

Case Report

Mesonephric adenocarcinoma of the uterine corpus

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Abstract: Mesonephric carcinomas are rare in the female genital tract and usually are found in sites where embryonic remnants of Wolffian ducts are usually detected, such as the uterine cervix, broad ligament, mesosalpinx and exceptionally rarely in the uterine corpus. To date, only four cases of mesonephric carcinomas arising in the uterine corpus have been described in literature. Here we report two cases of mesonephric carcinomas arising in a deep intramural location of the uterine corpus in a 55-year-old woman and a 62-year-old woman in Chinese populations. It is believed to be the first report in China. Both cases presented with a little postmenopausal bleeding. Before hospitalized, uterine curettages were programmed for both cases. The pathology reports were mesonephric adenocarcinoma. A total hysterectomy and bilateral salpingo-oophorectomy were performed. On gross examination, the tumors of both cases were confined to the myometrium. Microscopic examination found both tumors of these two cases were adenocarcinomas mixed with spindle cell component. The most primary histologic patterns of the mesonephric adenocarcinomas were tubular glands that varied in size and were lined by one to several layers of columnar cells. Immunohistochemically, the tumor cells expressed positive with CD10, calretinin, vimentin, cytokeratin (AE1/AE3) and epithelial membrane antigen (EMA); but expressions of ER and PR were completely negative. The peculiar location of mesonephric carcinoma of the uterine corpus may be misinterpreted as other histological type neoplasms. Awareness of this rare phenomenon and immunostaining for markers of mesonephric carcinoma can prevent from making a false diagnosis.

Keywords: Mesonephric carcinoma, uterine corpus, histologic patterns, immunohistochemistry

Introduction

The mesonephric or Wolffian ducts run parallel to the Mullerian ducts in the embryonic period. In male, the mesonephric ducts form the excretory duct systems (epididymis, vas deferens, seminal vesicles, and parts of the prostate and urethra). In female, the mesonephric ducts eventually regress in the absence of testosterone, and in the adult, there are only vestigial mesonephric remnants with no known function [1]. These remnants are usually found in the broad ligament, or in the lateral walls of the cervix and are uncommon in the vagina and uterine corpus [2]. Mesonephric adenocarcinomas can rarely develop in these remnants in the female genital tract. Most of them have been described in the uterine cervix, lateral wall of the vagina, broad ligament, mesosalpinx, and the ovarian hilum and exceptionally rarely in the uterine corpus [3].

Most patients of mesonephric adenocarcinomas present with abnormal bleeding, often with a visible uterine lesion. The tumors generally are widely infiltrative and often extended deeply. Mesonephric adenocarcinomas of the uterine typically show morphologic diversity similar to cervical mesonephric adenocarcinomas. The tumors can be either pure adenocarcinomas or adenocarcinomas that are mixed with a spindle component. The most common appearance has been termed the ductal pattern and consists of tubular glands that vary in size and are lined by one to several layers of columnar cells. Some of the gland lumens contain PAS-positive, diastase-resistant eosinophilic secretions. Other patterns that have been described include a retiform pattern, a tubular pattern, and a sex cord pattern. Mesonephric hyperplasia, often with atypical architectural and nuclear features, is often found at the periphery of the tumor or admixed with it [1, 4-7].

