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SHORT COMMUNICATIONS AND CASE REPORTS

A woman with synchronous cervical, vaginal and laryngeal squamous cell carcinomas and positive human papillomavirus type 16; case presentation with literature review

S. Georgieva[1], V. Iordanov[2]

[1]Oncotherapeutic Clinic, "Queen Giovanna" Hospital, Sofia; [2]Department of Gastroenterology, National Oncology Centre, Sofia, Bulgaria

Summary

During the last 25 years the development of cervical cancer and cancer of the anorectum has been related to human papillomavirus (HPV) infection. HPV infection is found in up to 99.7% of all cervical cancers. Head and neck squamous cell carcinomas (HNSCC) have also been related to HPV infection.

In this communication we present a 67-year-old female patient, nonsmoker, diagnosed with 3 synchronous cancers - squamous cell carcinoma of the uterine cervix, vagina and larynx.

The patient was found positive for immunoglobulin HPV 16 L1 using ELISA method.

We believe that in the presented case, the high risk HPV subtype 16 was implicated in the etiology of laryngeal, cervical and vaginal cancers.

We also think that HPV infection and related cancers could be prevented effectively by immunization.

Key words: anorectal cancer, cervical cancer, head and neck tumors, human papillomavirus

Introduction

During the last 25 years the development of cervical cancer has been related to HPV infection. HPV infection is found in up to 99.7% of all cervical cancers [1]. This virus has also been implicated in other epithelial tumors, such as those of the vulva, penis and anus, where it is found in 9-50% of the cases [2].

The development of HNSCC has also been related to HPV infection [3]. HNSCC have common predisposing factors: smoking, alcohol consumption, or both in combination, as well as chronic inflammation and gastroesophageal reflux disease (GERD) [3-5]. These factors induce hyperplastic inflammatory response, which is considered as a premalignant condition.

HPV is isolated also from benign and precancerous conditions such as skin verrucae, mucosal papilloma of the upper respiratory tract, and anorectal condylomata [6,7]. One of the variants of intraepidermal squamous cell carcinoma is Bowen's disease, where HPV-DNA has been isolated in 65% of the cases [8-16]. In preinvasive intraepithelial neoplasia of the vagina, HPV was isolated in 80% of the cases [9].

Thanks to the extremely fast development of diagnostic methods of molecular biology, our understanding of HNSCC tumorigenesis has increased tremendously. Using these methods, HPV is isolated from precancerous and dysplastic tissues, as well as from advanced tumors [8]. For example, using polymerase chain reaction (PCR), HPV-DNA is detected in 40-70% of HNSCC [5]. In contrast, HPV-DNA is found in only 1% in normal epithelial cells [5,6,10]. Gillison et al. found that only 25% of recurrent HNSCC were positive for HPV-DNA and that patients who were moderate or heavy drinkers had better prognosis and improved disease-specific survival [11].

Correspondence to: Dr. Victor Iordanov. Department of Gastroenterology, National Oncology Centre, 6, Plovdivsko pole Street, Sofia, Bulgaria.
Tel: +359 2 807 6342, E-mail: vic300@gmail.com

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Case presentation

A 67-year-old female patient, gravida 3, para 3, 1 abortion, nonsmoker, was diagnosed with 3 squamous cell carcinomas: cervical cancer (pT1bN0M0), vaginal cancer (T *in situ*) and laryngeal cancer (T *in situ*). Cervical cancer was diagnosed accidentally after routine gynecologic examination, when she was found to have a cervical erosion 1 cm in size. On examination, the uterus was atrophic without fixation. No infiltrations were found in the parametria. Piver's radical hysterectomy (class III) was performed under general anesthesia and histology confirmed low differentiated squamous cell carcinoma, penetrating the entire cervical wall. In the resected material vaginal carcinoma *in situ* was also found. The parametria were infiltration-free. The uterine corpus and endometrium were atrophic. No abnormalities were found in the tubes. Pelvic lymph nodes did not bear metastases. The postoperative period was uneventful and the patient was discharged.

One month after the operation the patient was admitted for chemoradiotherapy. The cumulative dose of external pelvic radiotherapy was 50.4 Gy. Chemotherapy included cisplatin 30 mg/m^2 weekly. Additionally, intravaginal brachytherapy with ^{192}Ir was delivered in 2 fractions of 5 Gy.

