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Four cases of mesonephric adenocarcinoma of the cervix: a rare histology

Quatro casos de adenocarcinoma mesonéfrico do colo uterino: uma histologia rara

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Abstract

Introduction: *Mesonephric adenocarcinoma of the uterine cervix is a rare tumor, originating from remnants of the mesonephric duct. The differential diagnosis from other cervical carcinoma can be challenging. The existing data in the literature, regarding clinical history, diagnosis, prognosis and treatment is scarce.*

Methods: *Four patients diagnosed with mesonephric adenocarcinoma of the cervix were treated at our institution. The clinicopathological data of these patients was collected.*

Results: *The patients presented postmenopausal metrorrhagia at diagnosis. Three patients underwent type C radical hysterectomy and pelvic lymphadenectomy, being staged (FIGO) as pIB1, pIB3 and pIIB, respectively. One patient was under surveillance, one patient underwent adjuvant treatment (radiotherapy and brachytherapy) and the third patient was restaged, stage IV, initiating palliative chemotherapy. One patient, stage IIIC1, underwent radical radiochemotherapy and brachytherapy. The patient presented regional and distant recurrence, and it was decided systemic treatment.*

Histologically, the tumors presented a mixture of patterns including papillary, glandular with the presence of spindle cells in two patients. The immunohistochemistry showed expression of CAM 5.2, CD10, vimentin, GATA3, calretinin, absence of expression of WT1 and hormone receptors, and p53 wild-type.

Conclusions: *The rarity of this disease raises challenges in its management, namely diagnosis, prognosis and therapeutic approach.*

Key-words: *Mesonephric adenocarcinoma; cervix cancer; multidisciplinary.*

Resumo

Introdução: O adenocarcinoma mesonéfrico do colo uterino é um tumor raro, com origem em remanescentes do ducto mesonéfrico. O diagnóstico diferencial com outros carcinomas do colo uterino pode ser difícil. Os dados existentes na literatura sobre a história clínica, diagnóstico, prognóstico e tratamento são escassos.

Métodos: Foram identificadas, retrospetivamente, 4 doentes diagnosticadas com adenocarcinoma mesonéfrico do colo uterino tratadas na nossa instituição e recolhidos os seus dados clinico-patológicos.

Resultados: As doentes apresentavam metrorragia pós-menopausa ao diagnóstico. Três doentes foram submetidas a histerectomia radical tipo C e linfadenectomia pélvica, sendo estadiadas (FIGO) como pIB1, pIB3 e pIIB, respetivamente. Uma doente ficou em vigilância, uma doente realizou tra-

tamento adjuvante (radioterapia e braquiterapia) e a terceira doente foi re-estadiada, estadio IV, tendo iniciado quimioterapia paliativa. Uma doente, estádio pIIIC1, realizou radioquimioterapia radical e braquiterapia. Recidivou regionalmente e à distância, sendo decidido tratamento sistémico. Três doentes encontram-se vivas, duas sem evidência de doença, e uma falecida com evidência de doença.

Histologicamente, os tumores apresentavam uma mistura de padrões incluindo papilar, glandular, com presença de células fusiformes em duas doentes. A imunohistoquímica mostrou expressão de CAM 5.2, CD10, vimentina, GATA3, calretinina, ausência de expressão de WT1 e recetores hormonais, e p53 "*wild type*".

Conclusão: A raridade desta doença torna desafiante a sua orientação, nomeadamente o seu diagnóstico, prognóstico e abordagem terapêutica.

Palavras-chave: Adenocarcinoma mesonéfrico; cancro do cérvix; multidisciplinaridade.

Introduction

Malignant mesonephric adenocarcinoma is a very rare tumor of the female genital tract that arises from mesonephric remnants. Mesonephric (Wolffian) ducts degenerate during female embryonic development, but remnants can be found in approximately 8 to 20% of women. The remnants may persist in the ovarium hilum, the broad ligament, the mesosalpinx, or the lateral wall of the uterine cervix or vagina. They can sporadically give rise to cysts or more rarely to neoplasms.[1] Mesonephric adenocarcinoma is one of the few subtypes of cervical cancer that is not related to HPV.[2] There are few cases reported in the literature, with limited available data, regarding the clinical behavior, diagnosis, prognosis and treatment management. We present 4 cases of women diagnosed with mesonephric adenocarcinoma of the cervix, including clinical presentation, pathologic findings, treatment and follow-up.

