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CASE STUDY

Vertically transmitted HPV-dependent squamous cell carcinoma of the external auditory canal

Case report of a child

Miroslaw Snietura[1] · Liliana Chelmecka-Wiktorczyk[2] · Slawomir Pakulo[1] · Agnieszka Kopec[1] · Wojciech Piglowski[1] · Grazyna Drabik[3] · Bogdan Kosowski[4] · Lukasz Wyrobek[5] · Agata Stanek-Widera[1] · Walentyna Balwierz[2,6]

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Abstract
Background There is much evidence that high-risk human papillomavirus (HPV) plays a causative role in a subset of head and neck squamous cell cancer (HNSCC) in adults. HPV-positive tumors behave differently even in their response to treatment and are therefore a distinct subset. Both HPV-positive and HPV-negative tumors of the head and neck region are usually in the domain of adults and cases in children are rare; thus when a 2-year-old child was diagnosed with this cancer in the external auditory canal, an in-depth assessment of the tumor was considered necessary.
Case report A 2-year-old girl was born to a HPV-positive mother who was diagnosed with cervical cancer during pregnancy. The child was delivered by caesarean section and the mother died of her cancer 7 months after delivery. After the diagnosis of locally invasive HPV-positive squamous cell cancer of the external auditory canal, the child was treated surgically, and with chemotherapy and radiotherapy. Full remission was obtained lasting up to 325 weeks since treatment was started, resulting in over 6 years of disease-free survival.
Conclusion This is the first case of advanced, HPV-related HNSCC in a 2-year-old child, in whom the tumor was located in the external auditory canal and who made a dramatic recovery after treatment with nonradical surgery, chemotherapy and radiotherapy. The child has currently been disease free for 6 years. This case supports the observation that HPV-related HNSCC tumors appear to respond favorably to treatment despite the patient's young age and the clinically advanced stage of the tumor.

Keywords Human papillomavirus · Ear canal · Vertical infection transmission · Chemoradiotherapy · Pediatrics

HPV-abhängiges Plattenepithelkarzinom des äußeren Gehörgangs nach vertikaler Virusübertragung

Fallbericht eines Kindes

Zusammenfassung
Hintergrund Es gibt reichlich Belege dafür, dass das menschliche Papillomavirus vom Hochrisikotyp (HR-HPV) in einigen Fällen von Plattenepithelkarzinomen des Kopf- und Halsbereichs (HNSCC) eine Schlüsselrolle spielt. HPV-positive Tumoren verhalten sich anders, auch bezüglich des Ansprechens auf die Behandlung. Deswegen stellen sie eine separate biologische Gruppe dar. Sowohl HPV-positive als auch HPV-negative Tumoren des Kopf- und Halsbereichs treten vor allem bei Erwachsenen auf und sind bei Kindern eine Seltenheit. Daher begründete die Diagnose eines Plattenepithelkarzinoms des äußeren Ge-

✉ Miroslaw Snietura, MD PhD
mirek@snietura.net

1 Tumor Pathology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Ul. Wybrzeze Armii Krajowej 15, 44-101 Gliwice, Poland

2 Department of Oncology and Hematology, University Children's Hospital of Cracow, Cracow, Poland

3 Pathology Department, University Children's Hospital of Cracow, Cracow, Poland

4 NZOZ Prosmed, Cracow, Poland

5 Department of Radiology, University Children's Hospital of Cracow, Cracow, Poland

6 Clinic of Oncology and Hematology, Polish-American Pediatric Institute, Jagiellonian University in Cracow, Cracow, Poland

