Seminars in Diagnostic Pathology (2010) 27, 241-260

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Seminars in
Diagnostic
Pathology

Nonendometrioid endometrial carcinomas

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KEYWORDS
Carcinoma;
Serous;
Clear cell;
Squamous cell;
Transitional cell;
Neuroendocrine;
Undifferentiated;
Endometrium

Clinicopathologic studies support a classification of endometrial carcinoma into two main categories (type I and type II). Type I cancers consist of endometrioid and mucinous carcinomas, with the former being the most common, whereas serous and clear cell carcinomas are the so-called "prototype" of type II cancers. Nonendometrioid carcinomas account for approximately 10% of endometrial carcinomas and differ from endometrioid carcinomas in terms of patient demographics, morphologic features, and biological behavior. Molecular studies have provided further insights into the differing alterations involved in the development and progression of these tumors. This review summarizes the characteristic clinical, morphologic, immunophenotypic, and molecular features of the various subtypes of nonendometrioid carcinomas and also highlights relevant conditions (both nonneoplastic and neoplastic) that should be considered in the differential diagnosis of these tumors.

Although nonendometrioid carcinomas represent a minority of all endometrial cancers, they are an important category of tumors, often associated with more aggressive biological behavior when compared with most endometrioid carcinomas (for example, serous carcinoma accounts for almost 40% of all endometrial cancer–related deaths). Furthermore, the molecular pathways involved in the pathogenesis of these tumors differ from that of endometrioid carcinomas. Among the nonendometrioid carcinomas, serous carcinoma is the most common, followed by clear cell carcinoma (CCC). Both are currently classified within the category of type II endometrial cancers, although recent studies have demonstrated that the two subtypes may exhibit divergent molecular alterations. Other less commonly encountered nonendometrioid tumors of the endometrium discussed in this review include transitional cell carcinoma (TCC), squamous cell carcinoma, and neuroendocrine carcinoma.

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doi:10.1053/j.semdp.2010.09.004

Serous carcinoma

Uterine serous carcinoma (U-SC) is the prototype of type II endometrial cancer and represents approximately 10% of all endometrial carcinomas.[1] Unlike type I carcinomas, which typically are seen in perimenopausal women with obesity and unopposed hyperestrogenism, U-SCs tend to occur in postmenopausal women, with a higher incidence in African American women, and are not associated with estrogen stimulation.[2] U-SCs have also been reported in patients with a history of breast cancer, including those treated with tamoxifen[3,4] as well as those with a history of pelvic radiation either for rectal or cervical carcinoma.[5-7] Occasionally, U-SC may develop in the setting of BRCA1/2 mutations or in association with hereditary nonpolyposis colorectal carcinoma (Lynch syndrome).[8-10]

Postmenopausal or abnormal bleeding is the most common clinical presentation, although some patients may complain of serosanguineous vaginal discharge. Occasionally, patients may also present with evidence of disseminated disease, including distant lymph node metastases[11] or an abnormal cervicovaginal Pap test.[12,13] These neoplasms are often associated with raised serum CA-125 levels[14] and rarely, raised serum carcinoembryonic antigen (CEA) levels[15] or

paraneoplastic hypercalcemia.[16] In approximately 35% of patients, preoperative ultrasound may not reveal a thickened endometrial stripe or mass;[17] therefore, despite reassuring imaging studies, persistent symptoms should still prompt further investigations such as an endometrial biopsy or curettage.

Pathologic features

These tumors may not be associated with uterine enlargement even in the presence of extensive myometrial and lymphovascular invasion because they tend to occur in postmenopausal women with small (atrophic) uteri (Figure 1A and B). Frequently, the tumor may not be grossly evident, especially when confined to an endometrial polyp.

Microscopic examination typically reveals a complex and irregular papillary architecture (Figure 2) with striking cellular pseudostratification, micropapillae formation (Figure 3), and budding of single cells (Figure 4). Slit-like spaces (Figure 5) secondary to poorly formed glands or compact growth of papillae, as well as solid nests or sheets of cells, are not as common as in the ovary. Some tumors may exhibit a striking glandular growth, simulating a well-differentiated endometrioid carcinoma at low-power magnification. The tumor cells (including those lining "pseudoendometrioid glands") typically display high-grade malignant features with a high nuclear-to-cytoplasmic ratio, prominent nuclear pleomorphism, enlarged hyperchromatic nuclei, and prominent nucleoli (Figure 6). Multinucleated forms are frequently seen. Mitotic activity is brisk including atypical mitoses. Some cells may have more abundant eosinophilic or clear cytoplasm or may display a hobnail appearance, mimicking a CCC, as has been described in the ovary.[18,19] Psammoma bodies are identified in approximately one third of the tumors but are usually less common than in their ovarian counterparts.

