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Pathology

Mesonephric Adenocarcinoma of the Uterine Cervix: A Rare Entity Not to be overlooked

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Abstract | **Original Research Article**

Mesonephric adenocarcinoma is a rare malignant tumor which derives from mesonephric embryonic remnants of wolffian ducts of the female genital tract. We describe a case of 59-year-old postmenopausal lady presenting with an abnormal vaginal bleeding misdiagnosed initially as undifferentiated papillary carcinoma. Imaging revealed a thickening in cervix of the uterus associated with pulmonary and peritoneal nodules. Histological features were consistent with mesonephric adenocarcinoma. Moreover, the tumor cells showed positive staining for CD10, GATA3 and E-cadherin, while progesterone receptor (PR) and estrogen receptor (ER) expressions were completely negative. For the locally advanced disease with multiple metastases, the patient underwent systemic chemotherapy as part of the therapeutic approach. Awareness of this rare tumor and its large admixture of morphologic patterns supported by immunoreactivity for mesonephric carcinoma markers, is crucial to prevent diagnostic errors, facilitate early therapeutic intervention and potentially improve prognosis.

Keywords: Adenocarcinoma, Mesonephric Remnants, Morphologic Patterns, CD10, Case Report.

INTRODUCTION

Mesonephric adenocarcinoma is a rare malignant subtype of epithelial tumors that originates from mesonephric remnants of the female genital tract: Wolffian ducts [1]. They are most commonly found in the stroma of uterus cervix, as well as the ovaries, fallopian tubes, broad ligament and less frequently present in the vaginal wall or within the myometrium [2].

Previous studies have shown that mesonephric adenocarcinoma can derive from mesonephric remnants of wolffian ducts regardless of their location. Determining the real incidence of this neoplasm is challenging, primarily due to its rarity and historical misclassification. Yolk sac tumors and clear cell carcinomas of the uterus corpus were previously sometimes labeled as mesonephric carcinomas, and mesonephric carcinomas themselves have often been mistaken for Müllerian tumors or mesonephric hyperplasia, leading to potential misdiagnosis. For these reasons, data on their clinical behavior, optimal management and prognosis remain limited [3].

Herein, we present a case of mesonephric adenocarcinoma of the uterine cervix with pulmonary metastases which has been misdiagnosed for a long time, in order to discuss the diagnostic challenges through our case and a review of the literature.

MATERIALS AND METHODS

A 59-year-old woman presented in 2020 in another hospital with postmenopausal vaginal bleeding. The medical history was negative. She menarched in 13 years old and had been married and gave birth to a healthy 03 kids. She had never smoked or drank and no familial history of malignancy was noted.

A CT scan was performed and showed a thickening in the uterus cervix associated with pulmonary nodules and peritoneal involvement. The pathology report of a cervical biopsy misinterpreted as invasive undifferentiated papillary carcinoma. A second biopsy of the peritoneal mass revealed a poorly differentiated carcinoma with a positive CK7, suggesting a gynecological origin. The patient was then lost to follow-up.

Twenty months later, the patient returned for consultation. MRI showed a mass in the uterus cervix infiltrating the parametrium and bilateral adnexa, along

with peritoneal carcinomatosis nodules and pelvic lymphadenopathy (Fig. 1). A biopsy of the cervical mass was performed.

RESULTS

Histopathological study of step serial sections of the biopsy sample showed a diffusely infiltrating tumor with ductal, tubular and retiform patterns. They are composed of tubular glands that varied in size and contained in some areas, eosinophilic intraluminal secretions which resembled the malignant counterpart of mesonephric remnants. These structures were lined by cuboidal cells exhibiting moderate nuclear atypia. (Fig. 2)

Immunohistochemical staining was positive for CD10 and GATA3, and focally positive for E-cadherin. Tumor cells were completely negatives for TTF1, WT1, progesterone and estrogen receptors (PR/ER) (Fig. 3). These immunomarkers confirmed the diagnosis of mesonephric carcinoma. The patient then underwent systemic chemotherapy as part of the therapeutic approach for locally advanced disease with multiple metastases.