Material and Methods

We conducted a unicentric retrospective review of patients with histologically confirmed mesonephric adenocarcinoma, treated in our Institution between 2011 and 2023. Medical records of all patients were collected, namely patients' comorbidities, clinical presentation of disease, staging and treatment. The site of recurrence and salvage therapies were recorded. Survival was calculated from the time of diagnosis. The Institutional Ethics Committee approved this study (CES. 018/024). The ethical standards displayed in the Declaration of Helsinki and its later amendments were followed.

Results

Four patients were diagnosed with mesonephric adenocarcinoma. Their clinical characteristics and therapeutic approaches are summarized in **Table 1**. The age at diagnosis ranged from 62 to 81 years, with an average of 70 years.

All patients presented with post-menopausal vaginal bleeding. Patient's physical examination revealed a polypoid/exophytic mass protruding into the cervical canal. Not visualized macroscopically lesions in the vagina or vulva. The parametrium tissue apparently not involved in all patients. The suspected lesions were biopsied. Histologically, the tumors had

Table 1. Patients' demographic characteristics, staging and treatment.

Patients' Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age	81	76	64	62
Surgical findings	Exophytic mass in the uterus cervix, measuring 14x14mm	Ulcero-vegetant neoformation in the cervix, measuring 51x25 mm	Mass in the uterine cervix, measuring 90x40 mm Lympho-vascular, parametrium and superior vaginal invasion	Conglomerate with 70 mm, adjacent to the common iliac artery
Pathological stage	IB1	IB3	IIB[a]	IIIC1
Initial treatment	Type C RH with PLND and BSO	Type C RH with PLND and BSO Adjuvant RT: EBRT 45Gy to pelvis and endovaginal BT Ir-192 HDR, 3x6Gy to VMS	Type C RH with LB and PLND and omentectomy	Diagnostic laparoscopy BSO and selective PLND Radical RCHT: EBRT 50.4Gy to pelvis (SIB 60Gy adenopathy); concomitantly cisplatin x6, and 2 applications of uterovaginal BT, Ir-192, LDR
Metastasis in the course of the disease	No	No	Distant	Regional and distant
Treatement after recurrence/persistance	NA	NA	Carboplatin/ paclitaxel x1	Carboplatin/ paclitaxel x6 + bevacizumab (since 4th cycle) >> maintenance with bevacizumab DP in 5 months >> Carboplatin/ gemcitabine
Status	Alive, without disease	Alive, without disease	Dead of disease	Alive, with disease
Follow-up (months)	11	5	3	25

Legend: BSO – Bilateral Salpingo-Oophorectomy; BT – Brachytherapy; DP – Disease Progression; EBRT: External Beam Radiation Therapy; HDR – High Dose Rate; LB – Lomboaortic lymph node; LDR – Low Dose Rate; NA – Not Applicable; PLND – Pelvic Lymphadenectomy; RCHT – Radiochemotherapy; RH – Radical Hysterectomy; RT: Radiotherapy; SIB – Simultaneous Integrated Boost; VMS: Vaginal Mucosa Surface.

[a] Re-staged after surgery, as stage IV.

Table 2. Immunohistochemical characteristics of cervix mesonephric adenocarcinoma.

Immunohistochemistry	Patient 1	Patient 2	Patient 3	Patient 4
CAM 5.2	Not done	+	+	+
Vimentin	-	+	+	Not done
PAX8	Not done	+	Not done	+
GATA3	-	+	Not done	+
TTF-1	-	+	Not done	-
CD10	+	+	+	+
P16	-	- (focal)	- (focal)	- (focal)
Calretinine	-	+	-	+
WT1	-	-	-	-
ER/PR	-	-	-	-
Desmine	Not done	Not done	-	-
p53	Wild-type	Wild-type	Wild-type	Wild-type

a mixture of patterns, including papillary, tubular, cordonal and nested, and in 2 patients there were spindle-cell areas. Tumor cells had amphophilic cytoplasm and moderate nuclear atypia, with vesicular chromatin, and inconspicuous nucleoli. Some tubules had eosinophilic luminal secretions. These morphological features were consistent with endocervical adenocarcinoma, HPV independent, favoring the hypothesis of mesonephric adenocarcinoma. Immunochemistry (**Table 2**) supported the diagnosis and showed expression of cytokeratin CAM 5.2, CD10, GATA3 and calretinin. They were negative for WT1 and hormone receptors. P53 had wild-type expression in all samples.

