Virology

Lec (10)

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Learning objectives

- ✓ To define papillomaviruses
- ✓ To classify this family
- ✓ To list types of disease cause by this family
- ✓ To clarify method of diagnosis and treatment

Papillomaviruses

Human papillomavirus (HPV) consist of more than 100 types, classified primarily on the basis of DNA restriction fragment analysis into two groups **low risk types** causes papillomas (which are benign tumors of squamous cells, e.g., warts on the skin) and **high risk types** especially types 16 and 18, cause carcinoma of the cervix and penis.

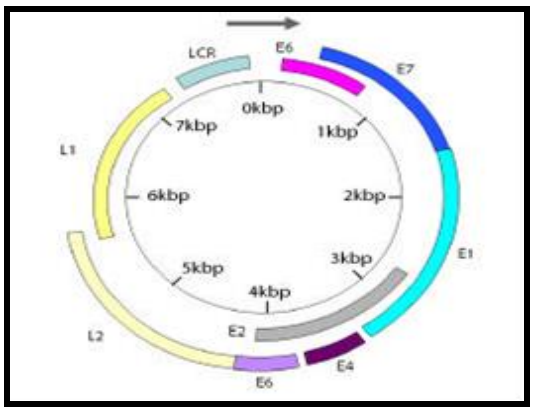
Most of the HPV prevalence figures are around genital infection. Human papilloma virus infection is the commonest sexually transmitted infection, and 25-40% of women between the ages of 15–25 years have evidence of HPV infection. There are an estimated 400 million cases of genital HPV infection worldwide. It is estimated that 250000 women die of cervical cancer each year with 500000 new diagnoses each year, 80% of which occur in the developing world

Important Properties

-Papillomaviruses are nonenveloped viruses with double-stranded circular DNA and an icosahedral nucleocapsid.

-The Papillomavirus genome is divided into an early region (E) and a late region (L).

-**Early region (E)** encoding various genes that are expressed immediately (early protein) after initial infection of a host cell, E1,E2 are responsible for replication of virus, E6, E7 which promoter cell growth by inactivation the tumor suppressor protein P**53**,P**RB** (retinoblastoma protein). **Late region (L)** encoding genes that are expressed L1, L2 proteins of capsid.



Route of spread

- Direct contact with infected material: usually introduced through abraded skin (e.g. sharing towels, swimming pools, walking barefoot). Common skin warts are normally transmitted by this route.
- Sexual: the main route of spread for genital warts is sexual, and therefore it is a sexually transmitted infection.
- Vertical: laryngeal papilloma or warts in children are usually due to transmission to the baby at the time of delivery if the mother has genital warts.

Summary of Replicative Cycle

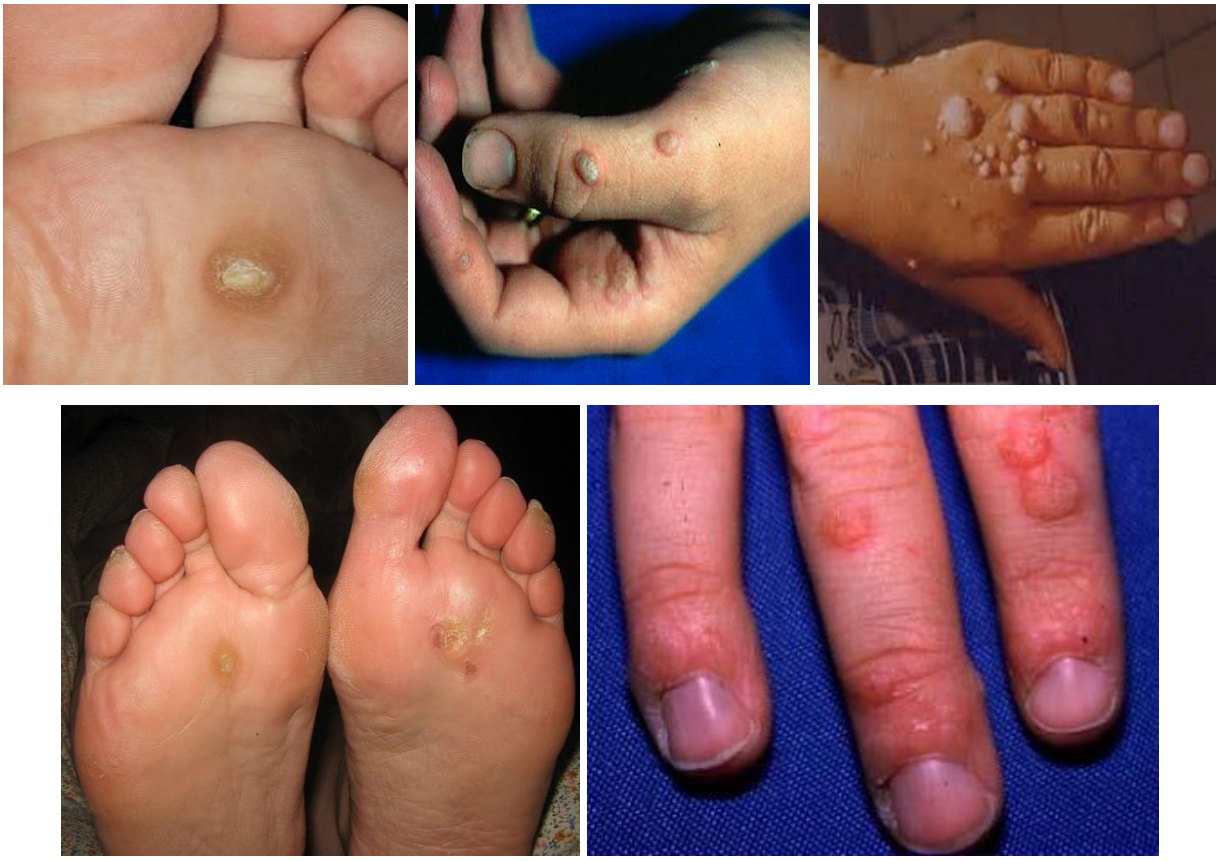
Little is known of the specifics of viral replication, because the virus grows poorly, if at all, in cell culture. In human tissue, infectious virus particles are found in the terminally differentiated squamous cells rather than in the basal cells. In malignant cells, viral DNA is integrated into host cell DNA in the vicinity of cellular proto-oncogenes, and E6 and E7 are overexpressed. However, in latently infected, nonmalignant cells, the viral DNA is episomal and E6 and E7 are not overexpressed. This difference occurs because another early gene, E2, controls E6 and E7 expression. The E2 gene is functional when the viral DNA is episomal but is inactivated when it is integrated.