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hörgangs bei einem 2-jährigen Kind die Notwendigkeit, die Krankheit eingehend zu untersuchen und zu beschreiben.
Fallbericht Wir berichten über ein 2-jähriges Mädchen, das von einer HPV-positiven Mutter geboren wurde, bei der während der Schwangerschaft Gebärmutterhalskrebs diagnostiziert worden war. Die Geburt erfolgte per Kaiserschnitt. Die Mutter erlag 7 Monate nach der Geburt ihrer Krebserkrankung. Das Kind wurde nach der Diagnose eines lokal fortgeschrittenen HPV-positiven Plattenepithelkarzinoms des äußeren Gehörgangs operativ und ergänzend mit Radio- und Chemotherapie behandelt. Erreicht wurde eine komplette Remission für mindestens 325 Wochen nach Beginn der Behandlung, sodass mehr als 6 Jahre keine Krankheitssymptome aufgetreten sind.
Schlussfolgerung Dies ist die erste Fallbeschreibung eines stark fortgeschrittenen HR-HPV-positiven HNSCC des äußeren Gehörgangs bei einem 2-jährigen Kind, bei dem nach Anwendung einer nichtradikalen chirurgischen Behandlung sowie einer Chemo- und Strahlentherapie eine spektakuläre Reaktion und ein aktuell 6-jähriges krankheitsfreies Überleben erreicht wurden. Dieser Fall bestätigt die Beobachtungen, nach denen HNSCC-Tumoren im Zusammenhang mit HR-HPV günstig auf die Behandlung ansprechen – trotz des klinisch fortgeschrittenen Tumorstadiums und des jungen Patientenalters.

Schlüsselwörter Humanes Papillomavirus · Äußerer Gehörgang · Vertikale Infektionsübertragung · Chemoradiotherapie · Pädiatrie

Introduction

The epidemiology of head and neck squamous cell carcinoma (HNSCC) in adults is changing. There is much evidence that human papillomavirus (HPV) plays a causative role in a subset of these cancers [4]. The incidence of HNSCC especially in the oropharynx seems to be etiologically related to HPV and has increased significantly in recent years [10]. HNSCC of the external auditory canal is rarely reported in adults and authors have not mentioned any relation to HPV. However, in pediatric cases, HNSCC is rarely seen and hitherto no case of this cancer has been reported to occur in the external auditory canal. This report presents the first case of HNSCC at this site in a 2-year-old child that was associated with active HPV infection in both mother and child. The mother was diagnosed with cervical cancer and was HPV positive during the pregnancy and died a few months after delivery. We suggest vertical transmission and early intrauterine infection with a causative role of high-risk HPV (HR-HPV) in the child leading to HNSCC in an anatomically rare location.

Case report

Present history

The patient is a 2-year-old child. In the 21st week of gestation the patient's mother was diagnosed as having squamous cell carcinoma of the cervix and was HPV positive (Fig. 1a, b). The child was delivered by caesarean section in the 27th week. The mother died of her cancer 7 months later. At the age of 20 months, the child developed the right facial nerve palsy and a month later she developed a chronic discharge from her right ear that was treated as a recurring and chronic external otitis for 3 months. She was then referred to the clinic for diagnosis and treatment.

Clinical investigation and diagnosis

On admission, a computer tomography (CT) of the mastoid process showed erosion of bone, sclerosis, and loss of aeration with dense fluid in the mastoid cells. The diagnosis of chronic otitis and secondary mastoiditis was made and local treatment was continued together with antibiotics. Nine weeks later a polyp-like growth was seen in the affected external auditory canal and surgical excision of the polyp was performed. Histopathological diagnosis from two pathology centers confirmed the diagnosis of squamous cell cancer (Fig. 1c, d).

Eleven weeks after admission, a CT of the head revealed that the cancer was directly involving the adjacent base of the skull mainly in the petrous part of the temporal bone and also penetrating into the middle and posterior cranial fossae, cerebellopontine angle, reaching the infratemporal fossa and the pterygopalatine fossa. The maximum dimensions of the tumor in the middle of the petrous part of the temporal bone was 61 × 50 mm. The CT revealed no distant metastases in the head and upper neck region (Fig. 2).

