Molecular Pathology
Predictive, Prognostic, and Diagnostic Markers in Uterine Tumors

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KEYWORDS
• Endometrial • Endometrioid • Serous • Adenocarcinomas • POLE • MSI

ABSTRACT

This article focuses on the diagnostic, prognostic, and predictive molecular biomarkers in uterine malignancies, in the context of morphologic diagnoses. The histologic classification of endometrial carcinomas is reviewed first, followed by the description and molecular classification of endometrial epithelial malignancies in the context of histologic classification. Taken together, the molecular and histologic classifications help clinicians to approach troublesome areas encountered in clinical practice and evaluate the utility of molecular alterations in the diagnosis and subclassification of endometrial carcinomas. Putative prognostic markers are reviewed. The use of molecular alterations and surrogate immunohistochemistry as prognostic and predictive markers is also discussed.

OVERVIEW

Knowledge of the molecular features of endometrial carcinoma has rapidly expanded in the last 5 to 10 years. This increase in information has led to several helpful diagnostic markers as well as future potential prognostic/predictive markers, both molecular and immunohistochemical. Recent large-scale genomic studies have led to a shift in the paradigm of endometrial carcinoma classification, with the recognition of distinct molecular groups that only partially overlap with the histologic classification. Historically, endometrial carcinomas had been divided into biological type I and type II pathways, but these are quickly being replaced. Hereditary endometrial cancer, namely Lynch syndrome, has raised the controversial question of appropriate prospective screening selection criteria in endometrial carcinomas. Various screening algorithms using mismatch repair immunohistochemistry (IHC) on tumor samples with or without *MLH1* promoter methylation testing are reviewed here.

HISTOLOGIC SUBTYPES OF ENDOMETRIAL CARCINOMA (WORLD HEALTH ORGANIZATION CLASSIFICATION)

Although the focus of this article is on the molecular features of uterine tumors, the histologic subtypes must first be considered in order to make the context useful for practicing pathologists. A comprehensive review of the morphologic characteristics of endometrial carcinomas is beyond the scope of this article; however, a brief description of the histologic types as defined by the World Health Organization (WHO)[1] is covered here as a basis for the remainder of the article.

ENDOMETRIOID ENDOMETRIAL ADENOCARCINOMA

Endometrioid is the most common histotype of endometrial carcinoma, and resembles normal proliferative-type endometrial glands with smooth luminal borders. Endometrioid carcinomas are divided into 3 grades based on architectural and nuclear features (International Federation of Gynecology and Obstetrics [FIGO] classification). Grade 1 (FIGO) endometrioid adenocarcinoma is composed of entirely, or greater than 95%, gland-forming tumor cells, with little or no ($\leq$5%) solid growth of tumor cells, and notably lacks significant (severe) nuclear atypia (**Fig. 1**A).

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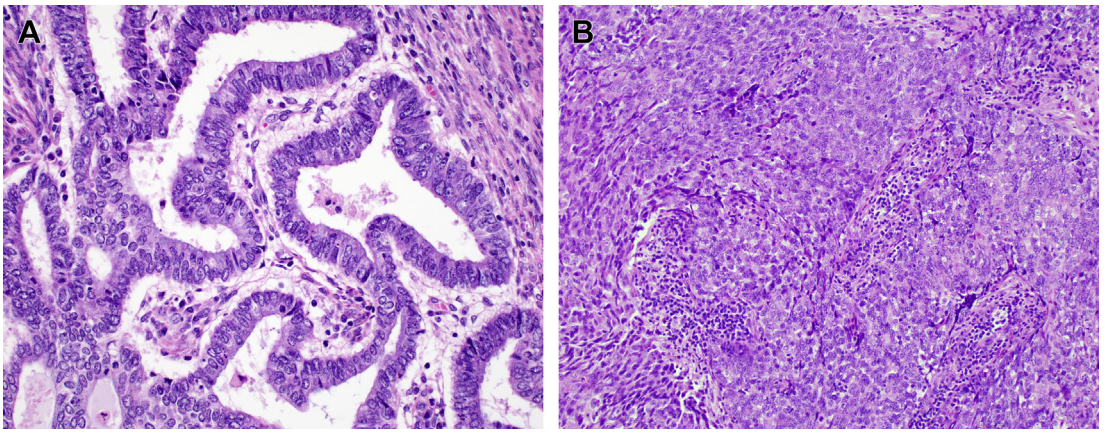

