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THE ORIGINS OF OVARIAN CANCER: MUCINOUS TUMORS

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Table of contents:

- Powerpoint handout
- Text handout: Mucinous Tumors Arising in Mature Cystic Teratoma
- Text handout: Distinction of Primary Ovarian Mucinous Tumors from Mucinous Tumors Secondarily Involving the Ovary
THE ORIGINS OF OVARIAN CANCER: 

MUCINOUS TUMORS

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Mucinous Tumors in the Ovary Other Than Primary Gastrointestinal Type

• Primary Seromucinous type:
  – Precursor: Endometriosis
  – ARID1A mutations

• Secondary origin:
  – 2 main groups:
    • Metastatic mucinous carcinoma (GI tract, pancreaticobiliary region, endocervix)
    • Secondary involvement in PMP (low-grade adenomatous mucinous neoplasm of appendix)
  – Ability to simulate primary ovarian tumors
    (carcinoma, borderline tumor, cystadenoma)
  – Potential for misclassification

Pathogenesis of Primary Ovarian Gastrointestinal type Mucinous Tumors

• Surface epithelial type
• Teratoma-associated

Surface Epithelial Type Mucinous Tumors

Pathogenesis of Surface Epithelial Type Mucinous Tumors

• Upper GI differentiation:
  – Morphology: Resembles gastric foveolar epithelium
  – Immunohistochemistry:
    • CK7-diffuse/CK20-variable (CK7 > CK20)

• W.H.O. Classification:
  – Cystadenoma
  – Borderline tumor (atypical proliferative, low malignant potential)
  – Carcinoma

Ovarian mucinous cystadenoma
Pathogenesis of Surface Epithelial Type Mucinous Tumors

- Type I pathway (dualistic model of pathogenesis):
  - Cystadenoma → Borderline tumor → Invasive carcinoma

- Morphologic evidence:
  - Cystadenomas with focal epithelial proliferation
  - Borderline tumors:
    - Within background of cystadenoma
    - With intraepithelial carcinoma
    - With microinvasion
  - Invasive carcinomas within background of borderline tumor
  - Tumors with admixed cystadenoma, borderline tumor, and invasive carcinoma

Pathogenesis of Surface Epithelial Type Mucinous Tumors

- Molecular evidence:
  - Cuatrecasas, *Cancer* 1997:
    - KRAS mutations in intestinal type ovarian mucinous tumors:
      - Tumors with different components:
        - Same mutations in cystadenoma + borderline tumor
        - Same mutations in borderline tumor + carcinoma
      - Conclusion: KRAS mutation is early event

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<th>Cystadenoma</th>
<th>Borderline tumor</th>
<th>Carcinoma</th>
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<td>Mutation Frequency</td>
<td>63%</td>
<td>83%</td>
<td>100%</td>
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Pathogenesis of Surface Epithelial Type Mucinous Tumors

- Progression pathway well accepted
- Precursors of mucinous cystadenoma?:
  - No normal mucinous component in non-neoplastic ovary
  - Metaplasia?:
    - Ovarian surface epithelium/epithelial inclusion glands → mucinous metaplasia → neoplastic transformation
    - Mucinous metaplasia would be rare in the ovary
  - Endometriosis?:
    - May show mucinous metaplasia
    - Significant association of endometriosis is with clear cell and endometrioid tumors, not mucinous tumor
    - Exception: Seromucinous tumors evolve from endometriosis
    - No definitive evidence of etiology for gastrointestinal type tumors
Precursors of Mucinous Cystadenoma?