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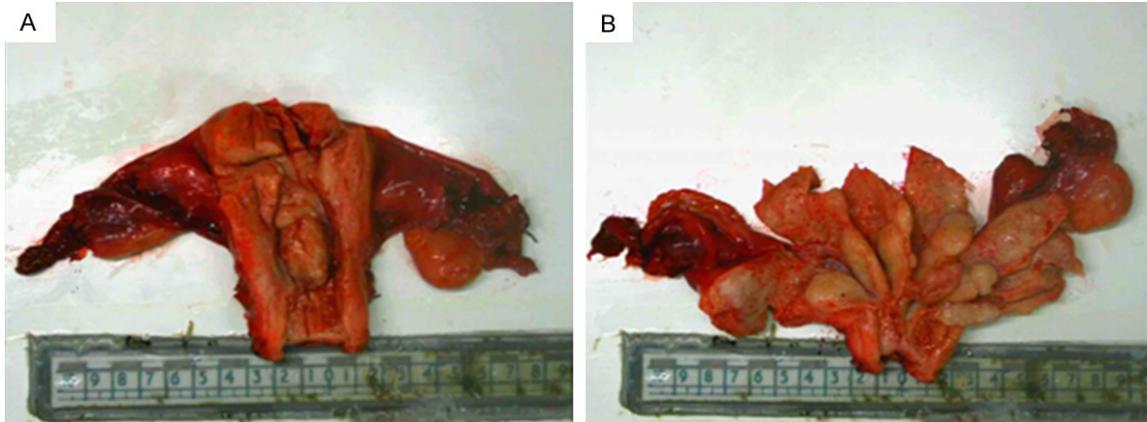


Figure 1. Gross image of the first case: a mass was located in the lower 1/3 portion lateral wall of the uterus to endocervix (A) with the sectioned surface of the mass (B).

The immunophenotype of the tumor cells was extensively studied in a recent report. Epithelial markers, including pancytokeratin, CK7, CAM5.2, and EMA, were universally present in the carcinoma cells. Vimentin was found in 70%, calretinin in 88%, and androgen receptor in 33%, whereas monoclonal CEA, estrogen receptor protein, progesterone receptor protein, and CK20 were absent. This profile is similar to what was found in mesonephric remnants [8]. A few other reported cases have shown focal CEA and CA125 positivity [7]. Recently, it has been suggested that CD10 may be diagnostically useful [9].

Here we present two unusual cases of mesonephric carcinomas arising in a deep intramural location of the uterine corpus in a 55-year-old woman and a 62-year-old woman.

Case report

Clinical information

The first case is a 55-year-old woman who presented with a little postmenopausal bleeding for 20 days without reason. She had past medical history of diabetes for 6 years, but had no hypertension and other diseases. She had no bad habit. She menarched in 14 years old and had been married and gave birth to a healthy baby in 31 years old. She had no positive family history except that her father was suffered from stomach cancer. 20 days before hospitalized, she went to see doctor in another hospital because of postmenopausal bleeding and uterine curettage was programmed. The pathology report of the hospital showed: poorly differenti-

ated endometrioid adenocarcinoma. Consultation in our hospital was considered mesonephric carcinoma. Her blood pressure was 150/100 mmHg. At pelvic examination, the uterus was a little big and mobile well, bilateral accessories had no mass. Sonography of the abdomen showed myoma of uterus and cyst of left ovary. She underwent hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy.

The second case is a 62-year-old woman who presented with a little postmenopausal bleeding for 1 year without reason and bleeding increased for two days. She had past medical history of hypertension for 20 years, but had no diabetes and other diseases. She had no bad habit. She had been married and had given birth to a healthy baby. Coincidentally, she had no positive family history except that her father was suffered from stomach cancer similar to the first case. Before hospitalized, uterine curettage was programmed for her. The pathology report was mesonephric adenocarcinoma. At pelvic examination, uterus was a little big and bilateral accessories had no mass. Sonography of the abdomen showed a lump of 58 × 38 × 37 mm in uterus. She also underwent hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy.

Gross findings

The uterus of the first case was measured about 10 × 5.5 × 4 cm. A 3.5 × 2.5 × 2 cm mass was located in the lower 1/3 portion lateral wall of the uterus to endocervix (**Figure 1**). The tumor was gray, showed a well-defined,

