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Case Report

Synchronous Urinary Bladder Urothelial Carcinoma and Transitional Cell Carcinoma of the Ovary: A Case Report

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Transitional cell carcinoma · Ovarian metastases · Bladder cancer

Abstract
Transitional cell carcinoma (TCC) of the ovary is a rare subtype of epithelial ovarian tumours defined as a tumour composed of epithelial elements, histologically resembling urothelium and its neoplasms. Ovarian metastases from primary urinary tract carcinomas are rare. The differential diagnosis of primary TCC of the ovary versus metastatic bladder TCC is challenging because of histological similarity. We present the case of a 49-year-old premenopausal woman who was initially diagnosed with non-invasive papillary urothelial carcinoma of bladder (NIPUC) and after 2 years with a synchronous TCC of the ovary while being investigated for suspected relapse. She underwent a radical cystectomy, total hysterectomy, bilateral salpingo-oopharectomy, and pelvic lymph node dissection. The final diagnosis of synchronous NIPUC of the bladder and TCC of the ovary was made by histopathology and immunohistochemical studies.

Introduction

Primary transitional cell carcinoma (TCC) of the ovary is an uncommon histopathological diagnosis, and it was first described as a separate entity from Brenner tumours of the ovary by Austin and Norris [1], with the first largest cohort presented by Eichhorn and Young [2]. Primary TCC of the ovary was reported as a subset of ovarian tumours with histologic features

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similar to those of malignant Brenner tumours, but the tumours lacked the associated benign, borderline, or proliferative Brenner tumour component, and prominent stromal calcification [1]. It also contained definite urothelial features and was therefore considered to behave more aggressively than malignant Brenner tumours. Since TCC of the ovary has close morphological similarities to TCC of the bladder and it behaves more aggressively than malignant Brenner tumours; Austin and Norris [1] concluded that ovarian TCC arises directly from the pluripotent surface epithelium of the ovary and from cells with urothelial potential, rather than from a benign or proliferative Brenner tumour precursor. In 2014, the World Health Organization (WHO) classification therefore regarded TCC as a separate entity and identified TCC as a morphological variant of high-grade serous cancer (HGSC). The pure form of ovarian TCC accounts for only 1% of surface epithelial tumours, but mixed carcinomas with a minor TCC component make up 3% and those with a predominant TCC component 5% of this group of tumours [3].

Histological examination remains the main tool for the diagnosis of these heterogeneous tumours and the differential diagnosis of closely related cancers. Hence, with revised classification of ovarian malignancies, it is important to report all rare subtypes to understand their biology and behaviour. We present the unusual case of a patient, who was diagnosed with a high-grade papillary non-invasive urothelial carcinoma of the bladder and subsequently with a separate new primary TCC of the ovary 2 years later.

Case Report

A 49-year-old woman presented with a 3-month history of haematuria and a diagnosis of high-grade non-invasive papillary urothelial carcinoma of bladder (NIPUC) (pTa) was made on the transurethral bladder resection (TURB) specimen. The TURB was complicated by bladder perforation, which required a laparotomy for repair. Further NIPUC was resected after 7 months. In view of the persistent disease, the patient underwent 6 cycles of induction therapy with Bacillus Calmette-Guerin. Six months after treatment, a re-look cystoscopy was performed and confirmed progression of the disease. The histology showed focal areas of superficial lamina propria invasion (pT1) of high-grade papillary urothelial carcinoma. A radical cystectomy was recommended due to the patient's young age and failure of Bacillus Calmette-Guerin therapy. A pelvic CT scan prior to surgery identified an increase of a previously described left adnexal lesion from 5 cm to 14 cm. The adnexal mass had developed complex features such as an irregular thick wall and a septum. The CA125 was found to be 69 IU/L and slightly elevated. The differential diagnosis was metastasis from the bladder cancer versus a synchronous ovarian and bladder malignancy. The patient had four cycles of neoadjuvant chemotherapy with carboplatin and gemcitabine prior to multidisciplinary surgery.

The operation included a total cystectomy with ileal conduit formation and a hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph nodes dissection. Intraoperatively, the right ovarian mass, measuring 22 cm had a smooth surface with focal disruption of the capsule and contained solid as well as cystic components. The histopathology showed high-grade TCC with focal glandular differentiation. The cells were arranged in papillae with atypical nuclei within a fibrous stroma. There was stromal invasion and vascular invasion together with abundant mitosis and focal glandular differentiation. There was focal perforation of the capsular surface with extravasation of mucin suggestive of focal ovarian surface involvement (Fig. 1). No background benign or borderline Brenner tumour was identified. Non-invasive high-grade papillary urothelial carcinoma was found in the bladder (pTa) (Fig. 2).