- **Brenner tumors?**:
  - Known association of mucinous tumors and Brenner tumors (mixed Brenner-mucinous tumor)
  - Brenner tumors may exhibit mucinous differentiation (metaplastic Brenner tumor)
  - Seidman, *Arch Pathol Lab Med* 2008:
    - Consecutive benign ovarian tumors with mucinous and/or transitional cell components
    - 25% mucinous tumors contained component of Brenner tumor
    - Walthard nests associated with 59% mucinous tumors vs. 28% controls (*p*<0.001)
    - Type of calcifications in mucinous tumors identical to those in Brenner tumors (spiculated)

- **Molecular evidence**:
  - Limited data in literature
  - Pejovic, *Gynecol Oncol* 1999:
    - Case report: Ovarian mucinous carcinoma associated with benign Brenner tumor
    - CGH analysis: Amplification of 12q14-21 in both components
    - Suggest clonal relationship
Pathogenesis of GI Type Surface Epithelial Mucinous Tumors

• Conclusions:
  – Origin from Brenner tumors:
    • Brenner origin represents at least 1 pathway
    • Question: *Are all GI type surface epithelial mucinous tumors of Brenner origin?*
      – Not all mucinous tumors have a Brenner component:
        • Overgrowth of Brenner component?
        • Non-Brenner pathways exist?
      – Further investigation warranted
  • A plausible concept
  • An identifiable source of mucinous differentiation
  • Other proposed origins: *Limited convincing evidence*

Teratoma-associated Mucinous Tumors
Pathogenesis of Primary Ovarian Mucinous Tumors: Germ Cell (Teratomatous) Origin?

- Known association between ovarian teratomas and mucinous tumors:
  - Teratomas: 2-11% contain mucinous tumors
  - Mucinous tumors: 3-8% contain teratomas
- Mucinous tissues within teratomas:
  - Colon
  - Appendix
  - Respiratory epithelium
  - Upper GI tract
- Proposal: Mucinous tumors may arise from teratomas
- Other somatic type tumors arising from teratomas:
  - Thyroid tissue  Papillary thyroid carcinoma
  - Squamous epithelium  Squamous cell carcinoma

Mucinous Tumors Associated With Teratomas

  - Abundant hypermucinous epithelium with goblet cells
  - Pseudomyxoma ovarii (48%):
    - Tumors resemble lower GI low-grade adenomatous neoplasms
  - Pseudomyxoma peritonei:
    - Exception to primary appendiceal origin
  - Histologic patterns:
    - Cystadenomatous
    - Proliferative:
      - Confluent glandular/villoglandular
      - Infiltrative, including signet ring cell carcinoma

Mucinous Tumors Associated With Teratomas

  - All possible CK7/CK20 coordinate profiles
  - 53% showed lower GI immunophenotype:
    - CK7(-)/CK20(+)
    - CK7-focal/CK20-diffuse
  - Significant association of pseudomyxoma ovarii with CK7(-)/CK20(+)
  - Similar morphologic & IHC findings: *McKenney, Am J Surg Pathol* 2008 (n=42)
Teratoma-associated: Resembles Low-grade Adenomatous Mucinous Neoplasm of Appendix

Teratoma-associated: Resembles Low-grade Adenomatous Mucinous Neoplasm of Appendix

Teratoma-associated: Resembles Low-grade Adenomatous Mucinous Neoplasm of Appendix

Teratoma-associated: Resembles Mucinous Borderline Tumor of Surface Epithelial Type

Teratoma-associated: Resembles Mucinous Borderline Tumor of Surface Epithelial Type

Teratoma-associated: Resembles Mucinous Borderline Tumor of Surface Epithelial Type
Mucinous Tumors Associated With Teratomas

- H&E + IHC: Many resemble lower GI tumors of the type more commonly encountered as secondary involvement in the ovary
  - Are not just tumor-to-tumor metastases:
    - Clinicopathologic features c/w primary ovarian origin (JHH + Stanford studies):
      - Generally young age
      - Presence of teratoma in all cases
      - Unilateral
      - Large
      - Lack other typical histologic features favoring metastases
        - (surface tumor, nodularity, LVSI/tumor in hilum)
      - Clinical work-up, gross sampling of appendix, follow-up:
        - No evidence of primary non-ovarian tumor
Lower GI type Mucinous Tumors Arising From Teratomas

- Teratomatous elements may be focal
- Teratomatous elements may not be found initially (for cases w/o evidence of non-ovarian primary):
  - May represent tumor overgrowth
  - Additional gross sampling necessary
- Regardless of teratomatous elements:
  - Comment section of pathology report: Secondary involvement should be clinically excluded

