
Helen J Trihia*

*Corresponding Author: Helen J Trihia, Department of Pathology, “Metaxas” Cancer Hospital, Piraeus, Greece

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Abstract

Background/Aim: Transitional cell carcinoma (TCC) is a rare subtype of ovarian epithelial carcinoma in which definite urothelial features are present, not associated with a benign or borderline Brenner component. A case of an advanced stage TCC of the ovary, misdiagnosed as a non-keratinizing squamous cell carcinoma of the vagina with secondary deposits in the liver and invasion of the large bowel, along with a literature review is presented.

Materials and Methods: A 48 year old woman with multiple sclerosis, presented with vaginal bleeding, abnormal cytology and constipation. Biopsy from an ulcerative lesion of the posterior fornix of the vagina was diagnosed as non-keratinizing SQCA.

Results: Hysterectomy, omentectomy, along with resection of the sigmoid and cystic mass of the left parametrium showed a TCC of the left ovary. The patient died two months after surgery.

Conclusion: Ovarian TCCs are uncommon neoplasms and a challenging diagnostic entity, especially in biopsy specimens.

Keywords: Transitional Carcinoma; Ovary; Squamous; Vagina; Misdiagnosis; Pitfall

Introduction

The group of the so-called transitional cell tumors (TCT) of the ovary includes the benign Brenner tumors, the borderline Brenner tumors, the atypical proliferating variant, the malignant Brenner tumors and the transitional cell carcinoma (TCC) of the ovary, non-Brenner type.

TCC is a rare subtype of ovarian epithelial carcinoma in which definite urothelial features are present, not associated with a benign or borderline Brenner component. Histopathological examination remains the only means used in the diagnosis of these heterogeneous tumors and in the separation of closely related tumors. A case of an advanced stage TCC of the ovary, misdiagnosed as non-keratinizing squamous cell carcinoma (SQCA) of the vagina with secondary deposits in the liver and invasion of the large bowel, along with a literature review, is presented.

Patient and Methods

A 48 year old woman, with multiple sclerosis, complained of vaginal bleeding, abdominal pain and constipation. In a biopsy from an ulcerative lesion of the posterior fornix of the vagina, performed elsewhere, she was diagnosed with a non-keratinizing SQCA of the vagina, grade II. The CT scan revealed multiple liver deposits and stenosis of the sigmoid colon because of an outer tumor mass. On several CT scans, a ‘cyst’ of the left ovary had been recognized since one and a half years, ‘probably benign’ (‘benign cyst’, ‘ovarian-salpingeal inflammatory disease’ or ‘benign cystadenoma’), which on last examination was measuring 8cm. Cystoscopy was unremarkable. She presented in our hospital, where a sigmoidoscopy with biopsy and liver FNB biopsy were performed.

The biopsy of the large bowel showed two nests of squamoid, non-keratinizing carcinoma in the lamina propria (Figure 1 and 2). The 'liver' biopsy (no recognizable liver parenchyma) was diagnosed as low differentiated squamous cell carcinoma (Figure 3 and 4). Exploratory laparotomy revealed a frozen pelvis. Sigmoidostomy was performed. Biochemical tests for tumor markers showed CEA: 14, AFP: 5, CA 125: 55, Ca19-9: 10, Tag72: 0.40, TPA: 200.

Figure 1: H&E stain: microscopic appearance of large bowel biopsy, where two nests of squamoid cells in the lamina propria are shown.

Figure 2: H&E stain: the same as figure 1, higher magnification.
Figure 3: H&E stain: liver biopsy: malignant neoplasm with features of squamous cell carcinoma, of intermediate to low differentiation.

Figure 4: H&E stain: similar as above, higher magnification.
The patient underwent chemotherapy (6 cycles of Poxene/Haloxan/Cisplatin). The disease responded favorably to treatment. There were no abdominal palpable findings.

Magnetic resonance imaging (MRI), 4 months after chemotherapy, showed, in the anatomic site of the left parametrium an enlarged cystic formation of 8x7x7 cm, with homogeneously thickening of the cyst wall and a solid area of 3 x 2 cm in the lower posterior wall of the cyst.

Hysterectomy with bilateral oophorectomy, omentectomy and resection of the recto-sigmoid, after six months of chemotherapy was performed. The patient recovered successfully and died two months after surgery, due to generalized intravascular coagulopathy.

