Transitional Cell Carcinoma of the Ovary: Report of Three Cases

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Background: We investigated retrospectively the records and tissue samples of patients with primary ovarian transitional cell carcinoma to determine clinical and pathologic features.
Methods: The records of 3 patients with ovarian transitional cell carcinoma were reviewed using data from several imaging techniques: transvaginal ultrasound, computed tomography, and magnetic resonance imaging. We also determined levels of several tumor marker molecules; and the level of carbohydrate antigen 125 (CA 125), was examined by means of immunohistochemistry.
Results: The tumors of 2 patients were classified as pure transitional cell carcinoma; in the remaining patient, as predominantly transitional cell carcinoma. All tumors were bilateral, and 2 of the 3 tumors formed solid masses. Areas of irregular high intensity signals were seen in magnetic resonance images of the solid parts of the tumors. All 3 tumors tested positive for CA 125; histochemical expression was confined to the tumor cell membrane and/or the cytoplasm in all cases. The tumors of all 3 patients tested negative for carcinoembryonic antigen (CEA), and second-look laparotomies did not reveal any residual neoplasms in any of the patients. The patients have been in a disease-free state for 34, 42, and 14 months, respectively.
Conclusion: Our results suggest that transitional cell carcinomas tend to arise bilaterally and to form solid tumors. Magnetic resonance imaging was a useful diagnostic modality in these cases. Transitional cell carcinoma was characterized by the presence of CA 125 and the absence of CEA.

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Key words: ovary, transitional cell carcinoma, magnetic resonance imaging, CA125, CEA

INTRODUCTION

Transitional cell carcinoma, a major type of ovarian carcinoma, is characterized by urothelial differentiation and the absence of a benign, metaplastic, and/or proliferating Brenner component. Austin and Norris[1] first classified transitional cell carcinoma of the ovary as an entity distinct from malignant Brenner tumors in 1987. Silva et al.[2] described 88 instances of ovarian carcinoma that contained areas of transitional cell carcinoma. Although the patient's prognosis may improve when the transitional cell carcinoma component of the tumor is predominant, because transitional cell carcinoma generally responds well to chemotherapy, the clinical significance of this observation remains to be clarified.[3,4]

Ovarian carcinoma consisting solely of transitional cell carcinoma is rare. We examined retrospectively the characteristics of 2 patients with pure transitional cell carcinoma of the ovary and 1 patient with ovarian carcinoma that was predominantly transitional cell carcinoma to clarify the clinical and pathological features of transitional cell carcinoma.

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PATIENTS AND METHODS

Ovarian malignancy was suspected during pelvic examinations performed on 3 patients to evaluate an increase in abdominal girth. The clinical features of the tumors of these patients were evaluated between 1991 and 1995 by transvaginal ultrasonography (Mochida, Tokyo, Japan) at Kurume University Hospital; by computed tomography (TCT-60A; Toshiba, Tokyo, Japan), by magnetic resonance imaging (SMT-50; Shimazu, Tokyo, Japan) (Table 1) and by assays of the serum tumor markers carbohydrate antigen 125 (CA 125), CA 72-4, basic fetoprotein (BFP), sialyl Tn antigen (STN) and carcinoembryonic antigen (CEA) (Table 2). After the ovarian neoplasms were diagnosed, each patient underwent a staging laparotomy consisting of a hysterectomy, a bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node adenectomy, and an omentectomy. Macroscopic examination showed no evidence of residual tumor tissue at the termination of the surgical procedure. Each

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Table 1. Characteristics of 3 patients with transitional cell carcinoma (TCC) of the ovary.

Patient no.	Age (y)	Gravida /Para	Stage (FIGO)	Tumor Size (cm)	Histologic component major	Histologic component secondary
1	67	0/0	IIb	rt. 20 × 20 × 15 lt. 10 × 10 × 15	TCC (100%)	—
2	45	3/2	IIIc	rt. 40 × 50 × 80 lt. 70 × 80 × 95	TCC (80%)	Serous (20%)
3	38	2/2	IIIc	rt. 16 × 15 × 12 lt. 12 × 10 × 10	TCC (100%)	—

rt., right; lt., left; FIGO, International Federation of Gynecology and Obstetrics.[5]

Table 2. Serum levels of tumor marker antigens in 3 patients with transitional cell carcinoma of the ovary.

Marker (diagnostic level)[a]	Patient no. 1	Patient no. 2	Patient no. 3
CA 125 (35 U/mL)	120 U/mL	3800 U/mL	970 U/mL
CA 72-4 (4.0 U/mL)	—	1740 U/mL	4.2 U/mL
STN (45 U/mL)	45 U/mL	2500 U/mL	36 U/mL
BFP (75 ng/mL)	79 ng/mL	260 ng/mL	83 ng/mL
CEA (2.5 ng/mL)	2.0 ng/mL	< 1.0 ng/mL	< 1.0 ng/mL

CA, carbohydrate antigen; STN, sialyl TN; BFP, basic fetoprotein; CEA, carcinoembryonic antigen. [a]higher level suggests malignancy.

patient received 5 courses of postoperative combination chemotherapy: cisplatin (70 mg/m^2), epirubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2).

