Extremely Rare Transitional Cell Carcinoma of The Round Uterine Ligament - Histopathogenesis, Immunohistochemical Analysis, Prognosis and Optimal Complex Treatment

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ABSTRACT

For the first time in the English medical literature is presented an extremely rare transitional cell carcinoma of the round uterine ligament. Transitional cell carcinoma (TCC) of the ovary was first defined by Austin and Norris in 1987. Malignant primary tumors arising in the uterine broad ligament are extremely rare. To date, its pathogenesis is unclear.

In the discussion we focus on the pathomorphological and immunohistochemical analysis of transitional cell carcinomas in the genital tract and their differential diagnosis from transitional cell carcinomas of the urinary tract / ureter and bladder.

Due to the high malignant potential, the prognosis is unfavorable and requires optimal complex treatment, including radical surgery followed by systemic chemotherapy.

Keywords

Transitional cell round uterine ligament carcinoma, Transitional cell ovary carcinoma, Histopathogenesis, Immunohistochemical analysis, Radical surgery, Systemic chemotherapy.

Introduction

For the first time in the English medical literature, we present a primary transitional cell carcinoma (TCC) of the round uterine ligament, and the other gynecological organs ovaries, fallopian tube and uterine body are without pathological changes. Although secondary involvement of the broad ligament by malignant tumours arising elsewhere in the abdomen is common, primary tumours in this location are rare [1]. Rare primary TCCs of the ovary are relatively common. Pure TCC was first defined by Austin and Norris in 1987 [2]. To date, its pathogenesis is unclear. TCC of the ovary has been described as a primary high grade carcinoma in which definite urothelial features are present but no benign, metaplastic and/or proliferating Brenner tumor can be identified [3]. In this article we will discuss the possible carcinoma histopathogenesis and will share our observations on the pathomorphology, immunohistochemistry, prognosis and complex treatment of this rare tumor.

The clinical case

In July 2009, on the occasion of a cystic formation in the area of the left adnexa in a 48-year-old woman, a total hysterectomy with bilateral adnexectomy has been performed. Postoperatively, the patient have undergone 6 courses of adjuvant chemotherapy (Ch) with gemcitabine and cisplatin. In May 2010, due to a painful formation in the left iliac region, a relaparotomy with tumorectomy, omentectomy and removal of implantable small bowel metastasis has been performed. Systemic Ch has changed according to the BEP scheme. Against the background of 2 courses of Ch, PET / CT reports progression of the disease.
From the examinations: Intraoperatively / July / 2009- In the left round uterine ligament / ligamentum rotundum / a cystic formation with dimensions of 35 mm was found, from which a purulent fluid leaked. After extirpation of the cyst, a total hysterectomy with bilateral adnexectomy was performed. Microscopic histological examination / 2009 - Round uterine connection with fragments of a thick-walled cyst, with an outer surface composed of connective tissue fragments; The inner surface of the cyst is upholstered with transitional cell epithelium with papillary architecture, in places with squamous differentiation; right ovary with cystic corpus luteum; left fallopian tube and left ovary with normal histological structure; right fallopian tube - normal histostructure; uterus with intramural leiomyoma and endometriosis; cervix with retention cysts of the cervical canal. Diagnosis: Moderately differentiated transitional cell carcinoma with squamous cell differentiation, tumor cells infiltrate the capsule of the cyst, but without reaching its serous surface (in the outer surface of the cyst, that to the abdominal cavity there are no tumor cells). Revision of the histological result - The wall of the cystic formation is composed of urban muscle elements with adipose tissue on the periphery, upholstered by overgrown broad papillary or solid structures; abundant lymphoid reaction with the presence of giant multinucleated cells. The tumor grows mainly in the cavity, single small sockets penetrate the cyst wall. Diagnosis: Moderately differentiated transitional cell carcinoma of the Mueller type, developed in the round uterine ligament (Figure 1).

Figure 1: Photomicrography of the round uterine ligament transitional cell carcinoma - presence of overgrown broad papillary or solid structures; abundant lymphoid reaction with the presence of giant multinucleated cells.

Examination of tumor markers CEA, CA 125, AFP, βHCG; CA 19-9 - normal; From 11.11.09 - Chromogranin A - 517 ng / ml (at norm 100 ng / ml); NSE is positive.

Intraoperatively / May / 2010 - Tumor formation with a diameter of about 2-3 cm and implantation metastasis of the small intestine with a diameter of 3-4 cm were found. An operation, including tumorectomy with total removal of the omentum and implantation small intestinal metastasis, was performed.

