Integration of human papilloma virus type 26 in laryngeal cancer of a child

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Abstract
Squamous cell carcinoma (SCC) in larynx is rare with children and adolescents. Usually larynx cancer is common with male smokers in the 7th decade. Among patients with no history of tobacco and/or alcohol consumption several factors have can play a role in the outbreak of laryngeal cancer: such as individual predisposition, radiation, gastroesophageal reflux, viral infection, dietary factors and environmental influences. In literature only few cases of laryngeal cancer with children are reported. Recent studies show that the most frequent laryngeal malignancy is the embryonal rhabdomyosarcoma. Besides the recurrent respiratory papillomatosis (RRP) based on an infection with human papilloma virus (HPV) types 6 and 11 (low risk) and types 16 and 18 (high risk) is known for a possible malignant transformation towards a SCC. HPV type 26 is only reported as low risk type HPV associated with cervical cancer.

Final diagnosis often takes a long time. Initial symptoms such as hoarseness, cough or shortness of breath are often referred to more typical pediatric diseases or laryngeal development.

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1. Introduction
Recurrent respiratory papillomatosis (RRP) is a serious disease in childhood. It is associated with the human papilloma virus (HPV) [7]. The most frequent HPV types, detected in RRP, are types 6 and 11. Approximately 1–2% of the patients with an early onset of RRP develop SCC in the upper respiratory tract. The HPV types 16 and 18 have been called high risk due to their direct association with genital cancer. Some studies and case reports also consider HPV type 11 as a high-risk virus because of the more aggressive development compared to HPV 6 types [5].

These patients were diagnosed in earlier stages and were more unlikely to show remission after surgery and/or radiation therapy. HPV 11 may play an important role in the genesis of laryngeal upper respiratory tract cancer. Usually RRP requires multiple surgical therapies, sometimes a spontaneous remission is found. However, in literature, multiple reports of development of RRP into an invasive carcinoma are given [4].

Usually SCC of the larynx is diagnosed in adult males with a history of risk factors such as extensive smoking, the exposure to irradiation or chemical carcinogens.

Children with initial symptoms such as hoarseness, dysphonia, dysphagia or recurrent upper respiratory tract obstruction demand a high degree of attention. Early laryngeal inspection and biopsies should be achieved [2].

Some studies show a malignant transformation of RRP towards SCC in 11% of the cases reported. Some carcinomas are diagnosed after a radiation therapy due to papillomatosis or adenoids [4].

In our study we present a 12-year-old boy with a SSC in his larynx. HPV could be detected in the tumor tissue, but there is no clinical or reported history of RRP.
2. Case report

A 12-year-old boy with a short history of dysphonia, no shortness of breath or dysphagia was presented for diagnosis. After a traumatic accident during a soccer game the dysphonia broke out and got worse during the following days. The laryngoscopy showed a polypoid tumorous lesion, completely consuming the left vocal chord (Figs. 1 and 2). The biopsy of the specimen revealed an invasive squamous cell carcinoma, well differentiated. The clinical staging (CT scan of thorax, abdomen and neck, ultrasound of neck and abdomen) showed a cT2 cN1 cM0 stage. The patient underwent a laser-guided chordectomy with bilateral neck dissection. The final staging was pT2, pN0, M0 and R0. Postoperative irradiation/chemotherapy were not performed. A microlaryngoscopic control after 1 month revealed a mild to severe dysplasia in the mucosal biopsy. This fact led to another resection in the vocal chord area. The final results of control biopsy a month later showed the mucosa free of dysplasia or tumor.

DNA of HPV type 26 could be amplified from the tissue of the SCC. The PCR technique was used to amplify HPV DNA from cell cultured tissue from the specimen. A special HPV sequencing revealed the DNA of HPV type 26. Li-Fraumeni-Syndrome could be ruled out by genetic analyses.

3. Discussion

The origins of SCC of the larynx with children were traditionally considered carcinogenic like in cases of irradiation, chemicals or smoking [1]. Then a chromosomal dislocation was found in young patients, which tend to develop cancer in childhood. In our case a 12-year-old boy developed a T2-vocal-chord SCC, but no history of papillomatosis and no cancerogenic factors were reported. However in most cases of laryngeal SCC the human papilloma virus of the types 6/11/18 and 33 could be identified [5]. A long history of RRP was reported in these patients whereas in this case no RRP has been diagnosed before. The first symptoms of hoarseness and a shortness of breath led to the diagnosis of an invasive SCC. We cannot be sure whether a malignant transformation of an undiagnosed papillomatosis caused the glottic SCC. For this reason the department of virology performed a PCR screen for all common HPV types. Interestingly HPV type 26 could be amplified in the tissue. This led to the interpretation that a papillomatosis possibly is the base of the tumor. The low risk HPV type 26 has only been associated with genital and not upper respiratory tract cancer before.

As to the mechanisms of transformation several factors seem to play an important part. The process seems to be triggered by the genetic disposition and the presence of HPV [3]. Regarding diagnostic management and options of therapy physicians should keep in mind the initial symptoms such as dysphagia, dysphonia, hoarseness or resistant cough in order to rule out a laryngeal tumor. In childhood approximately 70% of all malignancies concerning the larynx are of mesenchymal origin [6]. The RRP is the most common benign tumor in the glottis region in childhood. Former studies have shown the amplification of HPV types 6 and 11, 16, 18 and 33. Nevertheless the low risk types and especially type 11 show an increased potential of a serious clinical development. HPV subtype 26 is also regarded as low risk.

The therapy of juvenile larynx SCC should be performed just like with the adult patient. Surgical, oncological approaches and postoperative irradiation and/or chemotherapy play the most important role. In younger ages the decision for primary irradiation should be made rather carefully, the risk of secondary malignomas later in life should be kept in mind.

Our decision for the long-term follow-up was to determine short-term interval controls in the outpatient clinic. Regarding the progressive course of low-risk HPV associated carcinomas we started with 6 weeks intervals of ultrasound and laryngoscopy controls. The first endoscopy with biopsy was done after 1 and 6 months. Since there are no certain protocols for the long-term follow-up of HPV associated carcinomas with children we proclaim a rather conservative follow-up protocol.
4. Summary

RRP represents the most common benign tumor of the larynx in childhood. Infection may occur during birth or by respiratory infection. Mostly HPV 6 and 11 (low risk) and 16 (high risk) are found in RRP. Malignant transformation can be found even in “low risk” HPV subtypes. There are no cancerogenics in childhood, which shows that besides rare syndromes HPV in the RRP is the most common origin of SCC. A diagnosis at an early stage is important for the prediction of the RRP. In our case a HPV subtype 26 could be amplified in a “primary” SCC of the vocal chord. This HPV type has not been described as an origin for a SCC of the larynx.

References