The tumors of the 3 patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.[5] The histologic diagnosis of transitional cell carcinoma was based on the following characteristics of these tumors: thick papillary proliferations, a smooth luminal border, and projection of the tumor into empty cystic spaces. The epithelial cells that formed the papillae were polygonal. Focally, spindle cells and glandular lumina were observed. The neoplasms were graded according to the World Health Organization criteria for transitional cell carcinoma of the urinary tract.[6] An average of 20 sections from the tumor of each patient were examined histologically. The numbers of mitoses per 10 high-powered fields in the tumor tissue were examined.

Tissue specimens were fixed in 10% formalin, embedded in paraffin, and examined by immunohistochemical techniques for expression of the CA 125 antigen (OC-125; anti-CA125TM; CIS Bio International, Gif-Sur-Yvette, France).

RESULTS

Pathologic Features

All 3 patients had bilateral tumors. Upon gross examination, 2 of the 3 tumors were essentially solid masses; the tumor of the remaining patient was predominantly cystic with a solid component. The maximum dimension of the tumor was approximately 20 cm in patients 1 and 3, and more than 90 cm in patient 2 (Table 1) (Fig.1). The neoplasms in patients 1 and 3 consisted entirely of transitional cell carcinoma tissue, and the neoplasm in patient 2 was predominantly composed of transitional cell carcinoma tissue. Metastatic lesions of the omentum and the para-aortic lymph nodes in patients 2 and 3 were diagnosed histologically as transitional cell carcinoma. The histologic examination showed the presence of thick papillary proliferations with a smooth luminal border and projection into empty cystic spaces, which are similar to the characteristics of carcinoma of the urinary bladder. The epithelial cells forming the papillae were polygonal. No areas of benign Brenner tumor tissue were observed. All tumors were either grade 2 or 3 according to the World Health Organization grading system for bladder cancer. Vascular invasion and tumor necrosis were observed in each case. The average number of mitoses figures per 10 high-power fields in the tumor tissue ranged from 20 to 38 (Fig. 2).

Diagnostic Imaging

The bilateral tumors in patients 1 and 2 appeared to be virtually solid masses when the patients were examined by transvaginal ultrasonography. In T2-weighted magnetic resonance imaging procedures performed on the patients, solid tumors appeared as areas of irregular high-intensity signals, although they gave low-intensity signals in T1-weighted images. After intravenous administra-

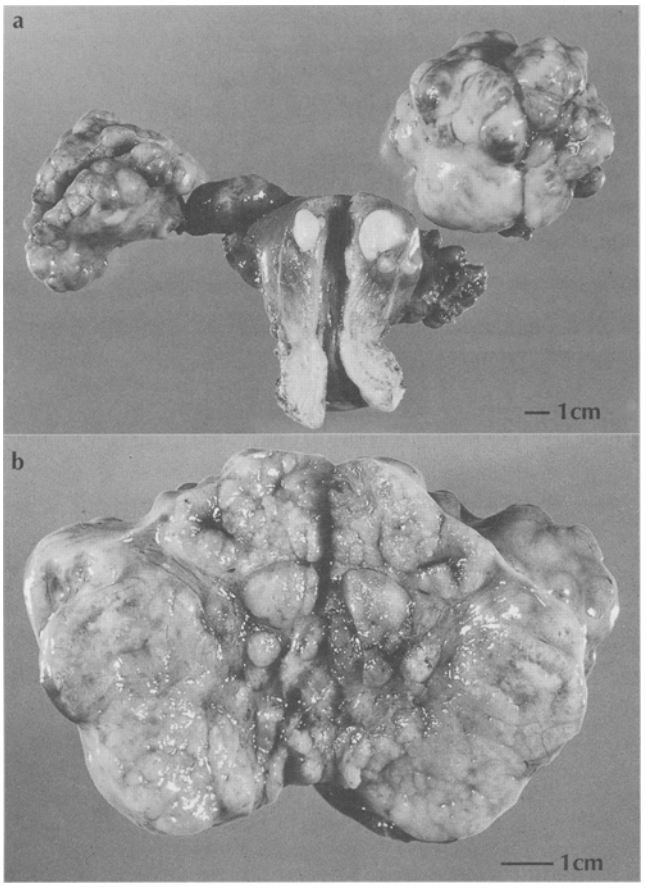

Fig. 1. Gross specimen of transitional cell carcinoma from patient 2. (**a**) Macroscopic examination showing bilateral ovarian tumors and normal sized uterine body with intramural myoma. (**b**) The cut surface of the left tumor, showing a multiloculated solid mass with focal hemorrhaging.