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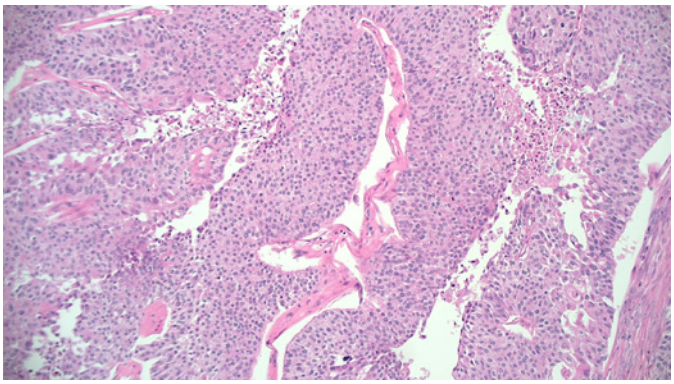

Fig. 1. The ovarian TCC is large and shows areas of necrosis on low power.

Immunohistochemistry (IHC) from the ovarian tumour showed strong and diffuse reactivity for GATA3 as well as CK7, and a moderate number of cells were staining for thrombomodulin, while only few cells stained positive for CK5/6. The ovarian tumour cells were negative for CK20, P16, p53, ER, mammaglobin, GCDFP-15, PAX8, WT1, uroplakin, and vimentin. The bladder tumour stained positive for CK7 with no staining for CK20. Based on the histology and immunohistochemical finding, the diagnosis of NIPUC of bladder with a synchronous primary TCC of the ovary was made. The contralateral adnexa, uterus, and pelvic lymph nodes and omentum were negative. The patient received adjuvant 4 cycles of carboplatin and paclitaxel. She remains free of disease 3 years after treatment. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533269).

Discussion

The clinical presentation of TCC of the ovary is similar to other types of ovarian carcinomas, and most common symptoms are abdominal distension and pain. Definitive diagnosis requires surgical resection and histopathological evaluation. The differential diagnosis of primary TC of the ovary versus metastatic bladder cancer is challenging and sometimes impossible. In our patient, the diagnosis of ovarian mass was an incidental finding during investigation for an NIPUC of the bladder.

To the best of our knowledge, there are no other published cases of synchronous TCC of the ovary and NIPUC. The ovaries are common sites for intra-abdominal metastasis, and TCC of the ovary may therefore be closely mimicked by metastatic disease as in our case. However, only about 6% of ovarian cancers found at laparotomy are secondary tumours from other sites, and metastatic TCC involving the ovary from the urinary bladder is extremely rare [4]. The distinction between metastatic and primary TCC ovary is important as the treatment and prognosis are different. In our case, the diagnosis of NIPUC of the bladder and its subsequent treatment delayed the diagnosis of the primary TCC of the ovary as it was thought to represent metastatic disease.

Mean age of patients newly diagnosed with TCC is 56 years, and 59% of TCC are unilateral [5], which reflects the characteristics of our case. The CA125 in our patient was increased which is a common feature for TCC and other epithelial ovarian carcinomas [6]. It normalized after surgical removal of the ovarian malignancy. We did not include HE4 and ROMA score in our case as the case was discussed at our MDT, and the decision was to go ahead with surgery in our gynaecological oncology department.

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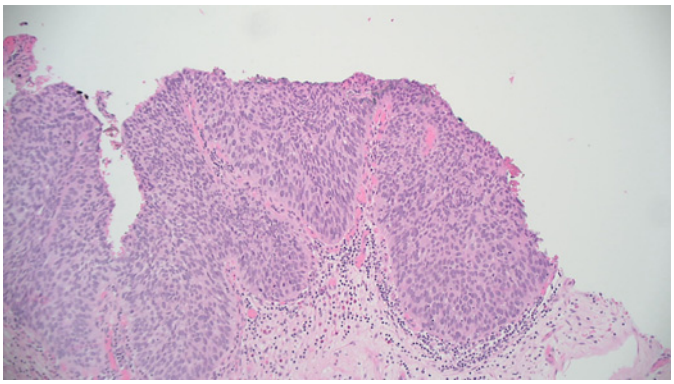

Fig. 2. Urinary bladder cancer ×10. The bladder urothelial carcinoma is small and shows no lamina propria invasion.

In our case, the ovarian TCC had histological similarities to the urinary bladder TCC, showing the same structural features such as papillae and microcysts filled with periodic acid-Schiff-positive mucus. But there were no bizarre giant cells, gland-like spaces, squamous differentiation, and psammoma bodies. Features observed by Eichhorn and Young [2] such as large eosinophilic nucleoli and longitudinal grooves were also not seen prominently in our case.

