Human Papillomavirus

- Human papillomavirus (HPV) is caused by a DNA virus from the *papillomaviridae* family
- Many HPV infection cause no symptoms and 90% resolve spontaneously within two years
- HPV can cause a variety of benign cutaneous proliferation, including common skin warts
- HPV also can cause malignant transformation of squamous epithelia
- In some cases, an HPV infection persists and increase the risk of cancer of the cervix, vulva, vagina, penis, anus, mouth, tonsils and throat

Virology

- HPV is a small, nonenveloped, double – stranded, circular DNA virus belonged to *papillomaviridae* family
- The virus genome is divided into 3 regions:

An early region (E1 – E8), a late region (L1-L2), and the viral long control region

- More than 200 HPV types have been recognize That classified according to type of epithelial they infect (cutaneous or mucosal)
- The mucosal HPVs also are subgrouped into low, high and moderate risk types. Depending on the frequency with witch they are found in invasive cancers

Virology…

- HPV infection is limited to the basal cells of stratified epithelium.
- HPV lesions arise from the proliferation of infected basal keratinocytes after minor skin or mucosal abrasion.
- *E*6 and *E*7 are oncoproteins that inactivate p53 and pRb proteins, these inactivation lead to dysregulation of the cell cycle and neoplastic transformation of the affected tissue
- Several months to years may elapse before squamous intraepithelial lesion develop
- Most HPV infection, including those with carcinogenic HPV genotypes typically resolve within 12months

Epidemiology

- More recently, HPV infection of genital tract has been recognized as the most prevalent sexual transmitted infection.
- Transmission

  -direct skin to skin contact

  -vaginal birth (vertical transmission)

  -objects
- Incubation period: approximately 3 months, but disease can appear weeks to years after exposure
- The highest rates of HPV infection are seen in females younger than 25 years old
- Risk factors for HPV infections

  - age of sexual activity

  -Smoking

  -immunosuppression

  -use of oral contraceptive

  -multiple sex partner

Epidemiology...

- HPV-associated malignancies in females

- in female ,HPV infection can progress to vulva ,vaginal , and cervical cancers

-cervical cancer remains the second Leading cause of cancer death in women worldwide

-All cervical cancers are HPV – associated

-With HPV 16 accounting for 50% of cases and HPV 12 for 20%. HPV 31,33,45,52,58,can estimated to cause 19%

-cervical cancer is Fourth most common cancer among females

-Half of the cases of vulvar cancer are HPV-associated(HPV 16,18)

-Vaginal cancer is much rarer than vulvar cancer

Epidemiology…

- HPV associated diseases in males

  -anal cancer in men who have sex with men (HPV 16,18)

  -penile cancer : less common in circumcised males

  -anogenital warts (condylomata acuminata)HPV 6,11

- HPV –associated oral and oropharyngeal cancers

  -oropharynx and base of the tongue and tonsils

- recurrent respiratory papillomatosis

  -most common benign laryngeal tumor in children

  -acquisition of HPV during Passage through the birth canal of an infected mother (HPV 6,11)

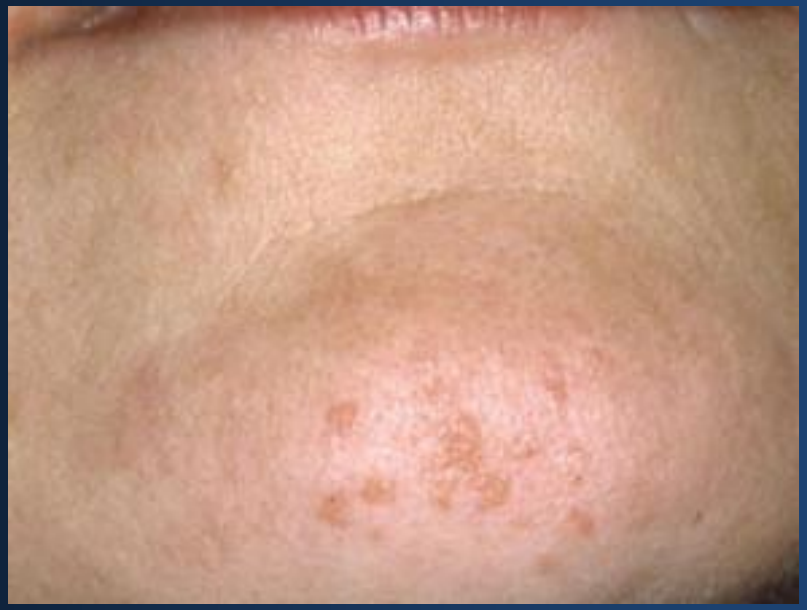
Clinical manifestations

- **cutaneous warts**

- common warts (verrucae vulgaris) ,are usually found on the hands and feet, well-demarcated ,dome-shaped papules with multiple conical projection (papillomatosis), cauliflower like surface.

-flat warts :do not have papillomatosis or hyperkeratosis ,most commonly found on the arms ,face ,or forehead .

