CASE REPORT

Advanced squamous cell carcinomas arising from mature cystic teratoma of the ovary: a retrospective case series at the Tohoku Gynecologic Cancer Unit

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Received: 15 January 2016 / Accepted: 5 March 2016 / Published online: 17 March 2016
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Abstract We retrospectively evaluated the clinical characteristics of a rare clinical condition of International Federation of Gynecology and Obstetrics (FIGO) stage III and IV squamous cell carcinomas arising from mature cystic teratoma of the ovary between October 1999 and September 2010 at member institutions of the Tohoku Gynecologic Cancer Unit. A total of nine cases (eight FIGO stage III and one FIGO stage IV) were included in this survey. The patients' median age was 56 years (range 46–74 years), and the median tumor diameter was 140 mm (range 95–250 mm). Five of eight patients were positive for cancer antigen (CA)-125, six of eight were positive for CA19-9, four of seven were positive for the carcinoembryonic antigen, and eight of nine were positive for squamous cell carcinoma antigen. Eight patients received postoperative therapy (five underwent chemotherapy, two underwent concurrent chemoradiotherapy, and one underwent radiation therapy alone). Two patients who received

complete surgery and concurrent chemo radiotherapy achieved disease-free survival. The median overall survival was 8.9 months. Univariate analysis showed that both the patients' age (<50 years or ≥50 years) and maximum diameter of the residual tumor (<1 cm or ≥1 cm and none or persistent) did not predict the patients' prognosis. These results suggest that complete surgery should be performed because disease-free survival was observed only in patients with no residual tumor, similar to the previous findings of large number retrospective study.

Keywords Squamous cell carcinoma of the ovary · Ovarian mature cystic teratoma · Malignant transformation · Clinicopathologic features

Introduction

Mature cystic teratoma of the ovary is a common benign ovarian neoplasm, but it has a malignant histology; mainly squamous cell carcinoma results from the malignant transformation. Hackethal et al. [1] conducted a systematic review of squamous cell carcinoma in ovarian mature cystic teratoma of previously reported 64 suitable studies, and reported that 67 % of patients had International Federation of Gynecology and Obstetrics (FIGO) stage I or II. Although we previously reported on a retrospective study of 20 cases of malignant transformation arising from mature cystic teratoma of the ovary at three Japanese institutions [2], detailed clinical characteristics of advanced stage squamous cell carcinoma are still unknown. Therefore, we conducted a retrospective study limited to FIGO stages III/IV squamous cell carcinoma arising from ovarian mature cystic teratoma at the Tohoku Gynecologic Cancer Unit.

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Cases report

We assessed patients' age; preoperative values of cancer antigen (CA)-125, CA19-9, carcinoembryonic antigen (CEA), and squamous cell carcinoma antigen (SCC); FIGO 1988 stage; maximum tumor diameter; surgical procedures; maximum tumor diameter of the residual tumor; postoperative therapy; and prognosis of squamous cell carcinoma arising from an ovarian mature cystic teratoma between January 2000 and January 2010, which had been collected by a mailed survey. The survival period was calculated between the date of surgery and the date of final follow-up.

We used the log-rank test for univariate analysis, and $p < 0.05$ was considered statistically significant. The protocol for the survey was approved by the ethics committee of each of the participating facilities. Table 1 shows the patients' clinical characteristics. The median age was 56 years (range 46–74 years), and the median maximum tumor diameter was 150 mm (range 95–250 mm). Two patients had stage IIIA, six patients had stage IIIC (one patient with para aortic lymph node metastasis and another five with abdominal dissemination), and one patient had stage IV (supraclavicular lymph nodes metastasis) squamous cell carcinoma. Five of eight patients (62.5 %) were positive for CA125 (>35 U/mL), four of seven (57.1 %) were positive for CEA (5 ng/mL), six of eight (75.0 %) were positive for CA19-9 (>37 U/mL), and eight of nine were positive for SCC (>1.5 ng/mL). Table 2 shows the treatment procedures and prognostic outcomes. One patient underwent a tumor biopsy, and 8 underwent cytoreductive surgery. Finally, four patients (44.4 %) achieved complete resection, 2 (18.2 %) achieved optimal resection (the maximum diameter of the residual tumor was <1 cm), and two had a suboptimal resection. Five patients underwent postoperative chemotherapy, two underwent concurrent

chemo radiotherapy with platinum agents, and one underwent radiation therapy alone. However, no evaluable responses were observed in patients with measurable diseases. The median overall survival time of all registered patients was 8.9 months with a median follow-up period of 8 months (range: 1–107 months). Univariate analysis showed that both patients' age (<50 years or ≥ 50 years: $p = 0.098$) and maximum diameter of the residual tumor (<1 cm or ≥ 1 cm: $p = 0.957$ and none or persistent: $p = 0.146$) did not significantly predict the patients' survival for FIGO stages III/IV squamous cell carcinoma arising from an ovarian cystic teratoma. However, complete surgery and chemoradiotherapy as an adjuvant therapy resulted in long-term survival in two patients.

