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TITLE: HPV Related Malignancies

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Slide 1:

Hello, my name is Deepika Sirohi. I am an Assistant Professor of Pathology at ARUP Laboratories and University of Utah. Welcome to this Pearl of Laboratory Medicine on "**HPV Related Malignancies**."

Slide 2:

Human papillomavirus is a small double stranded DNA virus with more than 200 genotypes and 16 genera. Of these, the alpha genotype is most frequently associated with cancers, although some of the other genotypes may be oncogenic in immunosuppressed states such as HIV infection and post-transplant states. Based on their oncogenic potential, Human papillomavirus have been classified into low risk and high risk with a third category of possibly carcinogenic. The low risk HPV includes types 6 and 11 while the high risk includes at least 12 different types. Of these, HPV types 16 and 18 account for approximately 70% of invasive cervical cancers.

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Human papillomavirus is the most common genital viral infection and is transmitted sexually. Infections of the anogenital region are most frequent with skin and oropharynx being some of the other sites involved. At these sites, the virus demonstrates an affinity for transitional zone mucosa such as the squamocolumnar (ecto- and endocervical) junction of the cervix and anorectal junction. Majority of the infections are transient and cleared by the immune system

over a course of 12-24 months. However, some progress to develop benign lesions (warts etc.) or in case of high-risk viruses to pre-malignant lesions that in some occasions could lead to cancers, if left untreated.

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HPV infections displays tropism for the basal layers of cutaneous and mucosal epithelium that has cells with stem cell like features. The virus gains entry into the cells through microtrauma and persists at low level in a non-integrated (episomal form) and may remain dormant. With cellular proliferation associated with differentiation and maturation, the virus replicates intracellularly expressing genes required for generation of new virions. During this phase, the virus lacks the cellular enzymes required for replication and is dependent on the host cell machinery.

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The viral replication is mediated by key genomic regions which includes an early region that encodes non-structural regulatory proteins for DNA replication: E1, E2, E4-E7; a late region encoding structural capsid proteins: L1 and L2; and a non-coding upstream regulatory region. The replication is initiated by E1 and E2. While the basic function of E1 is viral replication, E2 functions as a repressor of viral oncogenes E6 and E7. Persistent HPV infections of the high-risk type eventually result in viral integration that disrupts the functioning of E2 protein which in turn dysregulates the viral oncogenes E6 and E7 to initiate cellular transformation.

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The mechanism of action of E6 oncoprotein is through degradation of p53, which prevents activation of downstream targets and apoptosis; and overexpression of TERT that maintains telomere length and prevents cell death. E7 oncoprotein on the other hand binds to proteins of the retinoblastoma family, displacing E2F transcription factor resulting in cell cycle progression. It also causes the cells to progress through cell cycle by inactivating cyclin dependent kinases (CDK) inhibitors p21 and p27 and activating cyclins E and A. However, HPV alone is not sufficient for malignant transformation of cells, requiring additional genetic and epigenetic events.

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The risk for progression of HPV infection and malignant transformation is increased with persistent HPV infection, high-risk HPV types, increasing age, coinfection with other HPV subtypes, tobacco use and lower socio-economic status.

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Persistent high-risk HPV infection results in viral integration within the host tumor genome and is known to cause most cervical cancers. HPV has also been associated with a significant number of other anogenital cancers such as vulvar, vaginal, anal and penile and oropharyngeal carcinomas including those of the base of tongue and tonsils. On the other hand, low risk HPV infections have been associated with benign lesions such as genital and cutaneous warts and laryngeal papillomas as well as some low-grade pre-invasive cancers.

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Cervical cancers are a leading cause of cancer in women worldwide, after breast and colorectal cancers. Almost all cervical cancers are caused by HPV infection with HPV16 and HPV18 accounting for most cancers caused by HPV. The infection typically precedes the onset of cancer by decades with persistent infection progressing through stages of infection, pre-invasive cancer to invasive cancer over several years. Majority of the low-grade lesions resolve, however about 10-30% progress to pre-invasive high-grade lesions and subsequently invasive cancer.

Slide 10:

This slide depicts the HPV related changes that occur in cervical mucosa. Image A depicts a benign cervical mucosa with orderly maturation of the squamous mucosa. In image B, the cell layers show a disorderly maturation with significant cytological atypia involving approximately half of the mucosal thickness consistent with low-grade squamous intraepithelial neoplasia. Viral cytopathic changes are seen as koilocytic change. Image C shows marked cytological atypia involving the full thickness of the mucosa consistent with high-grade squamous intraepithelial neoplasia. Image D demonstrates a p16 immunohistochemical stain that can be used as a surrogate marker for HPV induced changes.

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The long disease course makes cervical carcinoma particularly amenable to screening and detection at an early stage. Screening methods recommended by the World Health Organization include molecular testing for HPV, cervical cytology and visual inspection with acetic acid. The prevalence of cervical carcinoma and the available resources in a given region guide the choice of screening methods adopted. The target population for cervical cancer screening are women in age group of 30-49 years, and may be extended to include younger women at high risk of developing cervical cancer. Recommended rescreening intervals after a negative result are 3-5 years for visual inspection with acetic acid or cytology and 5 years after molecular testing.

