

Malignant mesonephric tumor of the cervix with an initial manifestation as pulmonary metastasis: case report and review of the literature

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Summary

Malignant mesonephric tumor (MMT) is a relatively uncommon malignancy of the female genital tract. The diagnosis of metastatic MMT is difficult because cytological, pathological, immunohistochemical characteristics of MMT are under-recognized. The authors present a 55-year-old female with metastatic pulmonary nodules. The bronchial washing cytology revealed three dimensional clusters of bland epithelial cells with slight nuclear grooves. A corresponding lung histology had ductal or tubular clusters of epithelial cells with intraglandular eosinophilic materials. These epithelial cells were positive for immunohistochemical stain of CD10, suggesting metastasis from MMT. The cervical smear showed clusters of bland, gland-forming epithelial cells with intraglandular eosinophilic materials. On histologic examination, mesonephric adenocarcinoma with papillary and solid proliferation was identified in the uterine cervix. A review of the literature for 72 cases of MMT is also included. Clinical and cytopathological features of MMT are herein made available.

Key words: Malignant mesonephric tumor; Mesonephric adenocarcinoma; Uterus; Cytology; Pathology; Immunohistochemistry.

Introduction

Malignant mesonephric tumor (MMT) is a rare malignancy of the female genital tract. MMTs are derived from the mesonephric duct remnant, an excretory duct system of males that parallels to the Müllerian duct. The majority of mesonephric ducts regress, but some reveal as small remnants, cysts, and hyperplasia, and sometimes transform into malignancy [1]. MMTs are frequently found in the lateral wall of the cervix, rarely in the vagina, broad ligament and meso-ovaries [2]. The most common clinical manifestation of MMTs is vaginal bleeding. Initial metastatic presentation of MMT is rare. Diagnosis of the metastatic MMT is sometimes difficult due to the under-recognition of the cytological, pathological, and immunohistochemical characteristics of MMT.

Herein, the authors present a case of MMT of the uterine cervix in a 55-year-old woman with multiple pulmonary metastases. With a literature review of 72 cases of MMT, an improvement in the understanding of this rare entity will be achieved.

Case Report

A 55-year-old, gravid 2 para 2, menopausal woman was admitted with an incidental lung mass first identified during a routine health check-up. Her past medical history was lacking of pulmonary or gynecological symptoms. Chest computed tomog-

raphy (CT) revealed multiple scattered nodules in both lung fields (Figure 1A). Bronchial washing cytology and pulmonary wedge biopsy were performed.

The liquid based cytology (Thin-Prep) from the bronchus showed multiple clusters of epithelial nests in a background of numerous macrophages (Figure 1B). Cells were bland, round to oval, with regular nuclear membranes and relatively fine chromatin, exhibiting a high nuclear-cytoplasmic (N/C) ratio (Figure 1C). Occasionally, these cells had a slight nuclear groove with a small amount of dense cytoplasm. These cytological features suggested malignancy, especially adenocarcinoma. A corresponding wedge resection of lung tissue showed infiltrative tumor glands near the pulmonary vein (Figure 1D). The tumor was arranged in well-formed glands lined with cuboidal, hyperchromatic, and bland epithelial cells with frequent intraglandular dense eosinophilic materials.

Immunohistochemical analysis for cytokeratin (CK), CK7, CK8/18, and epithelial membrane antigen (EMA) were diffusely positive. CD10 was focally positive in the luminal area. Thyroid transcription factor (TTF)-1, napsin-A, estrogen receptor (ER), progesterone receptor (PR), calretinin, CK5/6, and p63 were all negative. The pathologic findings combined with CD10 expression implied a gynecologic tumor, especially mesonephric adenocarcinoma.

