediatric airway. Here, we would like to report a case of synchronous occurrence of laryngeal papilloma with neurofibroma in a child who presented with a life-threatening obstructed upper airway. The management primarily revolved around acute airway management and airway surveillance.

INTRODUCTION

It is uncommon to find both laryngeal neurofibromatosis and papillomatosis to exist synchronously within the airway. Juvenile laryngeal papilloma is known to be closely related to human papillomavirus (HPV) infections. However, laryngeal neurofibroma can either be attributed to a genetic inheritance, i.e., in neurofibroma type 1 and type 2 or as a sporadic occurrence resulting in isolated solitary lesions. To our knowledge, this dual synchronous occurrence, which presented as an airway emergency, has not been reported in literature thus far. Therefore, this case report details the co-existence of both these pathologies in a child with obstructive sleep apnoea who presented with an acute life-threatening respiratory distress.

CASE REPORT

A 7-year-old boy of mixed African-Malay descent, with underlying autism and morbid obesity (weight 134 kg, height 158 cm, Body mass index of 53) presented to the Sarawak General Hospital emergency department with features of impending respiratory collapse. Patient complained of productive cough with dyspnoea, orthopnoea, and progressive reduced effort tolerance for 5 weeks. He also had hoarseness since age 1 accompanied with noisy breathing since age 3, for which the latter was treated as bronchial asthma by a general practitioner, and there were no prior hospitalisations. Patient was drowsy on arrival, with presence of audible wheeze and reduced air entry upon auscultation. There were no abnormal skin lesions, e.g., café au lait spots, no bone deformities, and no obvious masses.

Blood gas analysis showed type II respiratory failure, and chest X-ray showed blunting of bilateral costophrenic angles and cardiomegaly. Bedside echocardiogram revealed dilated right heart with poor contractility. A working diagnosis of acute exacerbation of asthma and congestive heart failure secondary to chronic obstructive sleep apnoea was deduced, and initial treatments were instituted. As a result of failed non-invasive ventilation, he was intubated in the operation theatre in the presence of the otolaryngology team in the advent of anticipated difficult airway. He was preoxygenated with bilevel positive airway pressure and administered with total intravenous anaesthesia. Patient was placed in a ramped position and successfully intubated with cuffed endotracheal tube size of 6.5 mm assisted by C-MAC videolaryngoscope. Direct laryngoscopy and rigid tracheoscopy were performed by the otolaryngologist displayed presence of papilloma-like lesions at bilateral false cord, arytenoids, and laryngeal surface of the epiglottis including the anterior and posterior commissures (Figure 1a, 1b). There was no infraglottic involvement, and the glottic inlet was stented by the endotracheal tube. No tracheobronchomalacia seen. Debulking of the mass was done with cold instrument with multiple specimens sent for histopathological examination.

He underwent adenotonsillectomy at day 7 post-op, and two days later, he was extubated to bilevel positive airway pressure and continuous positive airway pressure subsequently. Flexible nasopharyngeal scope evaluation during extubation showed bilateral mobile vocal cord movement. Throughout this period, he developed lower limb deep vein thrombosis, nosocomial infection, and pressure sore as a result of prolonged immobilisation and underlying co-morbidities.

Histopathological examination of the specimens from the supraglottis and larynx revealed two different pathologies: squamous papilloma involving both false cords, arythenoids and laryngeal surface of epiglottis and neurofibroma at the anterior commissure. The squamous papillomatous lesions displayed proliferative well-differentiated squamous epithelium overlying the fibrovascular cores. These fibrovascular cores were infiltrated with mixed inflammatory cells and many ectatic blood vessels. The presence of intraepithelial neutrophils, with some areas showing reactive atypia, was observed. These squamous epithelial cells were negative for p16 (Figure 2a). The neurofibroma involving the

