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Case Report

Clinical analysis of 11 cases with squamous cell carcinoma arising from mature cystic teratoma of the ovary

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Abstract: Objectives: Due to its rarity, standard management for squamous cell carcinoma (SCC) arising from mature cystic teratoma (MCT) has not been achieved. We conducted a retrospective study to analyze the clinical characteristics, treatment and prognosis of SCC-MCT and to report our experiences with this disease. Methods: We identified 11 patients treated for primary or recurrent SCC-MCT at Zhejiang Tumor Hospital between 1995 and 2014. The patient's clinical characteristics, treatment, and prognosis were retrospectively evaluated. Results: Of the 11 cases, six patients were primary SCC-MCT and five were disease recurrence. The median age was 52 years (range 46-57 years). Mean tumor size was 10.3 cm (range, 11 ± 4 cm). Two cases had elevated level of SCC-antigen (SCC-Ag) and 4 cases demonstrated elevated level of CA125. Of the six cases with primary SCC-MCT, one case was stage IIC, and five were stage I. Three of them received adjuvant chemotherapy. The patient with stage IIC died of disease, and the overall-survival was 8 months. Of the five cases with disease recurrence, one patient refused treatment, and the other four patients received surgical resections followed by adjuvant chemotherapy or chemoradiation. Two patients died with overall-survival of 12 and 15 months. Conclusion: The overall-survival rate in patients with stage greater than I is extremely low. Therefore, early detection and adequate staging surgery are crucial for long-term survival.

Keywords: Ovarian cancer, mature cystic teratoma, squamous cell carcinoma, prognosis

Introduction

Mature cystic teratoma (MCT) is the most common ovarian germ cell tumor, accounting for 10-20% of all ovarian neoplasms. Malignant transformation of MCT is rare and occurs in 1-2% of this neoplasm, with squamous cell carcinoma (SCC) as the most common malignant change (80-90%). Other types of malignant transformation of the MCT include adenocarcinoma, carcinoma, melonamas, sarcomas, lipomas, and thyroid tumors [1]. Ovarian SCC, on the other hand, can arise from three different sources: SCC arising solely from an ovarian surface epithelium, SCC arising from MCT, and SCC arising from endometriosis [2]. Of these, SCC arising from MCT (SCC-MCT) is the most commonly encountered. Compared to benign MCT, malignant transformation of MCT occurs primarily in elderly women, with age range of 45-60 years [3]. The clinical presentations are similar to other ovarian tumors, including abdominal pain, abdominal distension from pelvic mass compression. And in some locally advanced cases, it can also include bladder and bowel symptoms. Preoperative diagnosis of SCC-MCT is very difficult. Diagnosis is usually made intra- and post-operatively by histopathological analysis. Therefore, re-staging surgery or cytoreduction is frequently needed. Patients in the advanced stage or with recurrent SCC, in which the lesions have spread beyond the ovary, have very poor prognosis. Standard treatment has yet to be established and there is no significant improvement in the overall survival rate of patients with SCC-MCT in recent years. In the present study, we examined and analyzed all cases of SCC-MCT in our institution for the past 20 years to better understand its clinical characteristics, treatment, and prognosis. We aimed to provide valuable information of the disease to enable better management of the disease in the future.

Table 1. Clinical characteristics of patients with initial presentation of SCC-MCT

Case	Age	Clinical feature	Re-staging	SCC-Ag (ng/ml)	CA125 (U/ml)	Tumor diameter (cm)	Stage	Chemotherapy	Prognosis	Survival (months)	Disease-free survival (months)
1	48	Abdominal pain	No	16.5	86.50	12.2	IIC	BEP	Advanced disease and death	8	1
2	61	Palpable mass	Yes	2.0	11.2	7.8	IA	NA	Alive	80	80
3	49	Palpable mass	Yes	NA	49.50	12.1	I	NA	Alive	36	36
4	67	Palpable mass	Yes	NA	11.40	7.8	I	DDP	No follow-up	NA	NA
5	45	Palpable mass	Yes	NA	26.20	10.1	I	BEP 4 cycles	No follow-up	NA	NA
6	45	Abdominal distension	Yes	NA	7.22	11.8	I	NA	No follow-up	NA	NA