During her stay at the department, the patient complained of hoarse voice. On further enquiry, she remembered to have had this problem during the previous 3-4 months. Her voice became even hoarser after the intraoperative intubation for her hysterectomy. On laryngoscopic examination, the patient was found to have an edematous and hyperemic vocal cord on the right, especially in its anterior 1/3, without paralysis. Those features were also clearly seen on CT scan (Figure 1). Biopsy confirmed carcinoma *in situ* in a hyperkeratotic squamous epithelium.

One month following chemoradiotherapy for her cervical cancer, the patient was admitted again for radiotherapy of the larynx. She received 66 Gy cumulative dose to the primary laryngeal tumor region.

Additionally, the patient was found positive for immunoglobulin HPV 16 L1 using ELISA method.

Sixteen months post-chemoradiation for the cervical/vaginal cancers and 14 months following radiotherapy for laryngeal cancer, the patient remains free of tumor recurrence.

Discussion

We believe that in the presented case the high risk HPV subtype 16 is implicated in the etiology of the 3 malignancies – cervical, vaginal and laryngeal squamous cell carcinomas.

HPVs are DNA viruses, from the Papovaviridae family (Figure 2) [17]. Their primary host is the basal layer of the squamous cell epithelium. The virus can multiply only in differentiating keratinocytes. Up until now more than 100 different subtypes of HPV are known [2]. Apart from differences in their structure, the subtypes differ in the clinical symptoms they cause [7]. According to their oncogenic potential HPV subtypes are divided into 3 groups: high risk subtypes: 16, 18; probably carcinogenic: 25, 53; and low risk subtypes: 6, 11.

Viral adhesion is the first step of any viral infection. In these localizations - cervix, vagina and vocal cords, the virus is enabled due to similarities in their

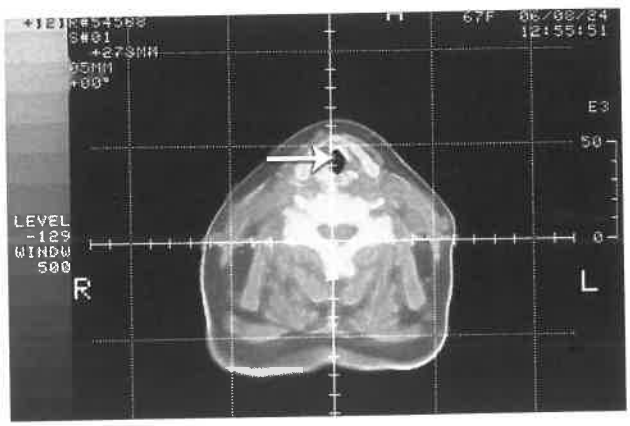


Figure 1. CT image showing edematous vocal cord on the right with carcinoma *in situ* (arrow).

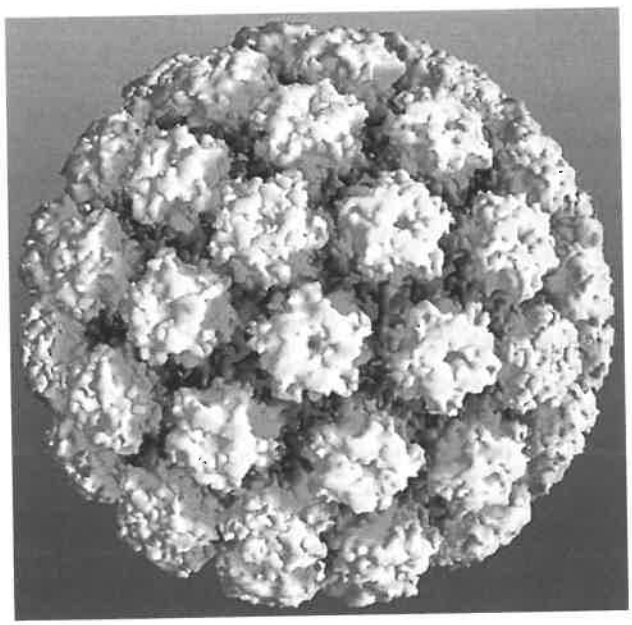


Figure 2. Atomic model of papillomavirus capsid (from Modis et al. [17]).

squamous epithelial cells. The next step is internalization and genome integration into the nucleus of the basal epithelial cell. Transcription of mRNA follows, encoding for viral proteins E5, E6 and E7, and later L1 and L2, known as replication proteins. Viral DNA is not replicated constantly, but it is still not known what causes its reactivation.