IHC staining may be of assistance to distinguish TCC of the ovary from TCCs of urothelial origin. CK20 and CK7 are useful markers for differentiating between TCC of the ovary and of the bladder, with CK7+/CK20+ profile being more common in urothelial carcinoma and CK7+/CK20− profile common in ovarian TCC. Additionally, the Mullerian marker CA125 is often strongly expressed in ovarian tumours but is absent in bladder TCC. Furthermore, ovarian TCCs are usually negative for urothelial markers, such as uroplakin III and thrombomodulin [7]. Unlike bladder TCCs, ovarian TCCs are often positive for vimentin and Wilms tumour protein (WT1), and this observation has supported the theory that many of these tumours are in fact variants of HGSCs and are not true TCCs [8]. Antibodies to S100 and GATA3 expression, which have all been demonstrated in bladder tumours have also been studied in ovarian TCC and while these markers are expressed in most cases of benign Brenner tumours, they are either weakly positive or negative in TCCs [9]. However, there is always limitation to the immunohistochemical workup. In our case, the ovarian tumour showed a mixed profile: on one hand, the CK7+/CK20− pattern and lack of expression of uroplakin were expected in the usual ovarian TCC; on the other hand, there was expression of thrombomodulin and GATA3 and lack of labelling with ER, PAX8, and WT1, more common pattern seen in urothelial carcinoma. It is important to combine immunohistochemical workup, and in fact, any workup, with the histological findings and the clinicoradiological findings. In our case, the finding of non-invasive papillary urothelial carcinoma in the cystectomy specimen, and history of very focal lamina propria invasion with no lymphovascular invasion in only one previous TURB specimen meant that it was very unlikely that the urothelial carcinoma had metastatic potential to result in a large ovary metastasis. Thus, more weight was given to the supportive IHC finding (such as CK7+/CK20− profile and negative uroplakin) over the non-supportive IHC finding. In our case, the expression of CA125 and lack of expression of CK20 supported the diagnosis of primary ovarian differentiation, favouring independent origins for the two tumours, rather than ovarian metastasis of the bladder TCC.

A common problem is also to distinguish moderate- and high-grade TCCs from other poorly differentiated serous carcinomas and undifferentiated carcinomas. Neoplastic cells

recognizable as transitional cells, papillae, and thick bands of neoplastic cells of the same type, and microspaces favour the diagnosis of primary TCC of the ovary [2].

An important means to advance our understanding of TCC would be to identify tissue biomarkers to be able to accurately distinguish between ovarian TCC and HGSC. A recent paper reported data obtained from proteomic analysis and found that claudin-4 (CLDN4), ubiquitin carboxyl-terminal esterase L1 (UCHL1), and minichromosome maintenance protein 7 (MCM7) were significantly higher, expressed in TCC than in HGSC of the ovary. The authors were therefore able to distinguish TCC from HGSC with those newly diagnosed proteomic markers [10].

The primary treatment of patients with TCC of the ovary is similar to that of other epithelial ovarian cancers. It consists of optimal surgical resection, followed by adjuvant platinum-based chemotherapy. Studies from MD Anderson suggested that TCC has a better prognosis than HGSC [11], possibly owing to better response to chemotherapy [12] and a less infiltrative invasion pattern. Subsequent work from a German group supported their findings and reported a significantly better prognosis compared to all other types of ovarian carcinomas after standardized chemotherapy [13]. The better prognosis was thought to be due to a more feasible surgical respectability, but less tendency to the bulky extraovarian tumour spread of TCCs was also reported in a published meta-analysis [14]. Consistent with this study few years earlier, Silva et al. reported that the estimated 5-year survival rate for patients with TCC of the ovary regardless the treatment was 37%, and this estimate was based on 88 patients, whereas for patients who received chemotherapy and surgery, it was 41%. Factors associated with survival for patients who received chemotherapy after surgery were the clinical stage, the percentage of TCC component in the primary tumour, and optimal cytoreductive surgery [15]. In our case, we achieved complete surgical resection of the tumour and good response to standard chemotherapy with no relapse after 3 years of follow-up. As we achieved complete surgical resection, we did not treat our case of NIPUC of the bladder with any of the immune-based combinations for advanced urothelial carcinoma.