Table 2. Clinical characteristics of patients with recurrent SCC-MCT

Case	Age	Initial treatment	Stage	Adjuvant treatment	SCC (ng/ml)	CA125 (U/ml)	Recurrent location	Recurrence interval (months)	Recurrent treatment	Status	Survival (months)
1	53	Total hysterectomy + bilateral salpingo-oophorectomy + omentectomy + appendectomy	Unknown	Doxorubicin and cis-platinum	NA	29.3	Pelvis	1	Refused treatment	No follow-up	NA
2	65	Pelvic mass + partial ileal resections	NA	None	NA	80.87	Small intestine	3	Hartmann's operation + partial small intestinal resection + CAP chemotherapy	No follow-up	NA
3	48	Total hysterectomy + bilateral salpingo-oophorectomy + pelvic and omentum resection + appendectomy	NA	CP 3 cycles	NA	12.5	Retroperitoneal lymph node	3	Laparotomy + DDP chemotherapy + radiotherapy	No follow-up	NA
4	61	Total hysterectomy + bilateral salpingo-oophorectomy + pelvic lymphadenectomy + cytoreduction	IIC	TP 3 cycles	1.2	8.5	Vaginal cuff	1	Pelvic mass resection + Dixon surgery + colostomy + BEP 6 cycles	Death	15
5	40	Laparoscopic ovarian cystectomy	NA	None	13.9	29.27	Pelvis; bladder; retroperitoneal lymph node; laparoscopic portsite	1	Ovarian cystectomy + partial cystectomy + TP chemotherapy + radiotherapy	Death	12

CAP- Cyclophosphamide, Adriamycin and Cisplatin. BEP- Bleomycin, Etoposide, and Cisplatin. DDP- Cis-diamminedichloroplatinum (II).

Materials and methods

Informed consent was obtained from all individual patients or their family included in the study. Between 1995 and 2014, 14 cases with SCC of the ovary were treated at our institution of Zhejiang Tumor Hospital in China. Of the 14 cases, 11 were cases of SCC arising from the MCT. A retrospective chart review was conducted. Identified cases were assessed for age, preoperative serum tumor markers, clinical presentations, histopathological findings, surgical and adjuvant therapies, disease recurrence and treatments, as well as overall-and disease-free survival. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 12.0.

Results

Of the 14 patients, eleven patients had SCC arising from MCT, two had SCC arising from ovarian surface epithelium, and one had SCC arising from ovarian endometriosis. Among the 11 cases with SCC arising from MCT, 6 were cases with initial presentation of SCC-MCT, and the other 5 were cases of recurrence. Tissue samples from all patients were reviewed by our pathologists in the Department of Pathology.

Clinical presentation

The median age of the 11 patients was 52 years (range 40-57 years). Of the 6 cases with primary SCC-MCT, 4 patients were presented with palpable abdominal mass, 1 patient experienced abdominal pain, and 1 patient showed abdominal distension. Among the 5 cases of recurrence, 1 patient was presented with metastases at the laparoscopic puncture site, 1 had mass at vaginal cuff, and 3 had pelvic mass extended to the colorectal and bladder.

Auxiliary examination

The mean tumor size was 10.3 cm (range, 11 ± 4 cm). All cases were tested with serum tumor markers. Increased levels of SCC-antigen (SCC-Ag) were observed in one case with primary SCC-MCT and in one case of recurrence. Four cases demonstrated elevated level of CA125.

Treatment and prognosis

As shown in **Table 1**. Among the 6 cases with initial presentation of SCC-MCT, primary surgical staging was performed in one case who was then classified as stage IIC. Re-staging was conducted in the other 5 patients. Four cases were classified as stage IA and one case as stage IC. Three patients received either intravenous chemotherapy with bleomycin, etoposide, and cisplatin (BEP) or intraperitoneal chemotherapy with cis-diamminedichloroplatinum (II) (DDP). Pelvic mass was detected in the patient with stage IIC disease after one course of chemotherapy. The patient died 8 months after diagnosis with 1 month of disease-free period. Among the 5 patients with stage I disease, 3 were not followed up, and the other 2 were alive with overall-survival of 36 and 80 months.

