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A guided tour of selected issues pertaining to metastatic carcinomas involving or originating from the gynecologic tract

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Abstract

Epithelial metastases originating from the gynecologic tract or secondarily involving it frequently display a different morphology when compared to the primary tumor. Furthermore, issues such as modes of metastasis, appropriate nomenclature and prognostic significance remain subjects of discussion and some skepticism. In this review, we will discuss: metastases to uterine adnexa; serous tubal intraepithelial carcinoma (STIC); serous borderline tumors; metastases from the uterine corpus; and “synchronous” endometrial and ovarian tumors. Three additional themes that will run through the discussions are those that are peculiar, although not restricted to the gynecologic tract: metastasis from non-invasive primary tumors, metastases that look benign and metastases that are benign or clinically indolent.

METASTASES TO THE UTERINE ADNEXA

Some metastases in the ovary that originate from malignant primary tumors exhibit a paradoxically low-grade appearance, mimicking cystadenoma or borderline tumor when metastatic to the ovary: metastatic pancreatobiliary adenocarcinoma and adenocarcinoma of the gallbladder; low-grade appendiceal mucinous neoplasm (i.e. well-differentiated mucinous adenocarcinoma of the appendix); human papillomavirus (HPV)-associated endocervical adenocarcinoma; and gastric-type endocervical adenocarcinoma, including minimal deviation adenocarcinoma of mucinous type.

Metastases from pancreatobiliary and gallbladder adenocarcinoma

Ovarian metastases from pancreatobiliary adenocarcinoma¹ and adenocarcinoma of the gallbladder² may show a low-power appearance of ovarian mucinous cystadenoma or mucinous borderline tumor of intestinal type (Fig. 1a), although when extensively sampled, most show areas diagnostic of carcinoma (Fig. 1b). Many such metastases also acquire goblet cells, which are not apparent in the primary tumors. When the metastasis contains both histologically benign and malignant components, the diagnostic challenge rests upon distinguishing a primary ovarian mucinous adenocarcinoma from a metastasis. When only

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benign-appearing and borderline-appearing components are present, the challenge obviously involves the distinction of a primary benign ovarian neoplasm or a metastasis from another source that mimics the former. The paradoxically bland appearance of metastases in the ovary (termed “maturation”) has been discussed in the literature,³ but the mechanisms underlying this phenomenon are largely the subject of conjecture. One hypothesis is that the ovary’s microenvironment, including its hormonal milieu, may play a role in modulating invasiveness and differentiation.⁴

Metastatic low-grade appendiceal mucinous neoplasm

Low-grade appendiceal mucinous neoplasm involving the ovary frequently manifests as large, benign-appearing glands composed of cells with abundant intracytoplasmic mucin.^{1, 5, 6} The presence of very tall columnar mucinous cells in glands with an undulating or scalloped contour and apparent separation of glands from underlying stroma can be helpful in diagnosis (Fig. 2a).^{1, 6} Stromal mucin dissection (pseudomyxoma ovarii, Fig. 2b) may also be present. Unlike pancreatobiliary adenocarcinoma, the primary appendiceal tumor usually has benign-appearing cytomorphology, although luminal distension by mucin and transmural mucin dissection are also usually present. Despite a benign appearance, low-grade appendiceal mucinous neoplasm involving the ovary is very frequently associated with pseudomyxoma peritonei, meaning that recurrences are common. Clinical outcomes differ, however, when comparing this tumor type to metastatic mucinous carcinomas with moderate or poor differentiation, as the latter carcinomas recur earlier and more frequently eventuate in death due to disease.^{1, 7–9}

Metastatic HPV-associated endocervical adenocarcinoma

Metastatic HPV-associated endocervical adenocarcinoma frequently has the architectural appearance of an ovarian borderline tumor of endometrioid type (when mucin-depleted, Fig. 3) or mucinous type (when mucin-rich), although careful study of the cytomorphology reveals features common to HPV-associated glandular neoplasia, namely pseudostratified, elongate and hyperchromatic nuclei with brisk adluminal mitotic figures (so-called “floating mitoses”) and abundant apoptosis (Fig. 3).^{10, 11} The lesion is frequently relatively well circumscribed, without destructive invasion of ovarian stroma. Complicating matters, the primary endocervical adenocarcinoma may not necessarily demonstrate destructive cervical stromal invasion and in some cases is represented only by adenocarcinoma in situ, which tends to be abundant and in some cases carpets most of the endocervix with variable non-invasive extension to lower uterine segment, endometrium and even fallopian tube.¹⁰ In other cases, the primary adenocarcinoma may show destructive or non-destructive growth patterns, the latter referred to as “pattern A” invasion.^{12–14} Linking together HPV-associated endocervical adenocarcinoma in situ or adenocarcinomas lacking destructive cervical stromal invasion with metastasis to the ovary has been the subject of some controversy, despite solid data indicating HPV infection by the same viral type in both sites and shared morphology. Even a rare case of HSIL/“squamous carcinoma in situ” has been reported to colonize endometrium, tubal epithelium and the ovarian surface.¹⁰ It is certainly plausible, if not likely, that these scenarios are examples of transtubal spread with ovarian implantation. Along these lines, it is interesting to note that in some studies, patients with HPV-associated endocervical adenocarcinoma involving ovary have event-free outcomes, although with

limited clinical follow-up,¹⁵ outcomes that might be expected of a non-invasive carcinoma with implantation.

