

Case Report

A Case Report about Generalized Verrucosis as an Unusual Clinical Presentation of a Disseminated HPV Infection, the Tree Man Syndrome, Case Study

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Human Papilloma Virus

Human Papilloma Virus (HPV) infection is very common. HPV is a group of more than 200 related viruses [1]. HPV is an infection of the basal epithelium and transmission can occur either by direct contact or during childbirth. More than 40 HPV types can be easily spread through direct sexual contact, from the skin and mucous membranes of infected people to the skin and mucous membranes of their partners [2]. They can be spread by vaginal, anal, and oral sex. Other HPV types are responsible for non-genital warts, which are not sexually transmitted.

Most sexually active women and men will be infected with some form of HPV at some point in their lives and some may be repeatedly infected [3]. For most people, HPV goes away on its own and does not cause any health problems [4], but for others who don't clear the virus, two categories of sexually transmitted HPV [5] include low-risk HPVs, which are not cancer causing, and high-risk, or oncogenic HPVs, which can lead to a cancer diagnosis. Malignancies found to be associated with HPV infection include cervical, vaginal, vulvar, penile and anal cancers as well as cancers of the oropharynx. HPV causes approximately 85-90 percent of anal cancers [6] and 90 percent of genital warts in both males and females.

Sexually transmitted HPV types fall into two categories [7]:

- Low-risk HPVs, which do not cause cancer but can cause skin warts (technically known as condylomata acuminata) on or around the genitals and anus. For example, HPV types 6 and 11 causes 90% of all genital warts. HPV types 6 and 11 also cause recurrent respiratory papillomatosis, a disease in which benign tumors grow in the air passages leading from the nose and mouth into the lungs.

- High-risk HPVs, which can cause cancer. About a dozen high-risk HPV types have been identified. Two of these, HPV types 16 and 18, are responsible for most HPV-caused cancers.

Pathogenesis

The pathogenesis of HPV involves viral particles which enter the epithelial cells at areas of micro trauma, actively targeting proliferating basal cells. As the infected cells migrate away from the basal layer, viral DNA is packaged into virions (infectious virus). When the epithelium is shed, viral particles are released and are able to infect other cells.

Human Papilloma Virus (HPV) infections cause a spectrum of clinical disease states, depending on the causative HPV and the characteristics of the infected host, especially the status of cell-mediated immunity.

Most high-risk HPV infections occur without any symptoms, go away within 1 to 2 years, and do not cause cancer. Some HPV infections, however, can persist for many years. The persistence of HPV infection in Epidermodysplasia Verruciformis (EV) is thought to be the result of an immunogenetic defect, which generates several cytokines capable of down-regulating cell-mediated immunity. Persistent infections with high-risk HPV types can lead to cell changes that, if untreated, may progress to cancer [2].

High-risk HPVs cause several types of cancer:

- **Cervical cancer:** Virtually all cases of cervical cancer are caused by HPV, and just two HPV types, 16 and 18, are responsible for about 70% of all cases.
- **Anal cancer:** About 95% of anal cancers are caused by HPV. Most of these are caused by HPV type 16.

- **Oropharyngeal cancers** (cancers of the middle part of the throat, including the soft palate, the base of the tongue, and the tonsils): About 70% of oropharyngeal cancers are caused by HPV. In the United States, more than half of cancers diagnosed in the oropharynx are linked to HPV type 16.
- **Rarer cancers:** HPV causes about 65% of vaginal cancers, 50% of vulvar cancers, and 35% of penile cancers. Most of these are caused by HPV type 16.

