Metastases to the uterus are rare, with a reported incidence of 5.9% for uterine corpus metastases and 0.3% for cervical metastases (1). Although they are usually seen in the context of widely disseminated disease, they may cause gynecologic symptoms such as abnormal vaginal bleeding or abdominal pain, thus mimicking a primary gynecologic neoplasm. This is particularly true if these symptoms precede the diagnosis of the primary tumor or the previous cancer history is unknown (2,3). Another challenge presented by these cases is that as most are carcinomas (3–5), there is a potential risk of overlapping histologic and immunohistochemical features with endometrial or cervical primaries. The following discussion addresses the histopathologic features of the most common metastatic carcinomas to the uterus and the ancillary studies most frequently utilized to determine the primary site.

**INTRAGENITAL METASTASES**

Ovarian and fallopian tube carcinomas are the most common sources of intragenital metastases involving the uterus (3), with the vast majority of them being serous carcinomas. Over half of the cases of ovarian serous carcinoma have extension of disease to the uterus. In most of these cases, the tumor is in the serosa with or without myometrial involvement or transmural involvement; however, in 18% of the cases the tumor involves the endometrium with or without myometrial involvement, the myometrium by itself, or the cervix (6). In addition, most cases of fallopian tube carcinoma are not recognized as such before surgery; however, they tend to have abnormal findings and/or carcinoma in Pap smears and uterine samples before surgery (7). Therefore, a subset of ovarian carcinomas and many cases of fallopian tube carcinoma can become a diagnostic challenge as they can present with abnormal vaginal bleeding, normal serum CA 125 level, and either fragments of a serous neoplasm (i.e., borderline serous tumor, low-grade serous carcinoma, or high-grade serous carcinoma) in an endometrial, myometrial, or
cervical sample or an abnormal Pap smear (7–13). Histologic clues to the presence of an upper gynecologic tract malignancy in the samples listed earlier include the presence of small clusters of neoplastic cells floating between fragments of benign endometrial or endocervical tissue or blood (Figs. 10.1–10.3, e-Figs. 10.1–10.9) and the presence of tumor cells within lymphatic spaces of the endometrium, cervix, or myometrium (Fig. 10.4, e-Figs. 10.10 and 10.11). Occasionally, the tumor may be seen within the endometrial or endocervical stroma adjacent to benign glands. The degree of cytologic atypia of the neoplastic cells ranges from absent to severe according to the primary tumor type (7,11). More challenging cases will show: (a) numerous psammoma bodies in the Pap smear or endometrial curettage as the initial presentation of an ovarian serous borderline tumor (14), (b) only involvement of the surface of an endocervical polyp (10) or endocervical epithelium mimicking thus an adenocarcinoma in situ (15), and (c) a combination of glandular and papillary patterns reminiscent of a primary cervical neoplasm (Fig. 10.5, e-Fig. 10.12) (13).

The differential diagnosis of serous neoplasms of ovarian or fallopian tube origin detected in uterine samples includes the following:

1. **Mesothelial cells and histiocytic aggregates:** A variety of immunoperoxidase studies are used in the distinction of serous from mesothelial proliferations, including calretinin, cytokeratin 5/6,
FIGURE 10.2 Small cell clusters floating within endocervical mucus of an endocervical curettage specimen; cells are uniform and bland; patient was ultimately found to have an ovarian serous tumor of low malignant potential.

FIGURE 10.3 Fragment of high-grade serous carcinoma adjacent to benign endometrium.
D2-40, and thrombomodulin as mesothelial markers and PAX-8, estrogen receptor, Ber-EP4, and MOC-31 as epithelial markers (Fig. 10.6, e-Fig. 10.13). A panel including multiple markers to distinguish mesothelial from epithelial cells is encouraged because
none of these stains are free of overlap. WT-1 is of limited value as it is expressed in mesothelioma and many ovarian carcinomas (16). Histiocytes can be excluded by a negative CD68 stain.

