Preinvasive squamous and glandular neoplasia of the cervix: an Update

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Topics

• Tricky squamous precursors of the cervix
• Classifying squamous intraepithelial lesions
• Early (superficial) adenocarcinoma in situ
• Adenocarcinoma in situ or invasive adenocarcinoma? The Silva criteria in diagnosis and management
• Gastric type adenocarcinomas of the cervix and their precursors
• Unusual adenocarcinomas of the cervix.
• Is it endocervical or endometrial adenocarcinoma?
• Unusual patterns of squamous differentiation and their significance.
Large Condyloma

• We have seen:
  – Large lesions mimicking verrucous carcinoma associated with HPV6
  – Large lesions associated with HPV 11 that metastasized
  – Large lesions that were p16 positive
Large (giant) condyloma
P16 positive condyloma
Verrucopapillary lesion of the cervix 5th decade
Verrucopapillary lesion of the cervix 5th decade

HPV 11
Verrucopapillary lesion of the cervix 5th decade

HPV 11
Verrucopapillary lesion of the cervix 5th decade

Patient had a biopsy proven nodal metastasis!

HPV 11
Verrucopapillary Lesions (Cx)

- Condyloma
- Very large condyloma
- Condyloma (rare) with invasion and spread
- Papillary HSIL
- Papillary/Transitional SCC
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ASCUS cytology, cervical biopsy
Diagnosis?

1. Benign mucosa
2. LSIL
3. HSIL
4. SIL of uncertain grade
p16ink4
Diagnosis?

1. Benign mucosa
2. LSIL
3. HSIL
4. SIL of uncertain grade
The Cervical Time Line

- 1960s – Age of CIS – hysterectomy
- 1970s-1990 – Age of cryo/laser (CIN1-CIN2)
- 1990-2010 – Age of LEEP for HSIL (CIN2-CIN3)
- 2010 – Age of p16, more cautious approach to CIN2
Current Recommendations

• P16ink4 staining is used **only** for cases that are suspected of being HSIL
• If p16ink4 staining is **positive** in such cases the diagnosis of **HSIL (CIN2)** is made.
• A conservative approach to CIN2 with a followup cytology is acceptable in young women (under 25?)
Facts

• The approach to CIN2 varies depending on the clinician.
• From 50-70% of LSILs will stain strongly for p16.
• Interobserver reproducibility for CIN2 is poor (k ~ .25). A CIN1 to one observer might be classified as CIN2 or borderline CIN2 by another.
• P16 has strong negative predictive value for HSIL.
• P16 is not recommended as a biomarker to predict if an LSIL will have an HSIL outcome.
So if:

- p16 stains 50-70% of LSILs
- CIN2 cannot be reproducibly recognized (i.e. an LSIL to one pathologist is an HSIL to another)
- P16-positive LSILs are not significantly more likely to have an HSIL outcome in follow-up studies

Will someone explain to me why p16 is useful as a marker in deciding whether a CIN1 or even a borderline CIN-1–CIN-2 lesion should be upgraded to CIN-2?
What is the underlying problem?

- The cervical mucosa is a land of heterogeneity
- It harbors ectocervical squamous, metaplastic squamous, reserve cell and squamocolumnar junction epithelium.
- All of these epithelium can be infected by a multiplicity of HPV types, producing a range of histologies
Origins of CIN

• Terms and significance
  – Squamocolumnar junction: known to be the site where the majority of malignancies and precancers develop
  – Transformation zone: The area between the “original” squamocolumnar junction and the current squamocolumnar junction.
  – Metaplastic epithelium: Any squamous epithelium in the region of the Tzone
Squamocolumnar Junction

• A specialized population of cuboidal cells of embryonic origin
The SC Junction Cell

Krt7
SCJ negative SIL

SCJ positive SIL
Ectocervix/TZ

SC junction

Endocervix

Focal induction of p63/keratin 5

Emergence of reserve cells (positive for SC junction-specific biomarkers)

Proliferation and squamous differentiation of reserve cells

Squamous metaplasia (negative for SC junction-specific biomarkers)
“Differential Risk”

Ectocervix/TZ → SC junction → Endocervix

- Focal induction of p63/keratin 5
- Emergence of reserve cells (positive for SC junction-specific biomarkers)
- Proliferation and squamous differentiation of reserve cells
- Squamous metaplasia (negative for SC junction-specific biomarkers)
“Differential Risk”

- Ectocervix/TZ
- SC junction
- Endocervix

1. Focal induction of p63/keratin 5
2. Emergence of reserve cells (positive for SC junction-specific biomarkers)
3. Proliferation and squamous differentiation of reserve cells
4. Squamous metaplasia (negative for SC junction-specific biomarkers)
SC Junction vs Tzone

Herfs et al PNAS 2012
90+% HSILs Come from the SC Junction

• Three major types of SIL
  – Ectocervical/metaplastic LSILs (SCJ-) = low risk
  – SCJ+ HSILs = high risk
  – SCJ+ LSILs = heterogenous group risk variable
What does this mean?

