

Update

IN GYNECOLOGIC ONCOLOGY



Pathology Updates in the Field of Gynecologic Oncology

Robert A. Soslow, Guest Editor

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Hereditary Non-Polyposis Colorectal Cancer

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Lynch syndrome, or Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is an autosomal dominant syndrome that predisposes its carriers to multiple malignancies including colorectal, endometrial, and ovarian cancers. Traditionally, HNPCC has been linked with colorectal cancer. However, in women with HNPCC, the incidence of endometrial cancer equals or exceeds that of colorectal cancer. In more than 50% of women with HNPCC, a gynecologic cancer is their first or sentinel malignancy. The identification of these patients is important because they and their family members may be at increased risk for developing synchronous and metachronous tumors, and could benefit from genetic counseling and appropriate surveillance measures.

The current guidelines for identification of individuals at risk for HNPCC focus almost exclusively on colorectal cancer. Similar guidelines to triage patients with endometrial cancer are absent.

Many parameters have been proposed as screening criteria for detection of endometrial cancer patients who may be at risk for HNPCC, including age and family history of HNPCC-associated tumors. However, the efficacy of these criteria is not known.

Previous studies from MSKCC have shown that the microscopic appearance of an endometrial carcinoma can suggest the possibility of HNPCC (Figures 1 and 2), and immunohistochemistry for DNA mismatch repair proteins is a sensitive and specific method of detecting it. Based on these observations, we have been performing immunohistochemistry for these proteins in endometrial carcinomas using the criteria of patient age and microscopic appearance of the tumor.

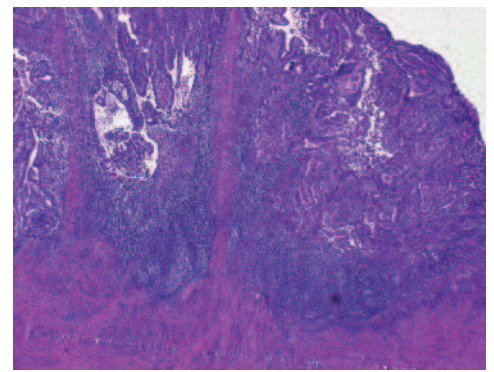


Figure 1: This endometrial tumor shows an extensive lymphocytic infiltrate. We have noticed that tumors with this appearance can be seen in patients with HNPCC.

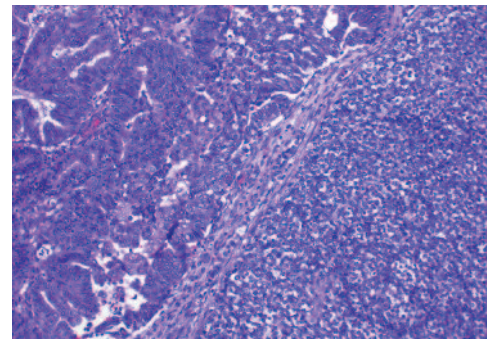


Figure 2: This endometrial tumor shows two distinctly different appearances. Such tumors with a heterogeneous appearance may also be suggestive of HNPCC.

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Histologic Subclassification of Ovarian Cancer

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The World Health Organization's (WHO) classification of ovarian tumors takes advantage of traditional histomorphologic features to recognize serous, mucinous, endometrioid, clear cell, transitional cell, and squamous ovarian neoplasms. We depend upon empirically derived conventions, not objective criteria, to synthesize the various features of these tumors. But as conventions change, so does our approach to subclassifying ovarian carcinomas. While one could argue that tedious subclassification of ovarian carcinomas is probably not worth the trouble given the current therapeutic options (i.e., most ovarian cancers are treated similarly and have a similar prognosis), I would make the point that reproducible subclassification of ovarian carcinomas is very important.

Emerging data support the idea that, instead of representing one disease with many faces, ovarian carcinoma constitutes at least several (perhaps dozens or more) distinct disease entities. Examples of these distinct diseases include the narrow spectrum of ovarian carcinomas

seen in *BRCA1* and *BRCA2* patients; the link between clear cell carcinomas in young patients and hereditary non-polyposis colorectal cancer (HNPCC/Lynch Syndrome); the biologic distinctiveness of low- and high-grade serous carcinomas; the molecular genetic pathways that link endometriosis with endometrioid and clear cell carcinomas; and etiologic relationships between serous borderline tumors and low-grade serous carcinoma, and between endometrioid borderline tumors and endometrioid carcinomas. Some of these relationships are currently clinically relevant; for example, it is increasingly recognized that mucinous, clear cell and low-grade serous carcinomas are intrinsically resistant to standard chemotherapeutic agents. Although specific therapies for each disease entity do not yet exist, standardizing diagnostic criteria will become essential as effective regimens are developed. Corollaries in other organ systems include the considerable data that link morphology, immunophenotype, and genotype in varieties of lymphoma, sarcoma, and renal neoplasia. The WHO classification of lymphomas is a model candidate for an objective and reproducible system for diagnosis [1]. A proposed classification scheme for ovarian carcinoma, based on similar premises, is described in a recent publication [2].