Microscopic histological examination /2010 - Tumor formation - Complex merging papillary and glandular structures with necrosis in the lumens are observed. In the empty spaces there are separate large and round, undifferentiated tumor cells with increased nucleus /cytoplasm ratio and numerous mitoses (Figure 2/A); small intestinal wall with infiltration of undifferentiated carcinoma; four pelvic lymph nodes with sinus histiocytosis; omentum with infiltration of undifferentiated carcinoma; Connective tissue densely sprouted from undifferentiated carcinoma.

From the immunohistochemical (IHC) analysis of tumor cells focal positive estrogen receptor (ER) expression (Figure 2/B) and diffusely positive Vimentin expression (Figure 2/C) were reported.

Figure 2: Photomicrography of recurrence of the round uterine ligament transitional cell carcinoma with metastases of the omentum and small intestine: A / complex merging papillary and glandular structures with necrosis in the lumens of H&E x100; B / IHC- focal positive expression for estrogen receptors (ER). Hobnail type cells are seen, which are positive for ER x40; C / IHC- diffuse positive expression for Vimentin x40.

CT of the abdomen / September 2010 (Figure 3) - cystic soft tissue formations with areas of necrosis - 1 / at the entrance of the pelvis on the left (infiltrating the intestine); 2 / above the left kidney at the level of the spleen. 3 / The cystic lesion in the area of the liver is reported as related to its parenchyma.

PET/CT / October 2010 (Figure 4) - At the level of the spleen soft tissue formation 54mm / 64 mm is reported, with a central zone of necrosis, with increased metabolic activity SUV 9.3, pressing on the stomach. At the entrance of the small pelvis a soft tissue formation with a central zone of necrosis measuring 66.2 / 44.5 mm, adjacent to the intestinal loops, close to the abdominal wall (m. Rectus abdominis) and medially from m. Iliacus. The lesion in the area of the liver is difficult to differentiate whether it covers its parenchyma or is located retrohepatic. Conclusion: PET/CT data for metastatic lesion in the liver, soft tissue metastatic lesions in the intestinal loops, as well as soft tissue formation at the entrance of the small pelvis on the left.
Figure 3: CT of the abdomen/ September 2010- Progression of the disease with metastatic lesion in the liver, soft tissue metastatic lesions in the intestinal loops, as well as soft tissue formation at the entrance of the small left pelvis.

In November 2010, following the onset of intraperitoneal metastases, fourfold elevated serum LDH levels have been observed.

Local status
Left-sided hydronephrosis with elevated urea and creatinine due to compression of the left ureter by a large left pelvic formation which required intraurethral stenting. The pronounced anemic syndrome had been corrected by blood transfusion, after that we started palliative decompressive radiotherapy. After total dose 46Gy in the area of pelvic implantation metastasis, a significant tumor reduction (over 50%) was reported, as well as a significantly reduced lymphedema in the area of the left lower limb and pelvis. The patient was referred for continued systemic Ch. The patient died of disease progression 3 months later.

Discussion
Malignant primary tumors arising in the uterine broad ligament are rare. By Gardner et al./1957 they are defined as a tumor with its primary location within or on the surface of the broad ligament, but entirely separated from the ipsilateral ovary, uterus and fallopian tube [4]. Among all the reported uterine broad ligament carcinomas, serous adenocarcinoma, clear cell adenocarcinoma and endometrioid adenocarcinoma are the most common histologic variants [5]. By 2016, 29 clinical cases with primary malignant carcinomas of the broad uterine ligament have been published, 2 transitional cell and 8 serous adenocarcinomas [6]. The primary endometrioid and clear cell adenocarcinomas of the broad ligament have their origin in the Mullerian ducts and arise from background endometriosis [7]. Paramesonephric ducts (or Mullerian ducts) are paired ducts of the embryo, that run down the lateral sides of the urogenital ridge and terminate at the sinus tubercle in the primitive urogenital sinus. In the female, they will develop to form the fallopian tubes, uterus, cervix, and the upper one-third of the vagina. During embryologic development, hormones control the development of the Mullerian ductal system and the Wolffian ductal system (which gives rise of the epididymis, vas deferens, seminal vesicle, and ejaculatory duct) [8]. Mesonephric duct is paired organ present during embryogenesis connecting primitive kidney to cloaca, which becomes part of male reproductive organs, known as Wolffian duct, archinephric duct, Leydig duct, nephric duct. They are localized anywhere in pelvic cavity, including broad ligament, cervix (20% of women), fallopian tube, lymph nodes, ovary [9].