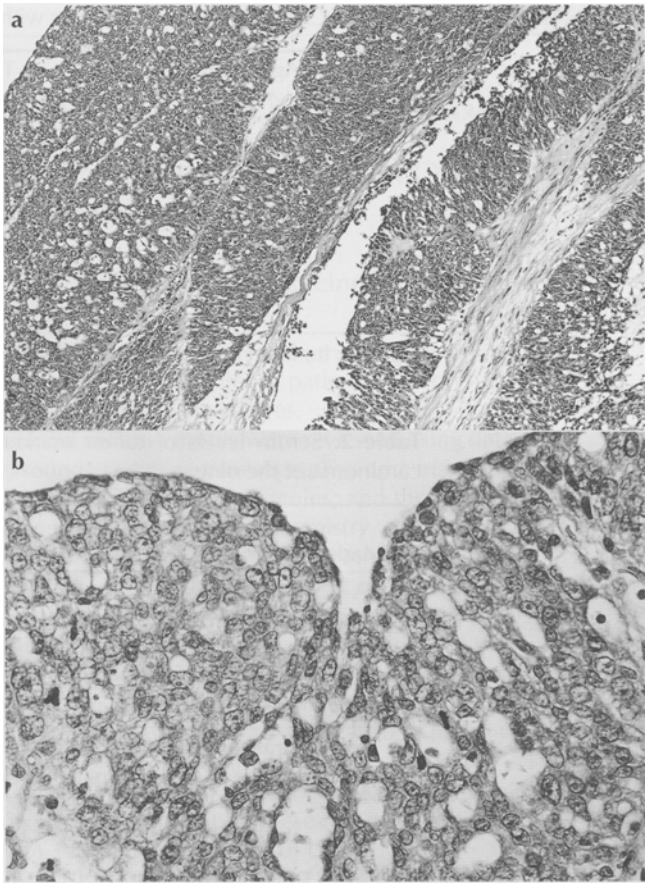

Fig. 2. Photomicrograph of transitional cell carcinoma from patient 1: thick papillary projections of transitional cell carcinoma of the ovary lined by multiple layers of epithelium showing a smooth luminal border (H&E; original magnification: **a**, × 40; **b**, × 100).

tion of a contrast medium, marked inhomogeneous enhancement of the tumor was observed (Fig. 3). A computed tomography scan showed a multiloculated cystic mass in the pelvis in patient 3. The septum was thick and was irregularly enhanced by the contrast medium.

Tumor Markers

Serum levels of the tumor antigen CA 125 were elevated in all 3 patients (Table 2). The serum level of CEA was less than 2.5 ng/mL in all patients. The serum levels of CA 72-4, STN, and BFP were near the level that suggests malignancy in patients 1 and 3. Immunohistochemical assays showed that expression of the CA 125 antigen was confined to the tumor cell membrane or to the cytoplasm of the tumor cells in all cases.

Clinical Outcome

The results of second-look laparotomies were negative for recurrence in all 3 patients. Patients 1, 2, and 3 have been disease-free for 34, 42, and 14 months, respectively.

DISCUSSION

Transitional cell carcinoma is a distinct histologic subtype of epithelial ovarian carcinoma.[1] Silva et al.[2] reported that urothelial differentiation was present in 9.4% of cases of ovarian carcinomas. Of the 88 cases of ovarian carcinoma associated with transitional cell carcinoma, pure transitional cell carcinoma was present in only 10 cases (11%). Primary ovarian transitional cell carcinoma can be distinguished histologically, not only from malignant Brenner tumors, but also from the more common high-grade serous carcinomas. Transitional cell carcinoma appears to be more chemosensitive and to be associated with a better prognosis than serous adenocarcinoma, but it is more aggressive than are Brenner tumors.[1,3,4] Only a few case reports of transitional cell carcinoma have been published in Japan.[7]

In the published literature, the age of patients with transitional cell carcinoma ranges from 28 to 87 years, with the mean age in the postmenopausal years.[1–8] There

