Early Surface Epithelial Neoplasms of the Ovary

Diagnostic Challenges and Controversies

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Precursor Lesions

Tumors of Low Malignant Potential (LMP)

Peritoneal & Omental Implants

PRECURSOR LESIONS

Precursor Lesions

- Surface epithelium & inclusion cysts
  - Epithelium & cysts adjacent to cancer
  - Contralateral ovary to one with cancer/LMP
  - Prophylactic oophorectomy (for family hx of ovarian or breast CA, BRCA 1 or 2 mutation)
  - Positive or susp cul-de-sac aspirate screen
- Benign & Borderline tumors
  - Serous
  - Mucinous
  - Others: Endometrioid, clear cell

Dysplasia of Surface Epithelium

Cell Stratification ***Loss of polarity***

Hyperchromasia ***Coarse chromatin***

- **Severe dysplasia rarely reported in association with small CA, but not in prophylactic cases**
- **Mild dysplasia seen by morphometry in prophylactic resections more than controls**
- **Few studies show mutation or upregulation of TP53, similar to high grade serous carcinoma**

(Bell & Scully 1994, Boyd 2003)

Metaplasia & Proliferative Lesions

Papillae and tufts

Stratification

Tubal metaplasia in cysts

Endosalpingiosis

- **A few conflicting reports**
- **? increased frequency of cysts**
- **Reported in inguinal endosalpingiosis**

(Salazar 1996, Tressura 1998, Carrick 2004)

Microscopic SE Carcinoma

- Rare reports of incidental findings
- Scully (1994) reported 14 cases, all unilateral and measured 1-7 mm, 10 were serous, and most were grade 2 or 3. About half of pts. died of disease, some after 10 yrs.
- Studies of BRCA1 or 2 patients showed only a few early ovarian CA, but more early tubal CA (Colgan 2003 & others)

Benign → Borderline → Invasive

- Mean age 44, 48 & 56
- 5X increase in incidence of benign tumors in close relatives of cancer patients
- Ultrasound evidence of mass increasing in size over time
- Combinations of more than one “phase” are not uncommon

Benign → Borderline → Invasive

- **LG serous CA (invasive micropapillary) is frequently associated with borderline micropapillary tumors & shares similar levels of expression of mutations in a progressive fashion, such as K-ras.**

- **HG serous CA is rarely associated with benign or borderline & has different expression levels of genetic mutations.**

(Smith, Sehdev 2003)

Gene Mutations

- **WT-1 gene rescues cells from p53-apoptosis. It is expressed in serous tumors of ovary, tube & peritoneum, but not in serous tumors of endometrium, or in ovarian mucinous, clear cell or Brenner.**

- **K-ras mutations separate serous carcinomas into LG invasive micropapillary (+ in 54%) from HG conventional serous CA which shows only native gene.**

(Hashi 2003, Singer 2003, Acs 2004)

Mutation	Benign	LMP	LG Ca	HG Ca
TP53	0-6%	uncom	uncom	60%
BRAF		50%	50%	0%
K-ras		high	high	v rare
LOH*	~10%			higher

**6p,6q,7p,7q,9p,9q,11p,11q,17p,17q*

Tumors of Low Malignant Potential:
Confusing Terminology; Uncertain Outcome

- Clinically “on the border of malignancy” (Pfannenstiel 1898)
- “On borderline between benign & malignant (Abel 1901)
- Semi malignant & borderline (Taylor 1929)
- Carcinoma of LMP (WHO 1973)
- Tumor of LMP (WHO & ISGP 1999)
- Atypical Proliferative Tumor (1990s)
- Borderline Tumors (WHO 2003)

Tumors of LMP: General Criteria

Significant change (at least 10% of tumor), with 2 or more of the following:

- Epithelial proliferation as tufting buds
- Stratification in papillae or glands
- Increased mitosis or altered distribution
- Mild to moderate nuclear / nucleolar atypia
- No stromal invasion

- **Microinvasion**: focal, <3mm, <10mm^2, has no impact on prognosis


Serous Tumors of Low Malignant Potential
cm

ST- LMP: Clinical Features

- 12% of all serous neoplasms
- Age 10-15 yr younger than CA (mean 38)
- Mean size 10 cm, 30-50% bilateral
- Often asymptomatic, 2/3^{rds} are stage I
- May recur 20 yrs after therapy
- Extraovarian spread in 17-30% of ST- LMP
- 10 year survival 75-98% (20% in frank CA)

Serous Tumors of Low Malignant Potential (LMP)

- Unilocular cyst with lush papillae
- 50% have surface papillae, and in 10% of cases, they are the only element
- 25% of stage I have surface papillae (Ic)
- Few have major solid fibrous component
- Variants include micropapillary, surface serous & adenofibroma

