

PHOTODYNAMIC THERAPY IN A PATIENT WITH HPV-ASSOCIATED LSIL OF THE CERVIX (CLINICAL CASE)

Filonenko E.V., Grigoryevykh N.I., Kaprin A.D.

P.A. Herzen Moscow Oncology Research Center – branch of FSBI NMRRС of the Ministry of Health of the Russian Federation, Moscow, Russia

Abstract

The article describes a clinical example of timely, safe and effective photodynamic therapy (PDT) in a patient diagnosed with human papillomavirus (HPV) CIN I-associated cervical cancer after ineffective vaccination with 4-valent Gardasil vaccine. Clinical case demonstrates the low effectiveness of HPV vaccination in patients with established HPV infection. In this patient, the lack of adequate treatment for about 1.5 years led to the development of HPV associated CIN I of the cervix. Center for Laser and Photodynamic Diagnostics and Therapy of Tumors and MRI P.A. Herzen, the patient underwent a course of antiviral PDT with the achievement of complete regression of dysplasia and complete eradication of HPV viruses. The patient tolerated the treatment well, without complications. The period of relapse-free follow-up is 19 months.

Key words: cervical dysplasia, CIN, photodynamic therapy, photosensitizer, HPV infection.

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Contacts: Filonenko E.V., e-mail: derkul23@yandex.ru

ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ БОЛЬНОЙ С ВПЧ–АССОЦИИРОВАННОЙ LSIL ШЕЙКИ МАТКИ (КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ)

Е.В. Филоненко, Н.И. Григорьевых, А.Д. Каприн

«Московский научно-исследовательский онкологический институт им. П.А. Герцена – филиал ФГБУ «Национальный медицинский исследовательский центр радиологии» Министерства здравоохранения Российской Федерации, Москва, Россия

Резюме

В статье описывается клинический пример проведения своевременной, безопасной и эффективной фотодинамической терапии (ФДТ) у пациентки с диагнозом ассоциированной с вирусом папилломы человека (ВПЧ) CIN I шейки матки после неэффективной вакцинации 4-валентной вакциной гардасил. Клиническое наблюдение демонстрирует низкую эффективность вакцинации против ВПЧ больных с установленной ВПЧ инфекцией. У данной пациентки отсутствие адекватного лечения на протяжении около 1,5 лет привело к развитию ВПЧ ассоциированной CIN I шейки матки. В Центре лазерной и фотодинамической диагностики и терапии опухолей и МР МНИОИ им. П.А. Герцена пациентке проведен курс противовирусной ФДТ с достижением полной регрессии дисплазии и полной эрадикации вирусов ВПЧ. Лечение пациентка перенесла хорошо, без осложнений. Срок безрецидивного наблюдения – 19 мес.

Ключевые слова: дисплазия шейки матки, CIN, фотодинамическая терапия, фотосенсибилизатор, ВПЧ-инфекция.

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Контакты: Филоненко Е.В., e-mail: derkul23@yandex.ru

Introduction

The role of human papillomavirus (HPV) persistence in the development of cervical cancer is now considered proven. For the prevention of cancer in these clinical situations, the currently accepted tactic is the use of the HPV vaccine. Clinical use of Gardasil was initiated in 2006, Cervarix in 2009. Since then, there has been a decrease in HPV infection in a young population of women aged 12-26 years who have been vaccinated, but prophylactic vaccination does not induce immunity in individuals with established HPV infection or neoplasms caused by HPV. The quadrivalent Gardasil vaccine is considered proven to be 99% effective against HPV and, as a result, is effective in preventing genital warts and genital warts caused by HPV types 6, 11, 16 and 18.

According to the literature, approximately 80% of sexually active women will contract some type of HPV infection during their lifetime, and in most cases this will be a transient, asymptomatic infection that is cured by the immune system within 6 months to two years. Only as a result of persistence of HPV infection can low or high grade cervical intraepithelial neoplasia develop, which can eventually progress to cervical cancer [1]. Given the above, timely and effective treatment of HPV infection is a technology for the prevention of cervical cancer.

We present a clinical case.

Clinical case

Patient N., aged 28, consulted a gynecologist in August 2019. Papillomavirus infection of the cervix (HPV) was diagnosed for the first time. PCR study for HPV revealed the presence of HPV types 31, 56 and 59 in the amount of 1.1×10^3 st.; 6.9×10^2 st.; 1.2×10^4 st., respectively. No treatment was given. During the re-examination on February 1, 2020, carriage of HPV type 31 was detected in the amount of 1.3×10^5 st., Type 59 – 6.9×10^5 st. HPV vaccination was recommended. From March to September 2020, the patient was vaccinated and twice revaccinated with the Gardasil-4 vaccine.

