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Clinical features and prognostic factors associated with malignant transformation of ovarian mature cystic teratoma

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Summary

Purpose: To explore the clinical characteristics and identify potential prognostic factors associated with malignant transformation (MT) of ovarian mature cystic teratoma (MCT). *Materials and Methods:* This study analyzed 23 patients with MT of ovarian MCT at the present center during a ten-year period. The data were analyzed using Kaplan-Meier method. *Results:* The incidence of MT of ovarian MCT was 1.3%. The mean follow-up time was 44 months. The overall five-year survival rate was 69.6%. Patient age, tumor size, histology type, disease stage, and postoperative residual disease had a significant prognostic impact on overall survival. Elevated CA125 was associated with adverse outcomes. *Conclusion:* Age of patient, size of tumor, serum CA125, CA199, CEA, and SCCA levels, and presence of HPV are potential predictors of MT of ovarian MCT. Intraoperative frozen section analysis is essential in cases of suspected MT. Patient age, tumor size, histology, disease stage, and postoperative residual tumors are important factors affecting prognosis. CA125 level is associated with a poor prognosis.

Key words: Mature cystic teratoma; Malignant transformation; Prognostic factor.

Introduction

Mature cystic teratoma (MCT) is the most common germ cell tumor of the ovary, accounting for 10-20% of all ovarian tumors [1]. Malignant transformation of ovarian MCT is extremely rare, occurring in an estimated 0.17-2% of MCT [1]. MCT are composed of well-differentiated tissues derived from three germ cell layers (endoderm, mesoderm, and ectoderm) [2]. Any MCT tissue component may undergo MT; however, squamous cell carcinoma (SCC) arising from the ectoderm compromises approximately 80% of MTs [3]. Less commonly reported malignancies include adenocarcinoma, carcinoid tumors, and melanoma [1, 4].

Management of MT of MCT is not standardized. Previous studies of MT arising from MCT were case reports or small case series; therefore, the clinical characteristics of patients, treatment outcomes, and factors affecting prognosis are not well defined. The objective of this study was to retrospectively analyze the clinical data of 23 patients diagnosed with MT of MCT to explore their clinical characteristics and identify potential prognostic factors associated with MT of MCT.

Materials and Methods

Patients undergoing surgery for ovarian MCT at the present institution between December 2004 and December 2014 were eligible for this study and patients with MT of MCT were included. Data from patients' medical records and pathology reports were collected by a retrospective chart review. Patients' age, parity, presenting symptoms, serum tumor marker levels, radiographic images, surgical procedure, intraoperative findings, histologic type, adjuvant chemotherapy, and prognosis were recorded. This study was approved by the ethical committee at the present center. Written informed consent was obtained from all patients and patient anonymity was be preserved.

Statistical analyses were performed using SPSS 22.0. Overall survival (OS) was estimated by the Kaplan-Meier method. Survival differences were assessed with the log-rank test. $P < 0.05$ was considered statistically significant.

Results

A total of 1,760 patients with ovarian MCT underwent surgery at the present center between December 2004 and December 2014. Of these, 23 cases were pathologically identified as MT, resulting in an incidence of 1.3% for MT of MCT. Among patients with MT of MCT, the median age at presentation was 48 (range, 23-71) years. Twelve patients (52.2%) were postmenopausal, and six patients (26%) were nulliparous; no patients were pregnant. All patients had unilateral ovarian tumors; the median tumor size was 12 cm (range, 3-20 cm). The most common clinical presentation was abdominopelvic pain or palpable abdominal mass (15/23; 65.2%). The remaining patients were asymptomatic, and the tumors were incidentally detected on routine examinations. None of the patients had undergone prior surgical procedure for MCT. All patients underwent gynecologic ultrasonographic evaluations, and five patients underwent CT of the abdomen and pelvis. Initially, all pa-

