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 cervixes
• 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
AIS OF GASTRIC TYPE

p16

p53
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
PrAP
Ectopic Prostatic Tissue in Cervix

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

• vaginal tubulosquamous polyp and ectopic prostatic tissue in cervix are same lesion

• probably derived from paraurethral Skene’s glands

• occasionally also see in vulva