ST-LMP: Histologic Criteria

- Papillary tufting, w/ complex hierarchical branching
- Small papillae often detach from larger ones as clusters of round eosinophilic cells
- Stratification up to 3 layers, ciliated cells
- Nuclei more round, w/ mild to mod. atypia, small nucleoli, mitosis rare (<4/10 HPF)
- Absence of frank stromal invasion
- Dx based on ovarian histology regardless of stage, extraovarian spread or behavior

Micropapillary Serous Borderline Tr

- 5-15% of serous borderline tumors. It is usually part of otherwise classic tumor, but a minimum of 5mm focus in a slide is required
- More bilaterality, surface lesions & implants
- Long thin papillae extend from broad cores in the cyst wall or surface → filigree or cribriform pattern, without hierarchical branching (Medusa)
- No HG nuclear atypia (unlike carcinoma)

ST-LMP: Treatment

- Stage I treated by surgery alone :
  - unilat SO, especially in young age
  - TAH, BSO in advanced stage
- Even if incompletely resected, more than 50% survive (unlike frank CA)
- Combination of stage III & invasive implants predicts a significantly worse prognosis, ? adjuvant Rx (Gilks 2003)
- Patients who die usually do so years after Dx, and most have extraovarian spread

10 yr Survival Rate of Ovarian Cancer

	Serous		*Mucinous*	
Stage	*LMP*	*Frank*	*LMP*	*Invasive*
I	96	54	98	67
I-IV	91	23	68	34

Peritoneal Implants

Histogenesis of Implants

Multicentric from peritoneum

Foci of endosalpingiosis

Metastatic ovarian borderline tumors

Peritoneal Implants

- 95% of patients with implants have exophytic surface serous tumors of ovary
- 60% of patients with surface tumors have implants (Segal, Hart 1992)
- Implants can be:
  - noninvasive epithelial or desmoplastic
  - invasive

Noninvasive Epithelial Implants

- Nests extend into fibrous septa between fat lobules, but maintain well defined contours
- Small submesothelial spaces filled with papillae
- Hierarchical branching of papillae
- Minimal nuclear atypia
- Psammoma bodies frequent
- No desmoplasia
- No effect on prognosis

Noninvasive Desmoplastic Implants

- Plastered on surface and lacks irregular destructive invasion of underlying stroma
- Over 50% of lesion is fibrous or granulation tissue; only a minor epithelial component
- Well defined deposits with a few glands, papillae & small epithelial nests
- Mild to moderate nuclear atypia
- No effect on prognosis

Invasive implants

- Destructive invasion of normal deep stromal tissues by glands & small nests that are disorderly distributed
- Implants have irregular tentacular contours
- Epithelial cells are dominant
- Marked nuclear atypia, similar to LG CA
- Mature or immature stromal desmoplasia

Invasive implants

- Uncommon, ~ 15% of late stage LMP trs.
- 50% recur, 10 y survival rate 35%
- Significant prognostic marker for FIGO II & III borderline trs
- Lesions should be sampled thoroughly, since implants are heterogeneous
- Biopsy must include deep tissues

SP Implant	Invasive	Noninv epith	Noninv desm
Contour	irregular deep	well defined between fat	well defined on surface
Pattern	glands small nests	small cysts full of papillae	gds, cysts, papillae
Epithelium	dominant	dominant	minor <50%
N. Atypia	marked as	minimal	mild to mod
Desmopl	present	absent	present
Inflammation	absent	absent	occasional
Prognosis	50% recur 35% 10yr S.	no impact	no impact

Invasive Implants: Issues

- Fibrous adhesions between fat lobules simulating invasion
- 25% of biopsies lack normal tissue
- Criteria of what constitutes invading epithelium are poorly defined. Single cells, clusters, cribriform or micropapillary patterns (Hart)

Outcome of Implants

- **Stabilize or regress**, with no impact on prognosis in most noninvasive and some invasive implants
- **Progress or recur** in 50% of invasive implants. Unusual if noninvasive
- **Transform to low grade** serous carcinoma

Aggressive ST-LMP with Extraovarian Implants

A few patients develop recurrence with aggressive behavior due to:

1-Original tumor misdiagnosed

2- Some tumors proliferate slowly, thus respond poorly to adjuvant Rx

3- A clone of invasive cells may start to proliferate after several years

Implants: Diff. Dx. I

Endometriosis:

- No nuclear atypia, papillae or psammoma
- Blood and macrophages.