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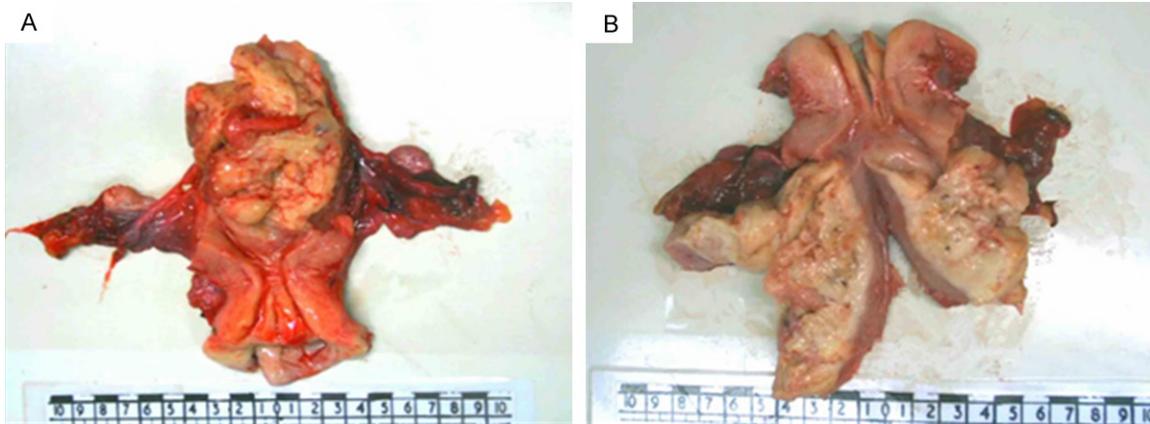


Figure 2. Gross image of the second case: a mass was located in the higher 2/3 portion of the uterus (A), with sectioned surface of the mass (B).

pushing margin and infiltration of the myometrium. The margin had a distance of 0.7 cm from serosa. No abnormalities were detected in the overlying endometrium, uterine cervix. Endometrium was smooth and thick as 0.1 cm. Cervix had no abnormality. Bilateral fallopian tubes both were 8.5 cm long and diameters were 0.6 cm. Fimbriae of uterine tubes were open. Bilateral ovaries could not be reliably distinguished from the normal appearance. Right ovary was measured 3.5 × 1.5 × 0.6 cm; left ovary was measured 3.5 × 2.5 × 1.8 cm. The sectioned surface of right ovary was solid, firm, and white to weak pink. The sectioned surface of left ovary was a cyst diameter of 2 cm.

The uterus of the second case was measured about 13 × 7 × 4.5 cm. An 8 × 7 × 3 cm mass was located in the higher 2/3 portion of the uterus (**Figure 2**). The tumor was swelled and like cauliflower and gray. It infiltrated the depth of the myometrium and the margin had a distance of 0.5 cm from serosa. No abnormalities were detected in the uterine cervix. Bilateral fallopian tubes and ovaries could not be reliably distinguished from the normal appearance.

Microscopic findings

Both tumors of these two cases were adenocarcinomas mixed with spindle cell component. The histologic patterns of the mesonephric adenocarcinomas were complicated. The appearance had been the ductal pattern and consisted of tubular glands that varied in size and was lined by one to several layers of columnar cells. Some of the gland lumens contained

eosinophilic secretions, which resembled the malignant counterpart of mesonephric remnants. There were also retiform pattern and sex cord pattern. Sheets of malignant spindle cell produced the solid pattern, which resided immediately adjacent to discrete glands. Despite a widely infiltrative pattern, large portions of the tumor had very little stromal response (**Figure 3**).

Immunohistochemical results

Immunoperoxidase studies were performed as follows: appropriate paraffin blocks representative of the pathological changes were selected for IHC. IHC was performed using the standard streptavidin-biotin-peroxidase procedure. Primary monoclonal antibodies against CD10, calretinin, vimentin, ER, PR, Ki67, cytokeratin (AE1/AE3) and epithelial membrane antigen (EMA) were applied to 4-mm thick 10% formalin-fixed, paraffin-embedded tissue sections. The sections underwent a process of deparaffinization, rehydration, and washing in xylene, graded alcohols, and distilled water, respectively. Blockage of endogenous peroxidase activity was performed after incubation with 3% H₂O₂ and a subsequent microwave antigen retrieval procedure was performed.

The tumor cells expressed positive with CD10, calretinin, vimentin, cytokeratin (AE1/AE3) and epithelial membrane antigen (EMA); but expressions of ER and PR were completely negative. Positive cells rate of Ki67 were less than 30% (**Figure 4**). These markers confirmed the diagnosis.

