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PEARLS OF LABORATORY MEDICINE

Pearl Title: HPV Related Malignancies

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Human Papillomavirus (HPV)

Small double stranded DNA virus

More than 200 genotypes, 16 genera

Alpha genotype- most frequently associated with cancers

Other genotypes might be causative in immunosuppressed states

Classification (based on oncogenic potential)

- Low risk- HPV6, HPV11: genital warts, papillomas
- High risk- 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59
- Possibly carcinogenic (uncertain oncogenicity)- 5, 8, 26, 30, 34, 53, 66, 67,68, 69, 70, 73, 82, 85, 97

HPV16 and HPV18: account for approximately 70% of invasive cervical cancers

HPV: Infection and Prevalence

Most common genital viral infection

Mode of transmission: sexually transmitted

Sites of infection

- Anogenital infections are most frequent
- Skin, oropharynx

Affinity for transitional zones: squamo-columnar junction in cervix and anorectal junction

Majority are transient and asymptomatic

Cleared by the immune system within 12-24 months

Some progress to develop benign lesions or cancers (HR HPV)

HPV: Life Cycle

- Tropism for basal epithelial layer of skin and mucosal squamous epithelium
- Infection through microtrauma
- Basal epithelial layer: stem cell like features
- Persists at low numbers in non integrated (episomal form) and may remain dormant
- Differentiation of epithelial cells: high copy number, expression of capsid genes and generate new progeny virions
- Dependent on host cell machinery for replication

HPV Genomic Structure

Three regions

- Early region: E1, E2, E4-E7: non-structural regulatory proteins for DNA replication
- Late region: L1 and L2 structural capsid proteins
- Non coding upstream regulatory region

E1 and E2: initiation of replication

E1: viral genome replication

E2: repressor of viral oncogenes E6 and E7

Viral integration → disruption of E2 → dysregulation of E6 and E7 viral oncogenes → cell transformation

HPV: Oncogenic Mechanisms

E6 oncoprotein

- Degradation of p53: prevents activation of downstream targets and apoptosis
- TERT expression (telomere maintenance)

E7 oncoprotein

- Binds to Rb proteins, displacing E2F transcription factor resulting in cell cycle progression
- Inactivates CDK inhibitors p21 and p27
- Activates cyclins E and A

HPV alone is not sufficient for transformation, additional genetic and epigenetic events necessary

HPV Infection Progression: Risk Factors

- Persistence of HPV infection
- High risk HPV types
- Age more than 30-years
- Coinfection with multiple HPV types
- Immunosuppressed states
- Tobacco use
- Low socio-economic status

HPV Related Malignancies

HR HPVs: Carcinomas: viral integration

- Cervical cancers
- Anogenital (vulvar, vaginal, penile, anal)
- Head and neck: oropharynx, tonsils, tongue

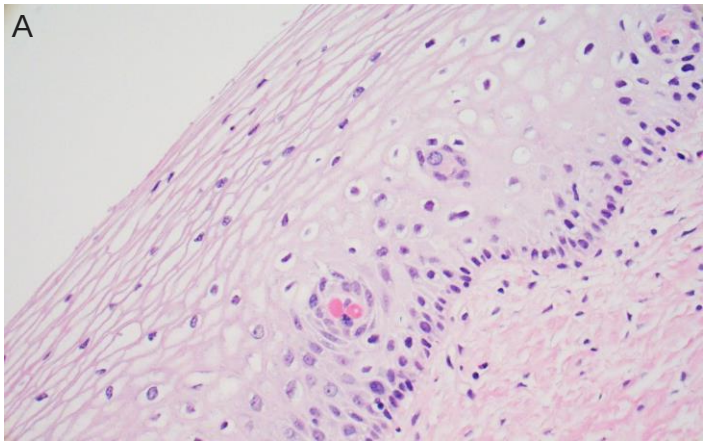
LR HPV:

- Genital warts (condylomas)
- Cutaneous warts (Verruca vulgaris)
- Laryngeal papillomas
- Low grade squamous intraepithelial lesions (LGSIL)

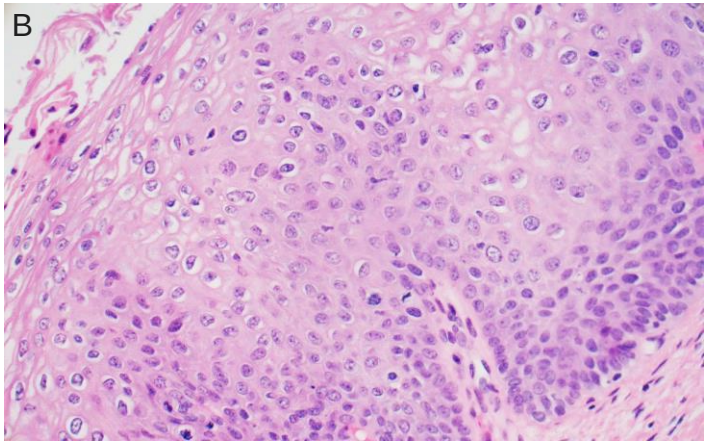
Cervical Cancer

- 3rd leading cause of malignancy in women
- Almost 100% HPV related
- HPV16, HPV18: most frequently associated
- SCC (90%), adenocarcinoma (10%)
- HPV infection precedes cancer by decades
- Persistent HPV infection progresses through stages of infection to pre-invasive to invasive cancer over several years
- Low grade lesions: most resolve
- 10-30%: progress to pre-invasive high grade lesions/ invasive cancer