• There are three types of SIL
  • Easy LSILs – mostly occurring in maturing metaplastic/ectocervical cells
  • Easy HSILs – Mostly occurring in SCJ epithelium
  • More problematic (L)SILs – occurring in SCJ epithelium
Three types of SIL

- SC junction negative LSIL
  - 90% agree
  - 50% HRHPV
  - 10% HPV16
  - CK7(-)

- SC junction positive LSIL
  - 50% agree
  - 100% HRHPV
  - 60% HPV16
  - CK7+

- HSIL
  - 90% agree
  - 100% HRHPV
  - 60% HPV16
  - CK7+
A different perspective

• Using this model it is possible to envision three types of SIL, easy HSIL, easy LSIL and problematic (L)SILs or QSILs, which arise in the SC junction.

• The diagnostic algorithm includes LSIL, HSIL and QSIL.

• With a little practice you can spot a QSIL.
Diagnosis?
Diagnosis

1. LSIL
2. HSIL
Diagnosis?
Diagnosis

1. LSIL
2. HSIL
Diagnosis?
Diagnosis

1. LSIL
2. HSIL
Three Approaches

1. Triage borderline with p16
2. Triage borderline with a second observer, p16 optional
3. Accept the fact that we cannot agree on what is CIN2 and classify difficult lesions as SIL of uncertain or indeterminate grade (CIN1-2)
Immature Metaplastic SILs are the ones that are the most difficult

- Uniform nuclear spacing, homogeneous nuclear morphology, nucleoli – LSIL
- Some nuclear overlap, mild anisokaryosis, inconspicuous nucleoli – SIL of indeterminate grade (QSIL)
- Nuclear crowding, anisokaryosis, no nucleoli - HSIL
Diagnosis: LSIL in metaplasia
Diagnosis: SIL of uncertain grade
Diagnosis: HSIL
Our approach at BWH

• If a borderline HSIL (CIN2) is encountered it is reviewed by a second observer
• If both observers feel the lesion is CIN2 it is classified as such (p16 is optional)
• If both observers are uncertain the diagnosis of “QSIL” is made
• QSIL = Squamous intraepithelial lesion of indeterminate grade (CIN1-CIN2).
• QSILs are generally followed
• P16 is reserved for excluding reactive
Reproducibility

• Three trainees
• Dx of LSIL, HSIL or QSIL
• Kappas = 0.65, 0.65, 0.25
• QSIL is not reproducible but honest
• P16 is reproducible but can be a false prophet
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Conventional (Classic) ACIS

- Nuclear stratification
- Nuclear hyperchromasia
- Nuclear enlargement
- Mitotic activity
- Apoptosis
- Strong biomarker staining (p16 and Ki-67)
Superficial (Early) ACIS

- Younger age group (mean 26 vs 38 yrs.)
- Less pronounced atypia
- Associated with columnar mucosa
- Strong biomarker staining (p16 and Ki-67)
- Integrated pattern of HPV by ISH

Witkiewicz et al AJSP 2005
Superficial (Early) ACIS
Differential Diagnosis of ACIS

- Mitotically active endocervical mucosa
  - Tall columnar
  - Normal mitoses
  - Minimal stratification
  - Normal contour
Reactive Endocervix
Reactive Endocervix

MIB1

p16
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32 year old with ACIS on biopsy
Diagnosis?

1. ACIS
2. ACIS with invasion
The problem with the cut-off of columnar cell invasion (Cx)

- AIS can expand into otherwise inconspicuous networks of crypts
- The underlying crypt architecture can be extensive in cases of co-existing benign glandular hyperplasias or tunnel clusters
- In the absence of desmoplasia a diagnosis can be extremely difficult
Invasive Patterns

- Invasion with altered epithelial morphology (budding or cluster type invasion)
- Invasion with preserved gland/epithelial morphology and altered architecture/stroma
- Invasion with preserved gland/epithelial morphology without altered architecture/stroma (controversial!)

Altered epithelial morphology

• Abnormal architecture
  – Small outpouchings or solid nests
  – Single cells
  – Fragmented glands

• Altered cytology
  – More abundant eosinophilic cytoplasm
  – Ill defined cell borders (syncytia)
  – Loss of polarity
  – Nucleoli

• Reactive stroma
  – Commonly associated with inflammation and desmoplasia
Variable Architecture, altered epithelial/stromal relationship

- Irregular glands
- Variable size glands
- Desmoplastic stroma
- Deep location
Extensive invasion (SILVA C)
Normal glands, no or minimal stromal reaction

- Lobular arrangements of glands
- Minimal stromal response
- Variable depth
- Patterns might mimic
  - Microglandular hyperplasia
  - Laminar hyperplasia
  - Lobular hyperplasia

This pattern has a ~0% recurrence risk

No (SILVA A in Diaz de Vivar et al)
No (or SILVA A in Diaz de Vivar et al)
No (or SILVA A in Diaz de Vivar et al)
Lobular Hyperplasia
Diagnosis

• Extensive adenocarcinoma in situ
• Focal invasive adenocarcinoma to a depth of 3 mm and involving the deep (radial) margin
• SILVA C
Focal Invasion (SILVA A)
Lessons Learned

• Extensive AIS can mimic invasive carcinoma (or a subset of invasive carcinomas without desmoplasia exists and does not metastasize)

• It is not common, but occasionally the areas that seem to be in situ with a uniform gland pattern will reveal cytologic changes heralding invasion.

