Transitional cell carcinoma of the ovary (Review)

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Abstract. Transitional cell carcinoma (TCC) of the ovary is a rare recently recognized subtype of ovarian epithelial cancer. Ovarian TCC has a modest response to chemotherapy, and metastatic TCC from the renal pelvis results in mortality. The clinical presentation is indistinguishable from other types of ovarian carcinoma. Histopathological examination remains the first tool used in the diagnosis of these heterogeneous tumors and in the separation of closely related tumors. Since it is generally accepted that surgical resection is the primary therapeutic approach, and patient outcomes following chemotherapy are better than for other types of ovarian cancers, it is a reasonable concept to detect tumors when they are still confined within the ovaries. Thus, the aim of this review was to describe typical cases of primary TCC, and to review the medical literature for information on TCC management in order to determine appropriate diagnostic methods and therapy.

Contents

1. Introduction

Ovarian cancer is the most lethal gynecological malignancy. Efforts at early detection and new therapeutic approaches to reduce mortality have largely been unsuccessful, since the origin and pathogenesis of epithelial ovarian cancer are poorly understood (1). Transitional cell carcinoma (TCC), a recently recognized subtype, resembles urothelium rather than ovarian surface epithelium (methothelium) (2,3). A small percentage of ovarian cancer types are accounted for by TCC, which has proven to be a distinct group with various histological and immunohistological patterns. Patients with TCC had better prognoses compared to patients with all other types of ovarian carcinomas following standardized chemotherapy (4). The aim of this review was to describe our typical cases of primary TCC, and to review the medical literature for information on TCC management in order to determine appropriate diagnostic methods and therapy.

2. General considerations

TCC of the ovary is a recently recognized subtype of ovarian surface epithelial cancer. TCC has been described as a primary ovarian carcinoma in which definite urothelial features are present, but no benign, metaplastic and/or proliferating Brenner tumor can be identified. TCC of the ovary was initally defined by Austin and Norris (5). These investigators reported a group of patients who had ovarian tumors presenting with histologic features similar to those observed in a malignant Brenner tumor, but the tumors lacked the associated benign Brenner tumor component. Pure TCC was thus distinguished from malignant Brenner tumor. In addition to not having a benign Brenner tumor component, TCC lacks the prominent stromal calcification (5-7). Since TCC of the ovary has close morphological similarities to TCC of the bladder and it behaves more aggressively than malignant Brenner tumors, Austin and Norris (5) 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 tumor precursor.

3. Incidence

The true incidence of TCC of the ovary remains unknown. Transitional cell tumors, including TCC, and benign and malignant Brenner tumors of the ovary represent ~2% of all ovarian tumors. Moreover, according to the World Heath Organization (WHO), depending on the histological pattern, these tumors are classified as benign, borderline or malignant Brenner tumors and TCC (8). Silva *et al* (9) observed the focal or diffuse TCC pattern in 88 of 934 ovarian cancers (9%).

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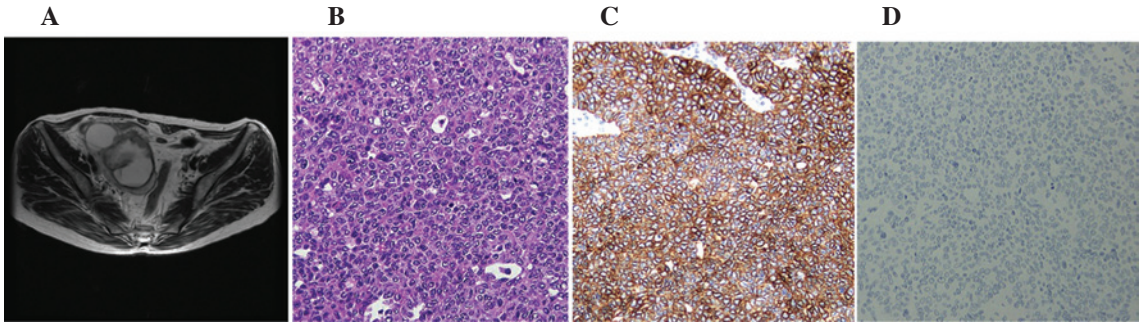

