

Malignant Transformation of Nonirradiated Recurrent Juvenile Laryngeal Papillomatosis

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Abstract

Very few cases of spontaneous malignant transformation of nonirradiated recurrent juvenile laryngeal papillomatosis (JLP) have been reported in literature. We document a case of invasive laryngeal carcinoma arising in pre-existing juvenile laryngeal papillomatosis. After multiple CO₂ Laser resections, a 29-year-old female, non-smoker, who had never received radiation therapy, developed a florid exophytic transglottic squamous cell carcinoma. Therefore, regular extensive biopsies and careful histopathological examination are required in cases of JLP. We also emphasize the need to maintain a high index of suspicion for malignant transformation in long standing cases.

Keywords: Juvenile laryngeal papillomatosis, Malignant transformation, Squamous cell cancer.

INTRODUCTION

Papillomas of the larynx are common benign epithelial tumors.¹⁻⁶ This disease includes two basic patterns: solitary laryngeal papilloma (SLP) and juvenile laryngeal papillomatosis (JLP); the latter illness is more common and tends to recur after excision.¹ Furthermore, 3 to 7% of these lesions undergo malignant transformation into laryngeal cancer.^{7,8} While the majority of JLP have an entirely benign appearance and clinical behavior, a small number of reports have been published on malignant transformation of these lesions. A cancerization of formerly irradiated juvenile papillomas is now a well-described entity but only few reports exist about the progression of non-irradiated papillomas to infiltrating squamous carcinoma. Laryngeal cancers may be very difficult to be diagnosed histologically and clinically early in the transformation process of JLP,³ and a solitary papilloma does not guarantee a good prognosis.^{4,9} Several recent reports suggest HPV types 6, 11, 16, and 18 are related to malignant transformation in JLP,^{3,6,8,10,11} but such instances are rare. Therefore, the role of HPV in the process of malignant transformation of laryngeal papilloma is still uncertain.¹² Other factors that have been implicated for the malignant transformation of the JLP are smoking, irradiation, exposure to other chemical

agents. Genetic mutation of p53 in association with integration of HPV-11 has been reported in histological malignant lesions. This association may promote progressive genetic instability that can lead to the development and clonal expansion of malignant lesion in JLP. Thus, not only papillomatosis but also some forms of its treatment have a potential for malignant transformation and this should be kept in mind.¹³

We present a case of a 29-year-old female, non-smoker, non-irradiated who underwent malignant transformation of long standing juvenile laryngeal papillomatosis. This case demonstrates the difficulty in making the diagnosis of malignancy and need to maintain a high index of suspicion. Also, a meticulous clinical and pathologic evaluation is emphasized.

CASE REPORT

A 29-year-old female, non-smoker, with history of multiple resections for juvenile recurrent laryngeal papillomatosis from age of thirteen years, presented to us with progressive hoarseness and mild stridor of 4 months duration. One of the histopathology reports when she was 20 years of age had shown associated carcinoma *in situ*. Rigid endoscopy examination of larynx (Fig. 1) revealed proliferative lesion