Mucinous Tumors Associated With Teratomas

- Molecular evidence:
  - Limited data in literature
  - Magi-Galluzzi, Mod Pathol 2001 (140A):
    - PCR of microsatellite polymorphisms on different chromosomes:
      - Ovarian mucinous cystadenomas associated with teratomas
      - Ovarian mucinous cystadenomas without teratomas
    - Conclusion: Mucinous cystadenomas associated with teratomas are of germ cell origin

Conclusions: Mucinous Tumors Associated With Teratomas

- Those resembling lower GI tumors:
  - Morphology & IHC distinct from surface epithelial type mucinous tumors
  - Pathogenesis independent of pathway for surface epithelial tumors (i.e., germ cell origin)
  - Importance of Dx: Misclassification as secondary involvement

Conclusions: Mucinous Tumors Associated With Teratomas

- Those resembling surface epithelial tumors:
  - Morphologic + IHC features identical to mucinous tumors w/o teratomas
  - Collision tumors?
  - Germ cell origin?:
    - Upper GI tissues and respiratory epithelium in teratomas
    - Morphology & IHC of surface epithelial type mucinous tumors c/w upper GI differentiation
    - Surface epithelial mucinous tumors w/o Brenner tumor component: Monodermal teratoma?
    - Further study warranted

Pathogenesis of Primary Ovarian Gastrointestinal Type Mucinous Tumors

THE ORIGINS OF OVARIAN CANCER: MUCINOUS TUMORS

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SUPPLEMENTAL INFORMATION:
Mucinous Tumors Arising in Mature Cystic Teratoma

Microscopic Features
Primary ovarian mucinous tumors associated with a mature cystic teratoma show a spectrum of histologic appearances.\(^1,2\) At the lower end of the spectrum, tumors display a cystadenomatous pattern. Proliferative tumors with architectural complexity and epithelial stratification resemble atypical proliferative (borderline) mucinous tumor of ovarian surface epithelial origin or low-grade adenomatous mucinous neoplasm of the appendix. Pseudomyxoma ovarii can be seen with some cystadenomatous and proliferative neoplasms. Compared to tumors without pseudomyxoma ovarii, neoplasms with pseudomyxoma ovarii more closely resemble lower gastrointestinal tract adenomatous tumors and tend to have hypermucinous columnar epithelium and abundant goblet cells. Other tumors may show goblet cell carcinoid-like morphology. At the upper end of the spectrum, the carcinomatous neoplasms may be of glandular or signet ring cell type. Pseudomyxoma ovarii can also be associated with goblet cell carcinoid-like tumors or carcinoma.

Immunohistochemical Features and Differential Diagnosis
Immunohistochemical stains for CK7 and CK20 show variable coordinate expression profiles.\(^2\) Tumors without pseudomyxoma ovarii and having cystadenomatous or proliferative patterns show a variety of CK7/CK20 profiles, including a CK7 diffuse/CK20 variable pattern (a pattern frequently seen in ovarian surface epithelial tumors). Those with pseudomyxoma ovarii and having cystadenomatous, proliferative, or goblet cell carcinoid-like patterns characteristically display a CK7(-)/CK20 diffuse or CK7 focal/CK20 diffuse profile (patterns typical of lower gastrointestinal tract tumors). A minority of these tumors histologically and immunohistochemically resembling lower gastrointestinal tract adenomatous tumors can have the clinical syndrome of pseudomyxoma peritonei without a tumor in the appendix. Parenthetically, it should be emphasized that although nearly all cases of pseudomyxoma peritonei are of appendiceal origin, rare cases are of primary ovarian origin due to an appendiceal-type mucinous tumor arising within a mature cystic teratoma. The carcinomas can have variable CK7/CK20 profiles, but some will show a CK7(-)/CK20 diffuse or CK7 focal/CK20 diffuse pattern.

