Gineco.eu [14] 77-80 [2018]
DOI: 10.18643/gieu.2018.77

Benign and malignant cutaneo-mucous pathology induced by human papillomaviruses

Abstract

Human papillomaviruses (HPV) represent a group of deoxyribonucleic acid viruses that contain over 150 distinct types which can cause proliferation of squamous epithelium of the skin and mucous membranes. These viruses are ubiquitous in humans and most often produce benign lesions, such as vulgar warts or condyloma acuminatum. Under certain conditions, depending on the viral strain involved and the susceptibility of the host, HPV can cause dysplastic and neoplastic lesions with fatal potential. Recent research has linked infection with certain HPV strains and cervical cancer, this type of cancer being one of the main causes of mortality in the female population. HPV infection and its clinical implications is therefore a real subject of interest, with potential for the development of numerous therapeutic options. This article aims to look over the main clinical aspects of the lesions produced by HPV and to provide information about the existing anti-HPV vaccines.
Keywords: *papillomavirus, wart, cervical cancer, vaccine, condyloma acuminatum*

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Introduction

Human papillomaviruses (HPV) are a group of double-stranded deoxyribonucleic acid viruses which belong to the class of Papovaviruses, with exclusive specificity for infected tissue and host, which multiply in the nuclei of infected epithelial cells. The current HPV classification system is based on similarities between the genomic sequences of the viruses and includes over 150 types of HPV associated with various types of clinical lesions or disorders[(1)].

Viral transmission happens through direct skin contact, trauma facilitating epidermal infection. With reference to the HPV group that presents anal and genital tropism, the current statistics estimate that more than 90% of the sexually active population will contact a certain type of HPV during their lifetime, in the majority of the cases the infection presenting spontaneous healing. An increased incidence and a wider extension of the skin lesions occurs in immunosuppressed patients, such as HIV-positive patients, organ transplant recipients, etc.[(1,2)].

Clinical manifestations

Vulgar warts are round, oval, hyperkeratotic, well-circumscribed lesions, found isolated or presenting a tendency to confluence, most frequently asymptomatic, of grey or pink color. They are predominantly located in areas prone to minor trauma, such as hands, fingers, knees, and are more common in children, usually being transmitted through hetero- and autoinoculation. The most commonly reported viral strains producing vulgar warts are HPV 1, 2, 4, 26, 27, 29, 41, 57, 65 and 77. The prognosis of the lesions is favorable, 65% of them spontaneously regressing[(3)].

Palmo-plantar warts are lesions that appear like slightly elevated papules or flat, discoid keratotic lesions which interrupt the normal palmo-plantar dermatoglyphs, the regeneration of these dermatoglyphs being a sign of healing. They are mainly located in pressure areas, and when they develop deep in the affected skin they can be very painful. The most commonly reported viral strains associated with the development of palmo-plantar warts are HPV 1, 2, 4, 60, 63. The prognosis is good, 30-50% of the lesions regressing gradually or spontaneously within 6 months[(4)].

Epidermodysplasia verruciformis is a rare, autosomal-recessive disorder which predisposes patients to a chronic and persistent infection with a highly oncogenic papillomavirus (HPV 2, 3, 5, 8, 9, 10, 12, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 36, 37, 38, 47, 50). Patients present a deficiency in cellular immunity, with skin carcinomas developing very frequently before the age of 40. The eruption is characterized by the persistence of numerous hyperkeratotic papules similar to warts, isolated or confluent, as well as of erythematous or hyperpigmented macules similar to the lesions that characterize pityriasis versicolor. The lesions are predominantly distributed on the face, hands, legs and the anterior trunk surface. Dysplastic and neoplastic lesions typical for squamous cell carcinoma are located mainly on the face, thus suggesting the additional carcinogenic effect of ultraviolet rays[(5,6)].

Received: *April 02, 2018*
Revised: *April 29, 2018*
Accepted: *May 06, 2018*

The treatment for non-genital HPV lesions includes topical treatment with 10% salicylic acid and lactic acid emulsions, for small lesions, or 40% salicylic acid and lactic acid emulsions, for larger lesions, imiquimod based creams, topical retinoids, cryosurgery with liquid nitrogen, electrosurgery (associated with a higher risk of scarring), or CO_2 laser surgery[7].

Oropharyngeal disorders induced by HPV may be subclinical but they may also raise serious health problems. Respiratory or laryngeal papillomatosis appears due to HPV 6 or 11 infection contracted during vaginal delivery and can be described as wart lesions present in the upper oropharynx and upper respiratory tract, usually associated with poor prognosis. HPV can also infect the mucous membranes in the oral and nasal cavities, causing benign or malignant neoplasms at this level[8].