Positron emission tomography/CT (PET/CT) and abdominopelvic CT revealed an enhanced mass (2.9 x 3.1 x 3.8 cm in size) in the uterine cervix and the left lower uterine body with abnormal fludeoxyglucose uptake (maximum standardized uptake value = 11.1) without evidence of lymphadenopathy (Figure 2A, 2B). Conventional Papanicolau (Pap) stained cervico-vaginal smears contained abundant large and small clustered epithelial nests harboring tubule and acinar structures (Figure 3A, 3B).

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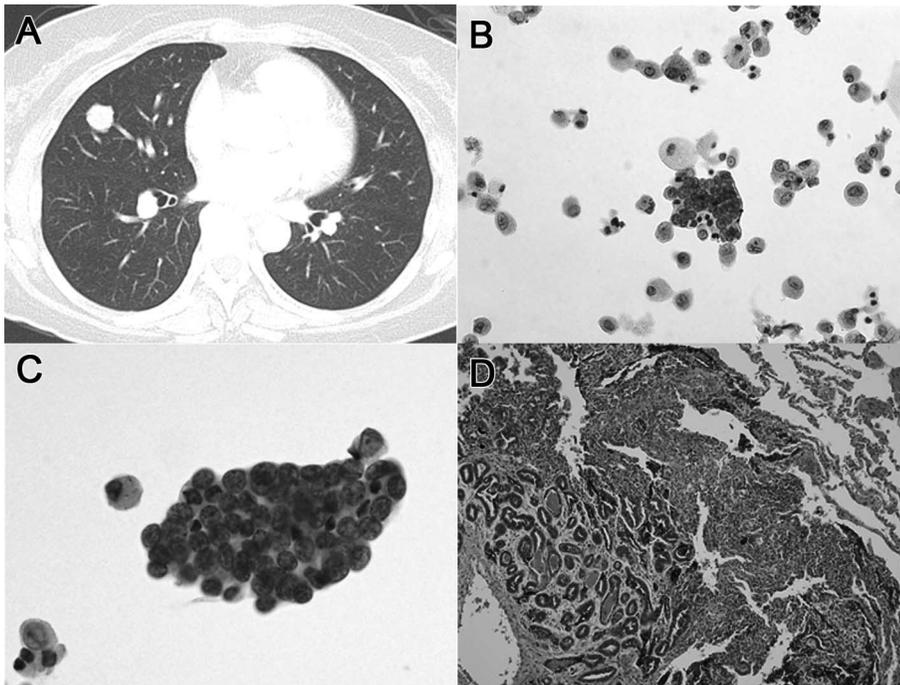


Figure 1. — A) Chest CT reveals multiple scattered nodules in both lung fields. The largest mass is in the right upper lobe. B) Liquid based cytology of bronchial washing (Papanicolaou stain) has three-dimensional clustered epithelial cells in the background of numerous macrophages. C) Nuclei are round to oval with an occasional nuclear groove, with fine chromatin and inconspicuous nucleoli, and a small amount of dense cytoplasm. D) A metastatic mesonephric adenocarcinoma located near the pulmonary vein in the lung parenchyma.



Figure 2. — Radiologic findings. A) PET/CT shows abnormal uptake in the right lung and uterus. B) The uterus reveals a heterogeneously enhanced ill-margined mass occupying the left wall of the cervix and the lower uterine segment.

Eosinophilic colloid-like materials were surrounded by epithelial cells (Figure 3C). Cells had bland, small to medium sized, round to oval nuclei with dense to pale cytoplasm (Figure 3D). Fine chromatin with occasional nuclear grooves were similar to those observed from bronchial washing.

A cervical biopsy and endometrial curettage were evaluated for the uterine mass. The cervix was occupied by mesonephric hyperplasia showing small proliferative and haphazardly scattered glands that grew inwardly as a papillary proliferation with intraglandular eosinophilic materials (Figure 4A). Endometrial curettage revealed multiple fragments showing papillary and

solid patterns (Figure 4B). Papillary clusters were lined with cuboidal to columnar epithelium with a high N/C ratio. Solid, spindle cell components were composed of polygonal and spindle-shaped cells lacking heterologous component (Figure 4C). Some glands were dilated and filled with eosinophilic materials (Figure 4D).