Patients were staged as clinical stage I (FIGO 2018). Three patients underwent type C radical hysterectomy and pelvic lymphadenectomy, with salpingo-oophorectomy. The margins were R0 for patients and the staging (FIGO 2018) was pIB1, pIB3 and pIIB, respectively.

Patient 1 presented a exophytic mass in the uterus cervix, measuring 14x14 mm, and 1 mm of cervical stroma invasion. No extension to parametrium or vaginal was observed, nor lympho-vascular invasion. Patient 2 had a ulcero-vegetant, hemorrhagic, neoformation along the cervix of the uterus, with 51x25 mm of extension and 20 mm of cervical stroma invasion. It was not observed lympho-vascular invasion or extension outside the cervix. The 3rd patient exhibited a mass in the uterine cervix, with 90x40 mm of extension and 14 mm of depth of cervical stroma invasion. It was observed lympho-vascular, parametrium and superior vaginal invasion.

Histologically, in the hysterectomy specimens, the diagnosis of endocervical mesonephric adenocarcinoma was confirmed. Similarly, there was a mixture of architectural patterns, including papillary, retiform, tubulocystic, glandular and spindle-cell (**Fig. 1**). Areas of squamous differentiation or intracytoplasmic mucin were not observed.

The 4th patient showed in the magnetic resonance a suspicious mass in the uterus cervix, measuring 30x28x28mm, occupying the anterior vaginal fornix and invading the anterior vaginal wall in its proximal two-thirds. No invasion of the

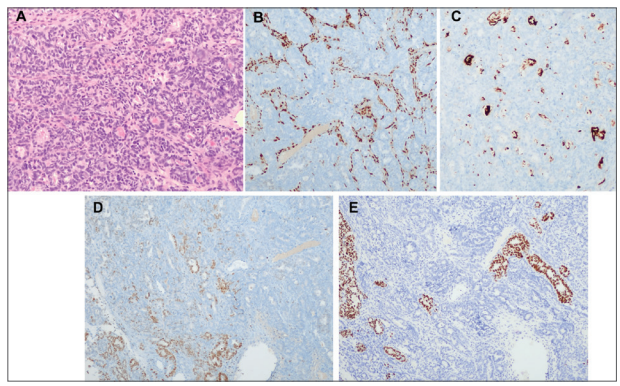

Figure 1. Histological and immunohistochemistry features of mesonephric adenocarcinoma from patient 2. **A** – Tubular and cordonal patterns, with focal dense eosinophilic luminal secretions. (H&E coloration; amplification 20x); **B** – Absence of estrogen receptor expression (positive internal control in cervical stroma) (amplification 10x); **C** – CD10 multifocal luminal expression (amplification 20x); **D** - GATA 3 nuclear multifocal expression (amplification 10x); **E** – TTF1 nuclear multifocal expression in an inverse pattern of GATA3 (amplification 10x).

parametrium or uterine body was observed. PET/CT ^{18}F-FDG exhibited hypermetabolism for the neoplasia in the uterine cervix and lymph nodes adjacent to the iliac external vessels. It was decided in a multidisciplinary team perform a diagnostic laparoscopy. Then, the patient underwent diagnostic pelvic laparoscopy, identifying a conglomerate mass, measuring 70 mm, adjacent to the common iliac artery. The patient underwent bilateral oophorectomy. Histologically, the tumor mass had morphological and immunohistochemical features consistent with a lymph node metastasis of the mesonephric adenocarcinoma diagnosed in the patient's previous uterine cervix biopsy. Thus the patient was staged as pIIIC1.