Anal and genital HPV infections are the most common sexually transmitted diseases. The receptivity of the population is general and over 90% of the sexually active population will contact a certain strain of the virus during their lifetime, although it is estimated that only 2% of those infected will present clinical lesions, respectively venereal vegetation. Four types of clinical manifestations have been described for anal and genital lesions: small, isolated or contiguous papules; condyloma acuminatum, which are cauliflower-like lesions; keratotic warts; abnormal papules/plaques, most commonly distributed on the cervix. The lesions can vary in size (from a few millimeters to giant lesions, especially in immune-compromised individuals) and colors such as pink, red, brown, or the color of the normal skin. With regard to the most frequently affected areas, these are represented by the frenulum, coronal sulcus, glans, foreskin, shaft and scrotum in men and labia, clitoris, perineum, vagina and cervix in women. The perineum and perianal regions are very commonly affected in both sexes[9,10].

The risk factors for contracting HPV infections are: the increased number of sexual partners, which augments the rate of occurrence for infections with multiple viral strains, increased frequency of sexual interactions, lack of condom use and the coexistence of other sexually transmitted infections. Condoms are not a 100% effective method for protection against HPV infection because the virus can also infect the uncovered tegument that comes into contact with the tegument of the partner, yet it significantly reduces the infection transmission and also protects against other sexually transmitted infections[11].

HPV infections can persist for many years in a latent state and the virus has the potential of becoming infectious intermittently, recurrent venereal vegetations suggesting a re-activation of a subclinical infection more often than a reinfection. The infectious potential of the viruses in the HPV group is high and the incubation period varies between 3 weeks and 8 months. The most commonly reported viral strains connected to venereal vegetations are: HPV 6, 11, 30, 42, 43, 44, 45, 51, 54, 55, 70[12].

The untreated venereal vegetations can evolve as it follows: they can spontaneously regress, remain unchanged or grow. The treatment and management of the anal and genital vegetations include: creams with 5% imiquimod, 0.5% podophyllotoxin based solutions, as well as liquid nitrogen cryotherapy, surgical excision, laser therapy. However, there is no treatment for the HPV carrier status and the treatment of the vegetations does not eradicate the virus, nor does it prevent cervical or other ano-genital types of cancer. Testing for other sexually transmitted diseases is also recommended when HPV specific clinical lesions occur. Also, anti-HPV vaccination is recommended for both girls and boys, preferably before the beginning of sexual life. Currently, there are several types of vaccines containing the most frequent viral strains among the population, both from the group of strains associated with benign genital lesions and from the group of highly oncogenic strains[13,14,15].

The venereal vegetations described above are therefore characterized by benignity and most often respond to treatment or spontaneously regress. However, the recurrent infection with specific HPV strains such as HPV 16, 18, 31, 33, 35, 39 is associated with an increased risk of developing dysplastic and neoplastic lesions. The most common dysplastic/neoplastic lesion is squamous cell carcinoma. This carcinoma can affect the vulva, cervix, penis or anus and it is characterized by flat erythematous papules, often with a tendency to confluence, or papules clustered in smooth, velvety, or smooth surfaces[16,17].

The diagnosis of HPV-induced genital lesions is based on clinical signs and confirmed by biopsy indicating epidermal proliferation with multiple and abnormal mitoses, atypical cells with large nuclei, dyskeratotic cells. Additional risk factors that contribute to the occurrence of squamous cell carcinoma, together with the infection with a highly oncogenic HPV strain, are: smoking, immunological deficits, personal history of condyloma acuminatum, obesity, prolonged use of oral contraceptives and intrauterine contraceptive devices, family history of cervical cancer induced by HPV, personal history of numerous natural births and *Chlamydia* infections[18,19].

A wide variety of treatment options are available for the treatment of malignant lesions, including 5% imiquimod cream, cryosurgery, electrosurgery, Mohs surgery and even hysterectomy with adnexectomy, in cases of invasive cervical cancer. When choosing the appropriate treatment, the physician must take into consideration the location and degree of invasion. Anti-HPV vaccination and the screening using Babeş-Papanicolau smear significantly reduced the incidence and the mortality of malignant lesions produced by human papillomaviruses, particularly cervical cancer lesions[20].

Caesarean delivery is recommended for pregnant women who have active HPV infection because vaginal born children present a high risk of developing genital warts and also recurrent respiratory papillomatosis throughout life. Also, during pregnancy there is a risk

that condyloma acuminatum lesions will have a faster growth rate than normal. In this case, the method of treatment must be chosen by the dermatologist, together with the obstetrician[21,22].