Metastatic gastric-type and minimal deviation mucinous endocervical adenocarcinoma

Endocervical gastric-type and minimal deviation mucinous adenocarcinomas are relatively uncommon tumors that are not associated with HPV. They represent approximately 10% of all endocervical adenocarcinomas, and may metastasize to ovary.^{16–18} Many gastric-type adenocarcinomas metastasize to the ovary in a pattern consistent with a moderately- or poorly differentiated mucinous adenocarcinoma, but some tumors may demonstrate a histologic appearance that is virtually identical to that of mucinous cystadenoma (Figs. 4a, 4b). In most cases, the presence of a mucinous adenocarcinoma in the cervix (Figs. 4c, 4d) along with a mucinous tumor involving ovary is likely to represent a metastasis from endocervix to ovary; however, caution is advised when the patient is known to have Peutz-Jeghers syndrome, as one must remain aware of the phenomenon of widely distributed “mucinous metaplasia” and multifocal mucinous neoplasia.^{19–23} Metastatic gastric-type and mucinous minimal deviation adenocarcinomas are malignant tumors with poor survival irrespective of the degree of differentiation in primary and metastatic sites.^{16, 18}

Approach to distinguish primary from metastatic tumors

The first step in distinguishing primary and metastatic disease in complicated cases is to assess laterality and ovarian tumor size, with approximately 90% of bilateral mucinous tumors and unilateral mucinous tumors measuring less than 12 cm being metastatic to ovary from another site, despite the presence of components that resemble benign or borderline tumors.^{1, 24–28} Occasional exceptions to this rule are metastatic colorectal adenocarcinoma (which almost always retains a malignant colorectal appearance in ovary) and metastatic HPV-associated endocervical adenocarcinoma, both of which may be unilateral and large. As this algorithm is not entirely sensitive or specific, it is also worthwhile to incorporate published histopathologic guidelines that help to recognize metastatic adenocarcinomas to the ovary: ovarian surface involvement, destructive stromal invasion of ovary, nodular growth pattern in ovary with retention of normal ovarian tissue between nodules of metastatic carcinoma, single cell invasion, signet ring cells and involvement of the hilum, particularly lymphovascular invasion in the ovarian hilum.²⁹ There are several papers describing the use of immunohistochemistry in distinguishing primary and metastatic ovarian tumors, but most concern metastatic colorectal adenocarcinoma versus endometrioid ovarian adenocarcinoma, a situation in which careful examination of H&E slides very frequently yields reliable diagnostic information, especially when confirmatory endometrioid features are required for a diagnosis of ovarian endometrioid adenocarcinoma.³⁰ Confirmatory endometrioid features include at least focal low-grade endometrioid adenocarcinoma, squamous metaplasia, endometrioid adenofibroma or borderline tumor and/or endometriosis; and approximately 90% of primary ovarian endometrioid adenocarcinomas are unilateral and large. Highly mitotically active glandular and cribriform tumors lacking confirmatory endometrioid features are much more likely to be colorectal-type adenocarcinoma (Fig. 5). In contrast to almost all primary ovarian mucinous and endometrioid adenocarcinomas, colorectal metastases express cytokeratin (CK)20 with limited or no CK7 staining³¹ and may exhibit aberrant expression of beta-catenin^{32, 33} and

racemase³² and/or SATB2 immunoreactivity.³⁴ The CK7/CK20 panel is also useful in recognizing low-grade appendiceal neoplasm involving ovary.^{3, 31} A CK7-negative/CK20-positive immunophenotype helps to recognize lower intestinal differentiation, rather than lower intestinal derivation. Two examples of this phenomenon are metastatic urachal cystadenocarcinoma of intestinal type^{35, 36} and primary ovarian mucinous neoplasia, either appendiceal-like or colorectal-like, arising in a mature ovarian teratoma.^{37–39}

A CK7-positive phenotype, with or without CK20 expression, can be seen a large variety of tumors, including not only primary ovarian mucinous adenocarcinoma, but also metastases from breast, lung, stomach, pancreas, biliary tract and gallbladder. Lineage-associated markers, such as GATA-3 and mammapsin in breast carcinoma and TTF-1 and napsin-A in pulmonary adenocarcinomas should be used when these tumors are suspected, but tumors from stomach, pancreas, biliary tract and gallbladder may be difficult or impossible to diagnose by immunohistochemistry alone. Loss of DPC4/SMAD4 expression can help to recognize approximately 50% of pancreatic ductal adenocarcinomas^{24, 40} and, much less commonly, biliary, gastric and rare colorectal adenocarcinomas.⁴¹ Retained expression is expected in primary ovarian mucinous neoplasia and examples of pancreatobiliary and gastrointestinal carcinomas lacking *SMAD4* mutation; in other words, retained expression is not diagnostically useful. Recently reported data also indicate that a variable percentage of primary ovarian mucinous tumors express PAX8 and/or ER/PR, unlike entities in the differential diagnosis.^{26, 42} Although it is possible that some of these tumors represent endometrioid adenocarcinomas with extensive mucinous differentiation rather than pure mucinous adenocarcinomas, a positive result is indicative of a gynecologic primary, while a negative result is non-contributory.