2. **Serous carcinoma arising in the endometrium**: This differential diagnosis applies to cases with high-grade cytology since serous tumors with low-grade features only arise in the ovary or peritoneum. WT-1 is the most reliable marker to make the distinction of a serous carcinoma of endometrial origin from one arising in the upper genital tract. Essentially, less than 20% of the cases of uterine and cervical serous carcinomas show nuclear expression of WT-1 (usually weak or patchy, although a rare case can be diffuse). In contrast, strong nuclear staining for WT-1 is noted in 76% to 97% of serous carcinomas of the upper genital tract (15,17,18).

3. **Adenocarcinoma of the uterine cervix**: Rarely, primary adenocarcinomas of the uterine cervix can show marked cytologic atypia reminiscent to the one seen in serous carcinoma or can represent a bona fide example of serous carcinoma (see Chapter 3). Human papillomavirus (HPV) testing is required in order to distinguish these primary cervical tumors from an upper genital tract metastasis, as most cases of cervical adenocarcinoma are associated with high-risk HPV (19). It has to be kept in mind that diffuse expression of p16 is seen in serous carcinomas with high-grade features regardless of the site of origin (cervix, endometrium, or upper genital tract) (20,21). In addition, a low-grade serous carcinoma arising in the ovary or peritoneum with cervical involvement can display glandular and

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**FIGURE 10.6** The cells in Figure 10.2 are negative for calretinin.
Metastatic carcinoM as to the Uterine cervix and corpus ——— 329

tic areas that can mimic a cervical primary. Attention to the lack of conspicuous mitotic activity or apoptosis as usually seen in cervical primaries and the expression of WT-1 and estrogen receptor in the context of a negative p16 will allow for the correct diagnosis (e-Figs. 10.14 and 10.15) (13).

4. Metastatic micropapillary breast carcinoma: This tumor, characterized by small papillae of tumor cells, usually with an intermediate to high nuclear grade, lacking fibrovascular cores and floating within stromal lacunae could potentially be detected in a uterine sampling and be mistaken for an upper genital tract primary. However, this type of tumor tends to metastasize to lymph nodes and not to distant sites (22). PAX-8 is the immunomarker of choice to distinguish micropapillary breast carcinoma from an upper genital primary since nuclear staining is seen in over 95% of ovarian serous carcinomas (23–25). Attention has to be paid to the fact that WT-1, a marker typically expressed in serous carcinoma of the upper genital tract, can be expressed in a small percentage of breast carcinomas (23). Use of CA-125 is of limited value. Although >90% of ovarian carcinomas have membranous staining with this marker, it is not considered specific as 10% to 30% of breast carcinomas as well as some cholangiocarcinomas and pancreatic carcinomas stain with this marker (26,27).

EXTRAGENITAL METASTASES

The most common primary sites of carcinoma metastatic to the uterus and cervix are the breast, colorectum, and stomach (3,4). However, pancreas, biliary tract, liver, lung, thyroid, and kidney can represent the primary site on an occasional case (28–38). The presence of histologic features not typically seen in uterine or cervical primaries such as numerous signet ring cells, a single-file cell arrangement, prominent dirty necrosis, nests of markedley eosinophilic cells, nests of clear cells associated with a distinct vascular pattern, or small and partially disrupted glands with clearing of the cytoplasm should raise the possibility of an extragenital origin and prompt the use of immunohistochemical markers to arrive at the correct diagnosis. The features of the more commonly encountered extragenital sources of metastases involving the uterus are discussed below.

In addition, immunoperoxidase stain expression patterns as related to the primary site are summarized in Table 10.1.

BREAST

Lobular carcinoma, the most common subtype of breast carcinoma metastasizing to the uterus (39), should be considered when dealing with a carcinoma composed of monotonous cells, arranged in solid or single-file
### TABLE 10.1 Immunoperoxidase Profile of Adenocarcinomas Involving the Endometrium and Cervix

