RECENTLY DESCRIBED VARIANTS OF LOWER GENITAL TRACT ADENOCARCINOMA AND THEIR PRECURSORS

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TO DISCUSS

• “gastric-type adenocarcinomas” of the cervix and their possible precursors

• vaginal adenocarcinomas and possible precursors
Cervical Epithelial Lesions (WHO 2014)

Squamous cell tumours and precursors
• Squamous intraepithelial lesions
  – Low-grade squamous intraepithelial lesion (HPV only, CIN 1)
  – High grade squamous intraepithelial lesion (CIN 2, CIN 3)
• Squamous cell carcinoma (keratinising, non-keratinising etc)

Glandular tumours and precursors
• Adenocarcinoma in situ (High grade CGIN)
• Adenocarcinoma
  – Endocervical adenocarcinoma, usual type
  – Mucinous carcinoma, NOS
    • Gastric type (including adenoma malignum / minimal deviation adenocarcinoma)
    • Intestinal type
    • Signet-ring cell type
  – Villoglandular adenocarcinoma
  – Endometrioid adenocarcinoma

  – Clear cell adenocarcinoma
  – Serous adenocarcinoma
  – Mesonephric adenocarcinoma
  – Adenocarcinoma admixed with neuroendocrine carcinoma
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NON-HPV RELATED CERVICAL ADENOCARCINOMAS

• emerging category of primary cervical adenocarcinomas (about 10-15%)
• tend to be older than HPV related adenocarcinomas
• **gastric type (including adenoma malignum)**
• clear cell carcinoma (most)
• mesonephric adenocarcinoma
• possibly intestinal type (some)
• HPV screening programmes will not detect
• HPV vaccinations will not prevent
• precursor lesions not well defined
ADENOMA MALIGNUM

- mucinous variant of minimal deviation adenocarcinoma (MDA)
- uncommon variant of cervical adenocarcinoma (1-3% of cervical adenocarcinomas)
- non-HPV related
- association with Peutz Jeghers syndrome
- highly differentiated
- thought to exhibit gastric/pyloric differentiation (HIK 1083/MUC6)
ADENOMA MALIGNUM

• risk of underdiagnosis as normal/hyperplastic endocervical glands
• risk of overdiagnosis- endocervical glandular hyperplasias, tunnel clusters, endocervicosis, mesonephric hyperplasia etc
• “flat” negative with hormone receptors (ER, PR)
GASTRIC TYPE CERVICAL ADENOCARCINOMA

• HPV negative variant of cervical adenocarcinoma
• included in WHO 2014
• cells with abundant clear or eosinophilic cytoplasm and prominent cell membranes; often lot of inflammatory cells
• poor prognosis with tendency to abdominal/adnexal dissemination and metastasis to other unusual sites (5 year survival 30 versus 77% for usual type)
• tend to present at higher stage
• may be associated with Tp53 mutations (often p53 aberrant- diffuse or null pattern)
• positive with gastric markers (but don’t need to diagnose)
• EMERGING AS SECOND COMMONEST FORM OF CERVICAL ADENOCARCINOMA
• PART OF SPECTRUM WITH ADENOMA MALIGNUM
pancreaticobiliary-like
IMMUNOHISTOCHEMISTRY

p53

p16

p53

-ER
OMENTAL METASTASIS
OMENTAL METASTASIS
OVARIAN METASTASIS
OVARIAN METASTASIS- p53
GASTRIC TYPE CERVICAL LESIONS- Advances in Anatomic Pathology 2013;20;227-237

**BENIGN**
lobular endocervical glandular hyperplasia (complex pyloric/gastric metaplasia)
simple gastric/pyloric metaplasia
type A tunnel cluster

**PREMALIGNANT**
atypical lobular endocervical glandular hyperplasia
adenocarcinoma in situ of gastric type

**MALIGNANT**
gastric type adenocarcinoma
minimal deviation adenocarcinoma

**SPECIFIC CONDITIONS**
synchronous mucinous metaplasia and neoplasia of the female genital tract
Peutz Jeghers syndrome
LOBULAR ENDOCERVICAL GLANDULAR HYPERPLASIA (LEGH)

