

RESEARCH ARTICLE

Characteristics and Treatment Outcomes of Patients with Malignant Transformation Arising from Mature Cystic Teratoma of the Ovary: Experience at a Single Institution

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Abstract

Background: Malignant transformation arising in mature cystic teratoma (MCT) is one of the most serious complications of MCT. Squamous cell carcinoma is the most common malignant change. Some clinical findings such as advanced age group and large tumor size are significant risk factors of malignant transformation. This study was conducted in order to evaluate characteristics, cell types, treatment and outcome of malignant transformation arising from dermoid cysts in our institution. **Materials and Methods:** A retrospective chart review was performed. General characteristics, operative data, procedure, operative finding and operative outcome were analyzed. Statistical assessment was performed with SPSS version 17.0, using mean, mode, median and percentage to describe those data. **Results:** During the 10 years period, 11 cases of malignant transformation from a total of 753 cases (1.46% incidence) of MCT were reviewed. Mean age of the patients was 41.2 years (SD 4.34, range 24-70). The most common presenting symptom was a palpable mass (8 cases; 72.7%). Primary surgical staging was performed in 4 patients (36.4%). Re-staging was conducted in the other 4. Complete cytoreduction was obtained in 45.5% (5 cases) and optimal surgical resection was obtained in 36.4% (4 cases). Mean tumor size was 14.1 cm. (SD 1.55, range 6-20). Squamous cell carcinoma was found in 36.4% (4 cases) and mucinous cancer in the other 4. More than half of them were stage Ia (54.5%, 6 cases). All patients whose stage more than Ia received chemotherapy (45.5%). Mean disease free survival was 5.53 years (1.32, 0.3-10). **Conclusion:** According to our study, the incidence of malignant transformation was consistent with previous studies. The common malignant transformation histologic types are both squamous and mucinous carcinoma which differed from previous reports. Early detection for early stage disease and optimal surgery are important for long term survival.

Keywords: Malignant transformation - mature cystic teratoma - dermoid - characteristics - outcome

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Introduction

Mature cystic teratoma (MCT) or Dermoid cyst is the most common benign ovarian germ cell tumors. Most MCT is identified during reproductive age (Curling et al., 1979; Ribeiro et al., 1988; Ulbright, 2008). MCT comprises 3 germ layers (ectoderm, mesoderm and endoderm) (Outwater et al., 2001; Rha et al., 2004). Most MCT patients are asymptomatic and usually found accidentally during routine pelvic examination (Peterson, 1957). However, some MCTs can cause symptoms and complications. The symptoms include acute abdominal pain due to torsion, rupture or infection and abdominal distension from pressure effect of the mass (Comerci et al., 1994; Lipson et al., 1996; Kido A et al., 1999; Hackethal et al., 2008; Chang et al., 2011).

Malignant transformation arising in mature cystic teratoma is one of the most serious complications of MCT. Although, the incidence of malignant transformation is

only 1-3%, the prognosis is very poor when malignant change occurs (Griffiths et al., 1995; Kido et al., 1999; Lai et al., 2005; Hackethal et al., 2008; Park et al., 2008). Malignant change can occur from any germ layers. The most common malignant transformation is commonly arising from ectoderm. Squamous cell carcinoma is the most common malignant transformation which is nearly 80% of malignant transformation (Sakuma et al., 2010). The other types of malignant transformation such as adenocarcinoma, malignant melanoma, transitional cell carcinoma and some sarcoma can also identify (Peterson, 1957; Hirakawa et al., 1989; Griffiths et al., 1995; Karateke et al., 2006; Iwasa et al., 2007; Hackethal et al., 2008; Park et al., 2008; Park et al., 2008;).