• Implication: Node dissection, recurrence risk, fertility
Redefining Invasive Endocervical Adenocarcinoma

- A: Extensive lobular growth without clear invasion (~25%) – no recurrences
- B: Focal invasion out of lobular nests (~25%) – 7% recurred
- C: Diffuse or confluent growth with stromal response (50%) – higher recurrence rate

** All recurrences in groups B and C had LVI!**

How do we approach these

• Lobular architecture, no desmoplasia – cannot confirm invasion (can cite the negative LN involvement from Silva et al)

• Focal invasion – scrutinize for LVI, give depth from the gland and from the surface, cite Silva et al.

• Unequivocal invasion – no qualification needed
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Glandular Neoplasia with Gastric Differentiation

- Lobular endocervical glandular hyperplasia
- Atypical LEGH (MDA in situ)
- Adenoma malignum (minimal atypia)
- WD adenocarcinoma, gastric type
LEGH
LEGH with atypical features

- Nuclear enlargement
- Irregular nuclear contour
- Distinct nucleoli
- Coarse chromatin texture
- Loss of polarity
- Occasional mitotic figures
- Apoptotic bodies and/or luminal nuclear debris
- Infolding of epithelium or distinct papillary projections
LEGH with atypical features
LEGH with atypical features
LEGH with atypical features
LEGH with atypical features
Minimal Deviation Adenocarcinoma
(Adenoma Malignum)

- Glands vary in size, shape
- Irregular angulated gland contour
- Infiltrative growth pattern
- Unusual orientation of glands near surface
- Deep extension
- At least focal atypia
- Reactive stroma
Significance of MDA

- Incidentally found
- Risk for recurrence
- HPV negative
- Associated with Peutz Jeghers Syndrome
- Can co-exist with lesions throughout the FGT
- Investigate all “gastric type” glandular lesions in the FGT or peritoneum with the cervix in mind.
Adenomyoma
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17 year old, cervical biopsy
Diagnosis?

1. Endocervical adenocarcinoma
2. Endometrial adenocarcinoma
3. Mesonephric carcinoma
4. Metastatic carcinoma
Diagnosis

Mesonephric Carcinoma of the Cervix

Implication: Outcome risk
Prostatic Metaplasia

Origin proposed to be misplaced Skenes glands (McCluggage)
Adenoid Basal Carcinoma

HSIL + Squamoid + Basaloid + Adenoid Differentiation
Favorable outcome without LN dissection
Solid forms of Microglandular Change
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Metastatic Endometrial Ca

Tambouret et al
Metastatic Serous Ca (Cx)
Metastasizing AIS

• AIS extending into the endometrial cavity
• Subsequent exam of the ovaries disclosed a metastatic adenocarcinoma
• Unusually good prognosis despite ovarian involvement

Ronnett 2008
Chang 2009
Endocervical vs Endometrial Adeno

- HPV
- P16
- P53
- Vimentin
- ER
Case 1

- Diagnosed as SCC of the cervix.
- Treated with Chemo-Radiation.
- Vaginal tumor 20 years later.
Endometrioid adenocarcinoma with clear cell features.

? Related to radiation 20 years prior

? Endometrial
Case 2

- Diagnosed as an endocervical adenocarcinoma.
- Treated with Chemo-Radiation.
- Recurrent cervical tumor 10 years later.
Case 2

p53

p16
Case 2. Diagnosis

- Probably a post radiation tumor or second primary
- P53 mutation excludes common endocervical carcinomas
Take home lessons

• Be aware that strong p16 staining can be encountered in both primary cervical and high grade endometrioid carcinomas
• Cautious approach to late recurrences following treatment for cervical carcinomas.
• Gastric type carcinomas involving cervix or entire genital tract will be p16 negative
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Curetting from menopausal women
Sixth decade curetting
All three represent?

1. Endocervical sampling
2. Endometrial metaplasia (ichthiosis uteri)
3. Endometrial neoplasia
Final Diagnosis

Grade I/III endometrioid adenocarcinoma of the endometrium with squamous differentiation

Implication: potential delay in diagnosis or wrong procedure (cone biopsy) if the lesion is interpreted as benign cervical tissue
Thank you for your attention!
Note that the pdfs are annotated with comments if when you review them