Figure 1. Primary TCC of the ovary (case 1). A 64-year-old postmenopausal woman presented with a 1-year history of progressive enlargement of an abdominal mass. Physical examination showed a pelvic mass. Abdominal ultrasound showed a pelvic mass measuring 6 cm with inhomogeneous echogenicity. (A) Horizontal T2-weighted MRI showed an inhomogeneous cyst on the right side of the pelvis, which was >70 mm in maximal diameter with a solid component. There was no evidence of lymphadenopathy. Prior to surgery, CA125 was elevated to 347 U/ml (normal, <35 U/ml), but other markers were all within normal ranges. Surgical staging procedures including total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and pelvic lymph node dissection were performed. The ascites were also sent for cytological examination. (B) Microscopic examination showed a malignant transitional epithelial lining of the right ovarian cyst. The final diagnosis was TCC, grade 3, FIGO stage IIc. Immunohistochemical studies showed that the tumor was (C) positive for CK 7 and (D) negative for CK20. The patient received six cycles of chemotherapy with paclitaxel-carboplatin following surgery, and has been disease-free for 1 year.

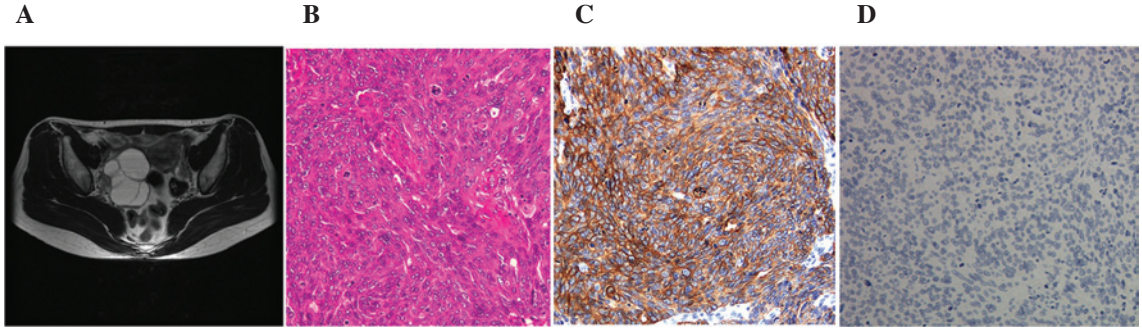

Figure 2. Primary TCC of the ovary (case 2). A 44-year-old woman with a right ovarian cyst was referred to the gynecology department. (A) The MRI (T2-weighted, horizontal) revealed a 5x6 cm multiple cystic mass in the right adenexa, suggestive of an ovarian tumor. There was no obvious metastatic foci in other organs. The levels of serum CA72-4 and CA125 were 7.7 U/ml (normal, <10.0 U/ml) and 12.9 U/ml (normal, <10 U/ml), respectively. (B) The right ovarian cyst was laparoscopically resected and diagnosed as TCC, grade 3 with serosal involvement. (C) Immunohistochemical stains for CK7 were positive; (D) but staining for CK20 was negative. The ascites cytology was reported to be positive. The patient was staged as FIGO stage Ic. One month following adenectomy, the patient was submitted for exploratory staging procedures including total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and pelvic lymph node dissection. The extensively sampled adnexal tissue was histologically uninvolved by the tumor. After recovering from surgery, the patient received six cycles of chemotherapy with paclitaxel-carboplatin. The patient is presently doing well without any recurrent disease for 2 years.

4. Diagnosis

The common presenting symptoms of TCC of the ovary are abdominal pain, abdominal swelling or distension and weight loss. Occasionally, the patient may present with uterine bleeding, back pain, bowel or urinary symptoms, as shown in our cases (Figs. 1 and 2). However, the clinical presentation is indistinguishable from other types of ovarian carcinoma (5,10). As described in detail by Eichhorn and Young (10), ovarian TCC typically shows undulating, diffuse, insular and trabecular growth patterns. The tumor cell nuclei were oblong or round, often exhibiting nucleoli with longitudinal grooves. The cytoplasm was often pale and granular, and was rarely clear or eosinophilic (Figs. 1 and 2).