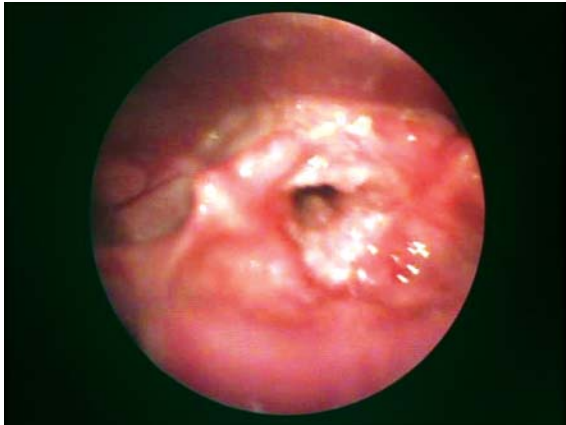


Fig. 1: Rigid endoscopic view of the left transglottic growth

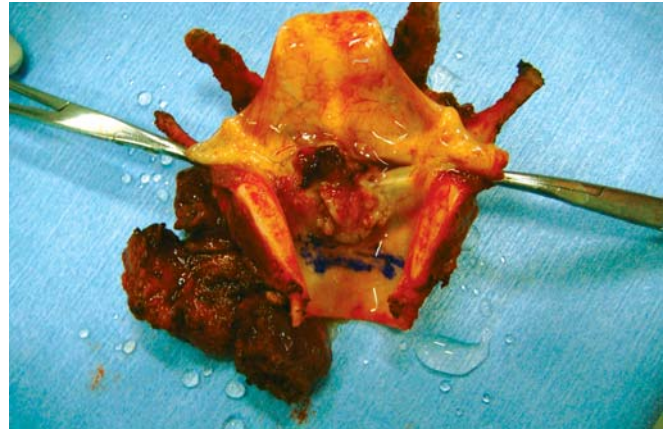


Fig. 3: Clinical picture of the total laryngectomy specimen

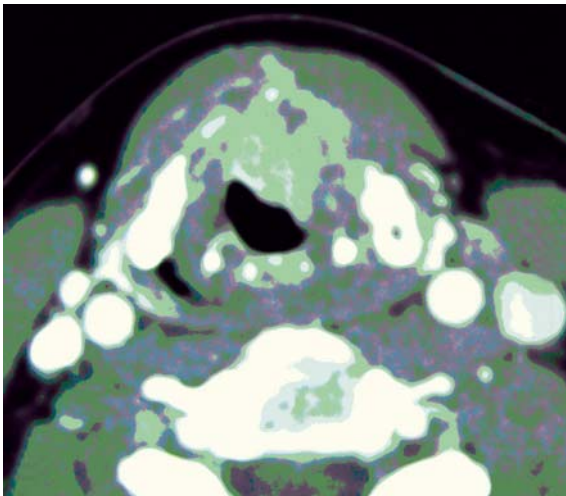


Fig. 2: Axial CT scan view of the transglottic lesion

of the left cord and anterior commissure with involvement of the anterior 2/3rd of the right true cord. There was significant supraglottic and subglottic extension of the disease with fixation of left hemi larynx. Examination of the neck did not reveal any lymphadenopathy. CT scan (Fig. 2) showed a large supraglottic enhancing mass involving the true cords, anterior commissure with significant subglottic extension. There was sclerosis of the laryngeal cartilage suggestive of erosion of thyroid cartilage. Metastatic work up did not reveal any distant metastasis. She was staged as cT4 NO MO transglottic cancer. Direct laryngoscopy confirmed the clinical findings. Histopathological examination of the punch biopsy was in favor of invasive squamous cell carcinoma. Neither conservative laryngeal surgery nor organ preservation with chemoradiotherapy was possible as there was gross thyroid cartilage involvement.

Wide field total laryngectomy was performed on her (Fig. 3). Postoperative period was uneventful. Final Histopathology revealed an ulceroinfiltrative tumor occupying supraglottis, glottis and subglottis. All the mucosal margins including the tracheal cut margin were free and well away from the tumor. Bilateral selective neck dissection did not reveal any lymph node metastasis. No adjuvant treatment was given to her. After two years of follow-up she is locoregionally well-controlled and there is no evidence of any papillomatosis in the lower respiratory tract.

DISCUSSION

Juvenile laryngeal papillomatosis presents clinically as recurrent and multiple papillomata which begin in infancy or childhood and possibly involute spontaneously in adolescence. Similar papillomatosis may occur in adults, but are usually solitary and less likely to recur following excision. Malignant transformation has been reported in only few cases without prior radiation therapy. The reported incidence is 2 to 3% of cases especially in the presence of known risk factors, such as smoking and irradiation.¹⁹⁻²¹ However, search of English literature revealed only few documented cases. The diagnosis of synchronous invasive carcinoma in the setting of papillomatosis is difficult to make both clinically and pathologically. But findings consistent with carcinoma *in situ* do not carry the same grave significance in a patient with Juvenile laryngeal papillomatosis.¹⁷ Juvenile form is associated with florid papillomatosis but no malignant change unless the lesion is irradiated.¹⁸ Patients in whom the disease follows a more aggressive course demonstrate the following findings:

- Persistence into adulthood.
- Airway obstruction with need for tracheotomy.
- Spread to subglottis.

Unfortunately, the treatment of laryngeal papillomatosis remains symptomatic in that as existing lesions are removed by surgery, new lesions arise *de novo* in adjacent sites or other areas of the larynx. At the same time, various chemical substances have been tried together with surgery or separately attempting to achieve better control of the lesions.

Our case illustrates the link between the phenomena by which virus may be the initiating event in the papilloma to carcinoma sequence. Laryngeal papilloma patients in Taiwan exhibit a relatively high conversion rate to malignancy.¹⁴ Patients who initially clear their HPV infection are at higher risk for developing laryngeal carcinoma when subsequently infected with HPV as compared with patients with persistent HPV-associated laryngeal papillomas.

Recurrent respiratory papillomatosis transformation to a malignancy is a rare occurrence, with roughly 40 cases reported in the literature. Of those in which HPV genotyping was obtained, 100% demonstrated evidence of HPV-11 infection. Reidy and colleagues, moreover, have provided evidence demonstrating the ability of HPV-11 genes to integrate into the host genome, a known mechanism underlying the malignant conversion of “high-risk” types of papillomavirus, including HPV-16 and HPV-18. These authors suggest that JLP patients with HPV-11, currently considered a “low-risk” virus, should be closely followed because of its known more aggressive clinical course¹⁵ and emerging capacity for malignant transformation.¹⁶

The present case is a good illustration of malignant transformation of the juvenile laryngeal papillomatosis, the importance of periodic biopsy and histopathologic review and fact that malignant transformation can occur even in absence of known risk factors like smoking and irradiation.

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