HPV-induced cervical cancer and anti-HPV vaccination

HPV are responsible for almost all cases of cervical cancer and a significant percentage of other genital cancers as well as localized cancers of the head and neck. Cervical cancer is the fourth most common type of cancer in the female population globally, the most frequent histological types being squamous cell carcinomas and adenocarcinomas[23].

In Romania, statistics from 2012 showed that cervical cancer is the second type of neoplasm in the female population aged between 15 and 44 years and it is the first cause of mortality within the same age group. Approximately 4300 new cases are diagnosed annually and 2000 deaths are attributed to this condition every year in Romania[24].

HPV prevalence increases with the severity of the cervical lesions. Statistics performed worldwide support the fact that the most commonly reported strains of HPV responsible for 70% of the cervical cancer cases are HPV 16 and HPV 18. The following most common strains, responsible for 20% of the cases of cervical neoplasms, are HPV 31, 33, 35, 45, 52, 58[25].

Mortality due to cervical cancer was significantly influenced by the occurrence of anti-HPV vaccines and Babeş-Papanicolau cytology screening. Babeş-Papanicolau smears are recommended for women from the age of 21 or at the latest 3 years after the beginning of sexual life and it is a minimally invasive, fast and inexpensive screening test. Testing is recommended annually and if three successive results are normal, testing is possible at intervals of 3 years, up to the age of 65[26].

Anti-HPV vaccines began to be used in the population since 2006 and are recommended before the onset of sexual life, but can also be used later, preferably up to the age of 25, due to the favorable immune response and the lower likelihood of already have contacted a papillomavirus. Currently, two types of anti-HPV vaccines are available in Romania. They contain virus-like particles which are derived from the viral capsid, have no infectious potential and stimulate the immune system of the receptor to produce antibodies against the most prevalent HPV strains in the population[27]. One vaccine acts against HPV 16 and 18, the strains most commonly associated with cervical cancer, and the second vaccine acts against HPV 16, 18, but also against HPV 6 and 11, most often associated with benign genital vegetations. They are given in three doses and the tetravalent variant of the vaccine is also recommended to be administered in the male population, because of its role in preventing the spread of viruses as well as its protective role against condyloma acuminatum genital lesions. It is important to inform the patients that the vaccines do not protect against all viral strains, so even vaccinated people are advised to use condoms, periodic clinical examinations in case of condyloma acuminatum or other cutaneo-mucous genital lesions, as well as periodic screening by Babeş-Papanicolau smear, for the female patients[27,28,29].

A study conducted in Sweden between 2006 and 2012 showed an 18.5% reduction in the incidence of condyloma acuminatum lesions in girls who had been vaccinated between 13 and 17 years of age. The vaccinated group covered about 30% of the population in the age group above mentioned. A decrease in the incidence of the lesions (16.6%) was also observed in the male population with ages between 15 and 29 years. A one-year delay was observed in the protective effect of the vaccine for the male population in the mentioned age group[30].

Another study conducted in India and published in 2018 argues that although the tetravalent anti-HPV vaccine is recommended according to the three-dose regimen, antibody titers also increase in double-dose or single-dose vaccines. Protective antibody titers in single-dose vaccinated girls were comparable to those of three-dose vaccinated girls, over a 7-year period. This suggests that monodose vaccination may be an alternative in the poor countries, the protective effect being comparable over a period of 7 years[31].

The vaccines against HPV are therefore a subject of interest and present further developing potential. A new type of vaccine containing nine viral strains (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) has been recently put on the market, presenting an expected 90% coverage of the most common strains present in the population responsible for genital and oral malignancies and genital benign lesions. This new vaccine is recommended in two or three doses as follows: girls and boys between the ages of 9 and 14 are recommended to receive 2 or 3 doses and boys and girls between 14 and 26 years are recommended to receive all 3 doses. Countries such as Canada, the United States of America and the United Kingdom have already included the new immunizer in their national vaccination schemes[32,33].

Conclusions

HPV are an extensive group of viruses frequently found within the population. The infection with certain strains can produce unaesthetic, highly contagious and sometimes difficult to manage lesions, or even premalignant and malignant conditions. Anti-HPV vaccination is a still a subject of high interest, with ongoing research being developed continuously and the results already being observed in vaccinated populations. However, none of the existing vaccines (bivalent, tetravalent, nonavalent) is able to provide complete protection and the need for periodical screening, even of vaccinated individuals, still exists. ■

Conflict of interests: The authors declare no conflict of interests.

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