Conclusion

Our case of synchronous TCC of the ovary and NIPUC of the bladder emphasizes the difficulties associated with distinguishing a primary TCC of the ovary versus metastatic bladder TCC. Clinical features and IHC studies are important in determining the final diagnosis. Gynaecologists should be aware that TCC of the ovary is a histological subtype of HGSCs and it needs to be differentiated from metastatic urothelial cancers when deciding the treatment. Neoplastic epithelial cells recognizable as transitional epithelium arranged in well-demarcated bands from the cystic spaces, papillary projections, and microspaces within neoplastic epithelium are important histological features. Although the microscopic examination has traditionally been the basis for diagnosis of this heterogeneous tumours, novel approaches increasingly utilize new IHC markers and molecular techniques to be able to distinguish closely related tumours and to make the correct diagnostic which guides patient management and improves outcomes. We hope that more similar cases will be published in the future in order to help clinicians to know how to manage these types of cancers.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of her medical case and any accompanying histological images. Study approval statement was not required for this study in accordance with local and national guidelines.

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Author Contributions

Authors (I.R., L.S., M.K.O.) have contributed to the care of the patient. Y.Y. has provided histological report. All the authors have edited the final draft.

Data Availability Statement

All data generated and analysed in this case report are included in this article and its online supplementary materials. Further enquiries about the case report can be directed to the corresponding author.

References

1 Austin RM, Norris HJ. Malignant Brenner tumor and transitional cell carcinoma of the ovary: a comparison. Int J Gynecol Pathol. 1987;6(1):29–39.
2 Eichhorn JH, Young RH. Transitional cell carcinoma of the ovary: a morphologic study of 100 cases with emphasis on differential diagnosis. Am J Surg Pathol. 2004;28(4):453–63.
3 Meinhold-Heerlein I, Fotopoulou C, Harter P, Kurzeder C, Mustea A, Wimberger P, et al. The new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. Arch Gynecol Obstet. 2016;293(4):695–700.
4 Bus MT, Cordeiro E, Anastasiadis A, Kliloueva NM, de la Rosette JJ, de Reijke TM. Urothelial carcinoma in both adnexa following perforation during transurethral resection of a non-muscle-invasive bladder tumor: a case report and literature review. Expert Rev Anticancer Ther. 2012 Dec;12(12):1529–36.
5 Ingin RJ, Andola SK, Zubair AA. Transitional cell carcinoma of the ovary: case series and review of literature. J Clin Diagn Res. 2014 Aug 8;8(8):FD07–8.
6 Ichigo S, Takagi H, Matsunami K, Murase T, Ikeda T, Imai A. Transitional cell carcinoma of the ovary (Review). Oncol Lett. 2012 Jan;3(1):3–6.
7 Logani S, Oliva E, Amin MB, Folpe AL, Cohen C, Young RH. Immunoprofile of ovarian tumors with putative transitional cell (urothelial) differentiation using novel urothelial markers: histogenetic and diagnostic implications. Am J Surg Pathol. 2003 Nov;27(11):1434–41.
8 Ali RH, Seidman JD, Luk M, Kalloger S, Gilks CB. Transitional cell carcinoma of the ovary is related to high-grade serous carcinoma and is distinct from malignant brenner tumor. Int J Gynecol Pathol. 2012 Nov;31(6):499–506.
9 Esheba GE, Longacre TA, Atkins KA, Higgins JP. Expression of the urothelial differentiation markers GATA3 and placental S100 (S100P) in female genital tract transitional cell proliferations. Am J Surg Pathol. 2009 Mar;33(3):347–53.
10 Tessier-Cloutier B, Cochrane DR, Karnezis AN, Colborne S, Magrill J, Talhouk A, et al. Proteomic analysis of transitional cell carcinoma- like variant of tubo-ovarian high-grade serous carcinoma. Hum Pathol. 2020 jul;101:40–52.
11 Sweeten M, Gershenson DM, Burke TW, Morris M, Levenback C, Silva EG. Salvage chemotherapy for refractory transitional cell carcinoma of the ovary (TCC). Gynecol Oncol. 1995;59(2):211–5.
12 Guseh SH, Rauh-Hain JA, Tambouret RH, Davis M, Clark RM, Boruta DM, et al. Transitional cell carcinoma of the ovary: a case-contro; study. Gynecol Oncol. 2014 Mar;132(3):64.

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DOI: 10.1159/000533269

13 Kommoss F, Kommoss S, Schmidt D, Trunk MJ, Pfisterer J, du Bois A, et al. Survival benefit for patients with advanced-stage transitional cell carcinomas vs. other subtypes of ovarian carcinoma after chemotherapy with platinum and paclitaxel. Gynecol Oncol. 2005 Apr;97(1):195–9.
14 Mackay HJ, Brady MF, Oza AM, Reuss A, Pujade-Lauraine E, Swart AM, et al. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. Int J Green Comput. 2010;20(6):945–52.
15 Silva EG, Robey-Cafferty SS, Smith TL, Gershenson DM. Ovarian carcinomas with transitional cell carcinoma pattern. Am J Clin Pathol. 1990;93(4):457–65.