Fig. 1. Endometrial endometrioid adenocarcinoma (H&E, 400×). (*A*) Grade 1 endometrioid adenocarcinoma is composed entirely or predominantly (95% or more) of gland-forming architecture. (*B*) Grade 3 endometrioid adenocarcinoma shows solid growth in at least 50% of the tumor, as shown here.

Importantly, areas of squamous differentiation must be excluded when determining the percentage solid growth. Grade 2 (FIGO) endometrioid adenocarcinoma is composed of a mixture of solid and gland-forming tumor, with the solid component comprising less than 50% but more than 5% of the tumor. Alternatively, an architecturally grade 1 adenocarcinoma may be upgraded to FIGO grade 2 based on the presence of significant severe nuclear atypia. Grade 3 (FIGO) endometrioid adenocarcinoma has poorly formed glands and is composed of greater than 50% solid growth (**Fig. 1**B), or the presence of severe nuclear atypia in the setting of an architecturally grade 2 tumor. However, the precise definition of severe nuclear atypia is not well defined and is subjective, leading to poor interobserver reproducibility.[2–6] Most clinicians accept striking cytologic atypia visible at 10× objective, present in most tumor cells, as the threshold for upgrading a tumor.[7,8]

SEROUS CARCINOMA OF THE ENDOMETRIUM

Serous carcinoma is the second most common type of endometrial cancer, and is histologically similar to the high-grade serous carcinomas of the ovary and fallopian tube. Serous carcinomas have a high nuclear to cytoplasmic (N/C) ratio with conspicuous nuclear atypia and high mitotic index (**Fig. 2**). Architecturally, they are typically papillary and micropapillary, forming characteristic slitlike spaces because of the lack of polarity. Irregular, infiltrative myometrial invasion is common. Serous carcinomas may also show glandular and/or solid growth patterns, causing diagnostic confusion with endometrioid carcinoma (discussed in more detail later).

CLEAR CELL CARCINOMA OF THE ENDOMETRIUM

Clear cell carcinoma is a high-grade malignancy, with similar morphologic features to its ovarian counterpart. Clear cell carcinomas are characterized by a variety of architectural patterns, including papillary, tubulocystic, and solid (**Fig. 3**). Hyalinized stroma is frequently seen and can be a helpful clue to making the diagnosis. The cells are large with typically clear to palely eosinophilic cytoplasm and have a bumpy hobnail appearance with large hyperchromatic and irregular nuclei and prominent nucleoli.

MUCINOUS ADENOCARCINOMA

Mucinous adenocarcinomas are very similar to endometrioid carcinomas; when greater than 50% of the tumor shows conspicuous mucinous differentiation, it is termed mucinous adenocarcinoma. These tumors are typically low grade and low stage, and may have strikingly bland cytomorphology.

UNDIFFERENTIATED/DEDIFFERENTIATED CARCINOMA

Undifferentiated carcinomas lack any amount of gland formation. Architecturally they are composed of solid sheets or vague nests, and the cells appear discohesive.[1] Hematopoietic malignancies, carcinosarcoma, and/or mesenchymal tumors are often considered in the differential diagnosis of undifferentiated carcinoma.[9] Dedifferentiated carcinomas are biphasic tumors consisting of an undifferentiated component as well as a (grade 1–2) well-differentiated endometrioid carcinoma component, and more than half of them show mismatch repair (MMR) deficiency by IHC.[9]