The formation of a wart by cell proliferation caused by infection of basement epithelial cells with human papillomavirus. Early gene expression leads to stimulation of cell division and terminal differentiation. This results in late gene expression and virus replication in a terminally differentiated, dying cell, which produces large quantities of keratin.

Clinical Findings

Papillomas of various organs are the predominant finding. These papillomas are caused by specific HPV types. For example,

1- **Skin and plantar warts** are caused primarily by HPV-1(foot warts) and HPV-2(hand warts) also HPV-4 cause the same disease.



2- Genital warts Ninety per cent of genital warts are due to HPV genotypes 6 and 11. Genital warts (**condylomata acuminata**) are the most common sexually transmitted infection (STI) and commonly occur in association with other STIs. The lesions may appear as papules or papillomatous, and the size may vary from small to very large especially when several lesions coalesce into one.

Affected areas in men:

- Penis - mostly around the glans and prepuce
- Urethra
- Anus and rectum - especially in those who practise receptive ano-rectal sex, e.g. men who have sex with men (MSM).

Affected areas in women:

- Vulva
- Vagina
- Cervix - typically flat lesions
- Anus and perineum.

Also cause respiratory tract papillomas, especially laryngeal papillomas, in young children by HPV types 6, 11, these occur in the mouth and larynx, as a result of vertical transmission at delivery from the mother's genital infection.

3- Carcinoma. Cervical cancer as well as premalignant lesions called intraepithelial neoplasia, are associated with infection by HPV types 16, 18, 31, 33, 35 and higher genotypes, and about 70% of all HPV associated cancers are due to genotype 16 and 18, the rest are due to the other HPV genotypes. Other cancers Squamous cell carcinoma of the penis, vulva, vagina and some laryngeal carcinomas are also associated with HPV infection.

Table 1. Human papilloma viruses and their associated lesions.

Lesion		*Associated HPV genotype*
Non-malignant lesions	Common warts	1, 2, 4
	Flat warts	3
	Genital warts	6, 11
	Laryngeal papilloma	6, 11
Premalignant lesions	Epidermodysplasia verruciformis*	2, 3 and others
Malignant lesions	Cervical cancer	16, 18, 31, 33, 35 and others

***Epidermodysplasia verruciformis** (EV) is a rare, inherited disorder that predisposes patients to widespread human papillomavirus infection and cutaneous squamous cell carcinomas. Although epidermodysplasia verruciformis 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 inherence, 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, wartlike lesions and reddish-brown pigmented plaques on the trunk, the hands, the upper and lower extremities, and the face are typical.

Malignant skin tumors, 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



Laboratory Diagnosis

1-Infections are usually diagnosed clinically.

2-moleculat techniques to detect the presence of viral DNA are commercially available such as DNA hybridization tests and PCR.

3-Diagnostic tests based on detection of antibodies in a patient's serum more common in patients with cancer.

Treatment and Prevention

1- The usual treatment for genital warts is podophyllin; alpha interferon is also effective and is better at preventing recurrences than are non-antiviral treatments.

2- Liquid nitrogen is commonly used for skin warts. Plantar warts can be removed surgically or treated with salicylic acid topically.

3- Cidofovir may be useful in the treatment of severe HPV infections.

4- A vaccine against four types of HPV was approved by the FDA in 2006. The vaccine, called **Gardasil**, contains the capsid proteins of types 6 and 11, which cause genital warts, and types 16 and 18, which are the two most common causes of cervical carcinoma. It is approved for use in females between the ages of 9 and 26 years. The role of cesarean section in preventing transmission of HPV from a mother with genital warts to her newborn is uncertain.