Endosalpingiosis:

- Papillary or tubular, 1 layer of ciliated low columnar cells. NO stromal cells
- Single cells rare, some psammoma bodies
- Nuclear atypia is mild, if any

Implants: Diff. Dx. II

Serous Ca Ovary & Serous Tumors of Peritoneum

- High grade nuclear atypia
- Necrosis

Mesothelial hyperplasia:

- Close to the surface
- Cells are low cuboidal or flat, with simple papillae
- Nuclei have smooth regular contours

Mesothelioma

- Unlikely in females. Hx of exposure
- Nuclear atypia


MUCINOUS TUMORS OF LMP

Mucinous Tumors of LMP: Issues

- Definition & criteria
- How much is an adequate sample?
- Tangential sectioning
- What constitutes invasion or microinvasion?
- Relation to pseudomyxoma peritonei
- Primary versus metastatic

Mucinous Tumors of LMP: Gross

- Described 30 yr ago (1973)
- Peak age is 30-40 yr (mean 35)
- Unilateral 90%; if bilateral rule out mets.
- Large tumors (mean 17cm), multilocular
- Heterogeneous, with foci of benign, LMP, microinvasive & invasive areas in same tumor, thus thorough sampling (1 slide per 1 to 2 cm) is critical to rule out occult CA

Mucinous Neoplasms

Benign→ Borderline → Carcinoma

- 74-90% of CA have benign mucinous epithelium
- CA-Intestinal type -68% show borderline areas
- CA-müllerian type 75-100% have borderline müllerian mucinous
- K-ras mutations similar in benign, borderline & CA areas of the tumor
- P53 mutation 13% in borderline, 40% in CA
- Most CA are associated with changes in RAS-RAF-MEK-ERK-MAP kinase signaling pathway

Mucinous Tumor of LMP: Course

- Almost all are stage I
- Extraovarian involvement in 15%
  - pseudomyxoma in intestinal type
  - subperitoneal implants in endocervical
- 10 yr. survival rate 96% (35% for CA)
- 2-4% of stage I recur or metastasize

Mucinous Tumors of LMP: Histology

- Daughter cysts close to large cysts
- Tufting, bridging, filigree, associated with mild stratification
- **Low grade nuclear atypia**. If HG, classify as intraepithelial CA
- Mitotic figures with altered distribution
- Granulomas, macrophages & giant cells
- Lack of capsular invasion
- Implants in peritoneum, tube & LN

Mucinous Tumors of LMP: Intestinal Type

- Most common type (90%)
- Cysts have smooth but thick wall
- Only a few papillae
- Some solid foci
- Epithelium includes goblet, gastric, neuroendocrine & rarely Paneth cells

Mucinous Tumors of LMP: Endocervical Type

- Less common (10%)
- Clinically similar to, and often mixed with, serous component
- Finer honeycomb than benign
- More papillae inside cysts or exophytic
- Pelvic endometriosis in 30% of cases
- Tall mucinous müllerian cells
- Polys in epithelium

Mucinous Tumors: Microinvasive LMP

- Foci are <3mm, with <10mm^2 surface area
- Small nest(s) surrounded by mucin, macrophages
- Seen in ~10% of LMP mucinous tumors
- No microinvasive LMP cases metastasized

- DDx: **Microinvasive carcinoma** has HG nuclear atypia, and involves larger areas.

Mucinous CystadenoCA

- Often starts as malignant change in 5-10% of adenomas. Suspect in solid areas
- Bilateral in 25%, but then R/O metastatic trs.
- Cells multilayered (>4 layers) & crowded, w/ bridging & cribriform pattern
- High grade nuclear atypia & mitosis
- Micropapillae without stromal core
- Pseudomyxoma is not a criterion

Mucinous CystadenoCA-2

- **Intraepithelial Carcinoma**
  - **<3mm/10mm^2**
  - **aka noninvasive or intraglandular carcinoma**
- **Frank Carcinoma**
  - **Solid irregular nests invade stroma destructively, associated with fibrosis & necrosis**

Peritoneal Adenomucinosis (PP)

- Benign or LMP glands & mucin that dissect between fibrous & omental tissues
- Only with intestinal type
- In 15% of cases of LMP, but also in adenoma & CA, so it does not indicate CA
- Not an indicator of ovarian malignancy
- Presence of glands worsens prognosis. All recurrent cases have glds & most have LG trs. of appendix

Most Peritoneal Adenomucinoses Originate from Appendix

- ~ 85% of recurrent cases are associated with mucinous adenoma, villous adenoma or low grade trs of appendix
- Synchronous trs (ovaries & appendix) are CK 20 pos. & CK7 neg., supporting that ovarian trs originate from appendix
- Rupture of ovarian trs. pre or intraoperatively almost never result in pseudomyxoma (3-19 yr)
- Mucin gene overexpression

Mucinous Tumors: DDx.

- Krukenberg
  - isolated signet ring cells
  - Rare glands
- Teratoma
  - often seen with benign mucinous trs
- Signet ring cell stromal tumor
  - No nuclear atypia
  - Absence of mucin

	CA125	CEA	CK7	CK20	Cdx2	HAM56	MUC5AC
Serous	+	-	+	-	-	+	
Mucin	+/-	+	+	+	+	+	+/-
Endom	+	-	+	-	-	+	
Colon	-	+	-	+	+	+/-	-
Stomach	-	+	+	+/-		+/-	+
Pancr	-	+	+	+		-	+
Append	-	+	+/-	+			+/-

Modified from Prat J, 2004