Ovarian mucinous tumors of germ cell origin with histologic and immunohistochemical features typical of primary lower gastrointestinal tract tumors can be misclassified as metastatic or secondary tumors involving the ovary. Thus, it is important to search for focal teratomatous components in such ovarian mucinous tumors in order to suggest a possible primary ovarian origin. Nonetheless, when problematic mucinous neoplasms in ovarian mature cystic teratomas histologically and immunohistochemically resemble lower gastrointestinal tract tumors, extensive sampling of the gross specimen and further clinical evaluation to exclude the rare possibility of a similar primary mucinous tumor in the appendix or colorectal region as part of a tumor-to-tumor metastasis (e.g., a primary lower gastrointestinal tract tumor with a metastasis to a co-existing ovarian teratoma) are recommended.

Primary ovarian mucinous tumors arising in a teratoma which histologically and immunohistochemically resemble lower gastrointestinal tumors are considered to be of germ cell origin. Tumors that are histologically and immunohistochemically analogous to ovarian surface
epithelial mucinous cystadenoma or atypical proliferative (borderline) mucinous tumor may have developed in the same ovary containing a teratoma as an independent tumor; however, it should also be considered that some of those mucinous tumors could be of germ cell origin as it is possible that they arose from upper gastrointestinal/pancreaticobiliary or sinonasal tissue in a teratoma, which would have histologic and immunohistochemical features similar to mucinous tumors of ovarian surface epithelial origin.

**Nomenclature**

For primary ovarian mucinous tumors histologically and immunohistochemically resembling lower gastrointestinal tract tumors, descriptive terminology that parallels the nomenclature for tumors in lower gastrointestinal sites (e.g., low-grade adenomatous mucinous neoplasm for ovarian tumors histologically and immunohistochemically analogous to those of the appendix) is preferred, considering that (a) terms such as borderline tumor or atypical proliferative tumor are used for surface epithelial tumors of the ovary, (b) these mucinous tumors are of germ cell rather than surface epithelial origin, and (c) they resemble their counterparts in the lower gastrointestinal tract.

**Clinical Behavior and Treatment**

Data on the behavior of mucinous ovarian tumors of germ cell origin are limited, but in the series of McKenney et al and Vang et al, patients with cystadenomatous and proliferative/low malignant potential tumors on follow-up remained well and disease-free. For ruptured primary ovarian mucinous tumors (with pseudomyxoma ovarii) which are the histologic and immunohistochemical counterpart of appendiceal low-grade adenomatous mucinous neoplasms, patients are at risk for the development of the clinical syndrome of pseudomyxoma peritonei, and further clinical evaluation and follow-up are prudent. In the two series mentioned above, mucinous carcinomas showed variable outcome but exhibited the potential for aggressive behavior.

**REFERENCES**


General Features Of Metastases Involving The Ovaries

Metastatic neoplasms involving the ovaries account for approximately 8% of malignant ovarian neoplasms in women undergoing surgery for an ovarian mass in the United States. Metastases derived from non-gynecologic sites are 11 times more common than those derived from female genital tract organs, with adenocarcinomas of gastrointestinal tract origin representing the most common type; however, a substantial number of metastases in the ovaries are of unknown origin.\(^1\)\(^4\) Metastases in the ovaries can present synchronously or metachronously with the primary neoplasm. Those presenting metachronously can do so subsequent to or prior to the diagnosis of the primary tumor. In the former situation, the diagnosis of an ovarian metastasis often is not difficult, particularly when the history of a prior non-ovarian malignant neoplasm is known to the pathologist and additional sites are involved by metastatic disease. In contrast, the latter scenario often poses a diagnostic challenge, particularly when metastatic disease appears to be confined to the ovaries and other characteristic features of metastatic disease in the ovaries are lacking. In exceptional cases, the primary site may not be identified until months or even years later. Thus, the typical, readily recognized ovarian metastasis presents as multifocal tumor in the setting of a known non-ovarian primary malignant neoplasm, but in some cases an ovarian mass can represent the first manifestation of metastatic disease from a clinically occult non-ovarian primary malignant neoplasm. On occasion, metastatic neoplasms can cause virilization, simulating a primary ovarian sex cord-stromal neoplasm. While relatively rare, this phenomenon is most frequently encountered with metastatic mucinous carcinomas, and the women can be relatively young and sometimes present during pregnancy.