Both glandular and spindle cell areas were diffusely positive for EMA and vimentin, focally positive for CK, p16, and p53, and negative for ER, PR, calretinin, and carcinoembryonic antigen (CEA) (Figures 5A-5C). The glandular component was diffusely positive for CK8/18 and focally positive for CD10 and CK7 (Fig-

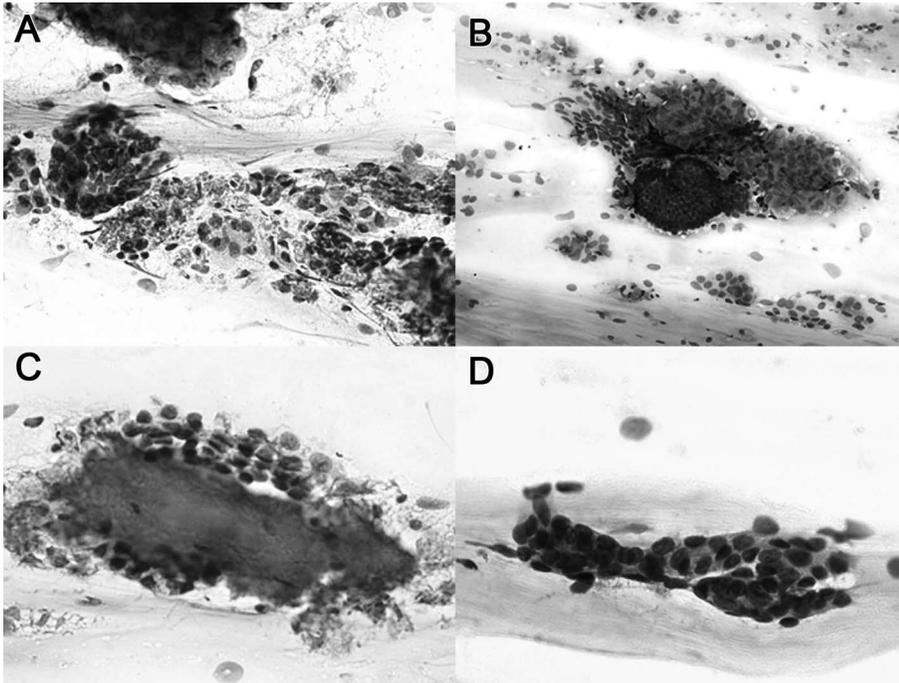


Figure 3. — Conventional smear of the uterine cervix (Papanicolaou stain). A) Large and small cellular clusters with scattered tumor cells show ductal and tubular structures. B) A few tumor clusters with peripheral palisading are identified. C) Colloid-like, granular, dense eosinophilic materials are surrounded by epithelial cells, forming glandular spaces. D) Round to oval nuclei with occasional nuclear groove have fine chromatin with a scant amount of lacy to dense cytoplasm.