Treatment

The first line of treatment was one cycle of induction chemotherapy with Velba and Vepesid (Fig. 4). This was followed by surgical resection for maximal tumor reduction by suboccipital craniotomy 2 weeks later (week 14 after hospital admission). Histology revealed incomplete resection with one occipital node metastasis (Fig. 1e, f). From week 14 to week 54, 10 cycles of chemotherapy (ifosfamide, carboplatin, paclitaxel) were administered. After 5 cycles of chemotherapy (week 34), CT revealed regression of the tumor with destruction of the temporal bone. From week 61 to week 69 adjuvant radiotherapy to the right external auditory canal was given with a total dose of 54 Gy in 30 fractions (Fig. 3). In week 73, the

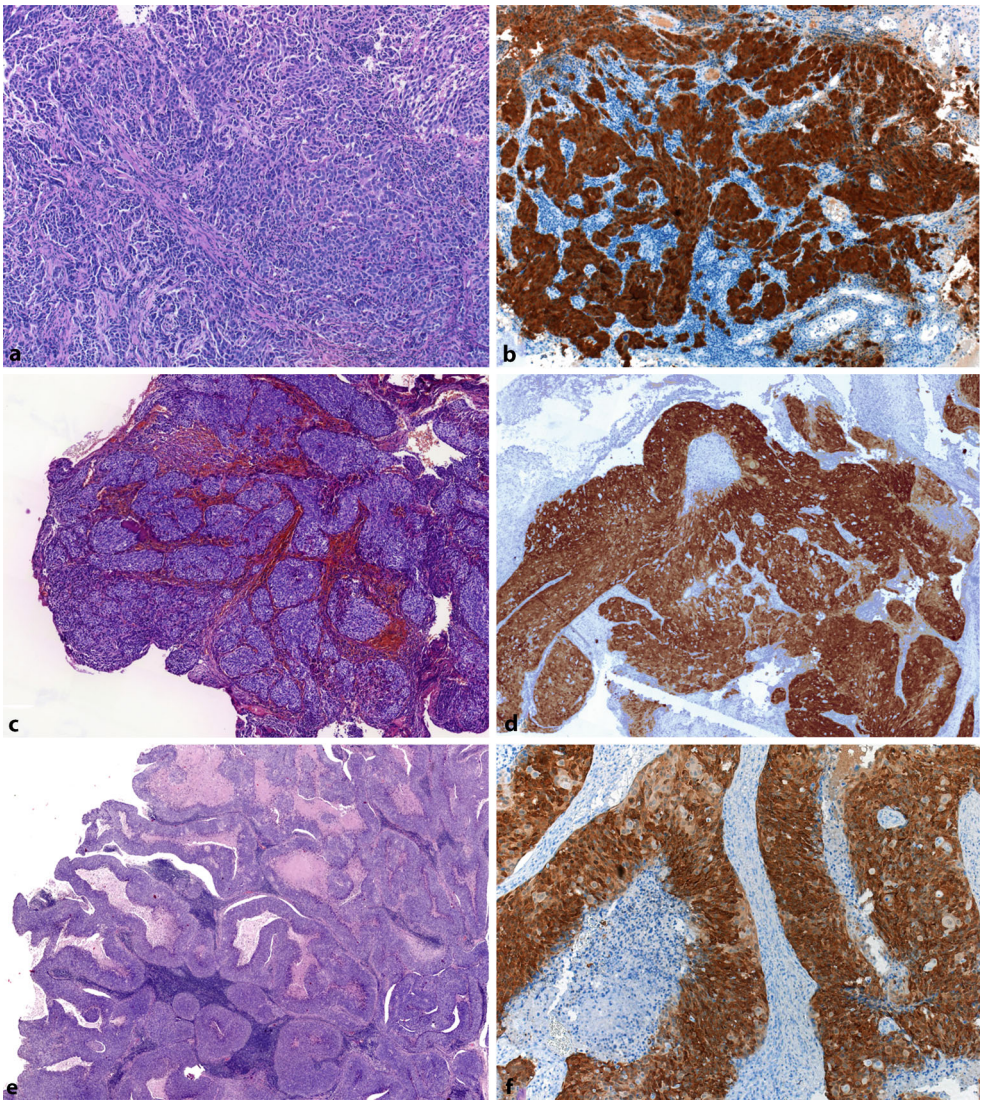

Fig. 1 Microphotographs of the representative tumor sections: **a**,**b** mother's cervical squamous cell carcinoma; **c**,**d** squamous cell carcinoma of external auditory canal of the child; **e**,**f** lymph node metastatic tumor. Staining: **a**,**c**,**e** hematoxylin-eosin, **b**,**d**,**f** immunostaining with anti-human $P16^{INK4A}$ monoclonal antibody clone E6H4™ (Roche mtm Laboratories AG, CINTech® Histology Kit)

11th and 12th cycle of chemotherapy was given (ifosfamide, carboplatin, and paclitaxel).