As shown in **Table 2**. In patients with disease recurrence, 4 cases previously underwent ovarian cystectomy and 3 received postoperative adjuvant chemotherapy. One case was managed with pelvic mass and partial ileal resections, followed by adjuvant chemotherapy. The average recurrence interval was 2.5 months. One recurrent case refused to be treated and was not followed up. The other 4 recurrent cases received cytoreductive surgery with adjuvant chemotherapy. Specifically, 2 cases underwent intestinal resection, 1 case underwent retroperitoneal lymph node dissection, and 1 case underwent urinary bladder cystectomy. All 4 cases received postoperative TP or BEP chemotherapy. One case also had radiotherapy. There were no follow-up on two of the patients and the other 2 patients died of disease. The overall survival for these 2 cases were 15 and 12 months, respectively.

Discussion

SCC arising from MCT of the ovaryis very rare. In fact, in our retrospective study, we found only 11 cases admitted to our institution over the past 20 years. Consistent with other study [3], our result showed that SCC-MCT affected elderly patients with median age of 52 years. The most common symptoms were abdominal pain, palpable mass, and abdominal distension. Most patients had palpable mass and received ultrasound examination on lower abdomen. However, physical examination and ultrasonography cannot give definitive diagnosis. In contrast, some imaging features of magnetic resonance imaging may be more helpful for preoperative diagnosis, such as solid components.

As our institute is specialized in oncology, most of our patients were referred for further evaluation or had disease recurrence. Therefore, of the 11 cases of study, only one patient underwent primary surgical staging, whereas the other 10 cases presented patients who underwent re-staging surgery or had disease recurrence. The patient with primary surgical staging was classified as stage IIC, and underwent oophorectomy followed by adjuvant chemotherapy of BEP. However, the patient died 8 months after diagnosis. Five patients who were referred from other local hospitals, underwent re-staging surgery. No residual tumor was detected. They were classified as stage I. Two received postoperative adjuvant chemotherapy with DDP or BEP. Presently, two patients are alive with overall survival of 36 and 80 months. The other five cases were patients with recurrent disease. Distant metastases were noted in the bladder, rectum, small intestine, retroperitoneal lymph node, vaginal cuff, and pelvis. Of these five patients, one refused treatment. The other four underwent cytoreductive surgery, and there were no residual tumors detected in three of them after surgery. All four cases received postoperative chemotherapy. Two cases received additional radiotherapy. Two patients died of disease with overall-survival of 12 and 15 months. Our analyses suggest that patient with stage greater than I or those with abdominal metastases have poor prognosis.

Strict histopathological analysis is necessary for a definitive diagnosis of SCC-MCT in patients. Pathological sampling on multi-site is required to reduce chances of wrong diagnosis. In one of our recurrent cases, patient initially underwent laparoscopic ovarian cystectomy at a local hospital and was diagnosed as benign MCT. However, when patient was referred to our institute, patient was presented with metastases at the laparoscopic port site, abdominal cavity, and bladder, indicating a misdiagnosis case of SCC-MCT. The misdiagnosis might be due to the large tumor size with multi germ layers, and consequently, the malignant area was not pathologically sampled. The metastasis at the pelvis may be caused by ruptured tumor and dissemination during laparoscopy. Therefore, preoperative examination to determine possibilities of tumor malignancy is crucial. Optimal surgical strategy, including complete tumor resection, may then be planned to prevent cyst rupture and dissemination. Multi-site biopsy, as well as Intraoperative and post-operative histopathological diagnosis are also important. In addition, immunohistochemistry staining with P63 CK5/6 might help to diagnose SCC.

Preoperative diagnosis of SCC-MCT can be indicated from the following: 1. Age: Malignant transformation arising from MCT is mostly observed in older women than those with benign tumor. The average age is over 50 years, and most of them are postmenopausal. 2. Tumor size: Large tumors are generally associated with increased risk of malignancy [4, 5]. Our analysis together with other studies showed that the tumor diameter of SCC-MCT is over 10 cm, bigger than benign tumor [5, 6]. 3. Preoperative serum tumor markers: Early research has reported elevated levels of SCC-Ag (81%), CEA (65%), CA199 (65%), and CA125 (60%) in SCC-MCT patients. However, the increases in CA125 and CA199 levels are also common in other ovarian tumor, so they were not used as indicators. Elevated levels of SCC-Ag have also been associated with poor prognosis and survival rate [7, 8]. 4. Preoperative imaging diagnosis: MRI can effectively distinguish between benign and malignant tumors. It can indicate the presence of a solid tumor or invasive growth. For example, imaging of an enhanced contrast of asolid component with transmural extension and invasion through the septa to the peritoneal area indicates malignancy [9]. A report has also shown fatty inhibition of T1 signal [10].