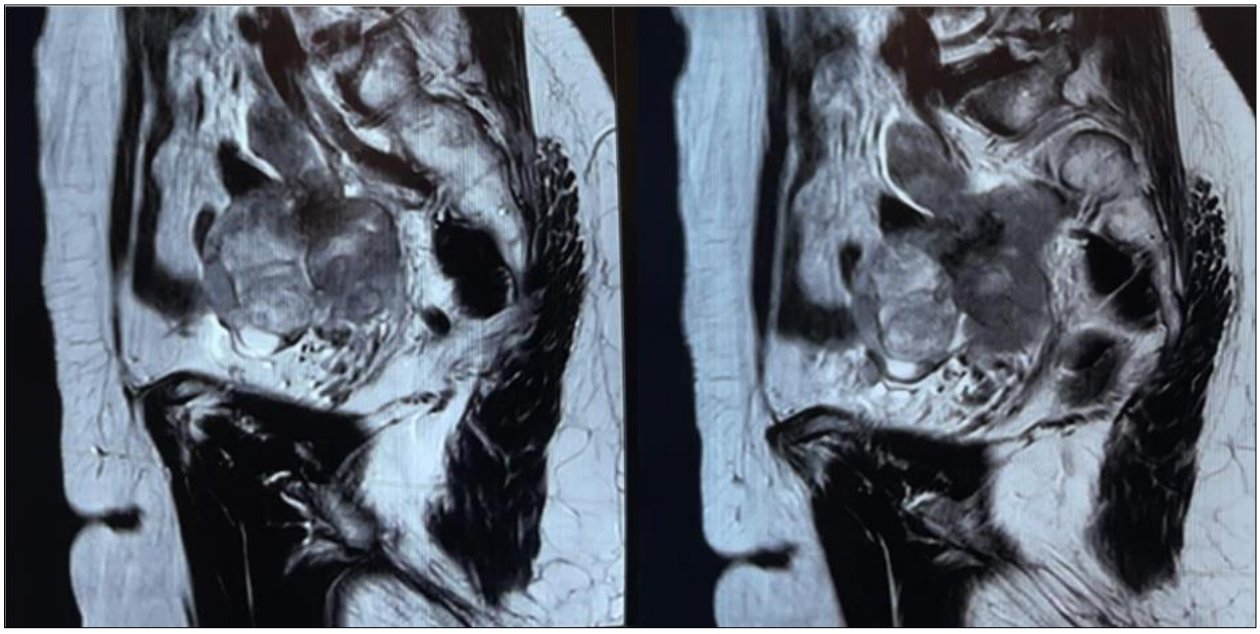

Figure 1: Axial T2 MRI images of the patient before treatment, showing the cervical tumor infiltrating the parametrium and bilateral adnexa

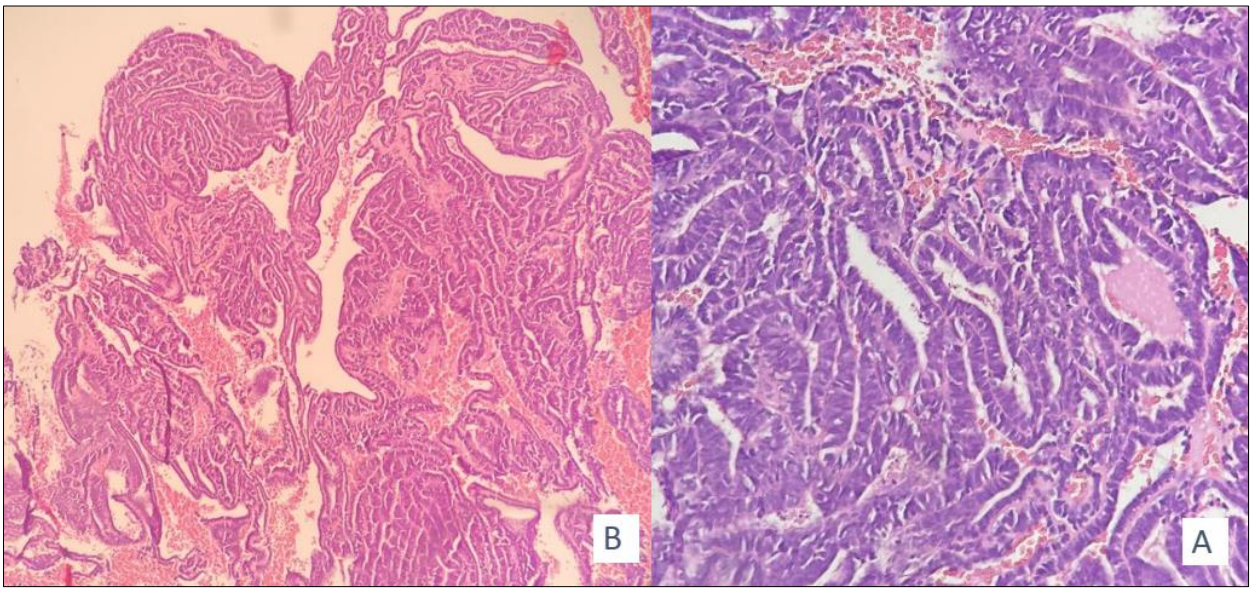

Figure 2: Histological aspects of mesonephric adenocarcinoma in Hematoxylin and Eosin staining (H&E) showing a combination of architectural patterns. (A) H&E x 10: tubular and ductal patterns. (B) H&E x 40: The tubules are lined by a single layer of cuboidal cells and possess intraluminal eosinophilic material

