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SQUAMOUS CELL CARCINOMA CERVIX

Pathology

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ABSTRACT

Squamous cell carcinoma cervix is a common cervical cancer seen usually in elderly age group. The most common type is keratinizing, other include, non keratinizing, basaloid, warty, papillary, lymphoepithelioma like, squamotransitional cell, and verrucous SCC. The most common etiological factor is HPV infection in particular HPV 16 and 18.Here we present 10 cases which highlights the common variant, histological pattern, age group and clinical presentation of squamous cell carcinoma.

KEYWORDS

human papilloma virus

Case series

- All 10 cases are above 50 yrs of age and presented with complain of bleeding per vaginum.
- Case 1 – 50 yr female, specimen – cervical biopsy (gross- greyish white firm tissue piece measuring 1× 0.5 cm.)
- Case 2- 62 yr female, specimen- cervical biopsy (gross- greyish white to greyish brown firm tissue piece measuring 1×1 cm.)
- Case 3- 65 yr female ,specimen – hysterectomy specimen with separately lying adnexa (uterus with cervix altogether measure 10 ×5×3 cm. endo – 0.1 to 0.2 cm, myo – 2.5 to 3 cm , cervical length – 3.5 cm and shows black patchy surface.)
- Case 4- 70 yr female, specimen- hysterectomy specimen (gross- uterus and cervix measure 9×4.5×3cm, cervical length is 2cm and is hard in consistency without apparent growth.)
- Case 5- 60 yr female, specimen – cervical biopsy measuring 1×1 cm
- Case 6- 55yr female, specimen – cervical biopsy measuring 1.5×1.5 cm
- Case 7- 52 yr female, specimen – cervical biopsy measuring 0.8×0.8 cm
- Case8- 62yr female, specimen- hysterectomy specimen (gross- uterus and cervix measure (9×4.5×3cm, cervical length is 2.8cm without apparent growth.)
- Case9- 65yr female, specimen – cervical biopsy measuring 1.5×1.5 cm.
- Case10- 56yr female, specimen – cervical biopsy measuring 1×1cm.

Diagnosis based on microscopic examination

Case 1: Non Keratinizing Squamous Cell Carcinoma

Case 2-10: Keratinizing Squamous Cell Carcinoma

figure1- Hysterectomy specimen from one of the case

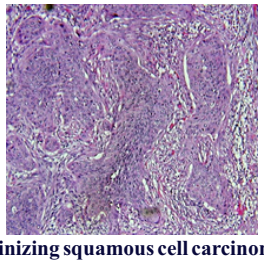

figure2-Non keratinizing squamous cell carcinoma

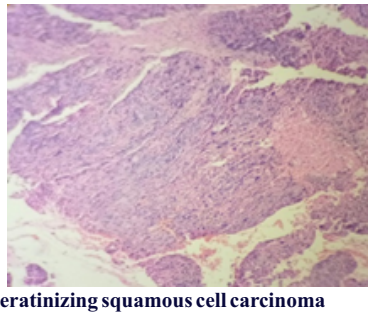

Figure 3- keratinizing squamous cell carcinoma

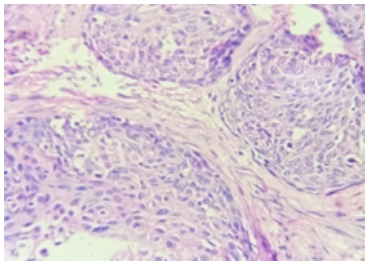

Figure 4- keratinizing squamous cell carcinoma

Introduction-

Squamous cell carcinoma of cervix is most common type of cervical cancer with keratinizing SCC as the commonest variant. Most of the patients are in 5th decade and above. Many present with post menopausal bleeding per vaginum. The common etiological factor is Human Papilloma Virus specially HPV 16 and 18.

Discussion-

- Definition -Malignant invasive tumor showing squamous cell differentiation (keratin formation, intercellular bridges.)
- Invasive squamous cell carcinoma is the most common malignant neoplasm of the uterine cervix.
- Mean age 51 years, uncommon before age 30 years but most cases are between 45 - 55 years of age.