Generalized verrucosis is an unusual clinical presentation of a disseminated HPV infection associated with severe immunodeficiency status. It has no definite age of onset but most probably seen in children to young adults ranging from 1 year old to 20 years old [8]. It is malignant when occurs at the age of 40-50 years. The percentages of cases seen, according to age group are the following: infancy- 7.5%, childhood- 61.5%, puberty- 22%. There are two forms of the syndrome as follows: The first form shows multiple plane warts. This form was widely distributed, and it does not show any malignancy transformations. The second form of the syndrome is induced by HPV-5 and sometimes HPV-8,9,14,20,24,28,47 and others. Although it is most commonly inherited in an autosomal recessive manner, sporadic, sex-linked, and autosomal dominant inheritance have been described. In those cases of autosomal recessive inheritance, there may be a history of consanguinity in the parents of the afflicted individual. In those cases of atypical inheritance, there may be an association with chronic lymphopenias. Regardless of the mode of inheritance, the phenotype of the disease is characterized by chronic infection with HPV. Widespread skin eruptions of flat-to-papillomatous, wart-like lesions and reddish-brown pigmented plaques on the trunk, the hands, the upper and lower extremities, and the face are typical. Malignant skin tumors (carcinomas), especially squamous cell carcinoma (in situ or invasive), develop frequently in these patients (30-70%), most commonly in sun-exposed areas starting between the ages of 20 and 40 years, which reflects the high-risk nature of the HPV infection. Skin cancers initially appear on sun-exposed areas, such as the face, neck, chest, and arms, reflecting the role of ultraviolet light and HPV infection in the promotion of skin cancer development [9].

Treatment: The treatment of HPV-related cancers often includes medical and surgical therapy.

Medical Care: No therapy for EV is definitive. Treatment of EV includes preventive measures, the most important of which is strict sun avoidance and protection, beginning as soon as the diagnosis is made. Nonsurgical therapies for the management of skin cancers include topical imiquimod and 5-fluorouracil, systemic retinoids, interferon, and 5-aminolevulinic acid photodynamic therapy. In advanced human papillomavirus (HPV)-related carcinomas, an experimental therapy involves treatment with a combination of 13-cis retinoic acid and interferon alpha or cholecalciferol analogues.

For localized multiple malignant lesions, auto transplantation of skin from uninvolved areas has been reported with success in preventing further development of cancers [9].

UV-B exposure, UV-A exposure, and x-ray irradiation should be avoided because radiation therapy often promotes the recurrence of more aggressive skin cancers.

Surgical Care: Surgical and electrosurgical removal and cryotherapy are used in the treatment of benign and premalignant skin lesions. Surgery is also indicated for treatment of malignant lesions. If skin grafting is necessary, the graft should be from sun-protected skin [9].

The Prevention: HPV Vaccines

Health education and prevention is necessary to reduce cancers related to HPV infections. Education on abstinence and vaccinations are two methods proven to be effective. The role of the health care provider is to educate adolescents regarding the risk of sexually transmitted disease and ways to protect themselves from HPV-related cancers such as the cases reviewed in this exhibit.

There are safe and effective vaccines recommended to prevent these health problems from happening. Three vaccines are approved by the FDA to prevent HPV infection: Gardasil, Gardasil 9, and Cervarix. All three vaccines prevent infections with HPV types 16 and 18, two high-risk HPVs that cause about 70% of cervical cancers and an even higher percentage of some of the other HPV-associated cancers [2]. Gardasil also prevents infection with HPV types 6 and 11, which cause 90% of genital warts. Gardasil 9 prevents infection with the same four HPV types plus five additional high-risk HPV types (31, 33, 45, 52, and 58).

In addition to providing protection against the HPV types included in these vaccines, the vaccines have been found to provide partial protection against a few additional HPV types that can cause cancer, a phenomenon called cross-protection. The vaccines do not prevent other sexually transmitted diseases, nor do they treat existing HPV infections or HPV-caused disease.

The FDA has approved Gardasil and Gardasil 9 for use in females ages 9 through 26 for the prevention of HPV-caused cervical, vulvar, vaginal, and anal cancers; precancerous cervical, vulvar, vaginal, and anal lesions; and genital warts. Gardasil and Gardasil 9 are also approved for use in males for the prevention of HPV-caused anal cancer, precancerous anal lesions, and genital warts. Gardasil is approved for use in males ages 9 through 26, and Gardasil 9 is approved for use in males ages 9 through 15. Cervarix is approved for use in females ages 9 through 25 for the prevention of HPV-caused cervical cancer.