The criteria used for tumor grading and for separating borderline tumors from carcinomas

depend on histologic subtype. For example, although it is commonly assumed that the presence of invasion separates borderline tumors from carcinomas, this is not always assumed in the case of serous carcinoma, in which high-grade malignant cytologic features (even without stromal invasion) generally trigger a carcinoma diagnosis; nor is it assumed in the case of clear cell carcinoma, in which papillary architecture (again without an obvious stromal response to invasion) in the right context defines carcinoma. So-called expansile invasion qualifies for carcinoma in the endometrioid and mucinous realms, although its equivalent in serous tumors, extensive micropapillary architecture, is not universally accepted as evidence of carcinoma. As for grading, none of the commonly used grading schemes is applicable to clear cell carcinomas, and the MD Anderson grading scheme pertains to serous carcinomas alone.

Serous carcinomas, frequently Wilms' tumor antigen-1 (WT1) positive, are morphologically diverse and mimic other tumors. Most transitional cell carcinomas are closely related to them. Mucinous carcinomas are very uncommon and should only be diagnosed after extraovarian primaries are excluded; true ovarian mucinous carcinomas are usually low stage. Intestinal and müllerian mucinous (seromucinous) tumors are histogenetically and clinically distinct. Ovarian endometrioid carcinomas almost always resemble endometrioid carcinomas of endometrium, express estrogen receptors (ER) but not WT1, and are frequently low grade and low stage. Ovarian clear cell carcinomas, negative for ER and WT1 and lacking p53 overexpression, have a limited morphologic repertoire and are frequently low stage at presentation. In summary, clinical biology, immunohistochemistry and genotype can be used to enhance diagnostic objectivity. ■

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Table 1. Ovarian surface epithelial carcinoma characteristics

Carcinoma Type	Morphologic features and associations	Phenotype
Serous	Wide spectrum of morphologic features Fallopian tube intraepithelial carcinoma associated with high-grade carcinoma Serous borderline tumor associated with low-grade carcinoma	+WT1, p53*
Intestinal mucinous	Glandular; at least focal intracytoplasmic mucin Intestinal mucinous borderline tumor also present	-ER, -WT1
Endometrioid	Glandular or papillary; "endometrial" appearance; Squamous differentiation, endometriosis, endometrioid adenofibroma or endometrial cancer also present	+ER; -WT1
Clear cell	Microcystic, papillary or adenofibromatous Endometriosis or clear cell borderline tumor also present	-ER, -WT1
Transitional cell	Broad papillae, solid sheets	+WT1, p53*

*Overexpression

Hereditary Non-Polyposis Colorectal Cancer

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We recently reviewed our prospectively accrued data to assess the efficacy of an algorithm with immunohistochemistry, age, and tumor appearance to detect endometrial cancer patients at risk for HNPCC. We observed that application of this algorithm appears to increase identification of patients with endometrial carcinoma who may be at risk for HNPCC.

We currently have several methods and resources available at MSKCC to test for HNPCC. One is immunohistochemistry for

DNA mismatch repair proteins; this test is performed in our routine pathology laboratory as well as in the pathology core research laboratory. In addition, microsatellite instability (MSI) analysis can be performed by PCR in the molecular genetics laboratory. Tests to detect DNA hypermethylation are expected to be online soon. Currently, genotyping studies are being performed at an outside facility.

In conclusion, it appears that application of an algorithm incorporating age, tumor appearance, and immunohistochemistry may be effective in detecting endometrial carcinoma patients at risk for HNPCC. Consideration

should be given to incorporating these criteria in a revision of the current guidelines for identification of patients at risk for heritable endometrial carcinoma. ■

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HPV-Unassociated Cervical Cancer

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The vast majority of cervical carcinoma is etiologically related to the Human Papillomavirus (HPV). Approximately 70% of cervical carcinomas are caused by two types of high risk HPV, 16 and 18. Most squamous carcinomas, adenocarcinomas, and some variants — including glassy cell, adenoid basal, and adenoid cystic carcinoma — are caused by high-risk HPV. There is a subset of cervical adenocarcinomas, however, that are thought to be unassociated with HPV. Although these entities are rare, it is important to be aware of them and to counsel patients appropriately, especially in the setting of HPV vaccination.

