Pathology of various uterine carcinomas

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Introduction

Currently, the histopathological classification of endometrial cancer is based on the 1996 General Rules for Clinical and Pathological Management of Uterine Corpus Cancer and the WHO classification of uterine corpus tumors. Also, the histogenetic clinicopathologic classification of endometrial cancer into Types I and II is widely accepted in terms of female hormone dependence. However, recent studies have provided new findings on the process of uterine carcinogenesis, some of which cannot be fully explained in terms of conventional Types I and II alone.

In this article, we outline recent findings in endometrial cancer from various perspectives for determining the histological type in routine pathological diagnosis.

1. Two types of endometrial cancer

Estrogen is closely involved in endometrial carcinogenesis. Endometrial hyperplasia and atypical endometrial hyperplasia are well known as precancerous lesions. However, not all cancers arise from precancerous lesions, and some develop independently of the hormonal status and endometrial hyperplasia. From these standpoints, the carcinogenesis of the two types of endometrial cancer is discussed separately.

Type I cancer commonly develops in relatively young, perimenopausal women. It is an estrogen-dependent tumor, and all generally accepted risk factors for endometrial cancer are involved in the development of this type of cancer. It takes a long time for this cancer to develop: endometrial hyperplasia and atypical endometrial hyperplasia occur as premalignant or concomitant lesions, and genetic abnormalities, such as K-ras and PTEN mutations and microsatellite instability (MSI), have been noted. Many of these cancers are low-grade, well-differentiated endometrioid adenocarcinomas, show minimal uterine wall and lymphovascular invasion, can be successfully treated with progesterone, and are associated with a relatively favorable prognosis. The incidence of multiple primary cancers, including ovarian, breast, and colorectal cancers, is high in patients with Type I cancer, some of whom have BRCA1 mutations.

Type II cancer develops in older women, and is not closely associated with general risk factors for endometrial cancer. It arises independently of hormones such as estrogen, has a short clinical course, and exhibits high-grade histological features with marked myometrial and lymphovascular invasion. The cancer is not accompanied by endometrial hyperplasia during its course, and the background endometrium is generally atrophic. The incidence of special types of endometrial cancer, such as serous and clear-cell adenocarcinomas, is high. This type of cancer cannot be effectively treated with progesterone, and is associated with a poor prognosis.

2. Dedifferentiated endometrioid adenocarcinoma

Type I endometrial cancer is clinicopathologically different from serous

adenocarcinoma; however, as seen in some serous adenocarcinomas, Type I and II cancers coexist in the same tumor. Thus, it is difficult to explain all endometrial cancers in terms of the two carcinogenic mechanisms alone. Studies focusing on the existence of different histological types that do not clearly correspond to either of the two types have been conducted. Such histological types include dedifferentiated endometrioid adenocarcinoma.

The histological grading of dedifferentiated endometrioid adenocarcinoma is mainly based on the degree of gland formation. Endometrioid adenocarcinoma is classified as poorly differentiated (G3) and undifferentiated if the extent of gland formation represents less than 50 and 0% of the total tumor area, respectively. Of course, the types of specimen and skill in the preparation of histological sections have some influence on the results of histological grading.

Some cancers that are conventionally classified as G3 show a similar morphology in glandular and solid areas. In other words, in these cancers, the nuclear grade is similar, and the difference in cellular differentiation (gland formation) is reflected in the histological grade. In the solid area, nests of adherent cancer cells are formed, which are often arranged in cords.

In contrast, some cancers show marked nuclear atypia in the solid area, in which the intercellular junction is loose, and mitotic figures are prominent in a necrotic background. These cancers are associated with a poorer prognosis than the above-described G3 endometrioid adenocarcinomas, and recent studies have proposed that well-differentiated adenocarcinomas characterized in part by the presence of

undifferentiated carcinomas be classified as dedifferentiated endometrioid adenocarcinomas similar to undifferentiated carcinomas without gland formation. An association between such a cancer and Lynch syndrome (see below) has also been noted. The possibility should be considered that tubular or papillary adenocarcinomas showing nuclear atypia that is disproportionately severe relative to the degree of differentiation are serous adenocarcinomas.

In view of the frequent development of carcinosarcomas in the uterine body, the concept of dedifferentiation is interesting because of its association with stem cells in various organs, which have been extensively discussed recently, and epithelial-mesenchymal transition (EMT).

3. The clinicopathological characteristics of serous adenocarcinoma

Most Type II endometrial cancers are special types of tumor, and the most typical histologic type is serous adenocarcinoma. It resembles ovarian serous adenocarcinoma, is characterized by complex papillary structures and cellular budding, is independent of a hormonal influence, and develops in older women. At the time of diagnosis, this tumor is often already advanced, and has markedly invaded the myometrium and vascular channels, with metastases to the cervix and outside the uterus. Even in the absence of such progression, the cancer recurs, leading to a poor prognosis.