Although, preoperative diagnosis of malignant transformation is difficult, it is important for management plan (Kikkawa et al., 1998). Some clinical finding such as peri-menopausal age group and tumor size larger than 9.9 cm may suggest malignant transformation (Tseng et

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al., 1996; Kikkawa et al., 1998; Takemori et al., 2003; Hackethal et al., 2008). The evidence supporting those finding is still inconclusive. Moreover, treatment of malignant transformation arising from dermoid cyst is also controversial. There is some evidence shows that if tumors spread out of the ovary, the prognosis will be poor (Miyasaki et al., 1991, Sakuma et al., 2010; Cheng et al., 2012).

From the observation of malignant transformation arising from MCT in King Chulalongkorn Memorial Hospital, there are some data different from the previous case series and reviews. This retrospective review was conducted in order to evaluate characteristics, cell types, treatment and outcome of malignant transformation arising from dermoid cyst in our institution.

Materials and Methods

After approval from Ethical committee was obtained. Retrospective chart review was performed. Retrospective review of patients whom diagnosis was malignant transformation arising in mature cystic teratoma of the ovary during 1 January 1993 to 31 December 2012 was conducted. The diagnostic criteria of malignant transformation arising in mature cystic teratoma were reviewed in all cases.

Patients' general characteristics such as age, race, presenting symptoms and underlying disease were reviewed. Operative data were recorded. Operative procedure, operative finding and operative outcome were also reviewed. Surgical stage was classified by using International Federation of Gynecology and Obstetrics (FIGO) system. Adjuvant treatment which included chemotherapy regimen and response rate was obtained. Disease free survival was also reviewed. All the date was determined from the date of surgery. Statistic process was performed by SPSS version 17.0. Mean, Mode, Median and percentage were used to describe those data.

Results

During 10 years period (1 Jan 1993 to 31 December 2012), all 753 cases of mature cystic teratoma were reviewed and we can identified 11 cases of malignant transformation arising from MCT. Our incidence of malignant transformation arising in mature cystic teratoma

is 1.46%. Mean age at the diagnosis time of the patients was 41.18 years (SD 4.34, range 24-70). All of the patients were Thai. Nearly half of the patients were nulliparous (5 cases, 45.5%). Only 2 patients (18.18%) were menopause. Most of the patients in this series do not have underlying disease (8 cases, 72.7%) and the others had hypertension and diabetes.

Most common presenting symptom was palpable mass (8 cases; 72.7%). The other presenting symptoms were pelvic pain and accidental finding during the routine examination. All of the patients were scanned with ultrasonography. Tumor marker was sent in some of the patients (6 cases, 54.5%) and the most common tumor marker sent was CA 125. Rising of CA 125 was found in 2 from 6 patients (33.3%). Primary surgical staging was performed in 4 patients (36.4%). Re-staging was conducted in the other 4 patients. Surgical complications were found in 3 cases. Complete cytoreduction was obtained in 45.5% (5 cases); optimal surgical resection was obtained in 36.4% (4 cases). Only 18.2% of the patients were suboptimal debulking surgery.

Mean tumor size was 14.09 cm (SD 1.55, range 6-20). Nearly most of the patients' (82.8%) tumors were larger than 10 cm. Half of the patients (54.5%) had tumor at right side of the ovary, while 36.4% was at left side. Only one patient had bilateral tumor.

Squamous cell carcinoma was found in 36.4% (4 cases). Mucinous carcinoma was also found in 36.4% (4 cases). More than half of them were stage Ia (54.5%, 6 cases); while, stage Ic was found in 2 patients (18.2%). Two cases were stage IIIc and another one was stage IIb. All patients whose stage more than Ia were received chemotherapy (45.5%). Most of them receive platinum based chemotherapy. Single agent carboplatin was administered to 1 case. Carboplatin and paclitaxel regimen was given to 2 cases. Cisplatin and 5FU regimen was assigned to 1 case and the rest regimen was cisplatin and paclitaxel. Three patients received complete 6 cycles and the entire patients who receive complete cycle attained complete remission. The other 2 patients whom stage IIIc received only 1 and 2 cycles and had to quit from protocol due to disease progression. Finally, both of them died, while the rest of the patients still survive without recurrence. Mean of disease free survival was 5.53 years (1.32, 0.3-10). Summary of patients' characteristic was demonstrated in Table 1.