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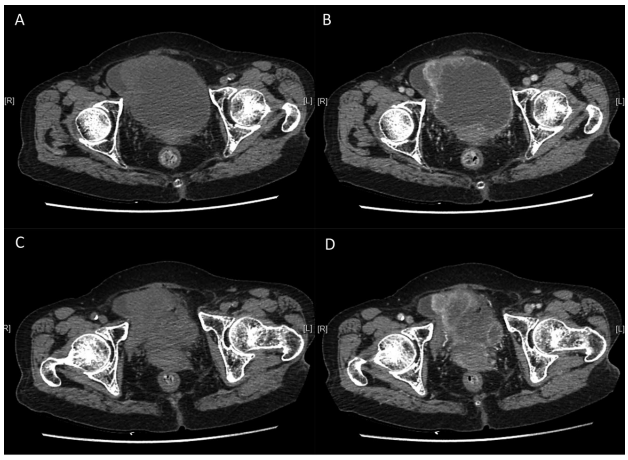

Figure 1. — CT showing large pelvic tumour. (A, C): Pelvic routine scan. (B, D): Pelvis enhanced scan.

Table 1. — *Pathologic subtypes and FIGO stage of patients with malignant transformation of ovarian mature cystic teratoma.*

FIGO Stage	Squamous cell carcinoma (n=15)	Carcinoid tumor (n=7)	Basal cell carcinoma (n=1)
I	53%	100%	100%
II	20%	0	0
III	20%	0	0
IV	7%	0	0

FIGO: International Federation of Gynaecology and Obstetrics staging system.

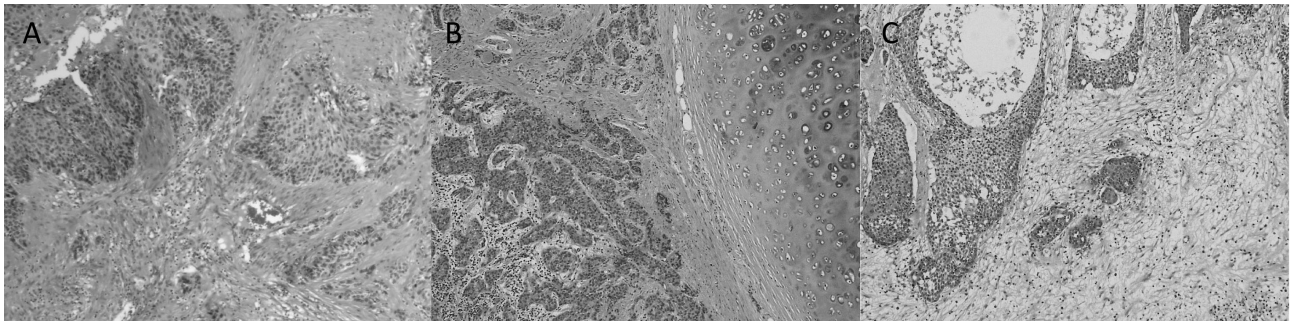

Figure 2. — Representative microscopic images of malignancy arising in MCTs (all hematoxylin and eosin stained, original magnification ×40). (A) squamous cell carcinoma, (B) carcinoid tumor, and (C) basal cell carcinoma.

tients were misdiagnosed as benign ovarian teratoma except one, who was diagnosed as suspected MT on CT (Figure 1).

Intraoperative frozen section analysis was used in 18 patients (78.2%). MT was successfully identified in 15 (83.3%) patients. Surgical staging involved total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), pelvic lymph node dissection, and omentectomy and/or appendectomy in 13/23 (57%) patients. In 7/23 (30%) patients, a fertility-sparing surgical approach was adopted, and postoperatively, there was no evidence of residual disease. One patient with a carcinoid tumor underwent TAH+BSO. Two cases with SCC only received debulking surgery because they were in late-stage disease and their weak condition did not allow staging surgery.

Staging was performed according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system. Sixteen (70%) cases were classified as Stage I, three (13%) cases were classified as Stage II, three (13%) cases were classified as Stage III, and one (4%) case was classified as Stage IV (Table 1).