Female adnexal tumors of probable Wolffian origin (FATWO) are rare tumors derived from the remnants of the mesonephric duct [10]. The current preferred terminology, according to the World Health Organization Classification of Tumors, is Wolffian tumor [11].

Female adnexal tumors of probable Wolffian origin has been reported as immunoreactive for pancytokeratin (AE1/3, CK1) (100%), CAM 5.2 (100%), cytokeratin 7 (88%), keratin 903 (17%), EMA (12%), estrogen receptor (78%), inhibin (68%), calretinin (91%), vimentin (100%) [12,13] and CD10 and negative for cytokeratin 20, epithelial membrane antigen (EMA), estrogen receptor (ER), progesterone receptor (PR), 34betaE12, and glutathione S-transferase [14]. Immunohistochemical staining with promising new markers and pathological investigation of the entire tumor are required to determine the malignant behavior of FATWO [10]. In their initial description of the tumor, Karminejad and Scully note that a Mullerian origin of the FATWO was improbable, despite its common location within the Mullerian-derived organs,
as the tumor does not closely resemble any neoplasm arising from a Müllerian duct derivative or surface epithelium of the ovary [15].

The Mullerian-origin broad ligament tumors and ovarian cancers can be confirmed by IHC. WT1, the most specific marker, is positive in 90% of the cases. IHC for CA-125 has a low specificity of 35%. The Mullerian-origin tumors also show positivity for ER, whereas the Wolffian-origin tumors show positivity for CD10, vimentin and calretinin, and negativity for ER [16]. An IHC analysis by Brady et al./2012 confirmed the above findings, but could not specifically suggest a Mullerian or Wolffian origin for the broad ligament tumors, as there occurs an overlap in the pattern of these markers [17]. As the broad ligament tumors are encased within the two layers of ligament, they tend to be asymptomatic during the early stages [16]. Similarly, their rupture, progression and metastasis are delayed because of the lack of their own vascular supply, in contrast to the ovarian tumors [18].

Malignant mixed mesodermal tumors, also called carcinosarcomas, are diagnosed mainly in postmenopausal women and are composed of mixed malignant epithelial and mesenchymal components, usually high grade [19].

Transitional cell carcinoma (TCC) of the ovary is a rare subtype of ovarian surface epithelial cancer classified under transitional cell tumors along with benign, borderline and malignant Brenner tumor [20]. TCCs have broad papillae lined by cells, some of which are recognizable as transitional cells; similar cells form undulating, thick bands. Scattered microspaces, which are often numerous, also favor a diagnosis of TCC [21]. Because TCC of the ovary has close morphologic similarities to TCC of the bladder and it behaves more aggressively than malignant Brenner tumor, Austin and Norris concluded that ovarian TCC arises directly from the pluripotential surface epithelium of the ovary and from cells with urothelial potential, rather than from a benign or proliferative Brenner tumor precursor [2]. Croft et al., concluded that almost all of the ovarian TCCs marked strongly for estrogen receptors (ERs), a characteristic that may help to differentiate these lesions from papillary urothelial carcinoma metastatic to the ovary [22].

The pure TCC of the ovary is a recently recognized subtype of ovarian surface epithelial cancer. It has been described as a primary ovarian carcinoma in which definite urothelial features are present but no benign, metastatic and/or proliferating Brenner tumor can be identified [23]. The tumors previously called transitional cell carcinomas of the ovary (not associated with benign or borderline Brenner tumor component) are now classified as variants of high-grade serous carcinomas. It has been proposed that ovarian TCC may represent a high grade serous carcinoma with morphologic features of transitional cell differentiation rather than being a distinct tumor type [24]. Ovarian TCCs are negative for CK20, thrombomodulin (TM) and uroplakin III, which are the antigens that are usually (CK20) or sometimes (TM and uroplakin III) detected in bladder TCCs [25]. Unlike bladder TCCs, ovarian TCCs are often positive for vimentin, CA-125 and Wilms tumor protein (WT1) [26]. The tumor cells showed nuclear positivity for WT1, cytoplasmic positivity for CK-7 and membrane positivity for Ber-EP4 [27]. Of the 88 clinical cases with ovarian TCC, 10 neoplasms were composed of only TCC, 48 were predominantly TCC, and 30 had foci of TCC but the predominant component was serous, endometrioid, undifferentiated, or unclassified adenocarcinoma. Tumor recurrences and lack of response to chemotherapy are often associated with a change in the histologic appearance of the metastatic lesions [28].