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Cytokeratin 7 (%)</th>
<th>Cytokeratin 20 (%)</th>
<th>PAX-8 (%)</th>
<th>WT-1 (%)</th>
<th>GCDFP-15(^a) (%)</th>
<th>MGB(^b) (%)</th>
<th>GATA-3 (%)</th>
<th>TTF-1(^c) (%)</th>
<th>Napsin A (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary(^d)</td>
<td>92–100</td>
<td>4</td>
<td>88–100</td>
<td>76–92</td>
<td>0</td>
<td>3–36</td>
<td>6</td>
<td>0–37</td>
<td>6</td>
</tr>
<tr>
<td>Endometrium(^d)</td>
<td>80–100</td>
<td>0–12</td>
<td>93</td>
<td>0–27</td>
<td>0</td>
<td>13–57</td>
<td>7</td>
<td>0–19</td>
<td>0–8</td>
</tr>
<tr>
<td>Breast</td>
<td>82–100</td>
<td>3</td>
<td>0</td>
<td>0–28</td>
<td>17–58(^e)</td>
<td>56–88(^e)</td>
<td>65–100(^e)</td>
<td>0</td>
<td>0–3</td>
</tr>
<tr>
<td>Colon</td>
<td>5</td>
<td>100</td>
<td>0</td>
<td>0–3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0–2</td>
</tr>
<tr>
<td>Stomach</td>
<td>38–55</td>
<td>50–73</td>
<td>0</td>
<td>0–3</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pancreas</td>
<td>92</td>
<td>62–74</td>
<td>8</td>
<td>0–3</td>
<td>0</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>0–4</td>
</tr>
<tr>
<td>Lung</td>
<td>100</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>2.5–4</td>
<td>8</td>
<td>64–82.5</td>
<td>83–87.5</td>
<td></td>
</tr>
<tr>
<td>Kidney(^f)</td>
<td>11–24</td>
<td>0–6</td>
<td>76–100</td>
<td>0–27</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>Bladder</td>
<td>11–63</td>
<td>29–89</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>84–100</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>98</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>97–100</td>
<td>5–7</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)GCDFP-15, gross cystic disease fluid protein-15.
\(^b\)MGB, mammaglobin.
\(^c\)TTF-1, thyroid transcription factor 1.
\(^d\)Higher percentage of staining in lobular carcinoma.
\(^e\)Serous and endometrioid carcinoma.
\(^f\)Papillary and clear cell types of renal carcinoma.
patterns or as single cells infiltrating the stroma with preservation of the endometrial or endocervical glands (Fig. 10.7, e-Figs. 10.16–10.19). In addition, some cases can show signet-ring cells that are also the hallmark of signet-ring cell carcinoma arising in the breast (40,41). Of interest, ductal carcinomas metastatic to the endometrium or cervix may lose their typical features (42). As mentioned earlier, micropapillary breast carcinoma (Figs. 10.8 and 10.9, e-Figs. 10.20 and 10.21) can be potentially encountered and this type of case can be mistaken for a metastasis not only from the upper genital tract but also from the lung or bladder (43). Immunohistochemical stains used to establish a breast origin for a given carcinoma include gross cystic disease fluid protein-15 (GCDFP-15), mammaglobin, and GATA-3. The staining pattern of GCDFP-15 is often only focal, and the protein has reportedly been identified in up to 55% of breast carcinomas overall (26,44,45). In contrast, mammaglobin is more sensitive, with expression reported in up to 88% of breast carcinomas, preferentially in lobular carcinoma. However, mammaglobin is less specific than GCDFP-15, with expression reported in ovarian, endometrial, and lung carcinomas (44–48). A newer marker, GATA-3, appears to have more specificity for breast carcinoma in the correct clinical setting. Over 90% of ductal and lobular carcinomas will have nuclear staining for GATA-3 (49,50). Additionally, less common breast carcinomas such as triple-negative tumors and metaplastic carcinoma may have nuclear expression of GATA-3 (49). As with mammaglobin, GATA-3 is also not entirely specific as it is expressed in the majority of bladder transitional carcinomas as well as in a minority of pancreaticobiliary, ovarian serous

FIGURE 10.7 Carcinoma cells in small clusters infiltrate the endometrial stroma in a patient with a history of lobular carcinoma.
FIGURE 10.8 Papillary clusters of atypical cells are present within the endometrial stroma adjacent to a benign endometrial gland. Morphology simulates high-grade serous carcinoma.