Metastases in the ovaries are readily recognized as such, even when another primary site has not been identified or is identified concurrently with the ovarian tumor, when they exhibit characteristic gross and microscopic features. Characteristic gross features of metastases in the ovaries include smaller size (often less than 10 cm), bilateral involvement, a nodular growth pattern, and presence of tumor on the surface and/or in the superficial cortex of the ovary. Nodular tumors typically are solid and compress the surrounding ovarian stroma. Characteristic microscopic features of metastases include an infiltrative growth pattern with stromal desmoplasia, a nodular growth pattern with involvement of the ovarian surface and superficial cortex, and hilar and lymph-vascular space involvement. The presence of signet ring cells almost invariably indicates metastatic carcinoma of gastrointestinal tract or breast origin although rare primary ovarian epithelial tumors with a component of signet ring cells without teratomatous elements have been reported.\(^5\)\(^6\) It should be noted, however, that primary ovarian carcinomas with a pure component of signet ring cell carcinoma probably represent tumors of germ cell origin in which the teratomatous components were overgrown by carcinoma. Certain other histologic features are characteristic of particular types of metastatic carcinomas, such as a garland pattern of epithelium draped along the periphery
of zones of so-called “dirty necrosis” in metastatic colorectal carcinoma. It should be emphasized that none of these individual features are pathognomonic and metastases are most easily recognized when a combination of features is present.\textsuperscript{7,8} In addition, certain microscopic features that might suggest origin of a neoplasm in the ovary are actually non-specific and can be seen in metastatic carcinomas. These include the finding of histologically benign-appearing and low-grade proliferative (cystadenomatous and atypical proliferative [borderline] type) mucinous epithelium in metastatic pancreatic, colorectal, and endocervical mucinous carcinomas, and stromal luteinization.

It is important to note that some metastases lack characteristic features of metastatic disease and share clinical, gross, and microscopic features with primary ovarian neoplasms. Thus, an ovarian mass involved by metastatic carcinoma can represent the initial clinical manifestation of disease, leading to surgical exploration by a gynecologist or gynecologic oncologist for a presumptive diagnosis of ovarian cancer. Occasionally, the ovarian tumor can be large, unilateral, and multicystic with a smooth surface, suggesting a clinical stage I primary ovarian neoplasm. These deceptive metastatic carcinomas can grow in confluent glandular/expansile or villoglandular patterns, without infiltrative growth, simulating primary ovarian atypical proliferative (borderline) tumors with intraepithelial carcinoma and well-differentiated carcinomas not only at the time of intraoperative consultation but also when examining multiple permanent sections. Thus, recognition of these neoplasms as metastases can be exceedingly difficult, particularly when the primary site has not been identified, and ancillary techniques are often required to establish the correct diagnosis. The distinction of primary and metastatic ovarian neoplasms is further complicated by the known occurrence of synchronous independent ovarian and non-ovarian neoplasms having similar histologic features. This situation usually involves synchronous endometrial and ovarian endometrioid tumors associated with endometriosis, in which the neoplasms are likely independent. However, in other situations, such as synchronous and metachronous ovarian and endocervical endometrioid and mucinous tumors, ancillary tests have provided evidence that the ovarian neoplasms are metastatic despite the presence of clinical, gross, and microscopic features suggesting the ovarian tumors are independent.

**Features Characteristic of Metastases to the Ovary:**

- Bilateral involvement
- Size < 10 cm
- Surface and/or superficial cortical involvement
- Infiltrative growth pattern with stromal desmoplasia
- Nodular growth pattern
- Signet ring cell component
- Hilar involvement or lymph-vascular space invasion
- Known history of non-ovarian primary tumor
Pathologic And Immunohistochemical Features Of Primary Ovarian Mucinous Tumors: Atypical proliferative (borderline) mucinous tumors of gastrointestinal type and mucinous carcinomas\textsuperscript{9-23}