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Besides cervical cancers, HPV-associated oropharyngeal cancers have also been associated with HPV16 infection in about 63% of the cases accounting for 95% of these cancers. Interestingly, despite a lower prevalence of HPV in the oropharynx, HPV associated cancers are more common than anogenital cancers. Younger age, multiple sex partners and male sex have been shown to be risk factors for development of HPV associated oropharyngeal cancers. These cancers have a predilection for base of tongue and tonsils; frequently show basaloid morphology and have favorable outcomes versus the non-HPV related cancers.

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Other HPV associated cancers occur in the anogenital regions and include anal cancers, penile cancers and vulvar and vaginal cancers. HPV accounts for 97% of HPV related anal cancers occurring more commonly in heterosexual men having sex with men and immunosuppressed individuals. 45% of penile cancers are caused by HPV and besides the high risk HPV; low risk types 6 and 11 are also causative. Vaginal and vulvar cancers on the other hand affect older women accounting for 40% of vulvar and 70% of vaginal cancers.

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An increasing number of immunocompetent individuals and immunocompromised patients especially in post-transplant are known to present with skin cancers. These have been associated with not only the α-subtype but also the less frequent β-HPV, potentiated by other carcinogens like UV light exposure. In cases of HPV infections, the E6 and E7 oncoproteins

prevent repair of UV induced DNA damage allowing deleterious changes to accumulate and predispose to malignant transformation.

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Besides cervical cytology, preventive strategies for HPV related cervical cancer also includes HPV vaccines, 3 of which have been FDA approved in US. Gardasil is a quadrivalent vaccine targeting HPV types 6,11,16 and 18 and has been approved for cervical cervical cancers and precancerous lesions, genital warts and precancerous anogenital lesions. Cervarix targets only HPV16 and 18 and is approved for prevention of cervical cancers and preinvasive lesions. Recently, FDA has also approved a 9-valent vaccine, which is effective against 5 additional HR HPV subtypes: 31, 33, 45, 52 and 58. The recommended vaccination schedule is 2 doses at age 11 or 12 years. It is also recommended for females 13 through 26 years who have not previously been vaccinated; males ages 13 through 21 and men up to age 26 if having sex with men or immunocompromised. The vaccines have been shown to be highly effective in preventing infections and development of dysplastic lesions. In general, the HPV vaccines are well tolerated and adverse reactions are rare. Most common adverse reactions are limited to local injection site reactions with systemic effects being extremely rare.

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Sensitive molecular assays are currently available for diagnosis of HPV infections and are used in conjunction with cervical cytology. The available assays include Hybrid Capture 2 (detects 13 HR HPV types); Cervista HPV HR (detects 14 HR HPV types); Cervista HPV16/18 (detects only HPV16 and 18); Aptima (detects RNA from 14 HR HPV types); Cobas 4800 (detects 14 HR HPV types) and BD Onclarity (detects 14 HR HPV types).

Slide 17:

HPV genotyping has the clinical advantage of identifying HPV type with resulting risk stratification as well co-infection with multiple strains. Most commercially available genotyping assays are based on amplification of a specific DNA region by polymerase chain reaction followed by genotype identification using a hybridization step with type-specific probes. Various hybridization methods are clinically used and include strip, microarray or luminex bead based formats.

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In summary, Human papillomavirus has been associated with several malignancies of which cervical cancers account for the large majority worldwide. Improved understanding of oncogenic mechanisms and the prolonged course of the disease makes it particularly amenable to screening and early detection and prevention in combination with highly effective vaccines.

Slide 18: References

1. Massad LS, Einstein MH, Huh WK et al. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis. 2013;17(5 Suppl 1):S1-S27
2. Pullos AN, Castilho RM, Squarize CH. HPV Infection of the Head and Neck Region and Its Stem Cells. J Dent Res. 2015;94(11):1532–1543
3. Li Y and Xu C. Human Papillomavirus-Related Cancers. In Q. Cai, Yuan Z, Lan K, editors, Infectious Agents Associated Cancers: Epidemiology and Molecular Biology. 1st Ed. Singapore: Springer Nature Singapore; 2017. p. 23-34
4. Hellner K, Dorrell L. Recent advances in understanding and preventing human papillomavirus-related disease. F1000Res. 2017;6:269
5. Brianti P, De Flammineis E, Mercuri SR. Review of HPV-related diseases and cancers. New Microbiol. 2017;40(2):80-85.
6. de Sanjosé S, Brotons M, Pavón MA. The natural history of human papillomavirus infection. Best Pract Res Clin Obstet Gynaecol. 2017;S1521-6934(17):30133-5
7. Centers for Disease Control and Prevention. Vaccination Schedules and Recommendations. https://www.cdc.gov/hpv/hcp/need-to-know.pdf. (Accessed December 2017).
8. Screening and treatment of cervical pre-cancer. In Comprehensive cervical cancer control: a guide to essential practice. 2nd Ed. World Health Organization; 2014.p. 129-149.
9. Tsakogiannis D, Gartzonika C, Levidiotou-Stefanou S, Markoulatos P. Molecular approaches for HPV genotyping and HPV-DNA physical status. Expert Rev Mol Med. 2017;19:e1.

Slide 19: Disclosures

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