FIGURE 10.9 Immunoperoxidase studies performed on the case referenced in Figure 10.8. A: Positive CATA-3 immunoperoxidase stain (nuclear expression); B: PAX-8 immunoperoxidase stain lacks nuclear staining (negative result).
Metastatic carcinoma, and endometrioid carcinomas (50). Because no single marker is perfect, GATA-3 plus one other breast marker should help confirm the diagnosis. Markers to exclude other entities in the differential diagnosis should be included to serve as additional confirmation.

**COLON/RECTUM**

Colorectal adenocarcinoma can involve the endometrium or cervix by direct extension from the primary, but may also be a hematogenous metastasis. Because colorectal adenocarcinoma shares histologic features with endometrioid adenocarcinoma (51) and intestinal-type endocervical adenocarcinomas (52,53), the absence of pertinent history could lead to a missed diagnosis. On histologic grounds, the admixture of normal endometrium, absence of preneoplastic or preinvasive changes such as hyperplasia/adenocarcinoma in situ, and the presence of disrupted glands, dirty necrosis, and marked cytologic atypia in the context of a predominant glandular pattern should raise the possibility of metastatic colorectal carcinoma (Figs. 10.10 and 10.11, e-Figs. 10.22–10.24) (4). Diagnostic immunohistochemistry can confirm the diagnosis (51) as colon cancer is usually strongly positive for cytokeratin 20 and CDX-2 with absent to rarely minimal expression of cytokeratin 7 (e-Figs. 10.25–10.28) (54). Endometrial carcinoma usually has the opposite immunohistochemical profile. The immunohistochemical profile of endocervical adenocarcinoma with intestinal differentiation more closely resembles the profile of a lower gastrointestinal primary (53). Diffuse nuclear expression
of CDX-2 may be of limited utility in the identification of a colorectal primary because this marker may also be expressed in endometrioid adenocarcinoma and mucinous endocervical adenocarcinoma (e-Figs. 10.29 and 10.30) (53,55,56). Carcinoembryonic antigen (CEA) is also expressed in both colorectal and endocervical adenocarcinoma (53). Due

**FIGURE 10.10**  
A: Low-power image of colon carcinoma in a cone biopsy, tumor is deep within the cervical stroma;  
B: higher power image showing dirty necrosis.
to the potential for gastrointestinal marker staining in uterine carcinomas with mucinous differentiation (53), markers should be added to exclude a Müllerian origin including PAX-8 (previously discussed) and estrogen receptor. Carcinoma originating in the colon will be negative for both
PAX-8 and estrogen receptor (e-Figs. 10.31 and 10.32) (25,51). Because PAX-8 and estrogen receptor expression in endocervical adenocarcinoma is variable and less often positive compared with endometrial carcinoma, a p16 immunoperoxidase stain and in situ hybridization for high-risk HPV may have some utility in unmasking an endocervical primary. Not all endocervical adenocarcinomas with mucinous differentiation are HPV related; therefore, determination of the origin of carcinomas with mucinous differentiation in the uterus and equivocal features with regard to the primary site will be clinical.