Discussion

Advanced staged squamous cell carcinoma in mature cystic teratoma is a poor prognostic tumor. The prognosis of stages III and IV has been reported as follows: 2-year survival in 30 % with stage III and 0 % with stage IV [3]; and 5-year survival in 0 % [4] and 20 % with stage III, and 0 % with stage IV [5]. Furthermore, a recent systematic review [1] demonstrated that although the FIGO stage has a significant prognostic effect, the prognosis of patients with stage II was similar to that of those with stages III and IV. We previously reported the clinicopathologic features of 20 cases (FIGO stage I in 11, stage II in 4, and stages III and IV in 5) at three institutions (Miyagi Cancer Center, Kinki University Faculty of Medicine, and Tohoku University Graduate School of Medicine) between 1988 and 2008 [2]. We found that the overall 1-year survival was 70 %, and the prognosis of this tumor was closely related to the patients' age, FIGO stage, and attainment of optimal cytoreduction, which is similar to the results of previous

Table 1 Clinical characteristics

No.	Age (years)	FIGO (1988) stage	Tumor diameter (mm)	CA125 (U/ml)	CA19-9 (U/ml)	CEA (ng/ml)	SCC (ng/ml)
1	49	IIIA	140	86	68	NE	50.6
2	58	IIIA	140	11	NA	2.6	17
3	68	IIIC	150	24	87.8	NA	2.2
4	46	IIIC	250	48	49.22	NA	10.6
5	50	IIIC	120	71.7	NA	11.9	NA
6	74	IIIC	200	51	248.3	9.7	2.4
7	40	IIIC	165	129	198	4.5	3.3
8	56	IIIC	150	NA	NA	NA	4.2
9	57	IV	95	NA	211	21.8	12

FIGO International Federation of Gynecology and Obstetrics, NA not available

Table 2 Treatment and prognosis

No.	Surgery	Residual tumor	Postoperative therapy	Best response	Prognosis
1	TAH + BSO + pOm	None	CCRT	NE	DFA
2	TAH + BSO	None	CT (BIP)	NE	DOD
3	TAH + BSO + Colostomy	1 cm<	CT (TC)	SD	DOD
4	TAH + BSO + pOm + app	<1 cm	CT (BEP)	NE	DOD
5	TAH + BSO + pOm + PLN + PAN	None	CT (TC)	NE	DOD
6	TAH + BSO + pOm + PLN	<1 cm	CT (TC)	NE	DOD
7	TAH + BSO + pOm + PLN + PAN	None	CCRT	NE	DFA
8	Biopsy	1 cm<	–	–	DOD
9	BSO + pOm	1 cm<	RT	SD	DOD

TAH abdominal total hysterectomy, BSO bilateral salpingoophorectomy, pOm partial omentectomy, app appendectomy, PLN pelvic lymph node dissection, PAN paraaortic lymph node dissection, RT radiation therapy, CT chemotherapy, CCRT concurrent chemoradiotherapy, TC paclitaxel and carboplatin, BIP bleomycin, ifosfamide and cisplatin, BEP bleomycin, etoposide and cisplatin, NE not evaluable, SD stable disease. DOD died of disease, DFA disease-free alive

studies [3–7]. However, our present study showed that these prognostic factors did not significantly predict the patients' prognosis for FIGO stages III/IV. Furthermore, although a systematic review [1] reported that postoperative radiotherapy did not show any benefit and it may adversely affect survival, two patients who achieved disease-free survival underwent postoperative concurrent chemo radiotherapy in our present survey. These results suggest that the indication of complete surgery and postoperative chemo radiotherapy may be one of the options for improving the long-term prognosis of advanced stage squamous cell carcinoma in mature cystic teratoma. Furthermore, although the detailed mechanisms are unknown, resistance to postoperative therapy is thought to be a poor prognostic factor in patients with this tumor. A recent phase III study reported that paclitaxel and carboplatin were useful for patients with metastatic or recurrent cervical cancer, and they were inferior to paclitaxel and cisplatin combination therapy [8]. Considering that the most frequent histological subtype in cervical cancer is squamous cell carcinoma, paclitaxel and carboplatin combination therapy concurrent with chemo radiotherapy would be considered a treatment option for this type of tumor. Furthermore, a recent phase II study (RTOG 0417) [9, 10] and NRG Oncology/Gynecological Oncology Group protocol 240 phase III study [11, 12] showed that the addition of bevacizumab to combination chemotherapy and definitive pelvic chemo radiotherapy contributes to improving the prognosis of patients with locally advanced squamous cell carcinoma of the uterine cervix. According to the results of those recent clinical trials, the treatment effects and feasibility of paclitaxel and carboplatin combination therapy concurrent with chemo radiotherapy and bevacizumab for

patients with advanced squamous cell carcinoma arising from an ovarian cystic teratoma are yet to be evaluated.

Previous studies [4, 13] have reported that the values of SCC and CEA, the patient's age, and tumor size are useful screening markers to detect malignant transformation of mature cystic teratoma. Furthermore, they have reported that significant differences were observed in the values of SCC, CA125, CEA, and CA19-9 between mature cystic teratoma and squamous cell carcinoma arising from an ovarian cystic teratoma [4]. We previously studied the value of serum tumor markers in 435 patients with mature cystic teratoma of the ovary, and reported that the respective mean values and frequencies of abnormal elevation for CA125, CA19-9, and SCC were 26.8 ± 21.5 U/mL, 246.8 ± 357.7 U/mL, and 1.6 ± 0.8 ng/mL; and 12.9, 50.6, and 4.6 %. Moreover, we also reported that although the values of CA125 and CA19-9 were significantly correlated with the maximum tumor diameter, the values of SCC were not influenced by the patient's menstruation status, occurrence site, and maximum tumor diameter [14]. The value of SCC in the present study showed that the mean value of SCC in a FIGO stage III/IV tumor was 17.9 ± 16.4 ng/mL, and the lowest value was 2.2 ng/mL. Considering that a previous review [1] reported that the values of serum tumor markers, including SCC, CA125, CA19-9, and CEA, had no correlation with the FIGO stage, a preoperative examination of SCC would be useful for diagnosing an advanced FIGO stage tumor and detecting malignant transformation from benign mature cystic teratoma.

Compliance with ethical standards

Conflict of interest The authors of this article declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparative ethical standards. For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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