MT histological subtypes included squamous cell carcinoma (SCC) (15/23), carcinoid tumor (7/23), and basal cell carcinoma (1/23) (Figure 2). Clinical characteristics of included patients stratified according to histological subtype are shown in Tables 1 and 2. Among the seven patients with carcinoid tumor, four cases were of the insular type, two cases were of the trabecular type, and one case was of the strumal type. On immunohistochemistry, all of the carcinoid tumors stained positive for synaptophysin (syn) and chromogranin, confirming the neuroendocrine phenotype (Figure 3A). Four cases were CD56 positive (57%). The proliferation index was determined by Ki-67 expression; among all carcinoid tumors, Ki-67 was < 1% (Figure 3B).

Serum tumor marker levels including cancer antigen CA125, CA199, carcinoembryonic antigen (CEA), and squamous cell carcinoma antigen (SCCA) were elevated in > 67% of SCC patients. Human papillomavirus (HPV) was found in 60% patients with SCC and 20% with carcinoid tumor. Serum tumor marker levels were not elevated and HPV was not found in the patient with basal cell carcinoma (Table 2).

Two patients had residual tumors. The largest residual tumor was > 1 cm. One patient underwent a second surgery for restaging because of incomplete resection. Fifteen patients with SCC and one patient with a carcinoid tumor received adjuvant chemotherapy with paclitaxel+platinum (cisplatin or carboplatin).

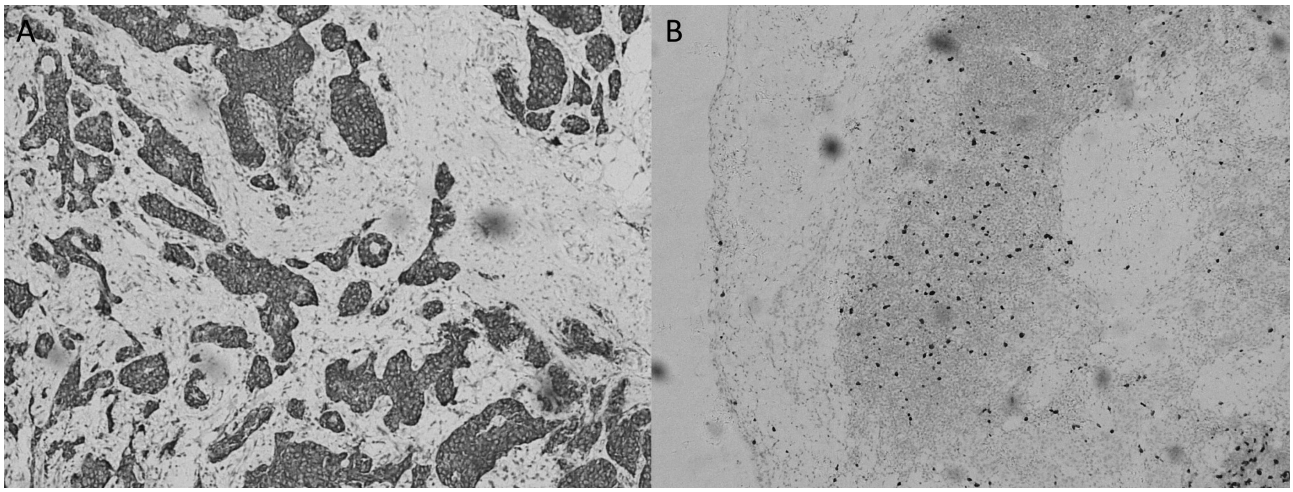

Figure 3. — Immunohistochemical study (A) neuroendocrine origin with strong positivity for syn. (B) Ki-67< 1%. IHC (×40).

Table 2. — *Serological marker levels of patients with different pathologic subtypes.*

	SCC	Carcinoid tumor	Basal cell carcinoma
CA125>35 (U/mL)	73.3%	14.3%	0
CA199>27 (U/mL)	72.7%	0	NA
CEA>3.4 (ng/ml)	66.7%	0	NA
SCCA>1.5 (ng/mL)	75%	0	NA
HPV(+)	60%	20%	0

CA: cancer antigen; CEA: carcinoembryonic antigen; SCCA: squamous cell carcinoma antigen; HPV: human papillomavirus; SCC: squamous cell carcinoma; NA: not available.

