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Dr. Kay Park declares she has no conflicts of interest to disclose.

Case 1

- 59 year old female with several month history of watery vaginal discharge
- Radical hysterectomy performed — no obvious mass
- Cervix was enlarged and firm, entirely submitted for histologic evaluation

Pertinent Lab data

- History of normal Paps, most recently 8 months ago
- HPV negative
- Immunohistochemical profile — p16 focal, CEA(m) positive, ER/PR negative, CK7 positive (diffuse), CK20 positive (focal), CDX2 positive (focal)
**Immunohistochemistry**
- p16 focal
- CEA(m) positive
- ER/PR negative
- CK7 positive (diffuse)
- CK20 positive (focal)
- CDX2 positive (focal)

**Adenocarcinoma subtypes**

- *WHO (new edition)*
  - Usual
  - Villoglandular
  - Mucinous
  - Intestinal
  - Gastric (minimal deviation adenocarcinoma)
  - Signet ring cell
- Endometrioid
  - Minimal deviation endometrioid
- Clear cell
- Serous
- Mesonephric

**GASTRIC TYPE ENDOCERVICAL ADENOCARCINOMA**

- Villiglandular
- Mucinous
- Intestinal
- Gastric (minimal deviation adenocarcinoma)

- Mucinous adenocarcinoma that shows gastric type differentiation
  - Mesonephric
Not HPV related!

Special stains showed gastric mucin in cells.
Gastric type endocervical adenocarcinoma

- Why is it important to distinguish from usual endocervical adenocarcinoma? -- Not caused by HPV!
  - Diagnostic pitfalls
  - Syndromic association
  - Clinical behavior
  - Screening
  - Treatment
  - Vaccination

Diagnostic pitfalls

- Small biopsies, curettage or cytology
- Use of immunohistochemistry or HPV testing
- DDx upper GI/pancreatobiliary tumors
- Metastasis to ovaries mimic primary tumors


- p16 usually not block-like
- Intestinal markers frequently positive
- PAX8 can be negative in 32%
- HNF1beta not specific to clear cell carcinoma
- p53 abnormal 41%
MDA/Gastric type

- High frequency of ovarian mucinous tumors in MDA patients
- "Mucinous cystadenomas"
- "Mucinous borderline tumors"
- Synchronous vs. metastatic
- Increased risk of ovarian mucinous tumors or metastatic disease that is difficult to recognize pathologically

Metastasis

- Gastric type adenocarcinoma/MDA
- Goes to ovaries
- Mimic benign or borderline lesions

Metastasis to ovaries

- Adequate sampling essential
- Rule of 2 sections/cm mucinous tumors
- Sample grossly various areas
- Clinical history

Pancreatic adenocarcinoma

Less "gastric"
More "pancreatobiliary"
GYN Evening Specialty Conference Case 1

Gastric type adenocarcinoma

- Peutz-Jeghers syndrome
  - 10% of patients with MDA are reported as having PJS
  - Mutations in STK11 have been identified in sporadic cases of MDA
  - Non-MDA Gastric type adenocarcinoma also reported in PJS

- Significantly decreased 5-year disease-specific survival rate
- Significant risk for disease recurrence
- Conclusion: GAC is a distinct morphologic variant showing an aggressive clinical course
Other pathologic findings

- Higher stage at presentation
- Lymphovascular invasion
- Pelvic and para-aortic lymph node metastases
- Ovarian metastases
- Abdominal spread
- Other unusual sites
  - Liver
  - Brain
  - Lung
  - Bone
  - Omentum

Clinical features: summary

- Advanced stage at presentation (stage II and higher)
  - 59% v 11%
- High incidence of disease recurrence
  - 32% v 4%
- High incidence of distant metastases including abdominal
  - 19% v 3%
- High mortality rate
  - 39% v 8%

Screening

- Standard screening Pap and HPV testing
- Detection of precursor lesions
- What is the precursor lesion of gastric type adenocarcinoma and can it be detected before invasion?

Lobular endocervical glandular hyperplasia (LEGH)
a presumed precursor lesion

Nucci et al. AJSP. 1995;29:806-810
Mikami et al. Gynecol Oncol. 1995;57:504-511
Screening

- Nuclear enlargement
- Irregular nuclear contour
- Distinct nucleoli
- Coarse chromatin texture
- Loss of polarity
- Occasional mitotic figures
- Apoptotic bodies or nuclear debris in the lumen
- Infolding of epithelium or papillary projections with fine fibrovascular stroma

Looks like PanIN
Uncertain malignant potential

Atypical LEGH

Treatment

- Standard therapy for cervical cancer based on data from studies on HPV driven tumors
- Likely differences in response to chemo/RT in HPV+ vs HPV – tumors (e.g. Head and Neck SCC)
- Gastric type adenocarcinomas do not respond to standard therapies
- Targeted therapies based on molecular alterations

Vaccination

- Implications for screening
- HPV testing alone sufficient?
- False sense of security
- Awareness among GYNs and patients

How common is gastric type ECA?

- 10-30% of all endocervical adenocarcinomas
- Probably seeing them in your practice
- A cervical cancer that looks pancreatobiliary and is p16 negative

Summary

- *Gastric type adenocarcinoma* is a distinct subtype of endocervical adenocarcinoma not associated with HPV
- MDA is part of spectrum
- Specific morphologic features (pancreatobiliary)
- Gastric phenotype (neutral mucin)
- Aggressive clinical course
- Unusual distant sites of metastases, especially abdomen
- Immunohistochemical and histochemical stains may be of limited usefulness
- Not all cervical cancers are associated with HPV!
- May be part of hereditary syndromes (PJS)

Conclusion

- Cervical adenocarcinoma is a heterogeneous disease and not all cases are HPV positive
- Gastric type endocervical adenocarcinoma has different morphology, pathogenesis, immunohistochemical profiles, clinical outcomes
- Perhaps not as rare as once thought
- Implications for screening, vaccination and targeted therapy
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