Both types of primary ovarian mucinous tumors are usually stage I unilateral tumors and typically larger than 10 cm, with most reported mean sizes for atypical proliferative tumors ranging from 19 to 22 cm and for carcinomas, 18 to 21 cm. The external surfaces are usually smooth, and the cut surface is multicystic. The cysts are often filled with mucinous material or fluid, and internal surfaces are generally smooth, typically without grossly evident papillations. Solid areas are occasionally encountered, more often in carcinomas than in atypical proliferative tumors. Microscopically, the atypical proliferative tumors form complex organized cysts having basal/peripheral crypts and luminal differentiated villous structures lined by gastrointestinal-type mucinous epithelium with variable numbers of goblet cells. The epithelium typically most closely resembles gastric foveolar-type mucosa. Nuclear atypia generally ranges from mild to moderate, with enlarged, reactive-appearing nuclei and proliferative activity generally restricted to the crypts. The presence of marked nuclear atypia qualifies a tumor for a diagnosis of intraepithelial carcinoma. The carcinomas most often exhibit an exaggerated atypical proliferative growth pattern in which the glandular epithelium of the cysts is sufficiently crowded to form a confluent glandular/cribriform pattern. The complex, confluent labyrinthine growth pattern of the epithelium imparts an expansile rather than infiltrative appearance to the tumor. Some mucinous carcinomas exhibit destructive, infiltrative growth, but this pattern should raise concern for the possibility of a metastasis, especially when bilateral involvement and extra-ovarian disease are present.

Primary ovarian mucinous tumors typically exhibit diffuse expression of cytokeratin 7 (CK7). Expression of cytokeratin 20 (CK20) is variable, ranging from negative to multifocal positivity with patchy areas of negative epithelium. The only exception to this pattern is the mucinous tumors arising in ovarian mature cystic teratomas, which exhibit a lower gastrointestinal tract type immunoprofile (CK7-negative, CK20 diffusely positive) \textit{[also, see other handout on mucinous tumors arising in mature cystic teratoma]}. Primary ovarian mucinous tumors retain expression of Dpc4 and lack expression of hormone receptors (estrogen [ER] and progesterone receptors [PR]).

Features Characteristic of Primary Ovarian Tumors:

- Unilateral involvement
- Size > 10 cm
- Lack of surface and/or superficial cortical involvement
- Lack of nodularity
**Features Shared by Primary Ovarian Tumors and Metastases to the Ovary:**

- Cyst formation
- Areas of microscopic low-grade tumor suggesting a primary ovarian precursor lesion
- Necrosis
- Stromal luteinization

**Guidelines For Distinguishing Primary Ovarian Mucinous Tumors From Mucinous Tumors Secondarily Involving The Ovary And For Predicting Primary Site For Metastatic Carcinomas Of Unknown Origin**

**Intraoperative consultation**

The first step in evaluating mucinous tumors involving the ovaries is to assess gross and microscopic features, along with any available clinical information, to determine whether the tumor is likely primary or could be metastatic. This is often done at the time of intraoperative consultation under less than ideal circumstances. Frozen section diagnosis of mucinous tumors is challenging for several reasons. These include sampling limitations (it is generally not practical to examine more than one or two sections, yet tumors are frequently heterogeneous) and the aforementioned ability of metastases to simulate primary ovarian tumors. In addition, there is often pressure to render a definitive diagnosis to guide surgical staging decisions. Ideally, in the absence of prior relevant specimens in the pathology laboratory database, the pathologist should ask the surgeon whether the patient has had any other documented tumors. Regardless of the patient’s history, the pathologist should also ask whether the ovarian involvement is unilateral or bilateral and if there is any evidence of extra-ovarian disease. In some cases, the features will be sufficiently characteristic to allow for confident diagnosis of a tumor as primary or metastatic. Combined assessment of just size and laterality of mucinous carcinomas is quite useful for predicting whether a tumor is primary or metastatic, but evaluation of morphologic features as part of the diagnostic algorithm is equally important. Not infrequently, however, definitive diagnosis at the time of intraoperative consultation is not possible. The phrasing used to report frozen section diagnoses for difficult mucinous tumors will depend on a variety of factors, including the pathologist’s diagnostic impression, degree of certainty regarding that impression, and the needs of the surgeon. Certain intraoperative findings and gross or microscopic features should prompt additional communication between the pathologist and surgeon. The presence of extra-ovarian disease, bilateral tumor, gross or microscopic nodularity, garland pattern necrosis, or signet ring cells should prompt the pathologist to recommend evaluation of the gastrointestinal tract, the most common source of metastatic mucinous carcinomas in the ovary. The finding of mucinous ascites (pseudomyxoma peritonei) should prompt the surgeon to evaluate and remove the appendix. It is important for both pathologists and surgeons to realize that some mucinous tumors require not only multiple permanent sections but also ancillary diagnostic tests (immunohistochemistry, further clinical evaluation with imaging studies) for definitive diagnosis.
Synthesis of microscopic findings and immunohistochemical profiles