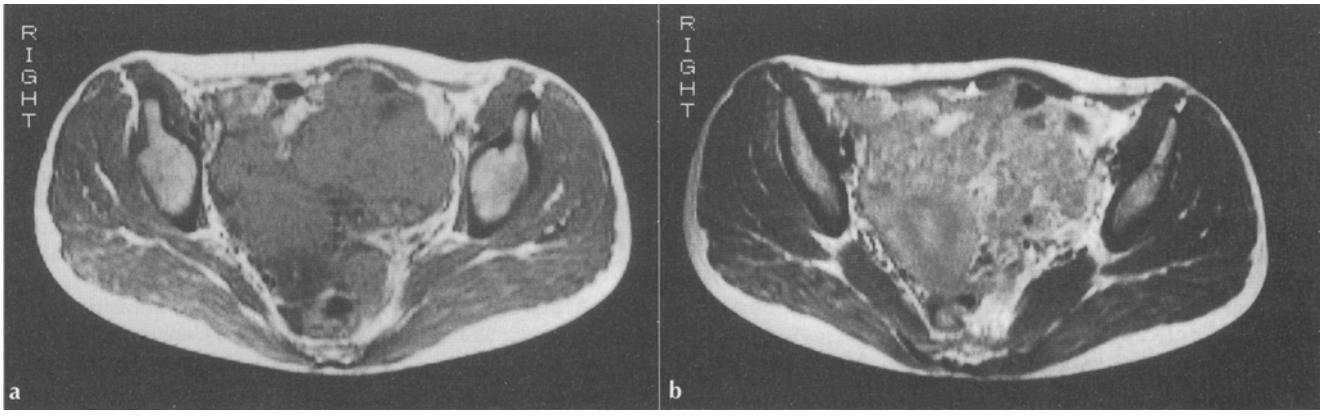

Fig. 3. Axial magnetic resonance imaging of patient 3. (**A**) Unenhanced T1-weighted (SE 500/20) image shows an almost solid mass with a low signal intensity. (**B**) Gadolinium- enhanced T1-weighted (SE 500/20) image clearly showing irregular high-intensity signals.

was no notable mean age difference compared with the mean age of patients with other types of adenocarcinoma. Austin and Norris[1] and Ayhan et al.[8] reported transitional cell carcinoma to be bilateral in 13.9% and 20%, respectively, of their cases. However, all 3 of our patients' tumors were bilateral. It has been reported that the cleavage plane of the tumors in the common epithelial malignancy was solid and cystic, but the proportion of solid and cystic tumors in transitional cell carcinoma was not specified. The tumors in our 3 patients were either solid or had a solid component. Assessment by means of magnetic resonance imaging or by use of serum tumor markers has not been reported in the literature. In our 3 cases with a high proportion of solid tumors, there were no specific findings in the tumors. Magnetic resonance imaging, however, is considered to be useful as a supplementary diagnostic method. The solid, purely transitional cell carcinoma of 2 of our patients tested positive for the presence of the antigen CA 125. However, the level of CA 125 expression was not high compared to that of tumors containing serous elements. Soslow et al.[9] reported that they located CEA by immunohistochemical methods in 68% of their cases of transitional cell carcinomas. In contrast, Ayhan et al.[8] could not demonstrate the presence of CEA in any of their patients. There is no literature on the immunohistologic determination of serum tumor markers. In all of our patients, serum CEA was negative. There are very few clinicopathologic studies to compare with our results. In our patients, the tumors showed bilateral growth and solid tumor tissue was dominant.

Prior to surgery, it is necessary to distinguish between primary and metastatic tumors, as well as other adenocarcinomas. In magnetic resonance imaging findings or tumor marker assays, the antigen CA 125 was present at moderate levels in the tumors of each of our patients, and CEA, which is usually found in metastatic tumors, could not be detected. Therefore, these tumor markers may be useful for differential diagnosis, although examination of the stomach and colon are also necessary. Further investigation is required.

Austin and Norris[1] have suggested that transitional cell carcinomas are most likely to originate directly from the coelomic epithelium, which can undergo urothelial metaplasia to transitional-type epithelium. The absence of stromal calcification, which is common in Brenner tumors, the more aggressive behavior of transitional cell carcinomas, and the association of transitional cell carcinomas with other common epithelial neoplasms provide support for this theory. The presence of OC-125 antibody in the cytoplasm of the transitional cell carcinomas in our cases suggests that ovarian transitional cell carcinomas may arise from the coelomic epithelium.

The transitional cell carcinomas in this report were of the papillary histologic type, which is the most common type of transitional cell carcinoma.[10] The tumors of 2 of our 3 patients were pure transitional cell carcinoma, which is a relatively rare situation. The tumors of all 3 showed the characteristic features of tumor necrosis and mitosis.

Previous case reports suggest that even patients with advanced ovarian transitional cell carcinoma respond to chemotherapy better than do patients with other types of adenocarcinoma, as long as both primary and metastatic lesions are transitional cell carcinoma.[3,4] Therefore, the histologic diagnosis of primary and metastatic lesions, as well as clinical staging of transitional cell carcinoma, is important. Patients in this report underwent staging laparotomies, which is the standard approach in patients with ovarian adenocarcinomas. All three patients have been without disease to date. Patient 2, who had multiple metastases greater than 3 cm in diameter in her lymph nodes, has shown no evidence of recurrence for

34 months. Patient 1, who had stage IIb disease with rectal invasion, has remained disease-free, after the completion of therapy, for 42 months.

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