The pattern of development of primary endometrial serous adenocarcinoma includes the transition of a mixture of serous adenocarcinoma and endometrioid adenocarcinoma (rarely clear-cell adenocarcinoma), carcinogenesis in the setting of an endometrial polyp,

and carcinogenesis in the background of endometrial atrophy with intraepithelial carcinoma. Regarding the latter two patterns, the presence of endometrial intraepithelial carcinoma (EIC) has attracted attention. In this condition, the superficial endometrial layer is covered with markedly atypical epithelium, like that of serous adenocarcinoma, and is considered a precancerous lesion for serous adenocarcinoma or the status of endometrial carcinoma in situ. Although the adenocarcinoma is noninvasive, it may develop at multiple sites, such as the cervix, fallopian tubes, ovaries, and peritoneal surface, or disseminate in the peritoneal cavity even in the absence of endometrial stromal invasion. Care should be taken not to overlook these lesions when making a pathological diagnosis. Once EIC has been diagnosed, it is necessary to conduct adequate tests to determine the stage of cancer.

Immunohistochemically, endometrial serous adenocarcinoma is often positive for p53, which, along with the presence of bizarre nuclei, may be useful for the identification of this histological type. It is characterized by p53 positivity, which is presumably not associated with HPV infection in cervical cancer, but is considered to result from cell cycle disturbances (therefore, the background endometrium is not positive for p53). Interestingly, it has also been shown that the staining characteristics of endometrial serous adenocarcinoma differ from those of ovarian serous adenocarcinoma with a similar morphology: the incidence of ovarian serous adenocarcinomas is high, whereas that of their endometrial counterparts is only 1/3; and the former adenocarcinoma is often positive but the latter adenocarcinoma is negative for ER and PgR. Regarding the development of ovarian serous adenocarcinoma, the presence of atypia in the fallopian

tube fimbria epithelium has attracted attention. This, along with the involvement of the tissue of origin and surrounding environment, is a subject for a future study. Endometrial serous adenocarcinoma is also often positive for erbB-2 (HER2), and PTEN expression is maintained.

The differential diagnosis includes tubulovillous endometrioid adenocarcinoma, a histological type. Serous adenocarcinoma contains a finer fibrous stroma, has a delicate papillary or micropapillary structure, and shows marked nuclear atypia. In addition, it is negative for hormone receptors (ER, PgR) and positive for p53, in sharp contrast to endometrioid adenocarcinoma. Serous adenocarcinoma often develops concurrently at the fallopian tubes, ovaries, and peritoneum, in addition to the endometrium. Clonality analysis of individual tissues can differentiate between the multicentric development of the adenocarcinoma and its metastatic seeding from a particular primary site. However, at the level of routine clinical practice, all we can do is to make a comprehensive judgment based on the distribution of cancer lesions and their degree of progression. Benign lesions need to be differentiated from the papillary or surface syncytial metaplasia of endometrial glandular cells, often presenting a cytodiagnostic challenge. The degree of nuclear atypia and status of p53 expression in cytology specimens aid in the diagnosis.

Additional Statement: Tis (FIGO stage 0, carcinoma in situ, preinvasive carcinoma)

This is a classification described in the TNM Classification 7th Edition. Essentially, endometrioid carcinoma refers to a carcinoma with stromal invasion; therefore,

theoretically, the so-called carcinoma in situ does not exist as a classification, but is applicable to EIC, which is localized in the superficial layer of the endometrium.

4. Clear cell adenocarcinoma and recent topics

Clear cell adenocarcinoma is a Type II endometrial adenocarcinoma that develops in elderly, postmenopausal women. Its incidence is reportedly slightly lower than that of serous adenocarcinoma. It is often advanced at the time of detection, and is associated with a poor prognosis, but an adenocarcinoma localized in the uterine corpus is associated with a more favorable prognosis than serous adenocarcinoma. However, since it is known that the tumor may recur more than 5 years after surgery, long-term follow-up is needed.

Histologically, the tumor is an adenocarcinoma composed of clear or hobnail cells, forming solid, tubulocystic, or papillary structures or their mixture. Sometimes, the cytoplasm is eosinophilic and granular. In general, the neoplastic cells show marked nuclear atypia (grade 2 or 3), enabling their differentiation from secretory endometrioid adenocarcinoma. They may show intra- and extracytoplasmic hyaline globules. The stroma is often eosinophilic and hyaline. This is due to the interposition of basement membrane material. Since the cytoplasm is rich in glycogen, it is PAS-positive and diastase-sensitive. No immunostaining markers specific for clear cell adenocarcinoma are known. The adenocarcinoma is usually negative for ER and PgR, and positive for p53, but not so often as serous adenocarcinoma. In addition, about half of clear cell adenocarcinomas are reportedly positive for p16. Staining for basement membrane

markers, such as laminin and type-4 collagen, although not cancer cell-specific, often aid in the diagnosis.