Patient 1, staged as pIB1, remained under surveillance until the end of the study (11 months). The patient 2 (stage pIB3) underwent adjuvant radiotherapy, receiving a total dose of 45 Gy to the pelvis, in 25 fractions, at 1.8 Gy per fraction (photons, energy of 6 MV, intensity modulated radiation therapy (IMRT)) (**Fig. 2**), and endovaginal brachytherapy, resorting to

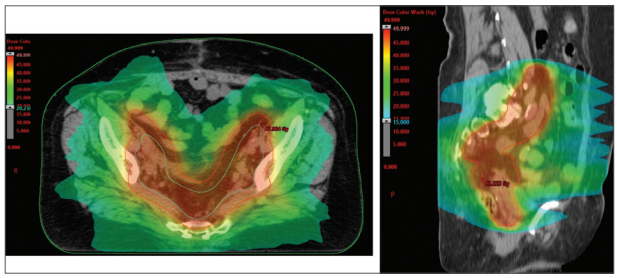

Figure 2. Axial and sagittal CT planning of external radiotherapy. The patient received a dose of 45 Gy to pelvis, in 25 fractions, with an intensity-modulated radiation therapy technique.

Iridium-192 source, using a vaginal cylinder, at high dose rate, in a total dose of 18 Gy, in 3 fractions, to the vaginal mucosa surface (3cm of extension), remaining with no evidence of disease. The 3rd patient was restaged after the surgery, with PET/CT (Positron Emission Tomography), and it was identified bone metastases (stage IV). She initiated palliative chemotherapy with carboplatin (AUC6) and paclitaxel (175 mg m^{-2}), dying 1 month later. Patient 4, staged as pIIIC1, underwent radical radiochemotherapy, receiving a dose of 50.4 Gy to the pelvis (60 Gy to iliac adenopathy), in 28 fractions, at 1.8 Gy per fraction, concomitantly with cisplatin, 40 mg m^{-2} in 6 cycles, and 2 applications of uterovaginal brachytherapy, with an Iridium-192 source, at low dose rate, performing 85 Gy to modified points A of Manchester. Ten months after initial treatment, regional and distant metastases were detected in PET/CT. The patient completed 6 cycles of carboplatin (AUC6) and paclitaxel (175 mg m^{-2}; reduction of paclitaxel dose to 75% at 4th cycle) associated with bevacizumab (15 mg kg^{-1}), since the 4th cycle. Five months after beginning the maintenance with bevacizumab, the disease progressed, and it was decided to change the treatment to carboplatin (AUC3) and gemcitabine (500 mg m^{-2}; reduction of dose to 50% at cycle 1, day 8). The patient completed 2 cycles until the end of the study.

After a median follow-up of 12 months (4 to 28 months), 3 patients were alive, 2 of them without evidence of disease and 1 patient had died with evidence of disease. Survival rate was 75% at 1 year of follow-up.

Discussion

The development of malignant mesonephric tumors of the female genital tract is very rare. Mesonephric adenocarcinoma occurs most often in adult women, with a mean age at diagnosis of 59 years.[3] The most frequent symptoms include abnormal vaginal bleeding or vaginal discharge. Abdominal pain or discomfort can occur in very rare cases that originate in the fallopian tube or ovary. The diagnosis is usually made on biopsy specimens, endometrial curetting, or hysterectomy specimens.[4] The diagnosis of mesonephric adenocarcinoma is often challenging and involves the differential diagnosis with clear cell carcinoma, mesonephric hyperplasia, malignant Mullerian mixed tumors, and endometrioid adenocarcinoma.[5,6]

World Health Organization defined mesonephric adenocarcinoma as a tumor with tubular glands lined by mucin-free cuboidal epithelium, luminal eosinophilic hyaline secretions with solid papillary, ductal or retiform architectural arrangements deriving from remnants of mesonephric ducts.[7] More than 20% of tumors had a biphasic variant of a mesonephric carcinoma, with sarcomatoid features.[4] Squamous and mucinous differentiation are normally absent. The tumors in our study showed the typical mixture of patterns described, including the presence of spindle-cell areas.

The immunohistochemistry profile helps in the differential diagnosis from others gynecological cancers. The published data described commonly expression of pan-cytokeratin, CK7, CAM 5.2, EMA, vimentin, GATA3, TTF1, PAX-8, calretinine and CD10. Usually, the tumor cells showed negative staining for estrogen and progesterone receptors, monoclonal CK20, CEA, p16; and, p53 wild type.[4,8,9] A positive immunostaining for CD10 indicates a mesonephric origin. HPV infection is strongly associated with the occurrence of cervical cancer; however, p16 is negative in mesonephric adenocarcinoma, as it is an HPV-independent tumor. PAX8 stains strongly in malignant mesonephric lesions, while in other cervical carcinoma types, it is variably expressed.[10] GATA3 seems to be highly sensitive and specific to mesonephric lesions, being positive in mesonephric carcinoma, but normally absent in the usual and gastric types of endocervical adenocarcinoma.[11] The lack of squamous cells associated with the presence of mesonephric remnants and negative staining for estrogen and progesterone receptors favors the diagnosis of mesonephric adenocarcinomas instead of endometrioid carcinoma of the cervix.