During the control PCR for HPV from 09/23/20, carriage of HPV type 31 was detected in the amount of 4.7×10^3 st., Type 56 – 8.6×10^5 st. Cytological examination for atypical cells on September 23, 2020 revealed ASC-US. The patient was left under dynamic observation. Cytological examination of smears from the cervix dated 12/04/20 revealed LSIL/CIN I, dyskaryosis, koilocytosis; PCR study for HPV – the presence of HPV type 31 in the amount of 4.1×10^3 st., Type 56 – 1.3×10^6 st.

The patient independently applied to the P.A. Herzen Moscow Oncology Research Center.

A cytological study was performed on December 17, 2020 No. 20/6-3009: a smear from the cervix – cells of the squamous epithelium of the intermediate and surface layers, in some of which there are signs of HPV infection, koilocytic transformation, metaplastic cells, elements

of inflammation, moderate mixed flora – conclusion – cytogram of moderate inflammation, squamous cells with signs of HPV infection and low-grade intraepithelial lesions – LSIL (CIN I); No. 20/6-3010: smear from the cervical canal – squamous epithelial cells, some of which have signs of koilocytic transformation, metaplastic cells, groups and clusters of cylindrical epithelium cells, blood cells, mucus – conclusion: squamous epithelial cells with signs of HPV infection and low-grade intraepithelial lesion – LSIL (CIN I). Immunocytochemical study No. 20/8-124 dated December 23, 2020 was performed using p16 and Ki67 markers. Some of the squamous epithelial cells showed a positive moderate expression of the p16 protein. The Ki67 proliferative activity index in squamous epithelial cells is low – conclusion: ICC data, together with cytological data, correspond to the picture of HPV-associated low-grade intraepithelial lesion – LSIL.

When viewed during the initial consultation at the P.A. Herzen Moscow Oncology Research Center – the external genital organs are formed correctly, the external opening of the urethra is without pathology; examination in the mirrors: the vaginal mucosa is not changed, on the mucous membrane of the cervix there is an endocervical ectopia around the external os up to 1.2 cm wide; PV: the cervix is not compacted, the uterine body is of a normal shape and size, dense, mobile, painless, the appendages on the left and right are not defined, their area is painless, the arches are free, infiltrates are not detected in the parameters, the utero-rectal depression is free, the rectovaginal septum is intact.

An MRI of the pelvic organs dated 01/10/21 with a targeted examination of the cervix showed an endocervix of a heterogeneous MRI signal, 2 to 3 mm thick, no volumetric formations of the cervix were detected. The vaults of the vagina and parameters are intact.

Ultrasound of the pelvic organs dated 01/12/21 (on the 9th day of the cycle) showed that the bladder was not changed. The uterus is 47.4x28.3x42.5 mm in size, the myometrium is homogeneous, the expansion of the arcuate veins of the uterine body up to 2.6 mm is noted; the endometrium is 8.3 mm thick, echopositive, homogeneous, the contours are clear, even. The thickness of the median structures of the cervix is up to 12.3 mm (duplication), with single small anechoic single inclusions, moderately pronounced vascularization. The cervical canal was dilated up to 1.5 mm due to anechoic contents. At the level of the isthmus, there are a few intra- and subendocervical cysts up to 4.3 mm in size. The left ovary is 32x20x25 mm in size, with follicles up to 19x11.4x18 mm, the right one is 29.4x14x24 mm, with follicles up to 7 mm in size. A meager amount of free fluid in the small pelvis is determined.

Taking into account the long-term persistence of HPV (about 1.5 years), the ineffectiveness of previously used therapeutic approaches, a decision was made at the council to conduct PDT.

In February 2021, a PDT course was conducted (Fig.).

At the control examination in July 2021, the mucous membrane of the cervix is smooth, uniform in color, there are no foci of ectopia of the cervical epithelium, a control cytological study was performed No. , groups of cells of cylindrical epithelium, cytogram without features; in scraping from the cervix – cells of the squamous epithelium of the surface layers without signs of atypia.

During the control examination in October 2021, another control cytological examination No. 7779000094 scraping from the cervical canal – NILM was performed; № 7779000093 scraping from the cervix – NILM; PCR study for HPV No. 7779000092 – HPV was not detected.

During the control examination in September 2022 – scraping from the cervical canal and cervix – NILM, PCR study for HPV – HPV was not detected.

The patient has been observed for more than 19 months without recurrence of LSIL, with complete eradication of HPV.