Follow-up

The child is in stable remission from week 73 to week 325.

Investigation for confirming human papillomavirus involvement

The need to determine the role of HPV in this rare case was compelling because of the history of HNSCC in the child and very probably HR-HPV involvement in the mother's cervical cancer. However, in this case the HPV-positive status was confirmed ex post and all the treatment was conducted without the knowledge of the viral commitment. All pathological samples that were formalin-fixed and paraffin-embedded from both mother and child were examined for protein $P16^{INK4A}$ which is considered a surrogate marker of high-risk HPV infection [7, 21, 25]. This was demonstrated by immunohistochemistry.

Immunostaining of all samples from the mother and child using CINTech Histology Kit (Roche mtm Laboratories AG) revealed strong homogenous chromogen concentration in cancer cells from both mother and child which is characteristic of HR-HPV infection (Fig. 1b,d,f). The presence and types of HR-HPV DNA in the tumor cells was confirmed using commercially available, Sacace HPV Genotypes 14 Real-TM (Sacace Biotechnologies Srl, Italy) which is a Real Time PCR Kit for quantitative detection and genotyping of the following human papillomavirus types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.

Briefly, the first step was to isolate the genomic DNA from all tumor tissue samples using Mag Core Genomic DNA FFPE One-step Kit and MagCore Nucleic Acids Automatic Extractor HF 16 Plus (RBC Bioscience Corp. Tai-

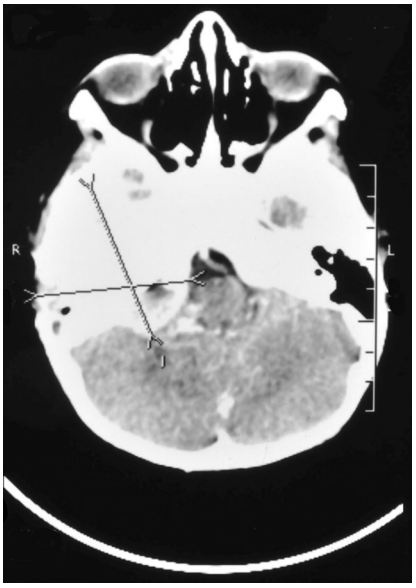

Fig. 2 Computer tomography of the child's head at the beginning of the induction chemotherapy in week 11 after admission to the hospital (see markers for tumor location)

wan). Next, a reaction mixture of 15 µl isolated DNA (25 ng/10 µl) was prepared and cycled in the ViiA7 Real Time Cycler (Life Technologies) according to the manufacturer's directions. The results obtained showed the presence of HR-HPV DNA of type 31 in all tested samples which includes the cervical cancer of the mother, the child's primary tumor of the external auditory canal, and the nodal metastatic site in the occipital region, thus, confirming the viral-related etiology of the disease.

Discussion

The incidence of HNSCC is increasing mainly in adults, whereby a relatively small number of pediatric cases have been reported and therefore are considered a rare entity [17]. In adults, the location of HNSCC in the external ear is less than 1 % of all head and neck cancers and clinical data is limited [14, 15, 28, 30]. To our knowledge, the present report is the first case of HNSCC in a very young, 2-year-old child. Primary risk factors such as smoking and alcohol consumption seem to lack direct meaningful impact in younger patients. However, recently HR-HPV infection has evolved to become a risk factor for HNSCC especially in young adults [9].

HPV in children can cause a wide range of cutaneous and mucosal infections [16, 27]. Most of them are asymptomatic and self-curing within a year. After the delivery of a baby, lesions in the cervical mucosa of the mother may become manifest. Some may have persistent lesions in the oral mucosa [3, 19, 20, 22]. The HPV infection can cause benign skin lesions such as skin warts, genital warts, respiratory papillomas, and low grade intraepithelial lesions [16]. It is still unclear how often HPV can cause high-grade intraepithelial lesions that sometime progress to invasive cancer.

