Neoplasia of the cervix

Ali Al Khader, M.D.
Faculty of Medicine
Al-Balqa’ Applied University
Email: ali.alkhader@bau.edu.jo
An overview of cervical neoplasia

- Most tumors of the cervix are of epithelial origin and are caused by oncogenic strains of human papillomavirus (HPV)

- HPV, the causative agent of cervical neoplasia, has a tropism for the immature squamous cells of the transformation zone

- Most HPV infections are transient and are eliminated within months by an acute and chronic inflammatory response

- A subset of infections persists, however, and some of these progress to cervical intraepithelial neoplasia (CIN)
Cervical neoplasia, pathogenesis

- HPV is detectable by molecular methods in nearly all cases of CIN and cervical carcinoma

- Risk factors for CIN & invasive squamous cell carcinoma:
  1- Related to HPV exposure:
    - Early age at first intercourse
    - Multiple sexual partners
    - Male partner with multiple previous sexual partners
    - Persistent infection by high-risk strains of papillomavirus
  2- Cigarette smoking
  3- Human immunodeficiency virus

...especially in progression from CIN to cancer
Cervical neoplasia, pathogenesis...cont’d

• HPV infection occurs in the most immature squamous cells of the basal layer

• Replication of HPV DNA takes place in more differentiated overlying squamous cells
  ...squamous cells at this stage of maturation do not normally replicate DNA, but HPV-infected squamous cells do, as a consequence of expression of two potent HPV oncoproteins: E6 & E7
E6 & E7

- **E6 & E7** gene products
  - Binds RB and release E2F from it
  - Also inactivates p21 & p27 (CDKIs)

So it will become free and induce cell proliferation

Degrad p53 (p53 is a tumor suppressor gene)

= cyclin-dependent kinase inhibitors

...When inactivated: cyclin-dependent kinases will induce cell proliferation
Cervical neoplasia, pathogenesis...cont’d

• More recently, somatically acquired mutations in the tumor suppressor gene *LKB1* were identified in more than 20% of cervical cancers
Cervical neoplasia, pathogenesis...cont’d
CIN (Cervical intraepithelial neoplasia)

• Usually precedes the development of an overt cancer by many years, sometimes decades

• CIN peaks in incidence at about 30 years of age, whereas invasive carcinoma peaks at about 45 years of age

• In many cases, even high-grade lesions fail to progress to cancer and may even regress...the regression rate is much higher in low-grade lesions
### Natural History of Squamous Intraepithelial Lesions (SILs)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Regress</th>
<th>Persist</th>
<th>Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSIL (CIN I)</td>
<td>60%</td>
<td>30%</td>
<td>10% (to HSIL)</td>
</tr>
<tr>
<td>HSIL (CIN II, III)</td>
<td>30%</td>
<td>60%</td>
<td>10% (to carcinoma)*</td>
</tr>
</tbody>
</table>

*LSIL, low-grade SIL; HSIL, high-grade SIL.*

*Progression within 10 years.*
Pap smear

• The most successful cancer screening test ever developed

• Cervical cancer no longer ranks among the top 10 causes of cancer deaths in U.S. women

  ...paradoxically, the incidence of CIN has increased to its present level of more than 50,000 cases annually. Increased detection has certainly contributed to this

• The recently introduced quadrivalent HPV vaccine for types 6, 11, 16, and 18 is very effective in preventing HPV infections...but Pap smear is still needed, Why?
CIN, some management notes

• CIN is asymptomatic and comes to clinical attention through an abnormal Pap smear result

• Followed up by colposcopy, during which acetic acid is used to highlight the location of lesions and the areas to be biopsied

• LSIL: follow up (conservative management)
• HSIL: surgery (e.g., cone biopsy)
Invasive carcinoma of the cervix

• Squamous cell carcinomas (75%)
  ...followed by:
• Adenocarcinomas and mixed adenosquamous carcinomas (20%)
  and
  small cell neuroendocrine carcinomas (less than 5%)

• All types are caused by HPV

• The relative proportion of adenocarcinomas has been increasing in recent decades
Cervical squamous cell carcinoma

• Peak incidence at the age of about 45 years

• Progression of CIN to invasive carcinoma is variable and unpredictable and requires HPV infection as well as mutations in genes such as \textit{LKB}
Cervical squamous cell carcinoma, morphology

• Range from microscopic foci of stromal invasion to grossly conspicuous exophytic tumors

• Barrel cervix...when the tumor encircles the cervix and penetrates into the underlying stroma
  ...easily palpated

• The grading is based on squamous differentiation

• The likelihood of spread to pelvic lymph nodes correlates with the depth of tumor invasion (less or more than 3mm) and the presence of tumor cells in vascular spaces
Cervical squamous cell carcinoma, clinically:

- Symptoms especially appear in those who were not previously screened

- Vaginal bleeding...e.g., postcoital bleeding
- Leukorrhea
- Painful coitus (dyspareunia)
- Dysuria

- Mortality is most strongly related to tumor stage

- Neuroendocrine carcinoma is bad

- Death in advanced disease is mainly due to direct invasion rather than metastasis, especially the invasion into bladder & ureter with resultant obstruction & renal failure
Thank You