Serous carcinoma typically arises in the setting of atrophic endometrium and origin in an endometrial polyp is also frequently described (Figure 7).[20-26] Extensive lymphovascular invasion and extrauterine extension may occur even when there is limited or absent myometrial invasion.[20,27-30] When there is myometrial invasion, a gaping gland appearance unaccompanied by any stromal reaction is frequently seen (Figure 8). One third of U-SC coexist with other subtypes of uterine carcinoma, usually endometrioid and, less commonly, clear cell or even neuroendocrine carcinoma.[31-34] Trophoblastic differentiation has also been reported.[35] Although a tumor is clinically regarded as a serous carcinoma if the serous component comprises >25% of the tumor volume,[19] any "serous" component should be indicated in the pathology report because even the presence of <10% of this histologic subtype (cut-off used by the most recent World Health Organization to define a mixed carcinoma of the endometrium) has significant therapeutic and prognostic implications.[36]

"Endometrial intraepithelial carcinoma (EIC)" or "intraepithelial serous carcinoma" has been proposed to be the putative precursor lesion of U-SC. This lesion, which may be found in isolation or, more commonly, adjacent to a focus of invasive serous carcinoma,[27,37] is characterized by replacement of the endometrial epithelium (surface and/or preexisting glands) by high-grade cells with a morphology similar to that of invasive serous carcinoma but with preservation of the normal architecture (Figure 9).[20,23,25,27,30,37-39] It is important to recognize that this lesion is not an "in situ" malignant neoplasm as: (1) it may be associated with high-stage disease and a fatal outcome even in the absence of endometrial stromal, myometrial, or

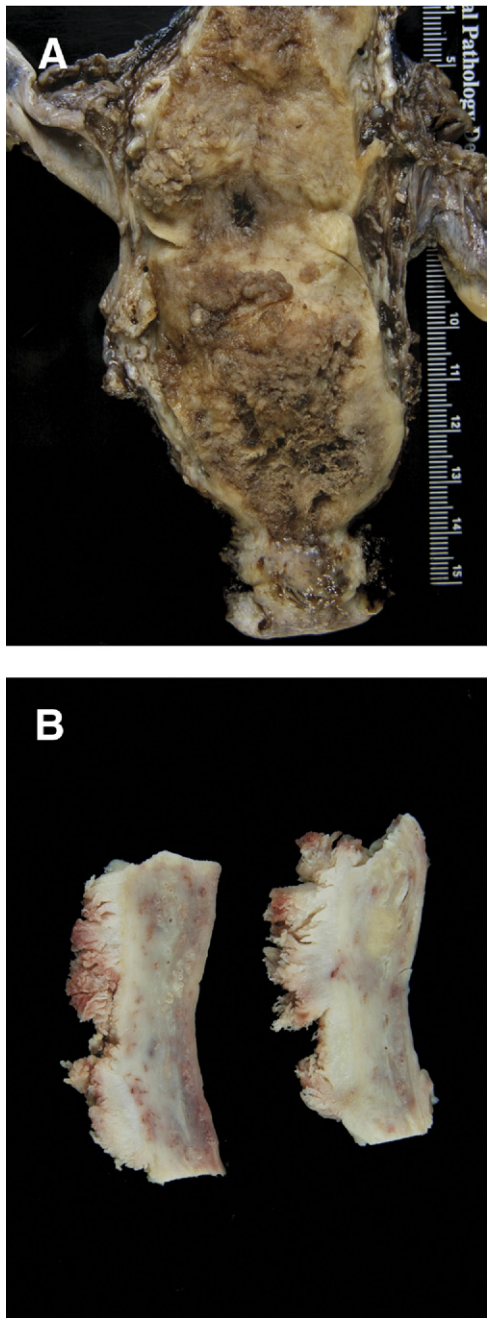

Figure 1 Uterine serous carcinoma. (A) The tumor extensively involves the endometrium. (B) The endometrium is thickened by a striking papillary tumor overlying an atrophic myometrium.