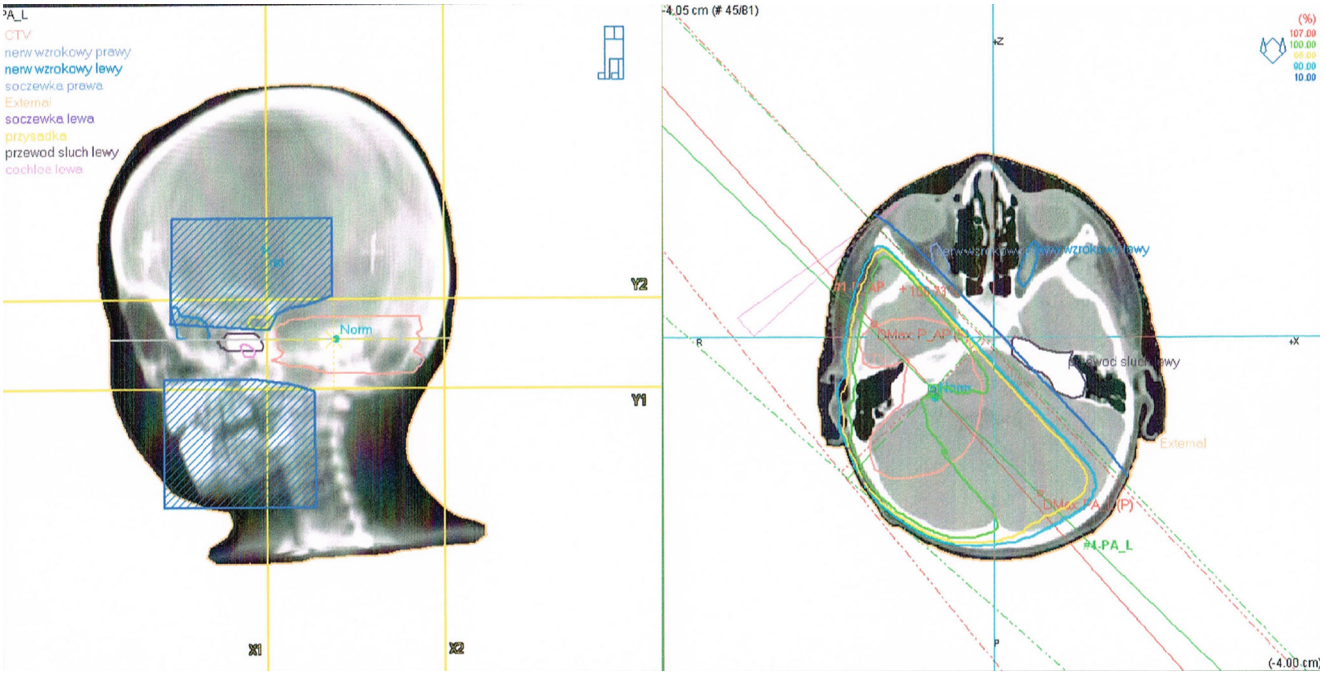

Fig. 3 Dose distribution during adjuvant radiotherapy

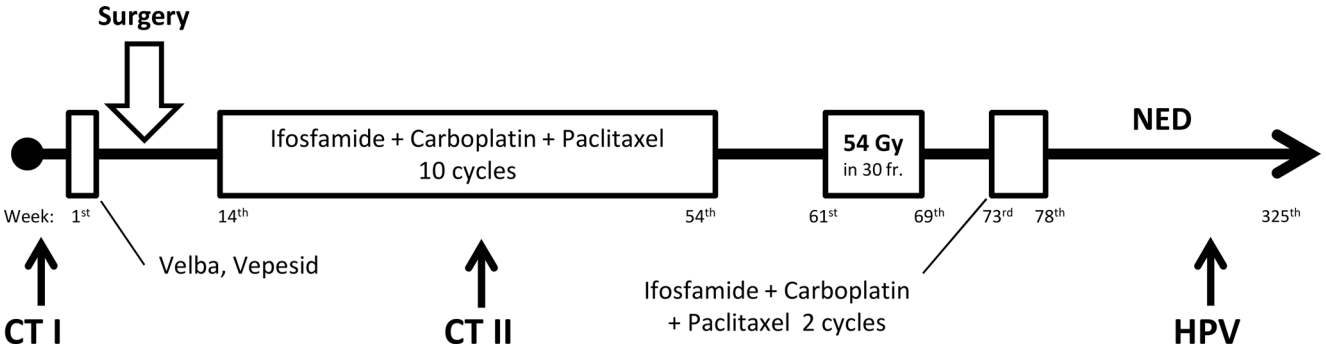

Fig. 4 Timeline showing treatment strategy, computed tomography imaging (*CT I* and *CT II*) and human papillomavirus (*HPV*) status assessment (*HPV*). *NED* no evidence of disease; *fr.* fractions

It is claimed that a vertical transmission between mother and child can exist but the exact routes and frequency have not been well established. Possible non-sexual transmission modes include vertical or horizontal transmission and auto-inoculation [26]. In the above described case, we assume that the transmission was vertical because the same HPV type 31 was present in both mother and child and was found in all pathologic tumor samples of these two subjects. The child was delivered prematurely to offset the risk of the mother infecting the child if it were to be delivered through the cervix which was diseased with squamous cell cancer. Furthermore, treatment to the mother's cervical cancer was started as early as possible after caesarean delivery. We recommend this management in such cases. In spite of the early caesarean section the child was infected and we must consider the possibility of intrauterine transmission through micro-tears [2, 29] in the fetal membranes or blood-borne via the placental barrier [23, 24, 29]. The possibility of mother infecting the child by direct skin to mucosal contact during suckling, kissing etc. could also be considered [3, 26].

In adults, HPV-positive tumors possess a different biologic subset of HNSCC with a different clinical behavior compared to HPV-negative tumors [1, 13]. HPV-positive tumors seem to respond better after radio- and chemotherapy even in advanced cases compared to HPV-negative tumors [5, 11, 21]. However, the risk of distant metastases is about the same in both HPV-positive and HPV-negative tumors [12, 18].

The external auditory HNSCC tumors are prone to a delayed diagnosis due to their anatomical position and the initial behavior as a local inflammation and can easily be misdiagnosed as an external otitis which happened in this case. Even a CT or MRI investigation should be carefully analyzed always keeping in mind the problem of local tumor development in an unrelenting chronic external ear infection. Such