**Results**

In the anatomic site of the left ovary there was a cystic tumor (Figure 5), measuring 10 x 8 x 4 cm, consisting of three smaller cysts (multicystic), with mostly smooth inner surface and with a solid area of 3 x 2 cm (Figure 6). The ‘cyst’ was in continuity with the lateral wall of the uterus. The posterior surface of the uterus, in the cervical portion was rough and in continuity with a large bowel segment, of 18 cm length. While opening the large bowel, at one margin, there was a tumor mass measuring 5 X 2,7 cm.
Microscopically, in sections examined from the cystic tumor, there were large cystic spaces with broad undulating papillae with smooth borders covered by multilayered transitional epithelium (Figure 7a-7c), as well as transitional cell nests in a fibrotic stroma (Figure 8a and 8b). Foci of comedo type necrosis (Figure 8b) and squamous cell differentiation (Figure 9a and 9b) were also present. The tumor was invading the serosa of the uterus and in continuity the co-excised vaginal fornix submucosally and likewise the large bowel wall up to the submucosa and lesser to the mucosa. There were multiple tumor emboli in the submucosa of the vagina (Figure 10) and of the large bowel (Figure 11). An obvious benign or borderline Brenner tumor was not recognized. Immunohistochemical stains were positive for Ker7 (Figure 12), Ker5/6, Ca125 (Figure 13), thrombomodulin (focally) and p53 and negative for Ker20, inhibin, uroplakin, vimentin, EMA and p63.
Figure 7c

Figure 7a-7c: H&E stain: microscopic appearance from the cystic tumor, showing cystic space with thin and broad undulating papillae covered by multilayered transitional epithelium.

Figure 8a


**Figure 8a and 8b**: H&E stain: microscopic appearance from the cystic tumor showing transitional cell nests in a fibrotic stroma with foci of comedo necrosis.

**Figure 9a**: H&E stain: microscopic appearance from the cystic tumor showing areas with extensive squamous differentiation.


Figure 9b: H&E stain: the same as 9(a), higher magnification.

Figure 10: H&E stain: microscopic appearance of the vagina, where tumor emboli in the submucosa (on the lower left) are shown.

**Figure 11:** H&E stain: microscopic appearance from the resection specimen of the large bowel, where tumor emboli in the submucosa are shown (on the left).

**Figure 12:** IHC: positive expression of the tumor for Ker7.
**Discussion**

The term ‘transitional cell carcinoma (TCC) of the ovary’ was proposed by Roth and Czemobilsky [1] for those primary ovarian carcinomas showing urothelial features without benign, metaplastic, or proliferating Brenner tumors. By this definition, this entity of carcinoma was separated from malignant Brenner tumor as well as undifferentiated carcinoma in 1987. Austin and Norris [2] compared 29 cases of TCC with 16 cases of malignant Brenner tumor and found that TCC was more aggressive than malignant Brenner tumor; as the former presented at a higher stage, as seen in our case, and behaved worse for a comparable stage. On the other hand, TCC responded favorably to chemotherapy and exhibited a better prognosis, as compared to non-TCC ovarian carcinomas of a similar clinical stage.

Ovarian tumors containing cells with transitional cell morphology were recognized in the 1999 and added as separate entity in the 2003 World Health Organization Classification of ovarian tumors [3] and include benign Brenner tumor, borderline and malignant Brenner tumor, and transitional cell carcinoma (WHO, 1999, 2003).

By definition, transitional cell tumors are the ovarian tumors composed of epithelial elements histologically resembling malignant urothelial neoplasms and do not have a component of benign or borderline Brenner tumor.

In 2013 WHO histological classification of tumors of the ovary [4], ‘transitional-like adenocarcinoma’ was categorized under malignant epithelial tumors, along with low grade and high grade serous adenocarcinoma.

In the new WHO Classification of ovarian cancers, published at 2014 by Robert Kurman and co-authors [5], the transitional cell type of ovarian cancer was removed.

TCCs of the ovary account for 1-2% of all ovarian tumors [6,7] and they arise directly from the pluripotent (coelomic) surface epithelium of the ovary through metaplastic changes and from cells with urothelial potential, rather than from a benign or proliferative Brenner tumor precursor and studies of its morphology are rare. TCC is the pure or predominant element in 6% of ovarian carcinomas [8]. Ovarian TCCs occur as partly cystic tumor, usually unilateral and bilateral in approximately 15% of cases [2] and are macroscopically indistinguishable from other surface epithelial-stromal tumors [2,8]. The great majority of TCCs occur in women 50 - 70 years old [9]. The presentation of women with TCC is the same as with other malignant ovarian tumors, pelvic mass, abdominal pain, abdominal swelling or distension, back pain, postmenopausal bleeding and bladder or bowel symptoms [2,8,10].