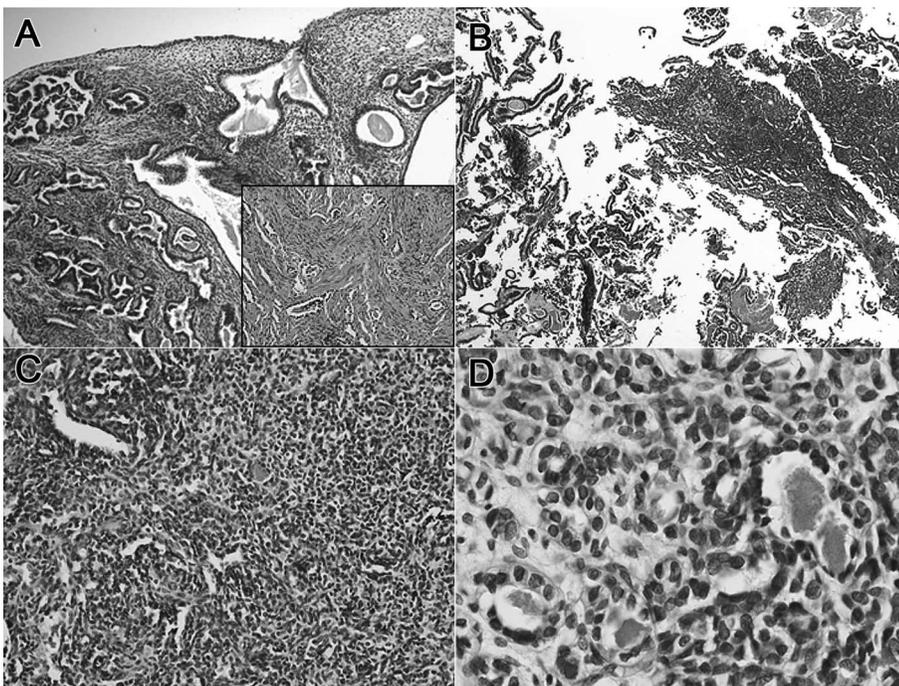


Figure 4. — A) Mesonephric hyperplasia in the cervix (inlet: mesonephric remnant). B) Fragmented papillary and solid tissue with necrosis from endocervix and endometrium curettage. C) Spindle component of closely packed oval to spindle-shaped cells interrupted by a few tubules. D) Round to oval tumor cells showing a tubular pattern with intraglandular eosinophilic secretions.

ure 5D). Spindle areas were diffusely positive for CD10 and CK7 and focally positive for CK8/18. Mesonephric hyperplasia and remnant were expressed similar to the glandular component, except for CD10, which was negative. HPV and EGFR studies provided negative results.

The patient was started on chemotherapy using docetaxel and cyclophosphamide for treatment of metastatic lung lesions. However she was subsequently transferred to other hospital.

Discussion

MMT is a rare gynecologic tumor, which is classified as a subtype of adenocarcinoma of the cervix and vagina or carcinosarcoma showing mesonephric adenocarcinoma accompanied by a sarcomatous component [3]. The cytological, pathologic, and immunohistochemical features of MMT is not well recognized that it would give

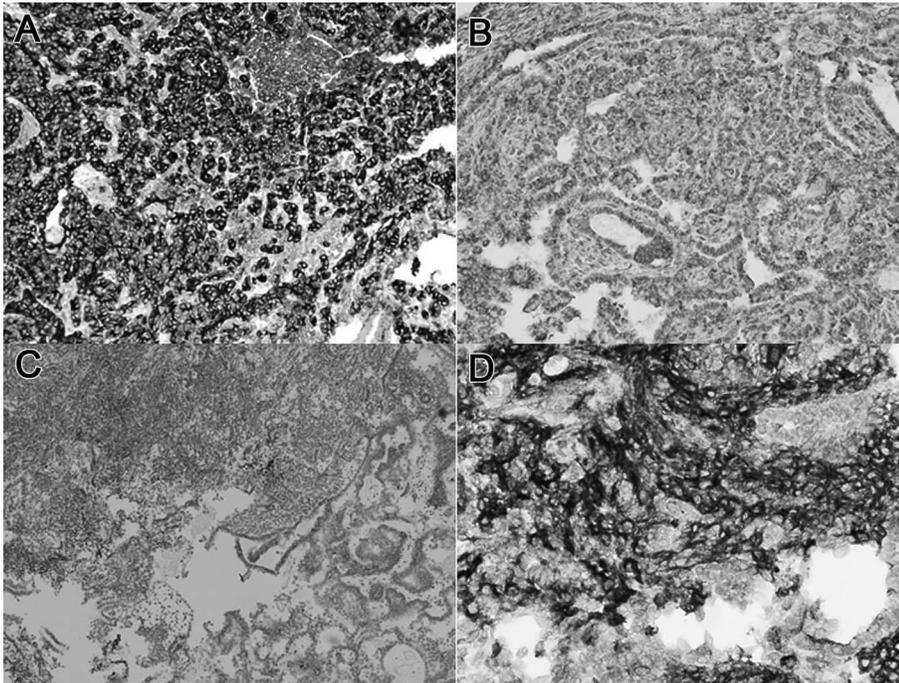


Figure 5. — Immunohistochemistry results. A) Diffuse expression of EMA. B) Diffuse membranous staining of vimentin C) Negative staining of CEA. D) Diffuse expression of CD10 on the spindle pattern and patchy expression on the glandular components.