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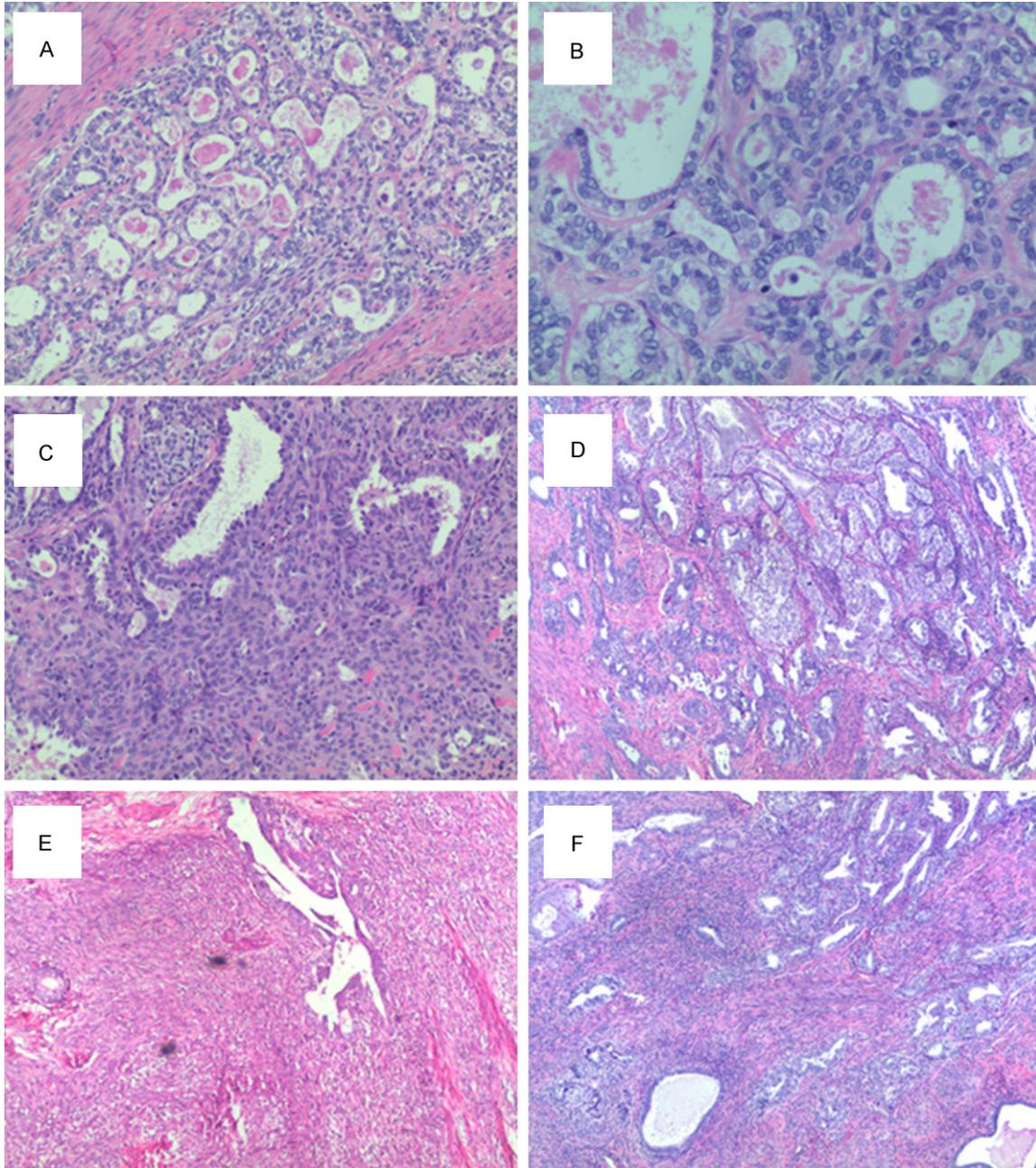


Figure 3. The most helpful histological pattern for diagnosis consists of large sheets of closely packed small round tubules, often with dense intraluminal eosinophilic secretions (A). With magnification of A, nuclear divisions can be seen (B). Sheets of spindle cells component are adjacent to the ductal pattern (C). Sex cord pattern are present (D). A sarcomatoid component consists of nonspecific malignant spindled cells (E). Mesonephric adenocarcinoma extensively infiltrates wall of uterus without any infiltration of cervical mucosa (F). (A \times 100, B \times 200, C \times 100, D \times 40, E \times 40, F \times 40).

