Metastatic Squamous-Cell Carcinoma of the Lung Arising in a 12-Year-Old Boy with Juvenile Recurrent Respiratory Papillomatosis of Neonatal Onset

Akciğerin Metastatik Skuamoz Hücreli Karsinomu; Neonatal Dönemde Ortaya Çıkan Tekrarlayan Respiratuvar Papilomatozis Olgusu; 12 Yaşında Erkek Hasta

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ABSTRACT

Juvenile recurrent respiratory papillomatosis is the most common benign neoplastic disease of the larynx in children, characterized by numerous squamous papillomas caused by Human Papilloma Virus type 6 and 11. HPV is thought to be acquired at the time of vaginal delivery from maternal genital condylomas. Juvenile recurrent respiratory papillomatosis can be protracted by surgical interventions performed to avoid airway obstruction and extend below the vocal cords as far as the main stem bronchi. Lung involvement in Juvenile recurrent respiratory papillomatosis seems to be more prevalent than non-systematic reviews have reported until now and progression to cancer occurs in a significant proportion of these cases at a younger age than previously reported. This would suggest that closer attention should be paid to these children. We report a case of malignant transformation in a 12 year-old boy followed-up since the birth for an invasive juvenile recurrent respiratory papillomatosis with pulmonary involvement. The presence of HPV 6/11 was demonstrated by PCR analysis performed on material obtained from a metastatic vertebral lesion.

Key Words: Human papillomavirus, Squamous cell carcinoma, Recurrent respiratory papillomatosis, Children

INTRODUCTION

Juvenile recurrent respiratory papillomatosis (JRRP) is the most frequent benign neoplastic disease of the larynx in children and adolescents (1). JRRP is characterized by numerous benign squamous papillomas of the respiratory tract, usually confined to the larynx and self-limited. Occasionally, the behaviour is more aggressive, with persistent, recurrent papillomas and spread to the inferior airways (2). This distal involvement has been reported to occur in the trachea in 2-26% of cases and in the lungs in 2.3 % of cases (3, 4).

The strongest risk factor for JRRP is a maternal history of genital papillomas transmitted during delivery. JRRP is due to infection with Human Papilloma Virus (HPV) mainly of type 6 and 11 (2,5,6,7). Although these HPV types are thought to be of «low risk» in the genitary tract, patients with JRRP can develop broncho-pulmonary carcinoma, especially those who receive radiation or cytotoxic drugs or subsequently smoke (8).
We report a new case of metastatic squamous cell carcinoma associated with HPV6/11 in a 12 year-old boy managed for a neonatal onset JRRP with pulmonary involvement.

CASE REPORT

Clinical data, since the birth of the child were available and reviewed. A Guyanese child presented with respiratory symptoms, shortly after birth. He was born at full-term and delivered vaginally. It is not known whether his mother had genital condylomas. These respiratory symptoms led to the discovery of papillomatosis affecting the whole upper airways (nose, trachea and bronchi). At the age of 4 months, he underwent a tracheotomy due to upper airway obstruction. A biopsy performed in Guyana confirmed benign papillomatosis. The patient referred to our institution at the age of 6 months and underwent a surgical management consisting in airway desobstruction with laser procedures and XPS shaver, without any improvement.

Medical therapy consisting in 15 cycles of intravenous administration of cidofovir was started in January 2001, followed by local injections into the larynx every month since April 2002 (7.5 mg/ml, from 10 to 20 ml each time). Between July and September 2007, he weekly received aerosols of cidofovir (30 mg each). No clinical response was obtained despite surgical and medical management, requiring 234 hospitalizations and 150 endoscopies under general anesthesia between 1997 and 2008. The tracheotomy could not be removed at any time.

At the age of 12 year-old, a follow-up computed tomography (CT) scan demonstrated a large pulmonary mass with mediastinal lymphadenopathies (Figure 1) and a lumbar spine (L2) lytic lesion (Figure 2). The pulmonary tumor was not accessible to biopsy or surgical resection and persisted after a broad-spectrum intravenous antibiotherapy. A fine needle aspiration (FNA) and a CT-guided fine needle-biopsy were then performed on the L2 lytic lesion. The cytologic material obtained was analyzed after MGG stain. Tissue for microscopic examination was fixed in formalin and processed routinely. Sections (5 µm) were cut from the paraffin blocks and stained with haematoxylin-eosin-saffron. FNA showed numerous differentiated squamous cells. Biopsies measured 10 mm in greatest length. Microscopic examination showed infiltration of bone by a carcinoma composed of sheets of polygonal tumor cells with abundant eosinophilic cytoplasm and vesicular nuclei, mild atypia and a low mitotic rate. Keratinization was focally present. A bone metastasis from pulmonary

Figure 1: Thoracic TDM showing pulmonary mass with mediastinal lymphadenopathies.