**STOMACH**

Gastric adenocarcinoma is often clinically silent with metastases often present by the time symptoms of disease develop. While disease symptoms are often related to tumor at the primary site, symptoms related to metastases that precede diagnosis of the primary frequently occur in gastric cancer, with diagnosis of metastatic carcinoma in an endometrial or cervical biopsy preceding discovery of the gastric primary (57–61). Most metastatic gastric adenocarcinomas to the uterus are poorly differentiated, commonly with signet-ring cell morphology (Fig. 10.12, e-Figs. 10.33–10.35). Tumor frequently permeates lymphatic spaces but may also be present in the endometrial or endocervical stroma with sparing of normal glandular structures (57,60,62). The differential diagnosis for these tumors includes signet-ring cell carcinomas from other sites such as the lower gastrointestinal tract, pancreas, breast, or bladder. In the endometrium, non-neoplastic signet-ring cells should be considered (e-Figs. 10.36 and 10.37) (63) as well as the rare case of endometrial adenocarcinoma, endometrioid or mucinous type, with signet-ring cell formation (64). In the endocervix, consideration should be given to the possibility of a rare primary signet-ring cell carcinoma of the cervix (60). Immunoperoxidase studies may be of some utility in establishing the primary site of a signet-ring cell carcinoma. The presence of cytokeratin 20 staining with or without concomitant cytokeratin 7 expression may suggest a lower gastrointestinal, pancreatic, or genitourinary origin (54). Tumors with exclusive cytokeratin 7 expression could be of either breast or upper gastrointestinal origin (e-Fig. 10.38). The addition of markers to further narrow the primary site such as hormone receptors and GCDFP-15 to establish a breast origin (40,41) may be helpful. GATA-3 is of limited use due to the potential for expression in both breast and bladder carcinoma (50). In the majority of cases, non-neoplastic signet-ring cells in the endometrium represent vacuolated, decidual cells or stromal histiocytes that can mimic carcinoma. A keratin stain should distinguish this artifact from metastatic carcinoma (63). For cases in which signet-ring cell carcinoma involves the cervix, a metastatic process must be excluded clinically before establishing the cervix as the primary site of disease (60,65).
Metastatic carcinoma to the uterine cervix and corpus

PANCREATICOBILIARY

Adenocarcinoma of pancreatic or biliary tract origin metastatic to the endometrium or cervix is uncommon, and may be more frequently found at the time of autopsy rather than biopsy (4). However, primary pancreaticobiliary adenocarcinoma, like gastric carcinoma, is often clinically silent until symptoms arise secondary to metastatic disease (4). In some cases, vaginal bleeding is the first sign of metastatic tumor following resection of the primary tumor (28,50,51). Rarely, the presence of widespread metastatic disease with extensive involvement of the uterus or cervix can clinically mimic an advanced-stage carcinoma primary in the uterus (Fig. 10.13, e-Figs. 10.39–10.41) (29). Histologically, similar to metastases from the stomach and breast, small glands and clusters or cords of cells permeate either the endometrial or endocervical stroma surrounding and sparing the native glandular structures. Immunohistochemically, pancreaticobiliary adenocarcinoma is typically positive for cytokeratin 7. Focal cytokeratin 20 and p16 staining can be seen while CEA expression is variable (e-Figs. 10.42 and 10.43) (54,66,67). Overall, this immunoprofile is not entirely specific and overlaps with primaries from multiple sites. When there is no past history of a primary elsewhere, an absence of PAX-8 expression may help exclude an intragenital metastasis or Müllerian primary, and a lack of GATA-3 expression may help exclude a breast primary. Ultimately, confirming a pancreaticobiliary origin for a metastatic carcinoma will likely be clinical due to the nonspecificity of the immunoperoxidase profile of these tumors.

FIGURE 10.12 Poorly differentiated gastric carcinoma with signet-ring cell morphology present in the endometrial stroma adjacent to a normal endometrial gland.
Of the primary sites discussed, metastatic lung adenocarcinoma involving the uterus is the least common (4). Nevertheless, it can represent a diagnostic challenge. Patients present with vaginal bleeding and a history of lung
carcinoma (34,35). The metastatic tumor usually shares histologic features with the primary lung tumor and the comparison of both tumors facilitates the correct diagnosis (Fig. 10.14, e-Figs. 10.44–10.46). Most lung adenocarcinomas are positive for cytokeratin 7 and negative for cytokeratin 20. In addition, approximately 70% of the cases show nuclear expression of thyroid
transcription factor 1 (TTF-1) and 80% show cytoplasmic staining for Napsin A (Fig. 10.15, e-Fig. 10.47) (68). However, it should be noted that endocervical and endometrial adenocarcinoma may have the expression of TTF-1 (69,70) and Napsin A (70). In some instances, the expression pattern of TTF-1 could be strong and diffuse (69). Therefore, it is important to use PAX-8 to

**FIGURE 10.15** Thyroid transcription factor 1 (TTF-1) in endometrial biopsy (A) and in the primary lung tumor (B).
exclude a gynecologic primary with aberrant TTF-1 expression whenever the diagnosis is in doubt or a lung primary tumor is unavailable for comparison.

REFERENCES


