Seminars in Diagnostic Pathology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Review article

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

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Introduction

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 to the ovary exhibit a paradoxically low-grade appearance, mimicking cystadenoma or borderline tumor: 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 adenocarcinoma[1] and adenocarcinoma of the gallbladder[2] 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 distinguishing a primary ovarian mucinous adenocarcinoma from a metastasis. When only benign-appearing and borderline-appearing components are present, the challenge obviously involves the distinction between 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

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https://doi.org/10.1053/j.semdp.2017.11.007

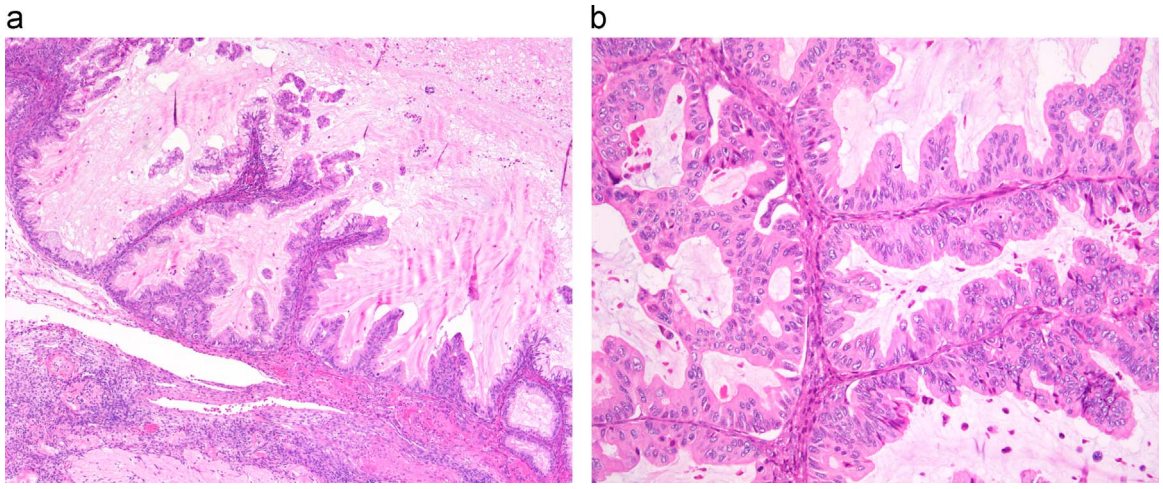

Fig. 1. Metastatic pancreatic ductal adenocarcinoma involving ovary. a) Low-power appearance mimicking ovarian mucinous borderline tumor. b) A focus in the same tumor that is recognizable as adenocarcinoma.

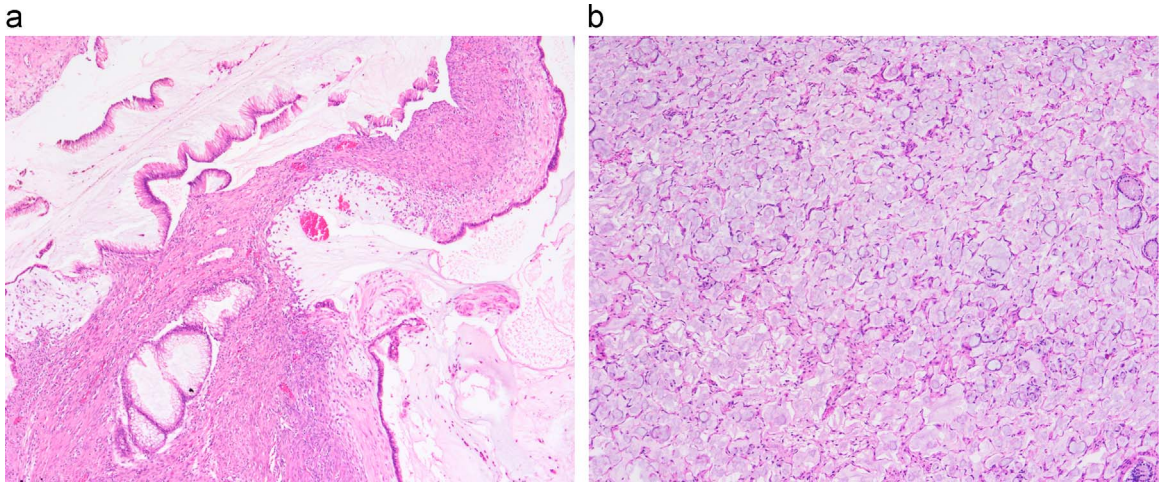

Fig. 2. a) Metastatic low-grade appendiceal mucinous neoplasm involving ovary. Glands are lined by tall columnar mucinous cells with a scalloped contour; foci of gland rupture with mucin extrusion into ovarian stroma are present. b) Pseudomyxoma ovarii - fragments of neoplastic mucinous glandular epithelium floating in mucin pools.

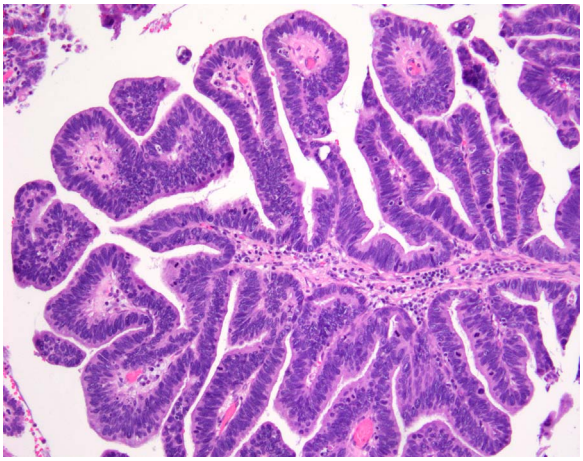

Fig. 3. Metastatic HPV-associated endocervical adenocarcinoma. This mucin-depleted tumor (high power of FIG 7) shows some morphologic overlap with ovarian endometrioid borderline tumor.

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