Figure 2: Spinal TDM: peripheral lytic lesion in L2.

Figure 3: Bone infiltration by well differentiated squamous cell carcinoma. (H&E Saffron; x40).
The course of the disease is unpredictable. Papillomas may regress spontaneously. An aggressive course may occur when papillomas spread to the distal airways and to the lungs, probably protracted by iterative surgical interventions performed to avoid airway obstruction. A systematic review of the literature analyzed 11 publications on 161 cases of lung involvement in JRRP. The pooled data showed the incidence of lung involvement in JRRP at 3.3% (from a cohort studies) and the incidence of malignant transformation at 16%. The median interval between the diagnosis of JRRP and that of lung involvement is 8 years (range <1-45 years) (4).

Malignant transformation may occur, either at the laryngeal, bronchial or pulmonary level. The median interval between the diagnosis of JRRP and that of cancer is 19 years (12 years in this case). The youngest child reported to die of lung cancer was 6 years old and 31% of the reported cases are diagnosed before the age of 18 years. The strongest risk factor for JRRP is a history of genital condyloma transmitted from the mother during delivery. HPV is the etiologic agent of respiratory papillomatosis. The virus is a 55 nm nonenveloped, icosahedron containing an 8 kb circular, covalently closed, double-strand genome. The genome consists of three regions: the long control region (LCR), which contains transcription regulatory sequences, the early and the late regions which are related to the phase of infection in which they are expressed (10). Gabott et al. evaluated HPV type and viral mutation occurring during the course of juvenile-onset recurrent respiratory papillomatosis in 199 papillomas excised from 47 children. Forty four children had HPV-induced papillomas, with type 11 accounting for 55%, type 6 for 43% and both type 6 and 11 for 2% (11).

Despite the epidemiological classification of type 6 and 11 HPV as low risk HPV’s, it has been reported in the literature that children with lesions containing HPV 11 have a more aggressive course than patients with HPV 6-associated lesions. HPV11 is associated with squamous cell carcinoma although HPV11 is uncommonly associated with the development of invasive carcinoma at other sites (12). Patients affected by HPV11 papillomatosis as in our case are younger, with a longer period of disease activity, require more surgical procedures and are less likely to go into remission than HPV 6-infected patients. These data suggest that HPV 11 may play a significant role in carcinogenesis in the larynx and respiratory tract, particularly in patients with JRRP. In summary, JRRP aggressiveness is in relation with two strong risk factors: the age at diagnosis of JRRP (laryngeal involvement) and HPV type.

Rady et al. demonstrated that the p53 genetic mutation was associated with integration of HPV-11 in histologically malignant lesions. This association may promote a progres-
sive genetic instability that can lead to the development and clonal expansion of malignant lesions in JRRP (2). In our case, immunohistochemical analysis showed positive nuclear staining for p53.

Patients who receive radiation or cytotoxic drugs or those who subsequently smoke may be predisposed to the development of broncho-pulmonary carcinoma (8).

In this observation, HPV may be an important risk factor in the development of squamous cell carcinoma as the child did not receive radiation or cytotoxic drugs. In addition, HPV 6/11 DNA was detected by PCR-analysis in the metastatic tumor cells.

Clearly, to date, not enough data are available on the association of HPV type, the possible variation in HPV or the development of mutations and progression to cancer.

To conclude, many issues need to be improved in JRRP: the understanding of the mechanisms underlying the lung involvement as well as the risks associated with different HPV types and the risk of progression to cancer, strategies for early diagnosis of malignant transformation and adequate follow-up. Randomized control trials and prospective cohort studies are warranted (12). Significant vaccine research is being pursued for JRRP (13). In the future, the incidence of JRRP and squamous cell carcinoma may be reduced by the wild use of quadrivalent HPV vaccine for prevention of HPV 6/11.

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