Pure TCC is distinguished from malignant Brenner tumor [11,12] and it behaves more aggressively, with frequent spread beyond the ovary at the time of diagnosis in over two-thirds of cases [8]. It has close morphological similarities to TCC of the urinary tract, but different immunophenotype (Ker20-, UROIII-/+, WT1+ versus Ker20+, UROIII+/-, WT1-) [11]. Ovarian TCCs are consistently cytokeratin 13 and 20 negative and WT1 (82%), CA125 and cytokeratin7 positive and rarely express UROII (6%) and thrombomodulin (18%). Most Brenner tumors show positivity with UROIII (82%) and thrombomodulin (76%), supporting the urothelial differentiation in these tumors [11]. Findings [13] have shown that p63 is expressed in benign and borderline Brenner tumors, but not in malignant counterparts and TCCs of the ovary suggesting that this antigen is a marker for the differential diagnosis of malignant Brenner tumors and TCCs. It has also been shown that Brenner tumors and TCCs follow different tumorigenic pathways, whereas borderline and malignant Brenner tumors are low-grade neoplasms with activation of the P13K/AKT pathway through EGFR, TCCs are high-grade tumors that have p53 mutations and p16 and p53 protein overexpression [13].

Metastatic TCC from the urinary bladder, or elsewhere within the urinary system, involving the ovary, is extremely rare [14]. There were six cases reported till 2012, as described by Lee., et al [7]. In all cases, secondary ovarian tumors were unilateral. The time interval to the appearance of ovarian metastases varied from synchronous to 4 years. The primary origin of lesions has prognostic significance as TCC of the ovary has a modest response to chemotherapy [6] and metastatic TCC from the renal pelvis results in mortality [7].

Histologically, TCCs typically are papillary with multilayered transitional epithelium and a smooth luminal border (‘papillary type’). A nested pattern characterized by malignant transitional cell nests irregularly distributed in fibrotic stroma (‘malignant Brenner-like’) has been described. It is characterized by large cystic spaces in 70%, broad undulating papillae with smooth borders in 60% and microspaces in 90% [6]. Foci of necrosis or hemorrhage are frequent. Mitotic figures are prominent. As in urothelial carcinoma, foci of glandular and/or squamous differentiation may occur. TCCs should be graded utilizing criteria for TCC of the urinary tract. Very commonly, transitional cell carcinoma is admixed with other epithelial cell types, primarily serous carcinoma. TCC lacks the prominent stromal calcification characteristic of some benign and malignant Brenner tumors [2,15,16].

The term TCC is not uniformly accepted, and overlapping features with other epithelial-stromal tumors, particularly serous carcinoma are present. It is important that strict histological criteria be applied to establish the diagnosis [17]. Not only an architectural but also a histological resemblance to transitional epithelium is required. The frequent association with epithelial-stromal tumors of other types strongly suggests a surface epithelial-origin [17].

Colorectal metastases are exceptional (0.338%) [18], represent a late stage of disease and reflect a poor diagnosis. It is much more common for colorectal mucosa to be involved by direct invasion or extension from neighboring organs, such as ovarian carcinoma, intraperitoneal seeding, or intraluminal or intramural dissemination. The pathologist should be alert for the possibility of secondary tumors when studying large bowel biopsies. Any therapy is usually palliative, but there are results that suggest that careful patient selection with primary site controlled and complementary therapy may be associated with prolonged survival after surgery.

The overall 5-year survival rate for TCC is 35%. Some, but not all, investigators have reported greater chemosensitivity and higher 5-year survival in patients whose metastases are composed purely or predominantly of transitional cell carcinoma [15,16,19]. Gershen-
son, et al.'s [20] concluded that advanced-stage ovarian TCC was significantly more chemosensitive and associated with better prognosis than poorly differentiated serous carcinoma.

There are a few examples of TCC arising in the cervix, endometrium, fallopian tube, broad ligament, paratubal cyst and vagina.

The metastatic pathways of the tumor simulate TCC of the bladder [2,16].

It is of note, that 84% of invasive vaginal carcinomas are secondary, usually from tumors from other pelvic sites, including the ovary, colon and urinary bladder [21]. Even 75% of vaginal SQCAs are secondary, usually from the cervix or vulva. Vaginal metastases may be the presenting sign of a distant tumor.

TCC of the ovary comprised a distinct entity of ovarian epithelial cancer till 2014, which we have to consider in case of transitional/squamo-transitional morphology and a cystic ovarian mass. It has to be distinguished from TCC of the urinary tract and malignant Brenner tumor, but it can also mimic other carcinomas, like in our case and it can be a very challenging diagnostic entity, especially in biopsy specimens.

**Conclusion**

Ovarian TCCs are uncommon neoplasms and a challenging diagnostic entity, especially in biopsy specimens.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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