diagnostic difficulties under uncommon clinical presentation.

The present authors reviewed the literature on MMT in the uterus and vagina using Pubmed (www.ncbi.nlm.nih.gov/pubmed) with the keywords ‘mesonephric’ and ‘wolffian’. The authors selected MMTs except for clear cell carcinoma of Müllerian origin, which was previously reported as mesonephric carcinoma. A total of 72 published cases (including this case) were identified (Tables 1 and 2).

Three-fourths of MMT in uterus and vagina were mesonephric adenocarcinoma. A malignant mesonephric mixed tumor (MMMT) comprised 18 cases, 22% of which had a heterologous component. The average patient age was 51 years (with a range of 1 to 81). The most common involvement site was the uterine cervix, followed by the uterine corpus, and the vagina. Tumors infiltrated or circumferentially encircled or grew in a polypoid pattern. The most common presenting symptom was vaginal (postmenopausal) bleeding. Other symptoms included hypermenorrhea, abdominal pain, lump sensation, abnormal Pap smears, and pelvic fullness. Two cases were initially identified as pulmonary metastases without gynecological symptoms including the present case [4]. The mean tumor size was 4.7 cm (0.9 to 14 cm). FIGO Stage I (all stages was IB) was most common and incidence rates for Stages II/III/IV were 20%, 7%, and 10%, respectively. Local recurrence was most common in the pelvic cavity followed by the vagina, abdominal cavity, and retroperitoneum. Lymph node metastasis was identified in 13% of cases. Distant metastases to the lung, bone, liver, distant lymph node, mediastinum, intestine, and ovary have been observed (18%).

The cytological features of MMT are only rarely reported in the literature. Some cases (4) had ‘negative for malignancy’ results due to an absence of involvement of the cervical surface [5-7]. Other cases had positive results, which were reported as adenocarcinoma (five cases), atypical glandular cells (two cases), and squamous intraepithelial lesion (two cases) [8-13]. Nomoto *et al.* [11] described cytological features of conventional Pap smear similar to the present case. Clusters of tubular, ductal, and sheet-like proliferation with small to medium sized round to oval, bland nuclei were observed. Characteristic intraglandular eosinophilic materials frequently filled the glandular spaces. Unfortunately, eosinophilic tumor diathesis was not always identified that one previous Pap smear cytology and the present liquid-based preparation did not reveal [11].

Mesonephric adenocarcinoma have variable architectural patterns, including tubular, ductal, papillary, solid, cribriform, sex-cord-like, retiform, and mixed [13]. Tubular structures lined by mucin-free cuboidal epithelium with a bland cytology are commonly exhibited [13]. The ductal pattern is composed of larger glands with papillae resembling endometrioid adenocarcinoma. Neoplastic cells are cuboidal to columnar without pleomorphism. Eosinophilic colloid-like secretions are common and characteristic features. MMMTs contain sarcomatous component, which is usually composed of a spindle cell proliferation. A heterologous component was also reported as osteosarcoma (two cases), chondrosarcoma (one case), and rhabdomyosarcoma (one case) [8, 14, 15]. A MMMT constituted 1/4 of MMT reported cases and 16% of cervical carcinosarcomas [16]. Three cases of metastatic lesions from MMMT confirmed by pathologic