Minimal deviation adenocarcinoma (MDA/adenoma malignum)

This is an extremely well-differentiated variant of endocervical adenocarcinoma characterized by mucinous glands, the majority of which have a deceptively bland appearance (Figure 1). The cervix is often grossly enlarged and may be firm or indurated. The diagnosis can be missed on curettings and small biopsies owing to the bland cytology, and a cone or hysterectomy is often necessary for the pathologist to visualize the architectural growth pattern and

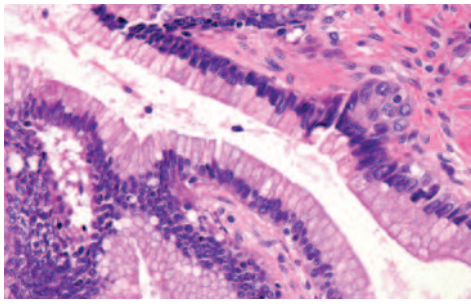


Figure 1: Minimal deviation adenocarcinoma (MDA/adenoma malignum)

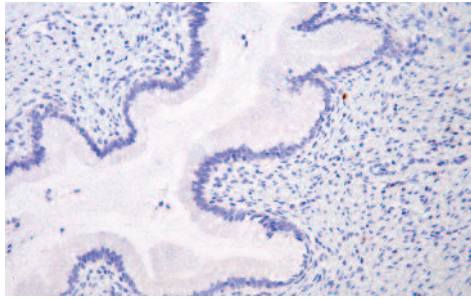


Figure 2: Minimal deviation adenocarcinoma p16 negative

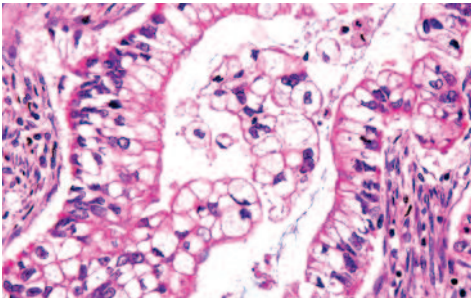


Figure 3: Gastric type adenocarcinoma

make the correct diagnosis. Multiple studies have shown that these tumors are not associated with HPV and, therefore, will not stain with p16 immunohistochemical marker (surrogate marker for high-risk HPV) (Figure 2)[1].

Gastric type adenocarcinoma

This is a recently described entity that is morphologically and immunohistochemically distinct from the usual type of endocervical adenocarcinoma (Figure 3). It is composed of cells with watery clear and/or pale eosinophilic voluminous cytoplasm with distinct cell borders and gastric immunophenotype (HJK 1083 positive). These tumors have been shown to have an aggressive clinical course, and it is postulated that MDA is an extremely well-differentiated form of gastric type adenocarcinoma. Not much is known yet regarding their immunophenotype, HPV status, or clinical significance; however, preliminary studies suggest that these are also not related to HPV infection (p16 negative) [2].

Clear cell carcinoma

Clear cell carcinoma of the cervix (Figure 4) is uncommon and most often thought of in the context of in utero exposure to Diethylstilbestrol (DES). However, it is now known that clear cell carcinoma can occur without DES exposure and shows a bimodal age distribution. The first peak is in younger women

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Distinguishing Breast Metastasis from an Ovarian Primary

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Ovarian metastases are associated with breast carcinoma in up to 30% of cases. However, ovarian masses in women with a history of breast cancer are more likely to represent primary ovarian cancer than metastatic disease by a ratio of 3:1. In patients with an ovarian mass and a history of breast cancer, it is imperative that we distinguish between a second primary versus a metastatic breast carcinoma to the ovary in order to provide appropriate therapy and render an accurate prognosis [1].

Breast cancer metastatic to the ovary may be of ductal or lobular type. Although the histopathology is often suggestive of a metastasis, the growth pattern of the tumor can mimic that of an ovarian neoplasm. Ductal carcinomas usually show a predominant tubular or

cribriform architecture, which may mimic ovarian endometrioid adenocarcinoma. A micropapillary growth pattern may simulate an ovarian serous tumor. A lobular metastasis with a diffuse or insular growth pattern may mimic a granulosa cell tumor.

Immunohistochemistry is useful in distinguishing carcinomas arising in the ovary and breast, but there is overlap in the patterns of immunoreactivity. Both ovarian and breast carcinomas are typically cytokeratin-7 positive and cytokeratin-20 negative. Hormone receptor positivity is not specific for a metastatic breast carcinoma since many primary ovarian and other gynecologic malignancies are commonly positive. Tornos et al reported that an immunohistochemical panel containing Wilms' tumor antigen-1 (WT1), CA125, and gross cystic disease fluid protein-15 (GCDFFP-15) was useful in the differential diagnosis of primary ovarian carcinomas versus metastatic breast cancer to the ovary. In their study, WT1 was positive in the majority (76%) of primary ovarian carcinomas and in none of the primary breast carcinomas. CA125 was positive in 90% (38/42) of the primary ovarian carcinomas and in 16%

(6/36) of the primary breast carcinomas. Fourteen percent (5/36) of the primary breast carcinomas and none of the primary ovarian carcinomas were positive for GCDFFP-15 [2].