By definition, carcinogenesis is a result of disorganization of intracellular signals during the process of cell proliferation, differentiation and apoptosis. In HPV infection, integrated DNA virus causes permanent genome defect, resulting in carcinogenesis [12].

The virus interacts with the cell through oncoproteins directed to certain components of the host cell. One such small protein is E6, containing only 150 amino acids and causing degradation of p53 oncosuppressor protein [9].

E7 has a similar role. The HPV E7 protein disrupts pRb control over E2F proteins, an important family member of transcription factors, allowing the activation of cyclin-cyclin dependent kinases (CDK) complexes, which ultimately causes unrestricted cell progression throughout G1 to S phases of the cell cycle [7,9,12].

Cervical cancer is a sexually transmitted disease caused by HPV infection, especially by subtypes 16 and 18. HPV DNA is found in more than 95% of preinvasive carcinoma *in situ* and its premalignant form CIN III and can be identified in both types of cervical cancers – squamous cell carcinomas and adenocarcinomas [13].

Anal cancer has also been related to HPV infection. Using PCR Frisch et al. found HPV in 88% of the patients with anal cancer [14]. They also found greater incidence of HPV in anal cancer in people who were promiscuous with early first sexual contact, especially anal, or people who were single and divorced, or women with a promiscuous partner. They concluded that HPV is a sexually transmitted disease and should be easily preventable.

Literature provides no much evidence of a relationship between HPV infection and laryngeal cancer. In more than 90% of the cases, laryngeal carcinoma is squamous cell. While most of the laryngeal surface is covered by respiratory columnar epithelium, only the true vocal cords and the lingual surface of the epiglottis are covered by squamous epithelium. That is why these areas are subjected to HPV adhesion and infection.

HPV 6 and 11 subtypes and other rarer low-risk subtypes have been found in recurrent laryngeal papillomatosis. This condition is characterized by multiple relapsing papules on the vocal cords which spread to other parts of the respiratory tract.

Laryngeal papillomatosis has distinct age predilection, seen mostly in patients before the age of 5 and between 20 and 30 years. This is related to the type of transmission - at birth and later during sexual contact. Laryngeal papillomatosis rarely progresses to malignancy, which is seen after many years of persistence and is facilitated by radiotherapy or smoking. In those cases, such malignant transformations are usually positive for HPV 6 and 11. This means that only under certain conditions HPV could exert its carcinogenic potential. HPV is a prerequisite, but not the only factor for papilloma development. Its role as a cofactor remains to be further explored [6].

Using *in situ* hybridization, viral DNA is localized in the nucleus of the preinvasive tumor cells, invasive carcinoma and metastatic lymph nodes. The reported rate of HPV-DNA detection in laryngeal carcinomas varies significantly - from 0 to 100% [6]. The exact percent is not known, because of great differences in the specificity of the HPV-detection methods used. When HNSCC are seropositive for HPV, they are subtype 16 in more than 90% of the cases [11].

Dahlstrom et al. found that seropositivity for HPV 16 was present in 58.6% of patients with oropharyngeal tumors and in 35.7% of those with laryngeal tumors [10]. They suggested that exposure to HPV 16 is a risk factor for HNSCC, particularly in non-smokers, like in our case [10,15].

HPV-positive HNSCC are found rarely in heavy drinkers and smokers [10,11]. Interestingly enough, all HPV-positive patients have better disease-specific survival in comparison to HPV-negative ones. This might be related to earlier detection, as HPV-positive tumors have protruding growth and lower invasive capacity [11,15].

Conclusion

These data extend recent molecular and epidemiologic studies which strongly suggest that HPV - positive HNSCC comprise a distinct molecular, clinical and pathologic disease entity, that is likely causally associated with HPV infection and could have markedly improved prognosis.

The presented case is noteworthy for the short time period among the diagnosis of the 3 synchronous squamous cell carcinomas in the same patient.

At the moment we are at "the beginning of the end" of the cervical cancer [16]. Our improved understanding of HPV-associated oncogenesis led to development of specific vaccine and improved prophylaxis. It means that those and other HPV-related cancers could be prevented by immunization.

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