Discussion

Mesonephric duct remnants are detected in up to 20% of cervixes removed during routine hysterectomy. Malignant mesonephric tumors are rare neoplasms of the female genital tract

derived from remnants of the mesonephric ducts. Mesonephric adenocarcinomas usually arise in the cervix and very rarely in the uterine corpus; as far as our knowledge, there were only 4 prior reports of primary mesonephric adenocarcinoma of the uterine corpus [1, 5-7].

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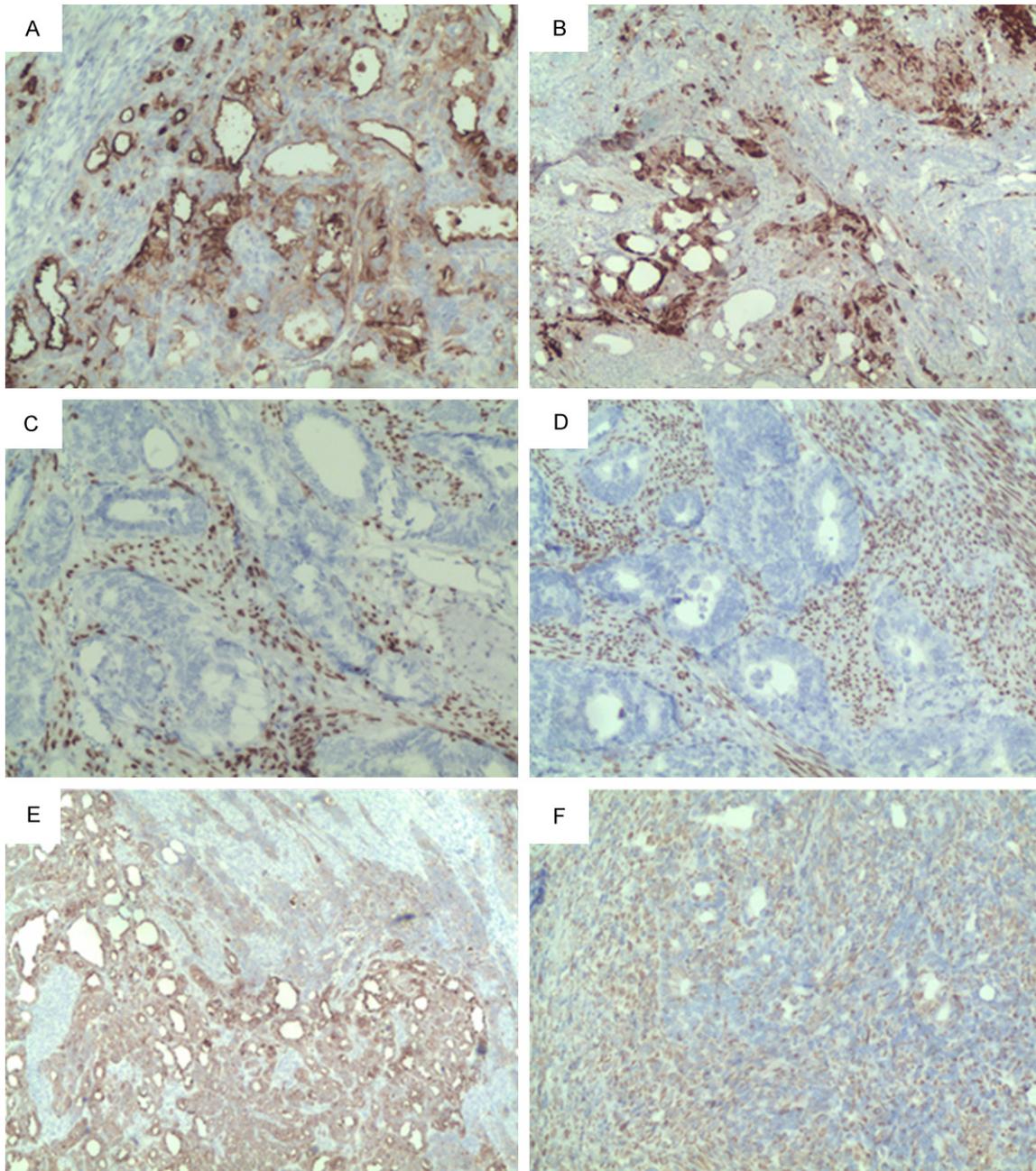