Table 1. — A literature review of malignant mesonephric tumors

Reference, year	Total No.	Site	Cytologic diagnosis	Pathologic diagnosis	Mesonephric remnant	Tumor size (cm)	FIGO stage	Local recurrence	LN metastasis	Distant metastasis
Buntine et al., 1979 [12]	1	Cervix	Adenocarcinoma	Mesonephric adenocarcinoma	+	2	IB	Vagina	–	–
Hinchey et al., 1983 [1]	1	Vagina (paravagina)	NA	Mesonephric adenocarcinoma	–	6	II	–	–	–
Valente et al., 1987 [18]	1	Cervix	NA	Mesonephric adenocarcinoma	+	3	IB	Pelvic cavity	–	Bone
Bloch et al., 1988 [14]	1	Cervix	NA	MMMT	+	3	IB	–	–	–
Gupta et al., 1988 [23]	1	Cervix	NA	Mesonephric adenocarcinoma	+	NA	III	NA	+	–
Ferry et al., 1990 [2]	4	Corpus	NA	Mesonephric adenocarcinoma	+	NA	NA	Vagina	NA	NA
		Cervix	NA	Mesonephric adenocarcinoma	+	NA	IB	Pelvic cavity	–	Bone
		Cervix	NA	Mesonephric adenocarcinoma	+	NA	NA	NA	NA	NA
		Cervix	NA	Mesonephric adenocarcinoma	+	NA	IB	Pelvic cavity	NA	NA
Lang et al., 1990 [6]	2	Cervix	Negative	Mesonephric adenocarcinoma	+	NA	NA	–	–	–
		Cervix	NA	Mesonephric adenocarcinoma	+	4.5	NA	NA	NA	NA
Stewart et al., 1993 [5]	1	Cervix	Negative	Mesonephric adenocarcinoma	+	NA	IB	–	–	–
Daya et al., 1994 [19]	1	Vagina (paravagina)	NA	Mesonephric adenocarcinoma	–	10	II	Paravagina	–	–
Yamamoto et al., 1995 [24]	1	Corpus	Negative	MMMT	+	14	IB	–	+	Hilar LN of lung
Clement et al., 1995 [13]	8	Cervix	NA	Mesonephric adenocarcinoma	+	2.5~6	IB	–	+	–
		Cervix	NA	Mesonephric adenocarcinoma	+		IB	Abdominal cavity	+	–
		Cervix	Atypical glandular cells	Mesonephric adenocarcinoma	+		IB	Abdominal cavity	–	–
		Cervix	NA	Mesonephric adenocarcinoma	+		IB	NA	–	–
		Cervix	NA	MMMT	+		IB	Retroperitoneum	–	Liver, bone
		Cervix	NA	MMMT	+		IB	–	NA	–
		Cervix	NA	MMMT	+		IB	–	NA	–
		Cervix	NA	MMMT	+		IB	NA	NA	–
Silver et al., 2001 [8]	11	Cervix	NA	Mesonephric adenocarcinoma			IB	NA	NA	NA
		Cervix	NA	Mesonephric adenocarcinoma			IB	NA	NA	NA
		Cervix	Squamous intraepithelial lesion	Mesonephric adenocarcinoma			IB	NA	NA	NA
		Cervix	NA	Mesonephric adenocarcinoma			IB	NA	–	NA
		Cervix	NA	Mesonephric adenocarcinoma			IB	NA	NA	NA
		Cervix	Atypical glandular cells	Mesonephric adenocarcinoma	+(10 case), –(1 case)		IB	Rectovaginal septum	–	NA
		Cervix	NA	MMMT			IB	NA	NA	Mediastinum
		Cervix	NA	Mesonephric adenocarcinoma			IB	NA	–	NA
		Cervix	NA	Mesonephric adenocarcinoma			NA	NA	NA	NA
		Cervix	NA	Mesonephric adenocarcinoma			IIB	Pelvic cavity	NA	NA
		Cervix	NA	Mesonephric adenocarcinoma			IVB	Bladder	+	Subhepatic, Ovary