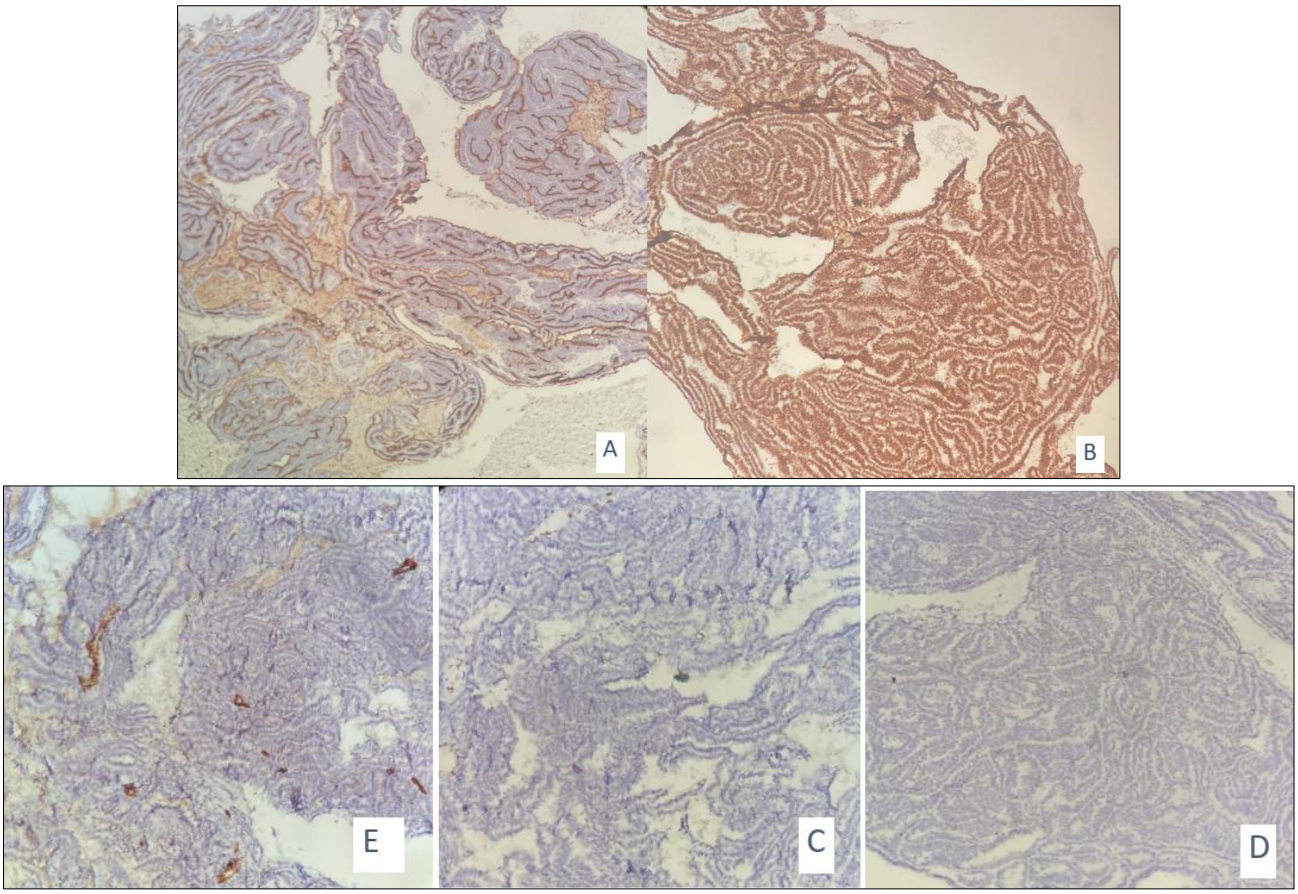

Figure 3: Immunohistochemical stains. A) Uniform CD10 immunoreactivity along the luminal surface. (B) Diffuse and strong nuclear GATA3 expression. (C) Lack of WT1 expression. (D) Lack of PR expression. (E) Lack of ER expression

DISCUSSION

During early embryonic development, between the third and the fourth week of gestation, two mesonephric ducts form and connect the mesonephros to the cloaca. In male embryos, exposure to testosterone promotes the differentiation of these ducts into the seminal vesicles, epididymis, ejaculatory ducts and vas deferens. In female embryos, the mesonephric ducts typically regress. Despite the regression, remnants of these Wolffian ducts, known as mesonephric remnants, can persist along the female genital tract [4].