Discussion

Currently, HPV is recognized worldwide as an etiological factor in the development of cervical cancer and precancerous lesions, whose DNA is found in 99.7% of cases [2]. Cervical cancer is the fourth most common cancer in women worldwide and the fourth leading cause of death among women [3]. There are HPV groups of “low risk” (type 6, 11, 42, 43), they are practically not detected in cervical cancer. The HPV group of “high risk”, which is isolated from cervical squamous cell carcinoma, includes viruses 16, 18, 31, 33, 35, 39, 45, 50, 51, 56, 58, 64 and 68 types [4]. Although some HPV infections may spontaneously resolve due to the work of the own immune system, studies have shown that “high risk” HPV infection is the main trigger for the development of lesions of the cervix [5]. Therefore, for patients with persistent high-risk infection for more than one year, timely treatment should be undertaken to prevent malignant lesions of the cervix. For patients with low-grade cervical disease, prompt and

aggressive treatment should be undertaken to promote negative HPV conversion and prevent further progression of cervical intraepithelial neoplasia (CIN).

The onset of CIN can be defined as a complex mechanism of uncontrolled cell division that may involve cellular changes and epigenetic factors such as HPV gene integration. In the presence of HPV infection, DNA mutates in cellular and other environmental conditions, which leads to the integration and triggering of mechanisms for the synthesis of viral DNA and host DNA. Therefore, viruses can elude the mechanisms of cellular and humoral immune defense, promote cell proliferation and inhibit apoptosis [6].

CIN includes a number of pathological changes such as abnormal cell proliferation, poor differentiation, nuclear anomalies, and increased mitosis in cervical epithelial cells upon HPV stimulation. CIN is closely related to and precedes cervical cancer (CC) [7].

Previously, it was customary to divide CIN into three degrees depending on the degree of tumor cell dysplasia, namely, CIN I – mild, CIN II – moderate and CIN III – severe dysplasia / cr in situ, which reflects the continuous pathological process of the occurrence and development of cervical cancer [8].

As part of the lower anogenital squamous epithelial terminology (LAST) standardization project, squamous intraepithelial lesions (SIL) have been used to rename HPV-associated squamous epithelial lesions of the lower genital tract, including the cervix, to low-grade squamous intraepithelial lesions, LSIL and high-grade squamous intraepithelial lesions – HSIL [9].

Squamous intraepithelial HSIL lesions without proper treatment have a high risk of progression to invasive cervical carcinoma. The choice of treatment method is determined individually depending on the prevalence of the process, age, and other factors. The main treatment options are cervical conization using laser, ultrasound, electro- and radiosurgical techniques, cryotherapy and photodynamic therapy [10]. With regard to the treatment

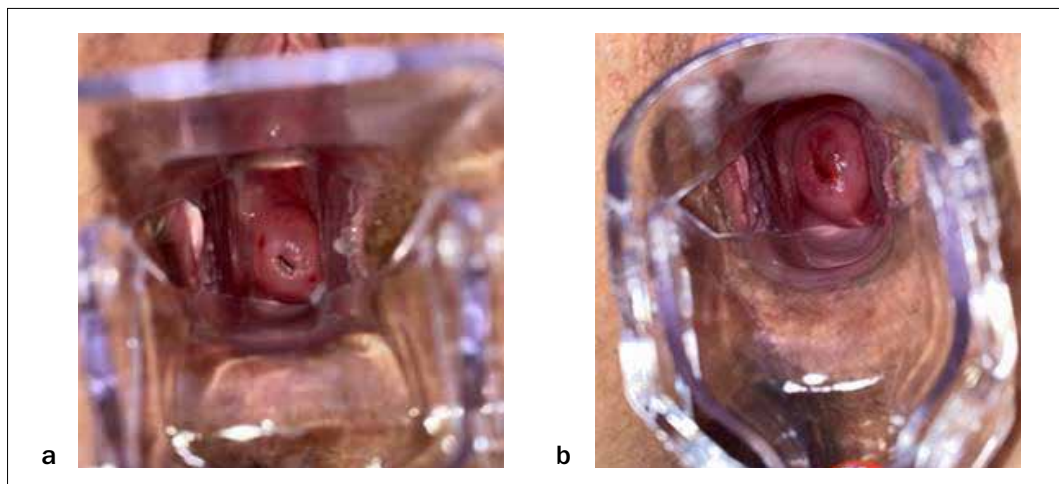


Рис. Фото шейки матки больной Н.: а – до ФДТ; б – 3 мес после ФДТ.

Fig. Photo of the cervix of the patient N.: a – before PDT; b – 3 months after PDT.

of LSIL, some experts believe that LSIL is only an instantaneous expression after HPV infection, which has different biological properties from malignant tumors with a high natural regression rate [11]. Rouzier R. et al. reported that 60-90% of LSILs can self-regress naturally within 2 years. While 30% of LSIL persist, at least 10% progress to HSIL [12].