Ordi et al., 2001 [25]	1	Corpus	NA	Mesonephric adenocarcinoma	-	8	IB	-	-	-
Kondi-Paftis et al., 2003 [26]	4	Cervix	NA	Mesonephric adenocarcinoma	-	NA	IB	NA	-	-
Montagut et al., 2003 [17]	1	Corpus	NA	MMMT	-	8	IB	Pelvic cavity	+	Lung, Peritoneum
Bague et al., 2004 [15]	9	Cervix	NA	Mesonephric adenocarcinoma	+	3	IB	NA	NA	NA
		Vagina	NA	Mesonephric adenocarcinoma	+	4	II	+	NA	NA
		Cervix	NA	Mesonephric adenocarcinoma	NA	6	IIA	NA	NA	NA
		Cervix	NA	Mesonephric adenocarcinoma	+	2	IB	NA	NA	NA
		Corpus	NA	MMMT	-	3.5	IB	NA	NA	NA
		Cervix	NA	MMMT	+	6	IIA	NA	NA	Intestine
		Vagina	NA	MMMT	NA	NA	NA	NA	NA	NA
		Cervix	NA	MMMT	-	8	IVB	+	NA	Bone
		Cervix	NA	MMMT	+	3.5	IB	NA	NA	NA
Angeles et al., 2004 [7]	1	Cervix	Negative	Mesonephric adenocarcinoma	+	3	IIA	-	NA	NA
Ersahin et al., 2005 [9]	1	Vagina	Squamous intraepithelial lesion	Mesonephric adenocarcinoma	+	0.9	IIIB	-	+	-
Marquette et al., 2006 [27]	1	Corpus	NA	Mesonephric adenocarcinoma	-	3.7	IB	-	-	-
Yap et al., 2006 [28]	1	Cervix	NA	Mesonephric adenocarcinoma	+	3.2	IB	-	-	-
Bifulco et al., 2007 [29]	1	Vagina	NA	Mesonephric adenocarcinoma	-	14	IVA (invasion to the bladder)	-	-	-
Wani et al., 2008 [4]	1	Corpus	NA	Mesonephric adenocarcinoma	-	8	IV	Pelvic cavity	-	Lung
Fukunaga et al., 2008 [30]	1	Cervix	NA	Mesonephric adenocarcinoma	+	4	IB	-	-	-
Kenny et al., 2012 [22]	8	Cervix (7 cases) Corpus (1 case)	NA	Mesonephric adenocarcinoma (7 case) MMMT (1 case)	+(2 cases)	NA	IB (2 cases) IIB (3 cases) IV (1 case) IIIA (1 case, Corpus) NA (1 case)	NA	+	Liver (1 case)
Lopez-Chardi et al., 2013 [10]	1	Cervix	Adenocarcinoma	MMMT	-	3	IB	-	-	-
Anagnostopoulos et al., 2012 [31]	1	Cervix	NA	Mesonephric adenocarcinoma	+	2	IB	-	-	-
Nomoto et al., 2012 [11]	2	Cervix	Adenocarcinoma	Mesonephric adenocarcinoma	-	5.2	IB	-	-	Lung
		Cervix	Adenocarcinoma	Mesonephric adenocarcinoma	+	1.5	IB	-	-	-
Menon et al., 2013 [32]	1	Cervix	NA	Mesonephric adenocarcinoma	+	3.4	IB	-	-	-
Meguro et al., 2013 [16]	1	Cervix	NA	MMMT	+	1.8	IIA	+	-	-
Tseng et al., 2014 [33]	1	Cervix	NA	MMMT	+	3	III	-	+	-
Ying et al., 2014 [34]	1	Vagina (vaginal-urethral interspace)	NA	Mesonephric adenocarcinoma	-	5	II	-	NA	-
Present case	1	Cervix	Adenocarcinoma	Mesonephric adenocarcinoma	+	3.8	IVB	NA	NA	Lung

NA, Not applicable; MMT, Malignant mesonephric mixed tumor; LN, Lymph node.