Figure 4. Immunohistochemical expression profiling of mesonephric adenocarcinomas. The tumor cells are positive for CD10 (A) Calretinin (B) but negative for ER (C) and PR (D) and also positive for cytokeratin (AE1/AE3) (E). A small part of tumor cells express vimentin (F). (A \times 100, B \times 40, C \times 100, D \times 100, E \times 40, F \times 100).

The present two cases are exceptional because of their locations. Although the first case has involved the lower uterine segment, it is considered that malignant mesonephric carcinoma arises in the uterine corpus. The carcinoma cells do not invade the top apex of cervix, but only invade the endometrium and myometritis.

Because of its rarity and morphologic diversity, the diagnosis of mesonephric adenocarcinoma

may be problematic, especially when presenting in limited (biopsy or curettage) material. Mesonephric adenocarcinomas are usually absent of specific morphologic, ultrastructural, or immunohistochemical features that would differentiate them from müllerian neoplasms, particularly if the adjacent mesonephric hyperplasia is not found in the vicinity. These tumors characteristically exhibit an admixture of morphologic patterns and may be confused with a

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variety of mullerian adenocarcinomas, including those of serous, endometrioid, or clear cell type [10-12]. Some tumors have a spindle cell component, potentially resulting in confusion with a carcinosarcoma (malignant mixed mullerian tumor) [13]. The presence of small glands or tubules with eosinophilic luminal colloid-like material, a common feature of mesonephric adenocarcinomas, may result in consideration of a thyroid-type neoplasm, especially in those cases with extrauterine extension and involvement of the ovary. Given this potential mimicry of other neoplasms, it is important to be aware of the immunophenotype of mesonephric adenocarcinomas, especially with regard to markers that are commonly positive in those adenocarcinomas that are in the differential diagnosis. A panel of immunohistochemical stainings, including ER, PR, CEA, vimentin, CD10, and calretinin, may be useful in the differential diagnosis [14].

Distinguishing mesonephric carcinoma from florid mesonephric hyperplasia can be difficult because the majority of carcinomas develop in the setting of diffuse mesonephric hyperplasia. In contrast to mesonephric hyperplasia, the carcinoma does not have a lobular architecture and the nuclei appear cytologically malignant [15]. The tubular pattern of mesonephric adenocarcinoma may closely resemble the diffuse form of florid mesonephric hyperplasia owing to the often inconspicuous stromal response in the former and the pseudoinfiltrative pattern of the latter. Helpful features supporting a diagnosis of adenocarcinoma include the presence of other morphologic patterns of mesonephric adenocarcinoma (solid or ductal), lymph-vascular space invasion, nuclear atypia, mitotic activity exceeding one mitosis per 10 HPFs, and necrotic luminal debris. Moreover, mesonephric hyperplasia is nearly always an incidental microscopic finding, whereas patients with mesonephric adenocarcinoma are more likely to be symptomatic and have a grossly apparent lesion. Ki-67 proliferation index and p53 immunostain may be useful in this differential diagnosis. The Ki-67 proliferation index of adenocarcinomas averages 15% [10].