Table 1. Characteristic of Malignant Transformation Arising in MCT

Case	Cell type	Age	Presenting symptoms	CA 125	Stage	Re-stage	Result	Adjuvant chemo	Cycles	Status
1	Adenocarcinoma	24	Palpable mass	1651	Ic	N	Complete resection	Carbo	6	Alive
2	Mucinous	28	Palpable mass	NA	Ia	Y	Complete resection	No	0	Alive
3	Squamous	36	Palpable mass	NA	IIIc	Y	Suboptimal	Cis-Tax	1	Dead
4	Squamous	34	Pain	NA	Ic	N	Optimal	Cis-5FU	6	Alive
5	Mucinous	33	Accidental finding	NA	Ia	N	Complete resection	No	0	Alive
6	Squamous	63	Palpable mass	31	IIIc	Y	Suboptimal	Carbo-Tax	2	Dead
7	Adenocarcinoma	45	Palpable mass	207.2	IIb	N	Optimal	Carbo-Tax	6	Alive
8	Adenocarcinoma	45	Palpable mass	24.54	Ia	N	Optimal	No	0	Alive
9	Mucinous	31	Accidental finding	NA	Ia	N	Optimal	No	0	Alive
10	Mucinous	42	Palpable mass	32.8	Ia	N	Complete resection	No	0	Alive
11	Squamous	70	Palpable mass	10.5	Ia	N	Complete resection	No	0	Alive

Discussion

In our retrospective study, we reviewed the clinical characteristics, treatment and prognosis of 11 patients diagnosed with malignant transformation arising in mature cystic teratoma of the ovary treated in our institution during a 10-year period. In general, malignant transformation of mature cystic teratoma has been reported with an average frequency of 1-2%. Squamous cell carcinoma is the most common transformation, followed by adenocarcinomas, carcinoid tumors, malignant melanomas, sarcomas, sebaceous carcinomas and thyroid papillary carcinomas (Pantoja et al., 1975; Tham et al., 1981). According to our study, we find the incidence of malignant transformation in our institution is 1.46% (11/753) which is consistent with previous studies but the most common malignant transformation histologic types in our study are both squamous cell and mucinous carcinoma which are different from previous report by Sakuma et al. (2010).

From several studies, the median age at diagnosis of malignant transformation of mature cystic teratoma of the ovary was 54-61.5 years, and tended to be older than that of its benign counterpart and most of them were in postmenopausal period (Kashimura et al., 1989; Kikkawa et al 1998; Rim et al., 2006; Dos Santos et al., 2007). That is not consistent with our study which finds that most of the patients are in premenopausal state and the median age at diagnosis is much younger (41.2 years). In general, most of the mature cystic teratoma of the ovary patients present with symptoms. The most common symptoms were abdominal pain, palpable mass and abdominal distension (Stamp et al., 1983; Hirakawa et al., 1989; Kashimura et al., 1989; Tseng et al., 1996). Most of our patients also presented with palpable mass and all of our patients were scanned with lower abdominal ultrasonography but unable to find any benefit for diagnosis of malignant transformation. Some imaging characteristics that may be beneficial in preoperative diagnosis of malignant transformation have been suggested in several studies; for an example, an area of solid component with contrast enhancement, transmural extension and irregular invasion through the septa to the peritoneal area which can be found in the cases of malignant transformation (Kido et al., 1999). Tumor size also has a role for prediction of malignant transformation from mature cystic teratoma of the ovary in imaging studies. Tumors with diameter more than 10 centimeters are associated with increased risk of malignancy in previous studies (Kikkawa et al., 1998; Yamanaka et al., 2005). In our study, the mean tumor size was 14.1 centimeters. Regarding tumor markers, squamous cell carcinoma (SCC) antigen seems to be the most useful tumor marker but from the evidences from many studies, it is still not sufficient to exclude malignant transformation preoperatively. However, in cases of recurrence, it has been shown to be useful because almost all reported cases have increased levels of SCC antigen, which usually preceded the clinical presentation by several months (Kimura et al., 1989; Tseng et al., 1996; Suzuki et al., 2000). Moreover, according to one previous study, approximately 60% of reported cases had a preoperative positive test result for CA125, and was found to be