A mixture of clear cell adenocarcinoma and serous adenocarcinoma or endometrioid adenocarcinoma exists. Regarding the histogenesis of endometrial carcinoma, it has been noted that, in addition to EIC as a type II endometrial carcinoma, microepithelial changes that are regarded as precancerous lesions often occur, but this awaits further study. Immunohistochemically, clear cell adenocarcinoma shows a tendency to be hormone receptor-negative and p53-positive, but this tendency is not as clear-cut as that of serous adenocarcinoma. In addition, about half of clear cell adenocarcinomas are reportedly p16-positive. Hepatocyte nuclear factor 1-β is a useful marker to differentiate this adenocarcinoma from other histological types, like in ovarian tumors.

5. Recent topics on mucinous adenocarcinoma

In mucinous adenocarcinoma, most cancer cells contain mucus, but pure mucinous adenocarcinoma is rare. The incidence of this adenocarcinoma varies from rare among endometrioid carcinomas to about 9% of stage I endometrioid carcinomas. It is also known that this adenocarcinoma often develops in patients who have received tamoxifen or progestin.

Grossly, mucus is rarely seen in large amounts, but the presence of intracytoplasmic mucus can be easily recognized by H&E staining. The tumor cells are high columnar, with their nuclei located basally. The cytoplasm is PAS- and mucicarmine-positive. Most mucinous adenocarcinomas are well-differentiated, but some contain

poorly-differentiated components. Similar to endometrioid adenocarcinoma, mucinous adenocarcinoma is generally associated with a favorable prognosis because of the high incidence of well-differentiated tumors.

This histological type should always be differentiated from benign mucinous metaplasia, microglandular hyperplasia, and cervical adenocarcinoma, and their differentiation in biopsy specimens is difficult. CEA and vimentin positivity, the absence of subnuclear vacuoles, mixed presence of foamy histiocytes, and increases in mitotic figures and MIB-1-positive rates are helpful in the differentiation from benign lesions. It is difficult to differentiate mucinous adenocarcinoma from cervical adenocarcinoma, particularly that of the lower uterine segment. Primary cervical mucinous adenocarcinoma is typically diffusely positive for p16 and negative for ER and PgR, whereas primary endometrial mucinous adenocarcinoma is negative or sporadically positive for p16 and positive for both ER and PgR, and vimentin positivity is also informative.

6. Squamous cell carcinoma

Pure primary squamous cell carcinoma of the endometrium is rare. It occurs more commonly after menopause, sometimes in association with cervical obstructive changes or pyometra. It is distinguished from primary cervical squamous cell carcinoma extending into the endometrium and endometrioid adenocarcinoma with marked squamous differentiation. It is histologically similar to cervical squamous cell carcinoma, and can develop into verrucous carcinoma. Although the prognosis of

primary endometrial squamous cell carcinoma is generally poor, that of verrucous carcinoma is favorable.

7. Undifferentiated carcinoma

This is a cancer that lacks a definite direction of differentiation, and does not correspond to any histological type. It is composed of large, giant, spindle, and small cells, and is generally associated with a poor prognosis[107]. Small cell (undifferentiated) carcinoma is a rare cancer that resembles small cell lung cancer, and is immunohistochemically positive for epithelial and neuroendocrine markers. The 5-year survival rate of patients with stage I undifferentiated carcinoma is about 60%, and that of those with advanced carcinoma is extremely poor.

8. Other cancers

Transitional cell carcinoma, hepatoid adenocarcinoma, and lymphoepithelioma-like carcinoma have been reported.

9. Mixed carcinoma

This carcinoma refers to a cancer that contains two or more histological types, and the minor component accounts for at least 10% of the entire tumor area. Pathological reports should describe the respective components. The prognosis of a patients with a tumor with over 25% of the area occupied by type II carcinoma (serous or clear-cell adenocarcinoma) is poor.

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Table. Two types of endometrial cancer based on carcinogenic mechanism.

	Type I	Type II
Age	Relatively young	Elderly
Exposure to estrogen	Present	Absent
Background endometrium	Endometrial hyperplasia Atypical endometrial hyperplasia	Endometrial atrophy
Molecular biological abnormalities	Microsatellite instability K-ras and PTEN abnormalities Intranuclear β-catenin accumulation	P53 abnormality Loss of heterogeneity at different sites
Histological type of cancer	Endometrioid adenocarcinoma (and its subtypes) Mucinous adenocarcinoma	Serous adenocarcinoma Clear-cell adenocarcinoma Undifferentiated carcinoma
Degree of cancer differentiation	Well to moderately differentiated	Poorly differentiated
Stage of cancer	Early	Advanced
Prognosis	Relatively favorable	Poor