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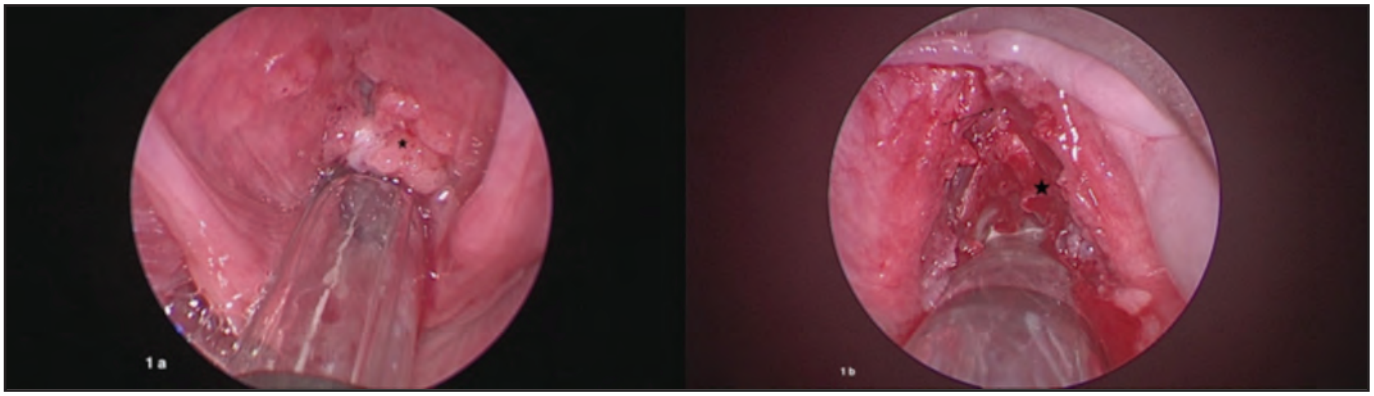

Fig. 1: (a) Intra-operative direct laryngoscopy 0-degree endoscopic view: Papillomatous lesions at bilateral false cords; asterisk denotes left false cord and arytenoids obstructing glottic inlet
(b) Post-debulking of the lesion showing the anterior commissure (marked by thin arrow) and right vocal fold (marked by black star)

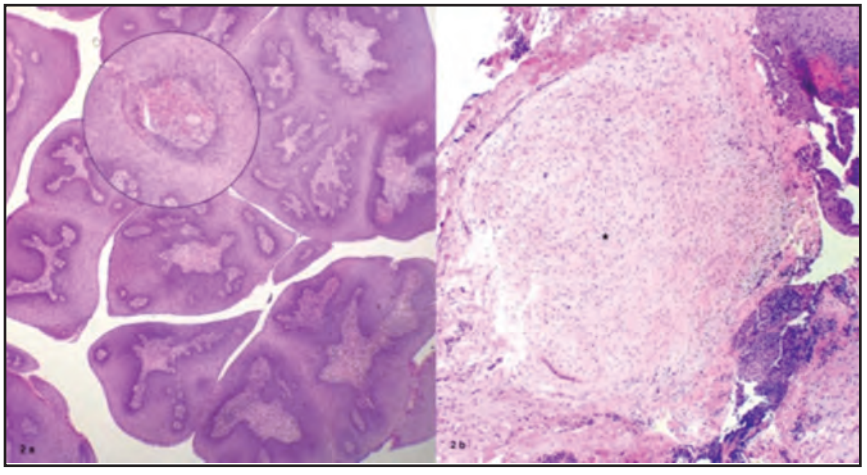

Fig. 2: (a) Haematoxylin and Eosin stain: Papillomatous lesions displaying proliferative well-differentiated squamous epithelium with arborising fibrovascular cores. Fibrovascular cores are infiltrated by mixed inflammatory cells with ectatic blood vessels; magnified lens
Original magnification x100
(b) Haematoxylin and Eosin stain: Neurofibroma with features of hyperplastic overlying squamous epithelium. Hypocellular proliferation of spindle cells with wavy bland nuclei. Cells are arranged in lose fascicles intermixed with bundles of collagen, denoted by black asterisk. Cells are positive for S100 stain
Original magnification x100

anterior commissure showed the presence of a poorly circumscribed lesion composed of hypocellular proliferation of spindle cells with wavy band nuclei. The cells were arranged in loose fascicles intermixed with bundles of collagen, which stained positive for S100 (Figure 2b).

He was discharged home with continuous positive airway pressure at eight weeks post-op, with only hoarseness evident. There was no stridor throughout the post-operative period. The final diagnosis upon discharge was severe obstructive sleep apnoea contributed by laryngeal papilloma and laryngeal neurofibroma causing severe respiratory distress. He is currently undergoing serial airway assessment to monitor disease progression and outcome.

DISCUSSION

Laryngeal papillomatosis (LP) was first described in children by Sir Morel Mackenzie in 1800, and later, Chaveliar Jackson introduced the term *'juvenile laryngeal papillomatosis'* (JLP) in 1940.[1] This benign laryngeal disease poses a management challenge owing to its tendency to recur and its unpredictable course. LP can be divided into two subtypes: juvenile and adult-onset LP, with the former displaying a more aggressive behaviour. The incidence of laryngeal papillomatosis is 4.3 per 100,000 children and 1.8 per 100,000 adults.[2] Juvenile LP shares a commonality with other respiratory disorders, resulting in frequent misdiagnoses as asthma or laryngotracheobronchitis in the emergency room.[3] Its presentation at a young age makes formal lung function test not feasible, thereby contributing towards challenges in making a correct diagnosis. The mean age of diagnosis is

2–9.[4] years, whereby children presenting later may have worsening dysphonia, stridor followed by respiratory distress4, as seen in our patient. Role of early laryngoscopic examination by the otolaryngologist is paramount in reaching a diagnosis, owing to the characteristic features of these papillomas, thereby preventing treatment delay. Histologically, papillomas are warty lesions with finger-like projection of stratified squamous epithelium with abnormal keratinisation and basal hyperplasia.