Table 3. — *Prognostic factors associated with malignant transformation of ovarian mature cystic teratoma.*

Characteristics	Five-year OS (%)	*p* value
Age (years)		
< 48	90.9	0.045
≥ 48	50	
Tumor size (cm)		
< 12	100	0.007
≥ 12	46.2	
Histology		
SCC	53.3	0.028
Non-SCC	100	
Disease stage		
I	100	<0.0001
II~IV	0	
Surgery type		
Radical	64.3	0.624
Non-radical	77.8	
Postoperative residual disease		
Yes	66.7	<0.0001
No	80	
CA125 (U/mL)		
< 35	100	0.003
≥ 35	41.7	

CA: cancer antigen; SCC: squamous cell carcinoma; OS: overall survival.

Mean postoperative follow-up was 44 months for living patients. In surviving patients, the five-year OS rate was 69.6%. At the final follow-up, 16 patients were alive with no evidence of disease. Univariate analysis revealed that patient age, tumor size, histology, disease stage, and postoperative residual disease had a significant prognostic impact on OS. Furthermore, CA125 was a prognostic factor (Table 3). The prognosis of patients whose serum CA125 level was elevated was significantly inferior to those whose serum CA125 level was within normal range.

Discussion

This study explored the clinical characteristics and identified potential prognostic factors associated with MT of ovarian MCT. In the current study, the incidence of MT of MCT was 1.3%; age of patient, size of tumor, serum tumor markers, and HPV positive were identified as potential predictors of MT of MCT, and patient age, tumor size, clinical stage, histology, and postoperative residual tumor were identified as important factors influencing the prognosis of MT of MCT. Furthermore, serum CA125 level was associated with a poor prognosis.

As MT of MCT is associated with poor prognosis, early diagnosis is essential; however, preoperative diagnosis of MT is difficult. Previous reports demonstrate that age of patient and size of tumor are potential predictors of MT of MCT. Tangjitgamol *et al.* reported that MT is more likely to occur in postmenopausal patients with a median age of 45–60 years [5]. Similarly, Desouki *et al.* found the average age of patients with MT was 48.7 years, compared to 38.8 years in patients with benign MCT, and the mean size of MT was 11.2 cm compared to 6.5 cm for benign MCT [6]. Some studies suggest that risk of MT is increased in tumors with diameters > 9.9 cm [2, 7]. In accordance with previous

reports, in the current case series, the median age of patients with MT of MCT was 48 (range, 23–71) years, and the average tumor size was 12 (range, 3-20) cm. The present authors propose that patient age and tumor size are associated with MT of MCT, and these factors should be considered in preoperative diagnosis.

Currently, the mechanism of MT of MCT is unclear. In a recent study, Chiang *et al.* revealed that HPV infection was associated with malignant transformation of squamous cell carcinoma (SCC-MCT). These authors found that HPV was localized to the tumor and adjacent reproductive tissues in four patients [8], suggesting that HPV infection is a causal factor that induces MT of MCT into SCC of the ovary. In the current case series, 60% of patients with SCC were positive for HPV, supporting the supposition that HPV infection is predictive of SCC-MCT.

Most patients with MT present with symptoms although some patients may be asymptomatic at diagnosis. The most common symptoms are abdominal pain, palpable mass, and abdominal distension [2, 9]. If the malignancy invades into surrounding organs, patients may present with fistula formation or symptoms of bowel obstruction [10, 11]. Approximately one-third of patients with an insular carcinoid tumor arising from MCT present with carcinoid syndrome, including cutaneous flushing, diarrhea, bronchoconstruction, and right-sided cardiac valve disease; these symptoms are especially common in patients aged > 50 years with tumors > 4 cm in diameter [12]. In the current case series, none of the patients with an insular carcinoid tumor arising from an MCT presented with symptoms of carcinoid syndrome.