SEROUS INTRAEPITHELIAL CARCINOMA

Serous tubal intraepithelial carcinoma

When serous tubal intraepithelial carcinoma (STIC, Fig. 6a) was first described, it was presented as an unequivocal precursor to high-grade serous carcinoma of the adnexa, despite some concerns that lesions with a STIC-like appearance might represent intraepithelial spread from another source, particularly the adjacent ovary.^{43, 44} There is now a large and convincing body of literature indicating that most STICs are precursors to invasive and/or metastatic high-grade serous carcinoma involving uterine adnexa and peritoneum. In support of their precursor status, retrospective studies have documented that the earliest form of serous neoplasia identified in risk-reducing salpingo-oophorectomy specimens and in the adnexa of specimens resected for non-neoplastic gynecologic conditions is nearly always in the fallopian tube in the form of STIC.^{45–48} Another line of histologic evidence is the occasional identification of STIC in association with high-grade serous carcinoma in fallopian tubes in risk-reducing salpingo-oophorectomy specimens as an incidental finding (Fig. 6b). Genetic analysis of normal tubal epithelium, STIC and matched invasive high-grade serous carcinomas have also supported that STIC is an unequivocal precursor to high-grade serous carcinoma.^{49–51} STIC is an example of a primary tumor that may involve other sites without invasion at the primary site. It is thought that the mechanism of metastasis to ovary involves exfoliation of neoplastic cells with implantation onto the ovarian surface or

into ovarian cortical defects that occur during ovulation (Fig. 6c).^{52, 53} Some peritoneal metastases are probably derived both directly from exfoliated STIC cells (Fig. 6c) or from the ovary. Patterns of distribution of high-grade serous carcinoma are characteristic of a tumor that originates in one site with subsequent multifocal metastasis.⁵⁴ High-grade serous carcinomas of the adnexa frequently involve bilateral ovaries smaller than 12 cm, with nodular growth patterns, surface involvement, frequent destructive stromal invasion and ovarian hilar lymphovascular invasion (Fig. 6d); as discussed above, such a pattern is consistent with the tumor representing a metastasis from another site.

Intraepithelial tubal metastases resembling serous tubal intraepithelial carcinoma

There exist tubal lesions with a STIC-like appearance that represent intraepithelial metastasis from an endometrial serous carcinoma or a contralateral adnexal high-grade serous carcinoma.⁵⁵ Complicating efforts to separate STIC from a STIC-like metastasis is the fact that there is no gold standard that distinguishes adnexal high-grade serous carcinoma from endometrial serous carcinoma. One can be more or less confident of an endometrial primary in a woman older than 60 years with an atrophic endometrial polyp containing a WT1-negative serous carcinoma,^{56–58} but exceptions to this profile exist. It will be worthwhile to study this phenomenon in more detail since treatment algorithms for endometrial serous carcinoma differ in many cases from those used for adnexal high-grade serous carcinoma. Intraepithelial tubal metastases resembling STIC may also originate from HPV-associated and unassociated cervix carcinomas (Fig. 7) and extra-Mullerian sites, such as colon, breast, appendix, stomach and pancreas, among others.⁵⁹ When the metastases exhibit the not uncommon pattern of flat architecture with high-grade cytologic atypia and aberrant P53 immunoreexpression, their resemblance to STIC may be pronounced. Some cases may be associated with stromal invasion.⁵⁹

Intraepithelial serous carcinoma of the endometrium

Intraepithelial serous carcinoma of endometrium (ISCE, Fig. 8) was described as a putative precursor to invasive endometrial serous carcinoma.^{60, 61} Subsequent to its initial description, several authors reported the coexistence of ISCE without invasive endometrial serous carcinoma and metastatic carcinoma to ovary and peritoneum^{61, 62} and clonal relationships between ISCE and metastatic carcinoma were demonstrated,⁶³ refuting the popular concept of multifocal Mullerian tumors. It has been estimated that 20–40% of ISCE cases lacking endometrial stromal or myometrial invasion are associated with extrauterine disease, as revealed by comprehensive staging surgery.^{62, 64, 65} Conversely, it has also been implied that some lesions with an ISCE appearance are drop metastases from the adnexa.^{66, 67} A WT1-negative ISCE-like lesion, involving an atrophic endometrial polyp, occurring in a woman older than 60 years is likely to be primary in the endometrium.^{56–58}