The WHO classifies invasive cervical squamous cell carcinoma into eight subtypes based on morphologic appearance: Keratinizing, nonkeratinizing, basaloid, warty, papillary, lymphoepithelioma like, squamotransitional cell, and verrucous

Pathophysiology / etiology

- Caused by high risk papillomavirus, in particular HPV 16 and 18
- Human papillomavirus (HPV): causes vulvar condyloma acuminatum (sexually transmitted), found in DNA of 95% of cervical cancers, 90% of condylomas and premalignant lesions
- High risk HPV types for cervical carcinoma: 16, 18, 31, 33, 35, 39,

45, 51, 52, 56, 58, 59, 68 and others
- Low risk HPV types for cervical carcinoma: 6, 11, 42, 44 (associated with condyloma)
- HPV acts via E6 and E7 genes, which differ in high vs. low risk HPV types; HPV is integrated in premalignant lesions with tumor DNA vs. present in episomes (not integrated) in condylomas; in HPV 16 and 18, E6 binds to p53, causing its proteolytic degradation; E7 binds to retinoblastoma gene (Rb) and displaces transcription factors normally bound by Rb; result is inactivation of cell cycle progression and inhibition of apoptosis control (1)
- Other cofactors are important, because (a) most with HPV don't get cervical cancer, (b) 10-15% of cervical cancer is NOT associated with HPV
- HIV or HTLV 1 infection adversely affect the prognosis, may be associated with rapidly progressive course
- Survivin, p16 (INK4a), COX2 and Ki67 play critical roles for development and progression of cervical cancer (2) Overexpressed SOX2 may play a role in carcinogenesis (3)
- Loss of TACSTD2 may contribute to squamous cell carcinoma progression through attenuating TAp63 dependent apoptosis (4)

- **Risk factors:**
- Early age at first intercourse, multiple sexual partners (5)
- Male partner with multiple prior sexual partners
- History of HSIL
- HLA associations in Mexican women (6)
- Cigarette smoking (7),
- Parity, family history, associated genital infections, no circumcision in male partner
- Oral contraceptives (some studies)

Prognostic factors
- Clinical stage, nodal status, size of largest node and number of involved nodes, tumor size, depth of invasion, endometrial extension, parametrial involvement, angiolymphatic invasion
- HPV negative patients do poorer
- Possibly S phase fraction
- Possibly tissue associated eosinophilia (poorer survival in one study)(8)
- Squamous cell carcinoma antigen serum level in patients with advanced disease (9)
- Not relevant: microscopic tumor grade, tumor type, angiogenesis
- Spreads usually through cervical lymphatics in sequential manner; via direct extension to vagina, uterus, parametrium, lower urinary tract, uterosacral ligaments; distant metastases to aortic and mediastinal lymph nodes, lung, bones, ovary (1%)
- 2/3 are stage I or II when diagnosed

Microscopic Description (histologic)
- Invasion characterized by desmoplastic stroma, focal conspicuous maturation of tumor cells with prominent nucleoli, blurred or scalloped epithelial-stromal interface, loss of nuclear polarity
- May have pseudoglandular pattern due to acantholysis and central necrosis
- Rare findings are amyloid , signet ring cells , melanin granules
- May have HSIL / CIN3 like growth pattern
- Grading does not correlate with prognosis and is optional
- Well differentiated: predominantly mature squamous cells with abundant keratin pearls, occasional well developed intercellular bridges, minimal pleomorphism, minimal mitotic activity
- Moderately differentiated: less distinct cell borders and less cytoplasm than well differentiated tumors; also more nuclear pleomorphism and more mitotic activity
- Poorly differentiated: small primitive appearing cells with scant cytoplasm, hyperchromatic nuclei and marked mitotic activity; no / rare keratinization; resembles HSIL .

Differential diagnosis
- Clear cell carcinoma: papillary and tubulocystic areas, hobnail cells, no squamous differentiation, may be associated with DES exposure
- Immature squamous metaplasia: uniform cell size and shape, no significant nuclear atypia
- Placental site nodule: well circumscribed nodules of intermediate trophoblast cells, no / rare mitotic activity, HPL+
- Small cell neuroendocrine carcinoma: diffuse infiltration of small cells with scant cytoplasm and hyperchromatic nuclei; often rosettes, trabeculae or ribbons; often crush artifact; immunoreactive for neuroendocrine markers
- Squamous metaplasia with extensive glandular involvement or marked decidual reaction: no atypia, no / rare mitotic figures; decidua is keratin-

- **Based on cytology smears:**
- Atrophic vaginitis with Thin Prep: similar background but no malignant squamous epithelial cells
- HPV related changes: no irregular shapes, no heavy keratinization, no tumor diatheses
- Keratinizing dysplasia involving endocervical glands
- Radiation related changes

- **Positive stains-**
- Keratin (almost 100%), CEA (90%), progesterone receptor, p63 , thrombomodulin, involucrin
- Mucicarmine (some but does not make them adenocarcinomas)

- **Negative stains-**
- p53 (usually), MDM2 gene, EBV (usually)

Conclusion-

Squamous cell carcinoma cervix is most common cervical cancer. Keratinizing variant is commonest.

Bleeding per vaginum is common clinical presentation Usually patients are in their 50's and above.

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