The following summary discussion is intended to provide guidelines for synthesizing particular combinations of microscopic patterns and immunohistochemical profiles to suggest likely primary sites for mucinous tumors suspected to be metastatic from undiagnosed primary neoplasms. A variety of glandular patterns and degrees of mucinous differentiation can be seen in metastatic mucinous carcinomas from different primary sites. Tumors with columnar epithelium exhibiting combined or hybrid mucinous and endometrioid-like differentiation suggest metastatic colorectal or endocervical adenocarcinoma whereas well-differentiated overtly mucinous glands with a more cuboidal appearance suggest metastatic pancreaticobiliary adenocarcinoma. Tumors producing abundant extracellular mucin can be derived from several sites, but those of appendiceal and colorectal origin are most common. Of these, those containing only low-grade adenomatous mucinous epithelium are virtually always of appendiceal origin and are associated with the syndrome of pseudomyxoma peritonei (mucinous ascites). Those containing carcinomatous mucinous epithelium are also commonly of appendiceal origin but also can be of colorectal, pancreatic, endocervical, or gastric origin. Those having a significant signet ring cell component are most often of appendiceal or gastric origin. Primary ovarian mucinous tumors with abundant extracellular mucin production are distinctly unusual and include the rare mucinous tumors arising in ovarian mature cystic teratomas.

The morphologic patterns can be used in isolation to suggest a potential primary site of origin for a given metastatic carcinoma, but evaluation in conjunction with selected immunohistochemical markers can provide additional discriminating information:
Distinction of Primary Ovarian Mucinous Tumors from Mucinous Tumors Secondarily Involving the Ovary

Diagnostic algorithm for ovarian mucinous tumors with glandular patterns
Distinction of Primary Ovarian Mucinous Tumors from Mucinous Tumors Secondarily Involving the Ovary

Diagnostic algorithm for ovarian mucinous tumors with signet ring cell patterns

Diagnostic algorithm for ovarian mucinous tumors with extracellular mucin production (PMP = pseudomyxoma peritonei)
A limited panel of antibodies is useful for distinguishing primary ovarian mucinous tumors from metastatic mucinous carcinomas and for distinguishing among the metastatic tumors. For the distinction of primary ovarian mucinous tumors from the metastases listed above, useful markers include CK7, CK20, Dpc4, and p16, whereas ER, PR, CA-125, and CEA, and are not useful. PAX8 has limited diagnostic value in the setting of mucinous tumors.

The utility of CK7 and CK20 for distinction of metastases from primary ovarian epithelial tumors is restricted to specific situations. In particular, coordinate expression of these cytokeratins is very useful for distinction of metastatic lower gastrointestinal tract (colorectal, appendiceal) adenocarcinomas from primary ovarian mucinous tumors. However, these markers do not distinguish metastatic upper gastrointestinal tract, pancreaticobiliary, and endocervical adenocarcinomas from primary ovarian mucinous tumors due to shared coordinate expression profiles. For those tumors that can share co-expression of CK7 and CK20, the staining patterns of these markers can be helpful for suggesting that one primary site is more likely than the other. In primary ovarian mucinous tumors (atypical proliferative and carcinoma), the CK7 staining pattern is almost always diffuse (staining of at least 75% of tumor cells and often more than 90%) whereas the CK20 staining pattern is variable, ranging from negative to positive but generally not so diffuse when positive; the rare exception is some mucinous tumors arising in ovarian mature cystic teratomas, which are diffusely positive for CK20 and negative for CK7. Lower gastrointestinal tract (colorectal and appendiceal) tumors are usually negative for CK7 and diffusely positive for CK20. Some appendiceal tumors and a small percentage of colorectal carcinomas can express CK7, but the staining pattern is usually patchy rather than diffuse, with the exception of some appendiceal carcinomas that exhibit diffuse expression of CK7. Therefore, positivity for CK7 should not be considered either proof of ovarian origin or evidence against lower gastrointestinal tract origin without considering the staining distribution in the tumor. In addition, it is critical to avoid letting immunohistochemical results determine that the ovary is the site of origin when the morphology clearly favors a metastasis (for example, diffuse CK7 expression in an appendiceal signet ring cell carcinoma or colorectal carcinoma with patchy strong expression of CK7).