The clinical case we presented is initially a moderately differentiated transitional cell carcinoma with pathohistological characteristics of serous papillary carcinomas of the ovaries or endometrium with the presence of papillary or solid structures; abundant lymphoid reaction and giant multinucleated cells (Figure 1). The presence of a neuroendocrine tumor component is evidenced by elevated serum levels of Chromogranin A and NSE. This indicates that this germ cell tumor is mixed transitional cell carcinoma with neuroendocrine tumor component. Observations suggest that the histogenesis of some cases of combined small and transitional cell carcinoma in the urinary bladder may be the same, as both can produce CA19-9 [29]. The studied tumor markers CEA, CA 125, AFP, βHCG; CA 19-9 were in normal values, which distinguish the presented tumor from ovarian, gastrointestinal and urothelial origin. Metastatic tumor formations after 1 year appear as undifferentiated carcinoma with already pronounced pathohistological and IHC characteristics of serous papillary carcinomas (Figure 2/A,B,C). The metastatic pathways of the tumor are mimicking the transitional cell carcinoma of the bladder which implicate a loss of the integrity of E-cadherin [2]. Loss of E-cadherin expression is associated with increased tumor cell motility and invasiveness [30], as well as with tumor progression, chemoresistance and metastases [25]. Epithelial to mesenchymal transition (EMT) contributes to tumor progression, cancer cell invasion, and therapy resistance [25]. The transcription profile induced by EMT acquires radio-resistance in tumor cells that share the properties of stem cells [31]. The tumor relapse can be explained by the mesenchymal transdifferentiated subpopulations of cancer cell nests that are induced by the fibroblastic stroma and are readily radio-resistant and chemo-resistant [32]. Diffuse IHC expression of Vimentin in recurrent transitional cell carcinoma shows, namely the cellular EMT of tumor cells (Figure 1/C). The hobnail type cells are very common for cervical, endometrial and ovarian clear cells carcinomas derived from mesonephros [33]. The mesonephros as a whole produces urine from the 6th through the 10th week of development. Despite the similarity in structure, function, and terminology, however, the mesonephric nephrons do not form any part of the mature kidney or nephrons [34]. Hobnail-like cells were focally positive for estrogen receptor and Wilms tumor gene protein in nearly all serous borderline tumors. Figure 2/B shows the presence of hobnail type cells in the recurrent tumor formation with positive IHC expression for ER. Hobnail-like cells in all clear cell carcinomas were completely negative for estrogen receptor and Wilms tumor gene protein [35].

All of these clinical data support the Mueller / paramesonephric origin of transitional cell carcinomas of the female genital tract, including the rare transitional cell carcinomas in the broad and
round uterine ligament. As a result of epithelial to mesenchymal cell transformation, transitional cell carcinomas of the female genital tract change their pathomorphological phenotype with the manifestation of immunohistochemical characteristics typical of highly malignant serous papillary carcinomas.

**Prognosis**
Favorable statistically significant prognostic factors in ovarian TCCs, were low clinical stage, predominant TCC in the primary tumor, and a negative second-look operation. Other prognostic indicators were the amount of residual tumor after the first operation and tumor differentiation [28]. In the multivariate analysis, the residual tumor after the salvage surgery in malignant ovarian germ cell tumors was the only significant variable associated with primary treatment failure (P = 0.0011, Hazard ratio = 29.046, 95% Confidence interval 3.832-220.181) [36]. In the presented clinical case, during the first operation the cyst had been torn and its contents were spread in the abdominal cavity. Despite the maximum visible radical surgery and adjuvant chemotherapy, tumor cells remained, which subsequently dedifferentiated after one year and caused disease progression.

**Optimal complex treatment**
Surgically treated advanced stage TCCs do not have a significantly better prognosis after platinum/taxane-based chemotherapy compared with serous endometrial ovarian carcinomas [37]. Ovarian carcinomas, containing predominant TCC pattern, have an excellent response to different chemotherapy regimens [38]. As the presented clinical case is a malignant mixed mesodermal tumor, it is necessary to perform maximally radical surgery with a volume of total laparohysterectomy with bilateral adnexectomy and omentectomy, followed by chemotherapy.

**Conclusion**
For the first time in the English medical literature is presented a primary transitional cell carcinoma (TCC) of the round uterine ligament. This cancer is an extremely rare malignant embryonic germ cell tumor of paramesonephric origin. Careful and rigorous pathohistological and immunohistochemical analysis is recommended for the diagnosis of these rare tumors. Achieving good recurrence-free survival requires radical surgery without residual tumor cells, followed by systemic chemotherapy. In R1 resection with residual tumor cells, the prognosis is unfavorable. Postoperative radiotherapy is not required due to the exceptional radiation resistance. Radiation therapy is performed only for palliative purposes.

**References**
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