All three vaccines are given through a series of three injections into muscle tissue over a 6-month period. In October 2016, the FDA approved a 2-dose schedule for boys and girls

initiating vaccination with Gardasil 9 at ages 9 to 14 years (the second dose is to be administered 6-12 months after the first). Those initiating the HPV vaccination series at older ages (including teens who begin getting vaccinated after they turn 15 years old) or who are immune compromised should still be vaccinated according to the 3-dose schedule.

Like other immunizations that guard against viral infections, HPV vaccines stimulate the body to produce antibodies that, in future encounters with HPV, bind to the virus and prevent it from infecting cells. The current HPV vaccines are based on virus-like particles (VLPs) that are formed by HPV surface components. VLPs are not infectious, because they lack the virus's DNA. However, they closely resemble the natural virus, and antibodies against the VLPs also have activity against the natural virus. The VLPs have been found to be strongly immunogenic, which means that they induce high levels of antibody production by the body. This makes the vaccines highly effective.

To date, protection against the targeted HPV types has been found to last for at least 8 years with Gardasil and at least 9 years with Cervarix. The duration of protection with Gardasil 9 is not yet known. ACIP recommends that women who have abnormal Pap test results that may indicate an HPV infection should still receive HPV vaccination if they are in the appropriate age group because the vaccine may protect them against high-risk HPV types that they have not yet acquired. However, these women should be told that the vaccination will not cure them of current HPV infections or treat the abnormal results of their Pap test.

Case Report

A 42-year-old male patient presented with Epidermodysplasia Verruciformis (EV) who had severe generalized verrucosis skin lesions for almost 10 years along with extensive warts over hands causing severe functional impairment as he couldn't take care of himself. (Figure 1)



Figure 1: On examination: A ten years history of progressively widespread worsening viral involvement (warts) over the trunk, limbs especially over both hand and mainly left hand was more severely affected with

difficult to use. The entire left hand is almost completely obliterated by extensive, deform, yellow-brown large keratotic masses originating from viral lesions making the skin hard and thickened. The hand is entirely functionless, as the lesion allow only limited movement. Similarly, but much less extensive, the same lesion exists on the right hand and other areas of the body (face and trunk).

He has no history of sexually transmitted diseases.

None of his family members, relatives or friends has the similar condition even at the present or in the past. Now he has a healthy all first line relatives. There is no history of the presence of risk factors. He is not taking any medications.

Laboratory Examination

- Lymphopenia (800 lymphocytes in blood count).
- Low level of IgM suggestive a primary immunodeficiency.
- HIV negative.

Assessment

- Generalized verrucosis secondary to a yet unknown primary immunodeficiency.

Plan

- Surgery to improve function of hands.
- HPV typing by PCR on a fresh tissue sample of a wart removed from the right forearm.
- Exome sequencing to reveal the genetic cause for the primary immunodeficiency.
- As there is no effective systemic treatment for this problem, removal of the extensive process surgically with cauterization of the base area will be done to reduce the viral load and perhaps restore some degree of the function, split thickness skin grafting versus secondary epithelialization depending upon the finding at surgery following removal.
- For like lesions, surgery is not a cure but it is an attempt to improve and control the situation and perhaps facilitate a better response to some sort of systemic treatment.
- In order to provide a partial protection against different HPV types that can cause cancer and to provide a additional protection against the HPV types included in these vaccines, a phenomenon called cross-protection, a vaccine called "Gardasil" is given.

Interpretation

A tree man syndrome is a rare disorder happening more frequently at a younger age in the general population. It is an unusual genodermatosis characterized by an autosomal recessive

inheritance pattern. Despite in our case, he is the only one who was afflicted with the disease and there is no other first relative afflicted, one of his previous generations of the family member should have the disease. Non-surgical therapies and surgical therapies are known to treat this disorder, but it is known to be lifelong disorder with no treatment to prevent new lesions from occurring. But it is important to reduce the risk of skin cancer. This a rare case of severe disfigurement of this patient illustrates the natural history of generalized verrucosis and was a result of a progress for many years before the initiation of therapy due to an underlying unknown primary immunodeficiency. In such situation, despite medical and surgical treatments can result in marked improvement in the general health of this patient, these lesions will continue to appear throughout life. Health education and prevention is necessary to reduce cancers related to HPV infections.

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