SEROUS BORDERLINE TUMOR

Non-invasive implants

Serous borderline tumors are associated with peritoneal and/or nodal disease in approximately 25% of cases,⁶⁸ with higher rates being reported for serous borderline tumor with micropapillary features, a tumor that is also referred to as “noninvasive low-grade

micropapillary serous carcinoma.”⁶⁹ Non-invasive implants may be seen in either scenario, but they are more characteristic of borderline tumors lacking micropapillary features (Fig. 9a). Studies assessing clonal relationships between ovarian serous borderline tumor and peritoneal implants have largely concluded that the implants are, in fact, derived from the adnexa.^{70–72} The best evidence links the ovarian tumor to peritoneal implants, but there is a theoretical construct that posits that some ovarian serous tumors themselves and endosalpingiosis derive from secretory tubal epithelium arranged in papillae and associated with psammoma bodies, so-called “papillary tubal hyperplasia”⁷³ or “papillary secretory cell outgrowth (SCOUT).”⁷⁴ Since most non-micropapillary serous borderline tumors with implants involve the ovarian surface,⁷⁵ it is not difficult to imagine direct extension and/or trans-coelomic spread of tumor to peritoneal surfaces. The presence of similar-appearing areas within the borderline tumor and, more importantly, on the tumor’s surface (termed “autoimplants”, Fig. 9b) ties desmoplastic implants to these microscopic areas within the borderline tumor.^{76, 77} For the practicing pathologist, it is unfortunate that desmoplastic non-invasive implants do not resemble large parts of the ovarian borderline tumor and also demonstrate features that in other circumstances would be equated with metastatic carcinoma, such as incomplete glands and nests of epithelium embedded in desmoplastic stroma (Figs. 9c, 9d, 9e). In contrast to most metastatic carcinomas, the implant rests on the peritoneal surface without invading underlying adipose tissue.⁷⁶ Ample clinical data demonstrate that desmoplastic implants do not behave like metastatic carcinomas.^{78, 79} Although patients with non-invasive implants, including desmoplastic implants, experience recurrence more frequently than patients whose disease is confined to the ovary, and rare patients experience progression of peritoneal disease over a period of decades, very few deaths due to disease are reported at 5- and 10-year follow-up.^{80–82} These data are recognized in the 2014 World Health Organization (WHO) classification,⁶⁹ which separates indolent non-invasive implants (termed “implants”) from malignant invasive implants (termed “low-grade serous carcinomas”).

***BRAF*-mutated serous borderline tumor with microinvasion and lymph node involvement**

Serous borderline tumors with *BRAF* mutations retain the expected borderline tumor architecture, but in addition feature polygonal eosinophilic cells that can become detached from the tumor’s intracystic papillae (Fig. 10a).⁸³ Although this sometimes leads to the low-power appearance of micropapillary serous borderline tumor, there are criteria, discussed below, that separate the two entities. Similar polygonal eosinophilic cells can be found in the stroma within the papillae of the borderline tumor (Fig. 10b), in lymphatic spaces and within the subcapsular sinuses of draining lymph nodes (Figs. 10c, 10d), where their appearance rarely resembles serous borderline tumor.^{84–86} Elegant experiments⁸³ have shown that these eosinophilic cells are terminally differentiated, non-proliferative and senescent, and therefore theoretically incapable of tumor progression; this validates the findings of most clinicopathologic studies that “pink cell microinvasion”, perhaps irrespective of extent, has no influence on clinical outcomes, and that lymph node involvement by borderline tumor does not significantly affect the disease course. Other types of microinvasion and lymph node involvement likely have a more sinister significance, as discussed below.