The presence of other morphologic patterns of mesonephric adenocarcinoma, adjacent mesonephric remnants, and an absence of squamous differentiation are features favoring a diagnosis of a mesonephric adenocarcinoma

than endometrioid adenocarcinoma. Some findings suggest that CD10 staining may be useful in defining tumors with mesonephric differentiation. In difficult cases, a panel of immunohistochemical stains, including ER, PR, vimentin, and possibly calretinin, may be useful in this differential diagnosis. Most mesonephric adenocarcinomas are immunoreactive with vimentin and calretinin, and do not express ER, PR. In contrast, most well-differentiated endometrioid endometrial adenocarcinomas express ER and PR [16].

Mesonephric adenocarcinomas may also be confused with clear-cell carcinomas because clear cell carcinoma may histologically overlap with mesonephric adenocarcinoma. Clear cell carcinomas of the uterine show varying degrees of cystic, papillary and solid patterns as well as clear cells and hobnail cells which are not usually seen in mesonephric neoplasms. Clear cell carcinomas may also exhibit prominent tubules filled with eosinophilic hyaline material [17]. The presence of mesonephric hyperplasia is not a feature of clear cell carcinoma.

The epithelial component of mesonephric carcinoma sometimes exhibits focal cellular budding similar to that seen in serous carcinomas. It should be distinguished from serous carcinoma. Most serous carcinomas are immunoreactive with P53 and WT-1 [18]. In contrast, mesonephric carcinomas do not express P53 and WT-1.

Both mesonephric adenocarcinomas and MMMTs in the current series had similar clinical features, although the latter tumors developed in slightly older patients. The uterine MMMT that presented as an endometrial polyp or carcinoma lacked mesonephric hyperplasia [19].

Uterine tumor resembling ovarian sex-cord tumor has been applied to a heterogeneous group of uterine mesenchymal neoplasms characterized by pure or predominant histologic patterns that closely resemble those of ovarian sex cord-stromal tumors [20]. Although these tumors may be histologically similar to mesonephric carcinomas, they rarely occur in the uterus, usually have a well-circumscribed pushing border, lack papillary architecture, and mesonephric rests are not seen in their proximity. In addition, they may exhibit smoothmuscle or endometrial stromal differentiation and are

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frequently immunoreactive for desmin and actin.

The differential diagnosis of uterine mesonephric adenocarcinomas also includes endometrial stromal nodules and low-grade stromal sarcomas. Although the latter tumors may present a tubular or nesting pattern, they are characterized by uniform collections of cells resembling the stromal cells of the proliferative endometrium, fine vascularization, and invasion of vascular spaces, all features that are absent in mesonephric carcinomas.

In our two cases, the histological morphological characters accord with mesonephric adenocarcinomas. In addition, the tumor cells expressed positive with CD10, calretinin, vimentin, cytokeratin (AE1/AE3) and epithelial membrane antigen (EMA); but expressions of ER and PR were completely negative. Positive rate of Ki67 was less than 30%. These markers confirmed the diagnosis.

Because of their rarity, the biologic behavior of the malignant mesonephric tumors is not well known. Until now, the first case has been survived without evidence of recurrence at 7 months after surgery. The second case is less than 1 month since operation. Of the 4 cases reported individually in the English literature so far, follow-up was from 9 months to 28 months without evidence of recurrence [1, 5-7]. In the cervix, stage I mesonephric carcinoma seems to have a more indolent behavior than other types of adenocarcinoma. However, high-stage tumors have had an aggressive course [10]. A few have been accompanied by extrauterine spread. Several tumors with a sarcomatoid component have metastasized, but it is unclear whether this pattern has particular prognostic significance. In the series of 11 cervical tumors (10 ACs and 1 MMT) published by Silver et al., two carcinomas were advanced stage, and 3 of 10 patients died of disease [9]. According to Bague et al., a total abdominal hysterectomy with salpingo-oophorectomy seems to be the treatment of choice.

In conclusion, mesonephric adenocarcinoma is characterized by morphologic diversity and an unusual appearance, and is almost always associated with mesonephric hyperplasia. In a problematic case of uterine carcinoma, this type of carcinoma should be included in the differential diagnosis.

Disclosure of conflict of interest

None to declare.

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