During routine hysterectomy, mesonephric duct remnants are found in up to 20% of cervices removed [5]. Their reported prevalence varies from 1 to 22% in adults and up to 40% in children [6]. They may expand into cysts and rarely, benign or malignant lesions [7].

Mesonephric adenocarcinoma is a rare non-mucinous and non HPV (human papillomavirus) related tumor [8]. It accounts for less than 1% of all tumors at this location [4]. They have been detected in uterine corpus [5] and cervix [3], broad ligament [9], urinary bladder [10], urethra [11] and urethral diverticulum [12]. Diagnosis is usually made on biopsy sample, endometrial curettage or hysterectomy specimen. Clinically, the most common symptom is abnormal vaginal bleeding or a cervical mass on pelvic examination [4].

The histopathological appearance is characterized by a mixture of morphologic patterns that may be confused with a large variety of other malignancies, leading to frequent misinterpretation. The more common pattern is the tubular, which consists of small, tightly packed and round to oval glands. Some of them may contain dense eosinophilic secretions within their lumens such as those observed in mesonephric remnants. This pattern should be differentiated from diffuse mesonephric hyperplasia [1-4].

Mesonephric hyperplasia may be present in the background of the tumor, it characterized by an intraluminal densely eosinophilic secretion. In contrast to mesonephric hyperplasia, mesonephric adenocarcinoma does not have a lobular architecture and the nuclei appear atypical with increased mitotic activity (>10/high power field). Additionally, the tumor shows areas of luminal necrosis debris and lymphovascular invasion. The p53 and Ki-67 immunomarkers may also prove useful in differentiating, the proliferation index is less than 1% in mesonephric hyperplasia compared to 15-20% in mesonephric carcinoma [13].

Furthermore, CA125 is negative in benign mesonephric structures but usually positive in mesonephric adenocarcinoma [13]. PAX2 is also

positive in mesonephric adenocarcinoma, but a diffuse and strong expression is more likely to be associated with benign mesonephric lesions [4].

The second most frequent pattern is the ductal, the tumor displays large glandular spaces, sometimes featuring intraluminal infoldings or papillary structures. These structures are lined by one or more layers of cells which needs to be distinguished from endometrioid adenocarcinomas and its minimal deviation variant [1-4].

Helpful features supporting a diagnosis of mesonephric adenocarcinoma than endometrioid adenocarcinoma include the presence of other morphologic patterns, adjacent mesonephric remnants, and an absence of squamous differentiation. In challenging cases, an immunohistochemical panel including PR, ER, vimentin, and potentially calretinin can be helpful in distinguishing between neoplasms. Mesonephric adenocarcinomas typically show positive staining for CD10, CK7, Pax8, cytokeratin (AE1/AE3), Epithelial Membrane Antigen (EMA), calretinin and vimentin, and negativity for PR and ER. Conversely, well-differentiated endometrioid adenocarcinomas usually express both PR and ER [5].

The retiform pattern is defined by elongated, slit-like branching tubules, which may contain intraluminal papillae with hyalinized fibrous cores. The sex cord like pattern is composed of cells arranged in cords and trabeculae, typically with scant cytoplasm. However, focal retiform and sex cord patterns are more common in adnexal tumors deriving from remnants of upper Wolffian duct [4].

Some tumors have a spindled cell component, a biphasic variant of mesonephric adenocarcinoma with sarcomatoid characteristics (malignant mixed mesonephric tumor, MMMT) [12], that should be distinguished from primary carcinosarcoma of cervix [13]. The presence of spindled or solid morphology is a pathological feature associated with a poorer prognosis [4].

The epithelial component of mesonephric adenocarcinoma sometimes exhibits focal cellular budding similar to that seen in serous carcinomas. Most serous carcinomas are immunoreactive with WT1 and P53. In contrast, mesonephric adenocarcinomas do not express WT1 and P53 [5].

Due to its rarity and histological variability, diagnosing mesonephric adenocarcinoma can be challenging, particularly when only limited tissue samples (such as biopsy or curettage specimens) are available. These tumors often lack distinct morphological and immunohistochemical features that clearly differentiate them from other tumors especially in the absence of adjacent mesonephric hyperplasia.

CONCLUSION

Mesonephric adenocarcinoma of the uterine cervix is a rare type of cervical neoplasm with only few cases documented in literature. Because of its morphologic diversity and unusual appearance, the diagnosis is challenging and usually confused with other malignancies, as a result, its true incidence is likely underestimated due to this frequent misclassification.

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