- very rare
- sometimes associated with Peutz Jeghers
- complex gastric (pyloric) metaplasia
- often high in endocervical canal
- positive with gastric markers
- may be difficult to distinguish from adenoma malignum
- “atypical” forms described (atypical LEGH) (cytologic and architectural abnormalities)
- atypical LEGH probably spectrum from mild reactive changes to precursor of adenoma malignum/ gastric type adenocarcinoma
- ALL GASTRIC LESIONS ARE FLAT ER NEGATIVE (useful in distinction of LEGH from other benign glandular lesions)
intestinal metaplasia
atypical LEGH
atypical LEGH
atypical LEGH
atypical LEGH
SIMPLE GASTRIC/PYLORIC METAPLASIA

- very rare but subtle
- positive with gastric markers (HIK1083, MUC6); ER negative
- one study- 0.7% of cervices
- pale eosinophilic rather than basophilic cytoplasm
AIS OF GASTRIC TYPE

• very rare and not well described
• subtle lesion
PROGRESSION

2009- AIS

2015- gastric type adenoca
AIS OF GASTRIC TYPE

MUC6
INTESTINAL TYPE AIS

• relatively common (most common after usual type)
• usually occurs in association with usual type
• intestinal phenotype predominantly occurs with premalignant or malignant endocervical glandular lesion (nuclear changes may be subtle)
INTESTINAL TYPE AIS

• AJSP 2013;37;625-633
• possibly 2 types- HPV associated and non-HPV associated
• non-HPV associated- older; p16 focal or negative, lower MIB1
• HPV associated; younger, diffuse p16, high MIB1
• non-HPV; possibly of gastric type
POSSIBLE ASSOCIATION BETWEEN NON-HPV RELATED CERVICAL ADENOCARCINOMAS AND LYNCH SYNDROME

• anecdotal cases
• gastric type/ clear cell carcinoma
• LUS endometrial carcinomas associated with Lynch syndrome
• non-HPV related cervical adenocarcinomas may arise high in endocervical canal
• no association between Lynch syndrome and HPV related cervical adenocarcinomas
WHO 2014- VAGINAL ADENOCARCINOMAS

- endometrioid
- clear cell
- mucinous (endocervical or intestinal type)
- mesonephric
TYPES OF PRIMARY VAGINAL ADENOCARCINOMA

• clear cell
• endometrioid
• serous
• endocervical-like
• intestinal
• gastric-type
• mesonephric
• Skene’s gland
PRIMARY VAGINAL ADENOCARCINOMA

- endometrioid, serous, clear cell, gastric, endocervical-like, mesonephric- always exclude primary elsewhere in female genital tract
- intestinal- always exclude large intestinal primary (even if confined to surface and seems to be pre-existing adenoma)
RECURRENT UTERINE ENDOMETRIOID ADENOCARCINOMA
ENDOMETRIOID ADENOCARCINOMA OF VAGINA

- AJSP 2007;31;1490-1501
- 18 cases
- many had prior hysterectomy
- association with unopposed oestrogens
- no DES history
- many cases had endometriosis
- good prognosis
GASTRIC TYPE VAGINAL ADENOCARCINOMA

• 2 cases published as such (1 with uterus didelphys) (others likely described as “mucinous” adenocarcinomas)
• both arose in adenosis (non-DES associated)
• identical to cervical adenocarcinomas of gastric type
• HIK1083 and MUC6 positive
• mutation-type p53
GASTRIC TYPE

HIK1083

MUC6
GASTRIC TYPE

p53
VAGINAL INTESTINAL TYPE GLANDULAR LESIONS

- AJSP 2014;38;593-603
- 14 cases- identical features to corresponding large intestinal neoplasms
- non-neoplastic polyps
- adenomas
- adenocarcinomas (often associated with adenoma)
- often positive with CK7, CK20, CDX2, CEA
CDX2
SKENE’S GLAND ADENOCARCINOMA

• extremely rare
• derived from periurethral Skene’s glands
• female counterpart of prostatic glands
• positive with prostatic markers
• PART OF SPECTRUM OF SKENE’S GLAND LESIONS IN LOWER FEMALE GENITAL TRACT
TUBULOSQUAMOUS POLYP OF VAGINA

• vaginal polyp
• usually postmenopausal
• most in upper vagina
• constant histology
Ectopic Prostatic Tissue in Cervix

• usually incidental microscopic finding
• usually in ectocervical stroma
• ? developmental anomaly, ? metaplasia
• positive with PSA and PrAP
VULVAL EXAMPLES

PSA
UNIFYING THEORY

• vaginal tubulosoquamous polyp and ectopic prostatic tissue in cervix are same lesion
• probably derived from paraurethral Skene’s glands
• occasionally also see in vulva