Highly sensitive real-time polymerase chain reaction is used to detect the presence of HPV. False negative results may occur when there is a low viral load. P16 (IKN4A) antibody expression as a biomarker is routinely used in combination with PCR to detect HPV. However, Huebbers et al reported a case of recurrent laryngeal papilloma linked to HPV, with no positivity to p16,[5] similar to this case.

Therefore, immunohistochemical detection of p16 alone is insufficient to prove the presence of HPV. As a result of poor laboratory resources and accessibilities in developing countries, the use of single methods to detect HPV, as done in our centre, may contribute to the false negative status.

JLP is commonly linked to HPV 6 and 11 subtypes, via intrapartum transmission. Despite this, its prevalence in pregnant mothers is only about 2%. Therefore, HPV infection may not be wholly responsible, and recent studies have shown immune response and some genetic susceptibility linked to the development of JLP.[6] Gelder et al found significant association with HLA DRB1x0102/0301 and DQB1*0201/0202 and increased inclination to JLP.[7] This may support the HPV-negative squamous papilloma presented in the biopsies from our patient.

Treatment of recurrent laryngeal papilloma is challenging and entails surgical and adjuvant therapies. Surgery aims to remove papillomas while preserving normal laryngeal tissue. It consists of repeated endoscopic microlaryngeal debulking surgeries with cold instruments, powered instruments such as microdebriders, lasers, or coblators. depending on the availability of resources and surgeon's preference.

Adjuvant therapies have been tried such as alpha interferon, bevacizumab, cidofovir, immunotherapy, and quadrivalent HPV vaccine to further improve the treatment outcome. Quadrivalent HPV vaccinations have shown to decrease the number of surgeries and increase the duration between surgeries.[8]

Laryngeal neurofibromas (LN) are benign tumours arising from Schwann cells and perineural cells and are extremely rare cause of paediatric upper airway obstruction. To the best of our knowledge, LN occurrence in the background of laryngeal papilloma, as reported in this index patient, has not been reported to date.[8]

Neurofibromas are classified as neurofibromatosis-1 (NF-1), neurofibromatosis-2 (NF-2), and spontaneous solitary lesions. The estimated prevalence of NF-1 is cited as 1 in 3000 patients and is transmitted in an autosomal dominant fashion; however, 30–50% patients are associated with spontaneous mutations with no family history.[9] They present in childhood with café-au-lait spots, learning disabilities, endocrine abnormalities, Lisch nodules, skeletal defects, axillary or groin freckling, or multiple cutaneous neurofibromas. NF-2 occurrence is also rare and typically presents in third decade of life.

There are only 62 paediatric laryngeal neurofibromas that have been reported worldwide.[6] Owing to their slow growth, patients may remain symptom-free for years or present at birth. The mean age of presentation is 4.1 years (0.8–12 years) with stridor being most common feature (44%) followed by hoarseness (12%). Most common site involvement in the larynx is the aryepiglottic folds and arytenoids as they are rich in terminal nerve plexuses. Features such as mimic papillomas until surgery reveal unanticipated histology. There is limited occurrence of neurofibroma in the vocal cord, which was reported in adults and not in children.[6] Here in our case, the anterior commissure of the glottis revealed the presence of a neurofibroma, thus postulating the possibility of an isolated spontaneous solitary neurofibroma, which is extremely rare. Tumour is believed to arise from the superior laryngeal nerve and/or from anastomosis with the recurrent laryngeal nerve. Histological features include slender spindle cells in collagenous stroma adjacent nerve fibres and axons and stain for S100 due to neurogenic origin.[6]

Treatment of LN depends on the site, size, and severity of presenting symptoms. Due to its infiltrative nature and poor margin control, the likelihood of recurrence is high as with papillomas. Therefore, mainstay of treatment includes surgical procedures that preserve laryngeal function while providing an adequate airway. Endoscopic approach either using cold-steel instruments or laser is used to address small, localised lesion. Large infiltrative lesions may require an open approach for a wider exposure, sometimes requiring tracheostomy.[6]

CONCLUSION

The irony of similar clinical presentation and behaviour of both JLP and LN as seen in this case were indeed challenging. Bearing in mind that both lesions tend to recur and may contribute to an obstructed airway, close monitoring with airway surveillance and follow-up is indeed at its utmost precedence.

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