The data regarding the biological behavior of this unusual tumor is scarce, so there is no sufficient data to recommend a specific protocol for the management of mesonephric adenocarcinoma. In general, it is treated similarly to cervical adenocarcinoma, according to the stage of the disease.[4] Most of the patients previously reported were diagnosed in early stages. In our study, 2 patients were diagnosed early (IB1 and IB3), but the other 2 patients presented with advance disease, stage IIIC1 and IV, respectively. The patients are usually treated with surgery (hysterectomy with or without bilateral salpingo-oophorectomy and pelvic lymphadenectomy) and with or without (neo-) adjuvant chemotherapy or radiotherapy.[4,11] Three of the patients, in this study, underwent surgery, followed by adjuvant treatment in stage IB3 and surveillance in stage IB1. The 3rd patient was re-staged after surgery and it was identified bone metastases (stage IV), initiating palliative chemotherapy. The patient 4 (stage IIIC1) underwent radical radiochemotherapy.

The prognosis of mesonephric adenocarcinoma is unclear, due to the small number of cases published in the literature. Dierickx *et al* [4] reported a review of the literature, in 2016, with 39 cases of mesonephric adenocarcinoma, observing a recurrence rate of 32% for stage I patients (70% of the sam-

ple). Their results suggest a worse prognosis for mesonephric adenocarcinoma compared to squamous-cell carcinoma and usual type adenocarcinoma (recurrence rates of 11% and 16%, respectively). The patients with spindle cell components were diagnosed at a more advanced stage, indicating a worse prognosis. One of the 2 patients with sarcomatoid features, in our study, had stage IV at diagnosis and died with evidence of disease. A recent multi-institutional study including 30 patients with mesonephric adenocarcinoma of the cervix demonstrated that 60% of the patients presented advanced stage (II-IV) at diagnosis, and half of them developed recurrence, most frequently at distance (56% to the lungs). The five-year disease-specific survival was 74%.[3] As previous referred, 2 of our patients were diagnosed at an early stage (IB1 and IB3) and 2 patients staged as IIIC and IIB, respectively. The last two developed distance metastases in the course of disease, and one died with evidence of disease. It seems important, to perform a complete stage of these patients, consider adjuvant therapy and maintain a close follow-up.

Finally, mesonephric adenocarcinoma is not associated with HPV. These tumors may not be diagnosed in cervical cancer screening based on the detection of high-risk HPV genotypes. Then, it is important to perform gynecological examination on all women's to avoid delay in the diagnosis of these patients.

Conclusion

Mesonephric adenocarcinoma is a very rare malignant tumor of the female genital tract, but should be remembered as a differential diagnosis for cervical cancer. The data regarding the disease is limited, namely clinical characteristics, pathological diagnosis, prognosis, and optimal treatment approach. Therefore, more data is needed to increase the experience in the management of these patients, particularly regarding early detection and adjuvant treatment.

Contributorship Statement / Declaração de Contribuição:

SC – Desenho e execução do estudo, recolha, análise e interpretação de dados, elaboração do manuscrito.

PV – Desenho e execução do estudo, recolha, análise e interpretação de dados, revisão crítica e alterações ao manuscrito.

CB, LC e LS – Desenho e execução do estudo, interpretação de dados, revisão crítica e alterações ao manuscrito.

SC – Study design and execution, collection, analysis and interpretation of data, preparation of the manuscript.

PV – Study design and execution, collection, analysis and interpretation of data, critical review and changes to the manuscript.

CB, LC and LS – Study design and execution, data interpretation, critical review and changes to the manuscript.

Ethical Considerations / Responsabilidades Éticas

The authors have no conflicts of interest to declare.

This work has not received any contribution, grant or scholarship.

During the entire research process, the confidentiality of the patients data was ensured.

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee of IPO Porto.

This article does not contain any new studies with human or animal subjects performed by any of the authors.

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