CA125 is clinically useful as a serum marker of tumor progression and recurrence, although early stages may be CA125-negative (Fig. 2). In the study by Ceauşu *et al* (11), 13 archived formalin-fixed paraffin-embedded samples of transitional cell tumors of the ovary were assessed using standard hematoxylin-eosin staining and the indirect tristadial ABC peroxidase immunohistochemistry method for 11 antibodies including CA125, cytokeratin (CK) 7 and CEA. Over 50% of the samples were malignant Brenner tumors, CA125 was positive in all malignant tumors (of Brenner type and TCCs), but not in the benign and borderline tumors, while CK7 was positive in approximately 70% of all cases. The two antibodies have shown a high sensitivity and low specificity, but do not correlate with each other. Recent findings (11,12) 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, and may also play a role in Brenner carcinogenesis. The aim of these studies was to detect tumors when they are still

confined to the ovaries, thereby increasing the likelihood of cure and reducing the mortality of the disease. The modalities that are currently in use to screen women are pelvic examination, imaging modality and measurement of serum CA125 (1) (Figs. 1 and 2), although case 2 was CA125-negative.

6. Treatment

Optimal surgical resectability followed by cisplatin-based chemotherapy may contribute to the survival benefit (4,6,7). The estimated 5-year survival following surgery for 88 patients was 37%, whereas for patients who received chemotherapy, survival was at 41% (6,7). Factors associated with survival for patients who received chemotherapy were the clinical stage, the percentage of the TCC component in the primary tumor and the results of second-look surgery. The predominance of TCC was a favorable prognostic factor and patients with higher clinical stages had poorer prognoses.

7. Prognosis

The relative effects of tumor biology and treatment strategies remain undetermined (6,7). Gershenson *et al* (13,14) concluded that advanced-stage ovarian TCC was significantly more chemosensitive and associated with better prognosis than poorly differentiated serous carcinoma. Kommoss *et al* (4) also documented that patients with TCC had better prognoses compared to patients with all other types of ovarian carcinomas following standardized chemotherapy. The metastatic pathways of the tumor simulate TCC of the bladder, which implicates a loss of the integrity of E-cadherin (5-7).

8. Metastatic TCC to the ovaries

The ovaries are common sites for intra-abdominal metastasis (15). Approximately 6% of ovarian cancers found at laparotomy are secondary tumors from other sites (15,16). Metastatic TCC from the urinary bladder, or elsewhere within the urinary system, involving the ovary is extremely rare (16). There have been six cases reported thus far, as described by Lee *et al* (17). In all cases, secondary ovarian tumors are unilateral. The time interval to the appearance of ovarian metastases varied from synchronous to 4 years. In the study by Lee *et al* (17), all cases received surgery, with the overall survival ranging from 3 months to 7 years. These cases favor metastatic ovarian tumors for the following reasons: definite histological evidence of a primary renal tumor, and deep stromal invasion. The origin of primary lesions has prognostic significance as TCC of the ovary has a modest response to chemotherapy (10) and metastatic TCC from the renal pelvis results in mortality (17).

Microscopically, metastatic TCC of the ovary resembles a primary ovarian TCC. Primary TCC accounts for 1-2% of all ovarian tumors (10,17). TCC of the ovary is a recently recognized subtype of ovarian surface epithelial-stromal cancer, and studies of its morphology are rare. The presence of a component of benign or borderline Brenner tumor confirms an ovarian primary tumor. TCC of the ovaries has mucin pools and thick papillae with smooth luminal borders, in contrast to the pseudo-papillae of tumor cell necrosis that is common in metastatic TCC (10,17). Another study has shown that the morphological similarity between transitional cell carcinoma of the ovary and its counterpart from the urinary bladder does not indicate any histogenic similarity, but CK7 and CK20, together with uroplakin III and WT1 may prove useful in distinguishing primitive TCCs of the ovary, and metastases from invasive TCC of the bladder to the ovary, the former being a variant morphology in the spectrum of surface epithelial carcinomas (11,18).

9. Conclusion

Microscopic examination remains the first tool in the diagnosis of these heterogeneous tumors and in the separation of closely related tumors. Primary TCC of the ovary is a relatively rare subtype of epithelial ovarian cancer. Surgical resection is the primary therapeutic approach, and patient outcomes following chemotherapy are better than for other types of ovarian cancers.

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