-plantar warts (verrucae plantaris):occur most commonly in adolescents and young adults, single lesion and have a highly Thickened corneal layer, painful, on the soles of the feet



Clinical manifestation …

- Epidermodysplasia verruciformis:
- autosomal – recessive dermatitis
- inability to resolve HPV – induced infection, cutaneous wart – like lesions
- two clinical types of warts are seen: flat warts, and reddish-brown macular Plaques on the face ,trunk, and extremities
- sometimes resembles pityriasis versicolor
- in about one-third of patients ,the lesions undergo malignant transformation into invasive SCCS

Clinical manifestation…

- Genital warts

-Genital tract HPV is the most common clinical manifestation of mucosal HPV disease

-It carries high rates of morbidity and mortality to both sexes by its oncogenic potential

-However condylomata acuminata or genital warts, which are the most common genital manifestations rarely develop into dysplastic lesions or invasive carcinoma

-90% of genital warts are caused by HPV types 6 and 11, and a small proportion by HPV -16

- Genital warts occur in multiples as flesh colored, pink, and or purple_ grey papules can also be pedunculated

-They found on the vulva, and in and around vagina, perineum , inner thigh and anus

-In males, genital warts can be found on the penis, scrotum, groin and upper thigh ,perineum and anus

-Genital warts are often asymptomatic but can cause burning , itching and pain.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Clinical manifestation…

- Recurrent respiratory papillomatosis(RRP)

-RRP is a rare potentially life - threatening condition caused by HPV types 6 and 11

-most common tumor of the larynx in children

-Infants and children with RRP acquire HPV infection during passage through an HPV – infected birth canal

-The most common site for RRP is the true vocal cord of the larynx , supraglottis and subglottic area , the disease may involve the trachea, palate , nasopharynx , and Paranasal sinuses

-Symptoms : hoarseness or a change in voice , infants and toddlers may have a hoarse cry , stridor , airway obstruction, respiratory distress , or difficulty in phonation

-the disease may involves the lungs and pulmonary nodules occur

-The main stay treatment of RRP is surgical debunking

-Interferon alpha is used in some cases

Diagnosis

- Most HPV infection are asymptomatic
- Typical appearance of common warts on the skin and condylomata acuminata in the anogenital area is sufficient to establish the clinical diagnosis of HPV infection
- Laboratory confirmation of HPV –associated lesions may be necessary for unusual manifestation, immunocompromised patients and for patients with suspected malignant lesions
- Electron microscopy can be used to detect Virion with typical papilloma virus morphology in cutaneous warts
- Culture and serology are not helpful

Diagnosis

- cytology:

-Pap smear for obtaining and staining exfoliated cervical cells:1-3 years interval in sexually active women

- colposcopy for women with abnormal pap smear or external anogenital warts

-cervix, vulva, and anus in female or urethral meatus, penis ,scrotum and anus in males are visualized for abnormal tissues

-the area then is soaked in acetowhite (3-5% acetic acid) for whitened plaques, HPV biopsy for histologic examination and detection of HPV DNA

-DNA hybridization /amplification method

-Commercially available PCR -based assay.

Treatment

- Most Hpv – associated Lesions will regress spontaneously in 1-2 years
- treatment for lesions which are large , multiple , recurrent ,painful ,and life Threatening
- surgical technique, traditional local excision, cryotherapy ,electrocautery, Curettage ,ultrasonication and laser Therapy.
- Mainstay of treatment for RRP is repeated surgical debulking,
- simple organic acids such as bichloractetic acid, trichloracetic acid or salicylic acid have shown some success in the localized treatment of skin and genital warts

Treatment…

- Immunomodulation: interferon topically ,intralesionally, or systemically
- Topical immunotherapeutic agents: imiquimod
- Retinoids and retinoic acid(analogs of vitamin A) was used to treat HPV –associated disease especially RRP
- Combination of interferon and retinoic acid
- Intralesional administration of cidofovir

Vaccination

- Three vaccines are available to prevent infection by some HPV types
- Cervarix : a bivalent vaccine targets HPV types 16 and 18 which cause 70% of all cervical cancers worldwide , also cause nearly 90 percent of anal cancers and a significant proportion of oropharyngeal, vulvar, vaginal and penile cancers. The vaccine prepared from virus-like particles of the L1 capsid protein.
- Gardasil: a quadrivalent vaccine targets HPV types 16,18,6,and11 .HPV types 6 and 11 cause approximately 90% of anogenital warts .a recombinant vaccine
- Gardasil 9: a nonavalent vaccine targets the same HPV types as the quadrivalent vaccine(16,18,6,11) as well as types 31,33,45,52,and58 cause an additional 20% of cervical cancer

Vaccination…

- Routine HPV vaccination is recommended at 11 to 12 years . it can be administered starting at 9 years of age
- For adolescents and adult aged 13-26 years who have not been previously vaccinated, catch – up vaccination is recommended
- CDC recommends two shots for those aged 11-12(0,6-12 months),and three doses for those 13 and older(0,1-2,6 months)
- Immunocompromised patients : three doses of HPV vaccine at(0, 1-2,6 months) >26 years:

-previously unvaccinated adults aged 27-45 years who have a low likelihood of prior HPV exposure

-Health care workers who have repeated exposure to HPV

- HPV vaccination during pregnancy is not recommended
- side effects: headache, nausea, vomiting, fatigue, dizziness, syncope, and generalized weakness.