Micropapillary serous borderline tumors

Micropapillary serous borderline tumors (Fig. 11a) are increasingly recognized as precursors to invasive implants/metastatic low-grade serous carcinoma.^{87, 88} There is incomplete agreement about cytoarchitectural features of this subtype of serous borderline tumor. Kurman's group requires a 5 mm expanse of confluent micropapillae lacking hierarchical branching,^{87, 88} The Massachusetts General Hospital group requires that the micropapillae be 5 times longer than they are wide, along with "grade 2" nuclei, usually round in shape and featuring a nucleolus.⁸⁹ Longacre's group stresses the importance of confluent papillae and/or micropapillae that completely fill a cystic space within the primary tumor,⁹⁰ similar to the "expansile invasion" criterion used for assessment of malignancy in endometrioid and mucinous ovarian tumors. Regardless of the precise definitions used, these tumors are associated with invasive implants/metastatic low-grade serous carcinoma in 25–50% of cases;^{87–89, 91, 92} this finding is used by some pathologists to justify the term "low-grade micropapillary serous carcinoma" for all such cases, even when unequivocal invasion is not identified within the ovary (in which case the prefix "non-invasive" is applied). In contrast to non-invasive implants of serous borderline tumor, peritoneal and nodal involvement by these tumors tends to have an infiltrative micropapillary appearance with surrounding retraction spaces (Fig. 11b); in lymph nodes, extension beyond the nodal capsule and subcapsular sinuses and effacement of lymph node architecture, sometimes with a stromal reaction, is seen (Fig. 11c).^{76, 84, 90} Microinvasion (tumor in ovarian stroma measuring less than 3 or 5 mm in greatest extent) with these characteristics should be distinguished from "pink cell microinvasion," described in reference to the *BRAF*-mutated tumors, because of legitimate concerns regarding differences in malignant potential; the WHO classification recommends the term "microinvasive carcinomas" rather than "microinvasion" for microscopic foci of invasive low-grade serous carcinoma.⁶⁹ Although most micropapillary serous borderline tumors/low grade micropapillary ovarian serous carcinomas with metastatic low-grade serous carcinoma feature both extensive non-invasive micropapillary growth and destructive stromal invasion in the ovary, there is a small proportion of cases lacking detectable stromal invasion within the ovary.⁸⁷ Although suboptimal sampling of the ovarian tumor accounts for some of these cases, there may be other mechanisms at work. For example, it appears that invasive implant/low-grade serous carcinoma may develop decades after definitive surgery showing non-invasive implants, which suggests either a new peritoneal primary, such as one originating in association with endosalpingiosis or progression of non-invasive implants to invasive implants.^{82, 92, 93} Studying a large cohort of cases diagnosed as invasive implants, one of the authors (RAS) recognized a subgroup of cases characterized by clusters of inverted micropapillae surrounded by clefted spaces within interlobular adipose tissue septa that lacked unequivocal invasion of subjacent adipose tissue; such implants are referred to as "implants indeterminate for invasion" by the Stanford group.^{80, 94} Clinical follow-up was compared with that of patients whose peritoneal implants were obviously invasive. The same proportion of patients eventually succumbed to disease, but the recurrence-free survival was longer in the non-invasive/indeterminate group, suggesting that some implants do, indeed, transform to invasive implants/low-grade serous carcinoma.

METASTASIS FROM THE UTERINE CORPUS

Two scenarios account for most metastatic endometrial carcinomas that do not resemble the primary tumor: intratumoral heterogeneity and microcystic, elongated and fragmented pattern (MELF) myometrial invasion with lymphovascular invasion.^{95–97} Interestingly, there appears to be a strong association between both these features and microsatellite instability.^{98, 99}

Intratumoral heterogeneity and metastases

The prototype of intratumoral heterogeneity is de-differentiated carcinoma, a tumor composed of endometrioid adenocarcinoma and a lymphoma-like, rhabdoid tumor-like or small cell carcinoma-like proliferation of medium-sized dissociated cells lacking any evidence of differentiation on H&E stains (Fig. 12a).^{100, 101} Attenuated epithelial differentiation can be elaborated with EMA and/or CK18 stains, but lymphoid, muscle and neuroendocrine markers are either lacking or only focally present in occasional cases. De-differentiation in this context is an example of epithelial-to-mesenchymal transformation (EMT),¹⁰² which in the endometrium involves expression of EMT markers and epigenetic downregulation of e-cadherin via the miRNA200 series.¹⁰³ This tumor type may be misdiagnosed as carcinosarcoma, grade 3 endometrioid carcinoma or combined endometrioid and small cell carcinoma.

Furthermore, what appears to be endometrioid carcinoma can metastasize in the form of undifferentiated carcinoma (Fig. 12b). Two clinicopathologic scenarios exemplify this diagnostic challenge. In the first, the undifferentiated component is removed by biopsy or curettage, so that when the patient undergoes hysterectomy by a different practitioner, there is a morphologic discrepancy between the residual tumor in the endometrium and that found in extrauterine sites. Similarly, retrospective review of tumors diagnosed as endometrioid carcinoma may disclose minute foci of undifferentiated carcinoma, accounting for the undifferentiated appearance of the metastases. The consequence of this degree of morphologic heterogeneity may be significant. Rarely, metastatic undifferentiated carcinoma is found before the patient is known to have an endometrial carcinoma, with the clinical presentation frequently being similar to lymphoma - patients may have systemic adenopathy, B-symptoms and an elevated serum LDH. As the rather small and dyshesive tumor cells may rarely express lymphoid associated markers on flow cytometry (unpublished observations) as well as CD138 by immunohistochemistry,¹⁰⁴ an erroneous diagnosis of lymphoma could be entertained. Endometrial biopsy should be considered in such cases, especially if the patient reports vaginal bleeding.

With only occasional exceptions, de-differentiated endometrial carcinomas and the related undifferentiated endometrial carcinomas have a very poor prognosis that compares unfavorably with outcomes of patients with grade 3 endometrioid carcinoma.^{101, 104} As these tumors may feature rhabdoid cells and have very frequent mutations in the SWI-SNF gene family, patients may theoretically benefit from certain forms of targeted therapy.^{105, 106} Furthermore, since approximately one-half of these tumors are mismatch repair-deficient or harbor hotspot mutations in the exonuclease domain of polymerase E,^{107, 108} it is possible that they may be targeted effectively with immunotherapy.