Due to the relatively low incidence of the disease, uniform consensus for SCC-MCT management has not been achieved. Multivariate analysis by Hackethal *et al.* demonstrated that tumor staging and optimal cytoreduction are correlated with prognosis. Therefore, it is recommended to perform re-staging surgery for those who have undergone only unilateral oophorectomy or oophorocystectomy. Patients with confirmed tumor stage IA have good prognosis and those who want to preserve their fertility can be managed with unilateral oophorectomy. Patients with tumor stages greater than 1A who had hysterectomy had better mean survival than those who did not have hysterectomy [11]. For stage II patients, omentectomy did not improve survival rate. Rather, lymphadenecto-

my improved survival rate (59.2 *vs.* 40.4 months). In the analyses, Hackethal *et al.* also indicated that ruptured tumor did not affect prognosis. Contradictorily, we found that laparoscopic cystectomy resulted in tumor dissemination, and patient showed worse survival rate. Therefore, patients with large tumor, and elevated SCC-Ag level should have laparoscopy cautiously.

In the treatment of SCC, the importance of radiotherapy and chemotherapy is still unclear. Chen *et al.* [8] found that chemoradiation was ineffective for stage I and II patients, but it prolonged the overall survival of stage III and IV patients. Ford *et al.* reported a successful treatment with multimodality therapy which includes surgical resection, followed by chemotherapy, and radiation in a stage IIC patient. This patient underwent optimal cytoreduction, including hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, and pelvic and pariaortic lymph node dissection. Postoperative examination confirmed that patient had bilateral tumor, which had invaded the uterus serosa and myometrium, and disseminated to the pelvic wall and mesentery. The patient then received 3 cycles of taxol (175 mg/m^2) and cisplatin (75 mg/m^2), followed by pelvic and pariaortic irradiation (4500 cGY). Radiation was performed concomitantly with chemotherapy of cisplatin (30 mg/m^2 per week), and cetuximab (400 mg/m^2 initial dose, followed by 250, 300, 350, 400 mg/m^2 per week). After radiation therapy, the patient received additional 3 cycles oftaxol (175 mg/m^2) and cisplatin (75 mg/m^2). The patient remained disease-free 5 years after diagnosis. In another report, Ito *et al.* [12] reported successful treatment with carbon ion radiotherapy (CIRT) in a stage IIC patient. The patient underwent hysterectomy and bilateral salpingo-oophorectomy, and received 6 cycles of taxol and cisplatin, but had disease recurrence. CIRT was given and patient remained disease-free for 53 months.

In most of our recurrent cases, patients were with advance metastases. Recurrences occurred at the pelvic within 3-4 months after initial surgeries. There was one case in which metastasis was observed at the laparoscopic portsite after one month of surgery. Although these patients underwent optimal cytoreductive surgery, the lack of effective postoperative adjuvant chemotherapy resulted in poor prognosis. We treated these patients with chemotherapies such as taxol combined with cisplatin (TP), bleomycin combined with etoposide and cisplatin (BEP), and cyclophosphamide combined with cisplatin (DDP). Tumor growth was suppressed. However, patients developed resistance to the chemotherapies. Once the courses of the treatment end, the tumor developed rapidly. Postoperative radiotherapy is the most effective treatment currently. However, radiotherapy can cause complications, including intestinal adhesions and obstructions.

In conclusion, the overall-survival rate in SCC-MCT patients with stage greater than I is extremely low. Therefore, early detection and adequate staging surgery are crucial for long-term survival. SCC patients with older age and tumor size over 10 cm should be cautious in choosing laparoscopic surgery. If laparoscopy is to be performed, spillage of cyst's content should be avoided. Standard postoperative treatment for SCC-MCT patients has yet to be established. When conventional treatment fails, targeted therapies and three-dimensional conformal radiotherapy can be applied to minimize radiotherapy-induced complication of intestinal adhesion and obstruction.

Disclosure of conflict of interest

None.

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