More recently, attention is being paid to antibodies to members of the pair box (PAX) gene family. The PAX family consists of nine members, PAX1–PAX9, each of which encodes a nuclear transcription factor. Antibodies to the PAX family have been shown to be useful in differentiating ovarian and breast carcinomas. The transcription factors are expressed in a spatial and temporal pattern during embryogenesis and are implicated in the control of organogenesis in several systems. PAX2 and PAX8 are expressed in the müllerian system, and PAX8 also regulates WT1 expression.

Two recent abstracts looked at the expression of PAX2 and PAX8 in ovarian and breast carcinomas. O'Connor et al found all subtypes of primary breast carcinomas tested for PAX2 expression were negative (26/26), while 100% (3/3) of ovarian papillary serous carcinomas were strongly positive. One ductal carcinoma metastatic to the ovary was also negative. Nonaka et al studied tissue microarrays consisting

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(mean age 26), and the second peak is in older women (mean age 71). One need not necessarily be young or have a history of DES exposure to be diagnosed with cervical (or vaginal) clear cell carcinoma. In a study of 4 clear cell cervical carcinomas, none showed evidence of HPV infection [1]. This suggests that there are non-DES- non-HPV-associated pathogenetic processes in these tumors. Clear cell carcinomas of the cervix are histologically identical to the ovarian and endometrial counterparts, showing hobnail cells with mild to moderate cytologic atypia and abundant clear to eosinophilic cytoplasm. These carcinomas can grow in three architectural patterns: tubulocystic, papillary, and solid.

Mesonephric adenocarcinoma

This is one of the rarest subtypes of cervical adenocarcinoma and is thought to arise from the mesonephric (Wolffian) duct remnants in the lateral wall of the cervix, often accompanied by the presence of mesonephric hyperplasia at

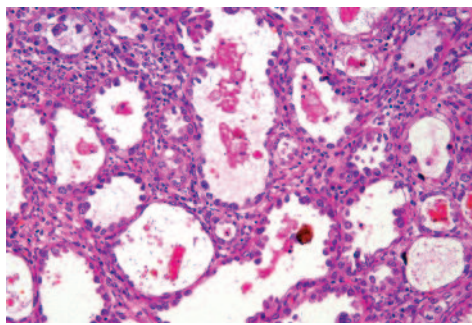


Figure 4: Clear cell carcinoma

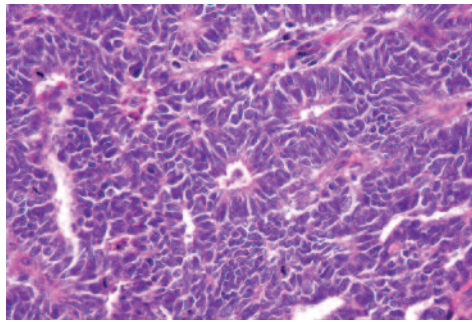


Figure 5: Mesonephric adenocarcinoma

the periphery of the tumor (Figure 5). The tumors usually show an infiltrative growth pat-

tern, sometimes with a nodular pushing margin. Spindle cells can be prominent and should be distinguished from carcinosarcoma. Owing to the rarity of the tumor, it is difficult to say with certainty the clinical impact of this variant. In a study by Silver et al, 7 of 11 patients had no evidence of disease after a mean of 4.4 years. Three of the patients died of disease between 0.8 to 6.2 years, all with distant metastasis or local recurrence. Because this tumor is so uncommon, it is most commonly mistaken for an endometrioid adenocarcinoma, especially on small biopsies or curettages. ■

Distinguishing Breast Metastasis from an Ovarian Primary
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of 135 cases of ovarian carcinomas and 213 cases of invasive breast carcinomas with PAX8 antibody. PAX8 reaction was found in 87% (117/135) of ovarian carcinomas. All breast carcinomas were completely negative for PAX8. PAX8 was better than WT1 for the diagnosis of all types of non-mucinous ovarian carcinomas, notably clear cell and endometrioid types, where WT1 expression is generally negative or focal.

Recognition of an ovarian tumor as a metastatic breast carcinoma requires adequate clinical history, careful evaluation of the gross and microscopic features and, when available, comparison with prior pathologic material. An immunohistochemical panel consisting of WT1, CA125, GCDFP-15 and PAX8, all

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STAFF NOTES

- The Gynecology Disease Management Team would like to congratulate **Douglas A. Levine, MD**, who was recently awarded a 2008 Geoffrey Beene Cancer Research Center grant for his work on "Integrated MicroRNA Genomics in Endometrial Cancer."

available in our laboratory, is effective in distinguishing most breast and ovarian cancers. ■

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