Thus, early detection and treatment of persistent high-risk HPV infection and dysplasia can effectively prevent the onset of cervical cancer.

Thanks to the knowledge that HPV is the main etiological factor in the development of cervical cancer, measures have been developed to prevent cervical cancer – a prophylactic vaccine against HPV has been developed and has been used in clinical practice since 2006 [13].

In Russia, two types of vaccines are available that are used for vaccination against HPV: tetravalent, which should protect against infection with four types of HPV – 6, 11, 16 and 18 (Gardasil is produced by the Dutch pharmaceutical company MSD Gardasil Merck Sharp and Domu B.V.), and bivalent – from two types of HPV – 16 and 18 (Cervarix is produced in Belgium by GlaxoSmith-Kline Biologicals). In Europe, in addition to these two and 9-valent vaccines are used, which acts against nine types of HPV – 6, 11, 16, 18, 31, 33, 45, 52, 58, most often detected in cervical cancer after HPV 16 and 18 types [14]. However, even with cross-protection and an increase in the number of HPV types covered by the 9-valent vaccine, any HPV vaccine does not protect against all HPV types that increase the risk of cervical cancer [15].

In cases where the patient is diagnosed as a carrier of HPV, the use of the vaccine is not justified. In a number of countries, such as China, Russia, Mexico, Italy, and others, photodynamic therapy of HPV-associated precancer and initial cervical cancer is actively used. The mechanism of action is based on the ability of a number of drugs – photosensitizers (PS) to accumulate in tumor tissue and, when interacting with light radiation of a certain wavelength, initiate damage and / or destruction of tumor structures due to a series of photophysical processes. The main targets of photodynamic exposure are tumor cells, the microvascular network of the tumor and the surrounding stroma, and cellular elements of the body's immune system that infiltrate the tumor [16]. Along with the antitumor effect of treatment, PDT also has an antiviral effect due to the selective accumulation of PS in cells infected with HPV, followed by their direct phototoxic destruction.

The Medical Research Ethics Committee of the International Peace Maternity & Child Health Hospital of China Welfare Institute approved a study of 115 patients with HPV-associated CIN, patients admitted to the hospital from October 2020 to June 2021. The average age of patients was 35.71 ± 2.51 years. Three courses of PDT were performed with an interval of 7-14 days with local application of the drug based on 5-ALA, followed by irradiation for 30 min with a power density of 80 mW/cm². The

overall cure rate and negative HPV tests was 79.0%. The follow-up period for patients ranged from 3 to 6 months after treatment [17].

In another study, PDT was performed on 30 Mexican women in one of the states of Veracruz at the age of 33. Based on cytological analysis, molecular tests, and histopathological evaluation of biopsy specimens, patients were divided into two groups: CIN I with high-risk HPV and high-risk HPV without CIN. Three patients withdrew from the study due to pregnancy. PDT was performed with a topically applied preparation based on 5-ALA, followed by irradiation of the cervix with a light dose of 200 J/cm². Histological examination of biopsy samples taken before PDT and 3, 6, and 12 months after treatment was performed. In the group of women only infected with HPV, the following results of PDT were achieved: 73% of patients got rid of the infection according to PCR data 3 months after PDT, 6 months after PDT. the number of patients with complete eradication of HPV increased to 80%. When observed for 12 months treatment outcome was maintained. In the HPV + CIN I group, 3 months after PDT, 42% of 12 patients showed complete regression of CIN I, when followed up for 12 months – there were no recurrences. In addition, 75% of HPV-infected patients with CIN I got rid of the infection according to PCR smears taken after 3 months, after 6 months the number of cases of complete eradication of HPV increased to 83%, this percentage remained constant for 12 months. In cases where, in addition to HPV infection, bacterial vaginosis was diagnosed, it was eliminated in 83% of patients after 3 months after PDT, the absence of vaginosis persisted for all 12 months observations [18].

In our clinical observation, we present the data of observation and treatment of a patient who, against the background of long-term persistence of highly oncogenic HPV types 31 and 56, developed cervical dysplasia – LSIL. An attempt by doctors at the place of residence to vaccinate Gardasil-4 could not achieve a positive result in relation to already existing viruses. PDT resulted in HPV eradication and LSIL cure.

Conclusion

The clinical observation presented in the article demonstrates the low effectiveness of HPV vaccination in the presence of persistent HPV infection, as well as the possibility and expediency of using antiviral PDT in these clinical situations.

There is also information in the world literature on the effective use of PDT with 5-ALA for antiviral purposes in women with HPV persistence in the absence of atypia of the cervical epithelium.

Thus, antiviral PDT with 5-ALA is a promising technology that can lead to the eradication of HPV infection and, as a result, the prevention of cervical cancer.

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