Dpc4 expression is retained in all primary ovarian mucinous tumors, but expression is lost in ~50% of metastatic pancreatic carcinomas. Thus, lack of Dpc4 expression distinguishes metastatic pancreatic carcinomas from primary ovarian mucinous tumors; this is useful because both ovarian and pancreatic mucinous tumors share the same pattern of CK7 and CK20 expression (diffuse positivity for CK7 and variable positivity for CK20). However, retained expression does not refute a diagnosis of pancreatic carcinoma. In addition, loss of Dpc4 expression appears to be rather specific for pancreatic carcinomas since colorectal, appendiceal, gastric, and endocervical carcinomas almost always retain expression.

Endocervical adenocarcinomas share microscopic features with primary ovarian mucinous and endometrioid tumors, and there is overlap in the CK7/CK20 immunoprofiles of these tumors. Thus, other markers are required to distinguish these tumors. Detection of HPV DNA is useful for distinguishing metastatic endocervical adenocarcinomas of usual type (those related to high-risk HPV infection) from primary ovarian carcinomas because studies on the association between HPV infection and
primary ovarian neoplasms have yielded almost universally negative results. The usual type endocervical adenocarcinomas demonstrate diffuse expression of p16 (always >50% and typically >75% of tumor cells staining moderately to strongly) in association with high-risk HPV infection. Diffuse p16 expression can distinguish these endocervical adenocarcinomas from most primary ovarian mucinous and endometrioid tumors and other metastatic adenocarcinomas having mucinous and/or endometrioid or endometrioid-like differentiation in the ovary because the latter two groups of tumors tend to be negative or exhibit patchy expression of p16. Those uncommon endocervical adenocarcinomas not related to HPV cannot be distinguished from primary ovarian mucinous tumors by HPV DNA detection or p16 expression.

Hormone receptor expression is not useful for distinction of primary ovarian mucinous tumors from most metastatic mucinous adenocarcinomas (those of colorectum, appendix, pancreaticobiliary tract, stomach, and endocervix) because all these tumor types, with the exception of a minority of endocervical adenocarcinomas, lack expression of ER and PR. Hormone receptor expression only distinguishes metastatic endocervical adenocarcinomas, which are most often negative, from primary ovarian endometrioid tumors and metastatic endometrial endometrioid carcinomas, both of which usually express hormone receptors.

The adenocarcinomas arising in the primary sites listed above account for the more commonly encountered metastatic mucinous carcinomas involving the ovary. Mucinous carcinomas occasionally, albeit uncommonly, arise in other organs, including breast, endometrium, small bowel, lung, and urinary bladder, and these sites should be considered when a non-ovarian primary cannot be found in the more commonly encountered primary sites. Occasional cases of metastatic lobular breast carcinoma involving the ovary may exhibit signet ring cell differentiation. Useful markers for diagnosing these tumors include CK7, CK20, ER, PR, GCDFP-15, and GATA-3. Expression of CK7 in the absence of CK20 is useful for distinguishing this type of breast carcinoma from lower gastrointestinal tract (colorectum, appendix) signet ring cell carcinomas; however, because the CK7+/CK20- immunoprofile does not distinguish these breast carcinomas from gastric signet ring cell carcinomas, the other markers are required as part of a diagnostic panel.

REFERENCES