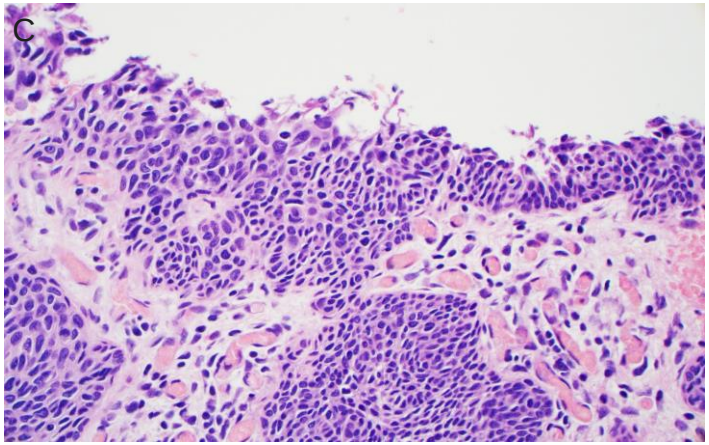
HPV Related Cervical Changes



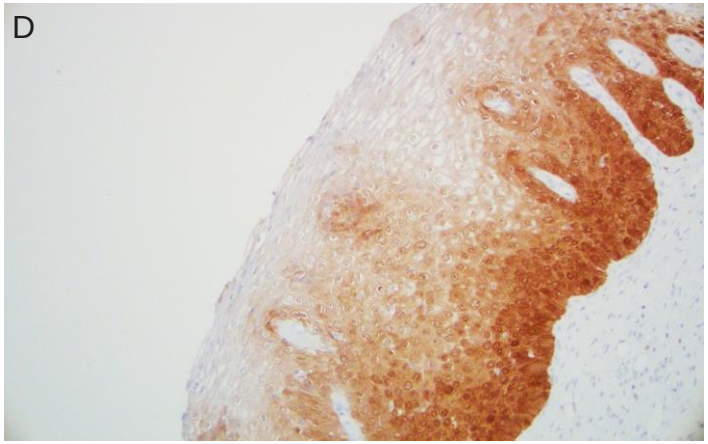
Benign cervical mucosa, H&E, 40x



Low grade squamous intraepithelial neoplasia, H&E, 40x



High grade squamous intraepithelial neoplasia, H&E, 40x



Positive p16 immunostain used as a surrogate marker for HPV induced changes, 20x

Cervical Cancer Screening- WHO Recommendations

Guided by prevalence of cervical carcinoma and available resources in a region

Highly effective in early detection

Target age: 30-49 years (younger if at high risk)

- Molecular HPV screening and visual inspection with acetic acid, > 30 years
- Cervical cytology: conventional pap smears/ liquid-based cytology, 30-49 years
- Visual inspection with acetic acid: < 50 years with visible squamocolumnar junction

Negative visual inspection with acetic acid or cytology:

Interval for re-screening: 3-5 years (increased to 5 years for older women)

Negative molecular testing:

Re-screening after 5 years

Oropharyngeal Cancer

- Oral HPV infection
- HPV associated: 63%; 95%-HPV16
- Despite lower prevalence of HPV infection, HPV associated oropharyngeal cancers more common than anogenital cancers
- Risk factors: Younger adults, multiple sex partners, males> females
- Common location: base of tongue, tonsils
- Basaloid morphology
- Favorable outcome

Anogenital Cancers

Anal cancers
- 97% HPV related
- Risk factors: men having sex with men (MSM), immunosuppresion

Penile cancers
- 45% HPV related, besides the HR HPV, LR HPV 6 and 11 also causative

Vulvar and vaginal cancers
- Older women
- Vulvar: 40% HPV
- Vaginal: 70% HPV

Skin Cancers

Squamous cell carcinomas

- Immunocompetent and immunocompromised (transplant recipients)

α and β-HPV

- Co-carcinogen with UV light
- HPV oncoproteins disable repair of UV induced DNA damage

HPV Vaccines: FDA approved

Quadrivalent vaccine (4vHPV) Gardasil (Merck)

- HPV types 6, 11, 16, and 18
- Cervical cancers and precancerous lesions
- Genital warts, precancerous anogenital lesions

Bivalent vaccine Cervarix (GlaxoSmithKline)

- HPV types 16 and 18
- Cervical cancers and precancerous lesions

9-valent HPV vaccine (9vHPV): 5 additional HPV types: 31, 33, 45, 52, 58

Recommended schedule of 2 doses:

- Vaccination starting at age 11 or 12 years
- Female ages 13 through 26 years
- Males ages 13 through 21 years
- Men up to age 26 if MSM/immunocompromised

Highly effective in preventing infections and development of dysplasia

Safety profile: well tolerated, adverse effects are rare

HPV Diagnosis

Hybrid Capture 2
- detects 13 oncogenic types of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

Cervista HPV HR
- detects 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

Cervista HPV16/18 detects only HPV16 and 18.

Aptima
- detects RNA from 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

Cobas 4800
- detects 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

BD Onclarity
- detects 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

HPV Genotyping

PCR based assays targeting a specific DNA region with identification of specific genotypes by a post-amplification hybridization with type-specific probes

Strip format

- INNO-LiPA HPV Genotyping Extra (Innogenetics, Gent, Belgium)
- Linea Array Genotyping Test (Roche Diagnostics, Indianapolis, IN)

Microarray-based format

- CLART® Human Papillomavirus 2 (Genomica, Madrid, Spain)
- PapilloCheck assay (Greiner Bio-One, Germany)

Luminex bead based-format

- xMAP platform (Luminex Corporation, Austin, TX)

Summary

HPV related malignancies

- Cervical
- Anogenital
- Oropharyngeal
- Skin

Preventive strategies

- Cervical cytology screening with HPV co-testing
- Vaccination

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Disclosures/Potential Conflicts of Interest

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