The clinical utility of these imaging tools for preoperative diagnosis remains unclear [13]. A malignant MCT is typically a mass with the appearance of a cystic teratoma, but a significant solid component [2]. Therefore, imaging that identifies an MCT with enhanced mixed signals through pelvis enhanced scan should be considered suggestive of MT, as shown in Figure 1. Identifying MT of MCT on ultrasound is challenging. In the current case series, all patients underwent gynecologic ultrasonography. Five patients also underwent CT of the abdomen and pelvis; however, only one case was suspected as MT of MCT on CT before surgery.

When an MCT transforms to SCC, serum levels of SCCA, CA125, CA199, and CEA are increased [14]. However, serum tumor markers may also be elevated in patients with benign tumours [15]. Evidence suggests that SCCA is the most useful marker in patients with SCC arising from an MCT. Mori *et al.* reported that the combination of patient age (> 40 years) and serum SCCA level (> 2.5 ng/mL) was 77% sensitive and 96% specific for MT of MCT [16]. A recent review article that analyzed 277 cases of SCC-MCT from 64 published studies found that 48 of 52 patients (86.5%) had high serum SCCA levels, and 36 of 51 patients (71%) had high CA125 levels [1]. In the present study, serum SCCA, CA125, CA199, and CEA levels were significantly increased in patients with SCC-MCT. Levels of serum tumor markers were not significantly increased in patients with carcinoid tumors or basal cell carcinoma arising from MCT. Although no studies have found significant correlations between the levels of tumor markers and FIGO stage [1], the present authors propose that increases in serum tumor markers levels are associated with MT of MCT, and serum tumor markers may have a major role in preoperative prediction of MT.

Intraoperative analysis of frozen sections is not a routine procedure associated with the management of MCT; however, it is a valuable tool and should be considered in patients with suspected MT of MCT. Intraoperative analysis of frozen sections has a sensitivity and positive predictive value of 80% and 100%, respectively, for malignancy [6]. Intraoperative analysis of frozen sections is especially relevant for carcinoid and adenocarcinoma tumors because an appendectomy can be completed as part of surgical staging [12].

MT of MCT is rare; therefore, large-scale randomized trials establishing effective postoperative treatment have not been conducted [1]. Previous studies support combination chemotherapy with paclitaxel and carboplatin as active agents, and have reported extended progression-free survival in most patients [2, 4, 17]. In the present case series, all patients in Stage I received adjuvant chemotherapy, and the five-year survival rate was 100%. Therefore, the authors recommend staging surgery and postoperative adjuvant therapy for MT of MCT. Yoshida *et al.* reported on 21 patients who received radiotherapy for advanced stage SCC arising from MCT. Two- and three-year survival rates were 43.3% and 34.7%, respectively, suggesting that radiotherapy or concurrent chemoradiotherapy may also have beneficial effects on this tumor [18].

Patient age, tumor size, histology, disease stage, and postoperative residual tumors are important factors affecting prognosis in patients with MT of MCT. SCC most commonly arises from MCT. In this study, SCC accounted for 65% of MT of MCT. The OS and five-year survival rates of patients with Stage I SCC-MCT were 53.3% and 100%, respectively, while the five-year-survival rate at Stage II-IV was 0. Carcinoid tumor accounted for 30.4% of MT of MCT. All cases were at Stage I, and the five-year-survival rate was 100%, suggesting that early stage carcinoid tumor has a good prognosis. Previous studies report the five-year survival rates of patients with Stage I and Stage II-IV SCC-MCT at 80% and 20%, respectively [1]. Despite the disparate findings between these studies and the present case series, the data indicate that tumor stage is an important prognostic factor in MT of MCT.

Conclusion

In conclusion, MT of MCT is rare, and preoperative diagnosis is challenging. Findings from this case series identified age of patient, size of tumor, serum CA125, CA199, CEA, and SCCA levels, and presence of HPV as potential predictors of MT of MCT. Intraoperative frozen section analysis is essential in cases of suspected MT. Patient age, tumor size, histology, disease stage, and postoperative residual tumors are important factors affecting prognosis. CA125 level is associated with a poor prognosis. For patients in Stage I, fertility-sparing surgery is a reasonable option, but close postoperative follow-up is required.

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