There are also more subtle examples of tumor heterogeneity that give rise to morphologically discrepant primary and metastatic endometrioid carcinomas. Soslow's group compared the FIGO grade, progesterone receptor (PR) status and DNA mismatch repair protein expression in matched primary and metastatic endometrial carcinomas.¹⁰⁹ Although serous carcinomas tended to remain stable morphologically and immunohistochemically, metastatic endometrioid carcinomas were often of higher FIGO grade and less frequently PR-positive compared to the primary. Interestingly, these tumors were highly likely to be mismatch repair deficient, both in the primary and metastatic sites. Retrospective review of the endometrioid primary disclosed grade heterogeneity within the tumor that theoretically accounted for the appearance of the higher grade component in extrauterine sites. This observation calls into question the wisdom of applying an average grade (i.e. FIGO grade) to cases showing clear-cut low- and high-grade components. In our practice, we diagnose endometrioid carcinoma with tumoral heterogeneity, and describe the different components (including their respective grades). Encouragingly, there is evidence that microsatellite unstable endometrial carcinomas are associated with more favorable clinical outcomes than microsatellite stable carcinomas, particularly when adjuvant therapy is administered.¹¹⁰ As with the microsatellite unstable undifferentiated carcinomas, it is also possible that such tumors might respond favorably to immunotherapy.

Lymph node involvement by endometrial carcinomas with microcystic, elongated and fragmented (MELF) pattern of myometrial invasion

The use of sentinel lymph node mapping and cytokeratin immunohistochemistry to detect occult nodal metastasis has revealed a significant number of clinically low- and intermediate-risk, low grade endometrioid carcinomas associated with isolated tumor cells (ITCs) or nodal micrometastases, using definitions from the breast literature.^{111–115} In most cases, the ITCs, particularly, resemble sinus histiocytes with abundant clear cytoplasm or activated lymphocytes with scant, dense eosinophilic cytoplasm (Fig. 13a).⁹⁵ The variable presence of a clear halo around the tumor cell(s) sometimes allows recognition of these cells at low power examination of H&E slides (Fig. 13a). Obviously, these cells do not resemble glandular, papillary or solid portions of the endometrial primary tumor, but they do resemble the lymphovascular tumor cells that are present in the context of MELF pattern myometrial invasion (Fig. 13b). A recent study reported expression of p16 and p21 with virtual absence of Ki-67 expression in tumor cells showing a MELF pattern, a pattern indicative of growth arrest or cellular senescence.¹¹⁶ Although it is difficult to study the natural history of such cases, especially because most gynecologists have recommended adjuvant therapy for these patients, there are now data that suggest that ITCs originating from FIGO grade 1 endometrioid carcinomas may be inert or clinically indolent.^{114, 117} The AJCC recommends staging ITC patients as N0i+, but FIGO is yet to make recommendations on this topic.¹¹⁸ The senescence and indolent behavior of lymph node metastases shows biologic and clinical similarities to nodal metastases of *BRAF*-mutant serous borderline tumor, as described above.

SYNCHRONOUS ENDOMETRIAL AND OVARIAN TUMORS

Synchronous = existing or happening at the same time

[Greek '*synkhronos*' (happening at the same time); from *syn* (together)+*khronos* (time)]

A patient who is found to have tumor in the endometrium and ovary at the same time is said to have synchronous endometrial and ovarian tumors. The differential diagnosis includes: an advanced stage tumor originating at one of these sites and secondarily involving the other (Fig. 14); or two low-stage tumors arising independently at each site. Clinical observations that some such patients had significantly better clinical outcomes than those with one advanced stage tumor^{119–121} lent support to the concept that at least in some patients with synchronous carcinomas, the two tumors were independent low-stage primary neoplasms. Proposed clinicopathologic criteria (Table 1) for determining the nature of synchronous tumors include numerous data points, are not highly reproducible, and are not strongly supported by evidence from comprehensive studies. Therefore the utility of these criteria in predicting clinical outcome is not unequivocally established.

Synchronous endometrial and ovarian carcinomas come in two major types, one in which low-grade endometrioid carcinoma of similar appearance involves both organs and a less common type in which carcinomas of obviously different histologic types and grades are present in endometrium and ovary. From a biological standpoint, what could possibly explain the emergence of synchronous tumors, particularly those of the same histologic type and grade? An inherited cancer predisposition syndrome is a possibility, but recently, Lynch syndrome was shown to account for only a small percentage of synchronous tumors.^{122–124} Investigators have long been trying to understand the relatedness of endometrial and ovarian carcinomas in this setting, with some studies arguing for independent primaries and others concluding that tumors with a synchronous appearance are really metastatic carcinomas from the endometrium.