a misdiagnosis, as in this case, led to deep tumor invasion through the skull bones which resulted in a lack of surgical radicality and the defeat of an earlier cure [32]. This particular case, which seemed hopeless at the outset, responded to a multimodal approach using all three arms of classical cancer therapy, namely surgery, chemotherapy and radiotherapy. Early full remission was achieved at the end of therapy in week 73 and full remission is still prevailing after 325 weeks since the start of the treatment.

With HPV positivity in mind, it is debatable if an overtreatment could occur or even some treatment de-escalation could be used in this case of a very young child. Unfortunately HPV status was not available during the treatment. Moreover, despite a better response of HPV-positive tumors to radio- and chemiotherapy, de-intesified combined modalities are not currently considered as standard treatment and their clinical performance is still subject of phase 2 trial investigations [5]. Due to locally advanced infiltration (61 × 50 mm), the decision of upfront chemotherapy had been taken. Chemotherapy, especially in children, is well tolerated and usually poses less risk of late complications compared to radiotherapy. Proton therapy and IMRT were not available for our patients at that time.

In the last decade vaccination against HPV has been available for young girls and boys to reduce the incidence of cervical cancers in later years and also to avoid transmission of HPV to the fetus [31]. Likewise young patients not eligible for vaccination benefit from herd effect protection in high coverage populations [6]. The impact of this vaccination in the general population is still too early to be fully appreciated and is the domain of the of the public health experts who need to seriously consider the prevention of HPV-induced diseases [8].

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Compliance with ethical guidelines

Conflict of interest M. Snietura, L. Chelmecka-Wiktorczyk, Sr. Pakulo, A. Kopec, W. Piglowski, G. Drabik, B. Kosowski, L. Wyrobek, A. Stanek-Widera and W. Balwierz state that they have no competing interest.

This article does not contain any studies with human participants or animals performed by any of the authors.

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