associated with poor prognosis and survival rates (Chen et al., 2008). In our study, we performed preoperative tests for CA125 for 6 patients and one third of them had positive level but we could not find the correlation with the survival. Since there still has been no SCC antigen test for clinical service in our institution, we cannot have the data for analysis.

Numbers of previous studies have found that malignant transformation of mature cystic teratoma has a poor prognosis. Stage, tumor grade, cyst-wall invasion, rupture, tumor dissemination, ascites, adhesion, growth pattern, vascular invasion, and tumor type other than squamous cell carcinoma have previously been suggested as prognostic factors.

Early stage and optimal cytoreductive surgery are reported to be good prognostic factors. Multimodality therapy including aggressive cytoreduction followed by chemotherapy and/or radiation therapy has been recommended by several authors (Peterson, 1957; Amerigo et al., 1979; Stamp, 1983; Hirakawa et al., 1989; Kashimura et al., 1989; Pins et al., 1996; Sakuma et al., 2010; Chen et al., 2012). From our study, we could perform optimal cytoreduction in most of the patients and only two patients who were in stage IIIc could not be optimally debulked. All of our patients whose stage more than Ia were received platinum-based chemotherapy for adjuvant treatment. This regimen was also reported in previous case series by Sakuma et al (Sakuma et al., 2010). Only two patients who could not be optimally debulked had disease progression during treatment and finally died of disease. It is consistent to previous reports that tumor optimal debulking was one of the factors that most significantly influenced survival and aggressive cytoreduction for advanced disease followed by adjuvant therapy might relate to good overall survival (Tseng et al., 1996; Chen et al., 2008; Sakuma et al., 2010). However The optimal adjuvant therapy for this disease has not been established. There has been some previous literature advocating adjuvant chemotherapy or concurrent chemoradiation therapy for patients with disease beyond the ovary owing to having longer survival times than those treated with surgery alone or with adjuvant radiation therapy alone (Chen et al., 2008; Park et al., 2008). We mainly used the platinum based chemotherapy in our institution due to its known activity against epithelial ovarian cancer and squamous cell carcinoma of the cervix (Omura et al., 1985; McGuire et al., 1996; Piccart et al., 2000; Zenetta et al., 2000). There were several previous studies supporting combination chemotherapy with paclitaxel and carboplatin as active agents in malignant transformation arising from mature cystic teratoma and reported that most patients had an extended progression-free interval (Eltabbakh et al., 1998; Ohtani et al., 2000; Powell et al., 2003; Dos Santos et al., 2007; Yamagami et al., 2007; Arioiz et al., 2008; Park et al., 2008; Sakuma et al., 2010). From those literatures, we mostly used combination chemotherapy with paclitaxel and cisplatin/carboplatin in our patients and found overall response rate around 60%. There were two stages IIIc patients who were unable to complete six cycles due to progression of the disease during treatment and finally died of disease while the rest of patients still

survive without recurrence.

In conclusion, our review has shown that stage and optimal cytoreduction are correlated with prognosis. Early detection and complete surgical resection are important for long-term survival. Since malignant transformation arising from mature cystic teratoma is a rare malignancy, we have limited cases for analyzing and finding definite conclusions regarding the proper adjuvant chemotherapy for this disease. However, combination platinum/taxane chemotherapy may lead to improved survival in advanced-stage disease. Future studies are needed for developing optimal treatment.

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