Understanding the derivation of endometriosis and its association with adenocarcinoma turns out to be important in understanding this scenario. There are reports describing that foci of endometriosis accompanying adenocarcinomas are usually not only clonal, but also clonally-related to the associated adenocarcinoma.^{125–127} A mouse model of endometriosis has been established using cancer driver genes, providing support for the idea that some examples of endometriosis are indeed cancer precursors.¹²⁸ Discussing a study reporting frequent *CTNNB1* (beta-catenin) mutations in synchronous endometrial and ovarian carcinomas,¹²⁹ Matias-Guiu¹³⁰ noted that one case in the series had a shared *CTNNB1* mutation, unlike the other cases that featured different *CTNNB1* mutations in each site. To account for this, he hypothesized that a focus of non-neoplastic endometrium acquired a *CTNNB1* mutation and, via trans-tubal spread, implanted into or onto the ovary in the form of endometriosis, which then acquired further mutations leading to the development of a *CTNNB1*-mutated endometrioid carcinoma in the ovary. The focus that remained in the endometrium evolved into an endometrioid adenocarcinoma with the same *CTNNB1* mutation. This discussion, for us at least, set the stage for a deeper understanding of “synchronous tumors.”

Two recent seminal papers on the topic using a next generation sequencing approach concluded that from a molecular biological perspective, most synchronous endometrial and

ovarian carcinomas are in fact metastatic carcinomas from one site to the other.^{4, 131} The authors showed that in every DNA mismatch repair-proficient endometrioid carcinoma studied, the endometrial and ovarian tumor in a given patient harbored a shared set of mutations that established the tumors as being clonally related. The tumors in each site subsequently acquired a further set of private mutations, supporting the idea that after tumor establishment at each respective site, the carcinomas underwent neoplastic progression independent of the other site. Interestingly, the rare synchronous tumors reported that lacked shared mutations were DNA mismatch repair deficient.

How can this new information be used in clinical practice? There are many unanswered questions, particularly in light of the recent genomic studies. However, since most previous studies have reported better survivals for tumors characterized as independent primaries than metastatic tumors, we should attempt to categorize synchronous tumors on clinicopathologic grounds, based on the best available pathologic criteria (Table 1).¹³² In future, our practice can be modified by results of integrated studies of clinicopathologic and genetic features of synchronous carcinomas, which should provide more information about the optimal combination of features that accurately predict clinical outcomes.

Conclusions

Many of the difficulties with metastases involving gynecologic tumors can be alleviated by a return to basics. Extensive tumor sampling, careful and detailed microscopic examination, judicious use of ancillary diagnostic techniques, correlation with clinical findings, awareness of the existence of new entities and research discoveries, and consultation with experienced colleagues are probably sufficient to solve most diagnostic problems encountered in practice.

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Summary. Key points about metastases in the gynecologic tract

Metastases whose appearance often differs from the primary tumor

- Metastatic pancreatobiliary and gallbladder carcinomas
- Low-grade appendiceal neoplasm involving ovary
- Metastatic gastric-type endocervical adenocarcinoma, including minimal deviation adenocarcinoma of mucinous type
- Desmoplastic implants of serous borderline tumor
- Isolated tumor cells (originating from endometrial endometrioid carcinomas with MELF-pattern invasion) in lymph nodes
- Recurrent DNA mismatch repair-deficient endometrioid adenocarcinoma with tumoral heterogeneity

Metastases that may look benign

- Metastatic pancreatobiliary and gallbladder carcinomas
- Low-grade appendiceal neoplasm involving ovary
- Metastatic gastric-type endocervical adenocarcinoma, including minimal deviation adenocarcinoma of mucinous type

Metastases that are benign or clinically indolent

- Desmoplastic implants of serous borderline tumor
- Isolated tumor cells (originating from endometrial endometrioid carcinomas with MELF-pattern invasion or BRAF-mutant serous borderline tumors) in lymph nodes
- A subset of metastatic HPV-associated endocervical adenocarcinomas involving ovary
- A subset of ovarian carcinomas identified synchronously with endometrial carcinoma

Metastases from non-invasive primary tumors

- Desmoplastic implants of serous borderline tumor
- A subset of low-grade, noninvasive micropapillary ovarian serous carcinomas with metastatic low-grade serous carcinoma (i.e. micropapillary serous borderline tumor)
- Serous tubal intraepithelial carcinoma associated with ovarian high-grade serous carcinoma
- Intraepithelial serous carcinoma of endometrium with ovarian and peritoneal metastasis

- A subset of low-grade endometrioid carcinomas with clonally related ovarian carcinoma
- A subset of endocervical adenocarcinomas in situ with ovarian metastasis

Figure 1. Metastatic pancreatic ductal adenocarcinoma involving ovary. a) Low-power appearance mimicking ovarian mucinous borderline tumor. b) Higher magnification demonstrates nuclear stratification, overlap and pleomorphism, along with numerous mitotic figures.

Figure 2.

a) Metastatic low-grade appendiceal mucinous neoplasm involving ovary. Glands are lined by tall columnar mucinous cells with a scalloped contour; foci of gland rupture with mucin extrusion into ovarian stroma are present. b) Pseudomyxoma ovarii - fragments of neoplastic mucinous glandular epithelium floating in mucin pools.