Table 2. — Clinical-pathological characteristics of 72 literature reported patients with malignant mesonephric tumors.

Characteristic	Case no. / Total no. (%)
Mean age (range)	51 years (1-81)
Mean tumor size (range)	4.7 cm (0.9-14)
Tumor site	
Uterine cervix	57/72 (79)
Uterine corpus	8/72 (11)
Vagina	7/72 (10)
Pathologic diagnosis	
Mesonephric adenocarcinoma	55/72 (77)
Malignant mesonephric mixed tumor	17/72 (24)
With heterologous component	4/18 (22)
Associated mesonephric remnant/hyperplasia	47/70 (67)
Tumor growth	
Infiltrative	40/60 (67)
Polypoid	20/60 (33)
FIGO Stage	
I (IB)	39/61 (64)
II	12/61 (20)
III	4/61 (7)
IV	6/61 (10)
Adjuvant therapy	
Radiotherapy	15/56 (27)
Chemotherapy	8/56 (14)
Radiotherapy + chemotherapy	10/56 (18)
Not given	23/56 (41)
Local recurrence	17/72 (24)
Lymph node metastasis	9/72 (13)
Distant metastasis	13/72 (18)
Outcome	
Free of disease	31/72 (43)
Alive with disease	10/72 (14)
Death due to disease	10/72 (14)
Not available	21/72 (29)

examination, which were all composed of an adenocarcinoma component [8, 13, 17]. Metastatic lesions from mesonephric adenocarcinomas (five cases including the present case) had similar (two cases), poor (one case), and well (two cases) differentiated histologic grade compared to primary lesions [8, 13, 18, 19].

Immunohistochemical evaluation aids differentiation of a mesonephric origin from tumors (Table 3). The CD10 marker, a cell surface marker has been suggested as a differential marker for a mesonephric origin [20]. CD10 is diffusely expressed in the endometrial stroma, and focally in endometrioid carcinoma and ovarian tumors [21]. The CD10 immunohistochemical result for MMT in this review was 22/34 (65%) in an uneven and luminal pattern [22]. CEA is generally expected to be negative in MMT and positive in endocervical adenocarcinoma; nine of 45 MMT cases were positive [6]. The MMT cases had patchy expressions of ER, PR, and HNF1- β in 4/24 (17%), 1/15 (7%) and 3/9 (33%) cases, respectively. EMA, vimentin, and cal-

Table 3. — A review of Immunohistochemical staining results of malignant mesonephric tumor.

Immunohistochemical marker	Present case	Positive expression No. / Total No. (%)
EMA	+	31/31 (100)
Vimentin	+	36/47 (77)
P16	+	8/11 (73)
Calretinin	–	19/28 (68)
CD10	+	22/34 (65)
HNF1- β	NA	3/9 (33)
TTF1	–	3/10 (30)
CEA	–	9/45 (20)
ER	–	4/24 (17)
CK20	–	1/10 (10)
PR	–	1/15 (7)

NA: not applicable.

retinin have shown diffuse positivity in 31/31 (100%), 36/47 (77%), and 19/28 (68%) of MMT cases. Many reported cases in the literature showed p16 expression (8/11, 73%) with no relation to HPV infection [22]. TTF-1 and CK20 expressions in MMT [3/10 (30%) and 1/10 (10%)] should be considered for evaluation of metastatic lesions. Result for Wilms tumor-1 (WT1) was all negative (0/9) (0%).

MMT sometimes presents a diagnostic difficulty due to lack of recognition of its specific morphology and immunohistochemical markers. As in the present case, bland cytological features with characteristic intraglandular eosinophilic materials give diagnostic clue to MMT. The CD10 immunohistochemistry has been suggested as a differential marker for a mesonephric origin. With a literature review of 72 cases of MMT, an improvement in the understanding of clinical and cytopathological features of MMT would be achieved.

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