Figure 3. Metastatic HPV-associated endocervical adenocarcinoma involving ovary. This mucin-depleted tumor shows some morphologic overlap with ovarian endometrioid borderline tumor.

Figure 4. Metastatic gastric-type endocervical adenocarcinoma involving ovary. Low-power (a) and high-power (b) views of ovarian metastasis showing mild cytoarchitectural atypia; in isolation, this tumor may be misinterpreted as mucinous cystadenoma. The primary cervical tumor from this patient shows irregularly-shaped, infiltrative mucinous glands (c) exhibiting cytologic atypia and associated stromal inflammatory reaction (d). [images courtesy of Dr. K. J. Park]

Figure 5. Metastatic colorectal adenocarcinoma involving ovary. This moderately differentiated nodular tumor shows a cribriform glandular architecture, and exhibits areas of necrosis.

Figure 6. Serous tubal intraepithelial carcinoma and high-grade serous carcinoma. a) Intraepithelial lesion exhibiting nuclear enlargement, pleomorphism, and disorganization, with scattered mitotic figures and apoptotic bodies; these features stand in stark contrast to the bland monolayer appearance of the residual benign tubal epithelium. b) Prophylactic risk-reducing salpingo-oophorectomy specimen showing STIC in association with high-grade serous carcinoma. c) STIC showing detachment of its constituent cells into the tubal lumen; such

exfoliation of neoplastic cells with implantation onto the ovary or peritoneum has been proposed as a means of dissemination of serous neoplasia at a very early stage in its evolution. d) Metastatic high-grade serous carcinoma involving ovary with a nodular growth pattern, including ovarian surface involvement.

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Figure 7.
Intraepithelial tubal metastasis resembling STIC. This metastasis originated from a HPV-associated cervical adenocarcinoma.

Figure 8.

Intraepithelial serous carcinoma of the endometrium. The intraepithelial carcinoma exhibits nuclear stratification, crowding, overlap and pleomorphism, along with conspicuous nucleoli, mitotic activity and apoptosis. The atypical features stand in stark contrast to the appearance of an adjacent benign endometrial gland (top left).

Figure 9. Serous borderline tumor and non-invasive implants. a) Serous borderline tumor of ovary. b) Autoimplant of serous borderline tumor on surface of ovary. c) Non-invasive desmoplastic implant of serous borderline tumor on fallopian tube. d–e) Non-invasive desmoplastic implants of serous borderline tumor composed of small numbers of incomplete glands and nests of epithelium, as well as psammomatous calcifications embedded in abundant desmoplastic stroma.

Figure 10. Serous borderline tumor of ovary with *BRAF* mutations. a) Typical appearance of ovarian tumor, which retains borderline tumor architecture, but in addition features polygonal eosinophilic cells that can become detached from the tumor's intracystic papillae. Similar polygonal eosinophilic cells can be found in the stroma within the papillae of the borderline tumor (b), as well as in the subcapsular sinuses of draining lymph nodes (c and d).

Figure 11.

Micropapillary serous borderline tumor of ovary. a) This example is composed of confluent micropapillae lacking hierarchical branching. b) Invasive implant (low-grade serous carcinoma) exhibiting an infiltrative micropapillary appearance with surrounding retraction spaces. c) Low-grade serous carcinoma involving a lymph node.

Figure 12.

De-differentiated carcinoma of endometrium. a) The tumor is composed of a well-differentiated endometrioid adenocarcinoma and a lymphoma-like, rhabdoid tumor-like or small cell carcinoma-like proliferation of medium-sized dissociated cells. b) Metastatic

undifferentiated carcinoma involving ovary – this tumor morphologically resembles the undifferentiated component of the uterine tumor in a).

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Figure 13.

Endometrial carcinoma with microcystic, elongated and fragmented (MELF) pattern of myometrial invasion. a) Metastatic carcinoma in lymph nodes resembles sinus histiocytes with abundant clear cytoplasm or activated lymphocytes with dense eosinophilic cytoplasm. b) Endometrial tumor showing similar histiocytoid cells invading myometrium singly and in small clusters.

Figure 14.
Metastatic endometrioid adenocarcinoma of endometrium involving ovary. This metastasis has a nodular growth pattern and exhibits an associated stromal reaction.

Table 1

Morphologic criteria for determining the likely nature of synchronous endometrial and ovarian tumors

	Metastasis	Independent primary tumors
Ovary size	Small	Large
Laterality of ovarian involvement	Bilateral	Unilateral
Multinodular ovarian involvement	Yes	No
Myometrial invasion	Deep	Superficial
Lymphovascular invasion	Present	Absent
Fallopian tube involvement	Present	Absent
Histologic type	More often high- grade endometrioid, serous, clear cell or carcinosarcoma	More often low-grade endometrioid

(based in part on ¹³²)