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Malignant transformation arising from mature cystic teratoma of the ovary: A report of six cases

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Abstract

Aim: Malignant transformation of mature cystic teratoma (MCT) is an uncommon complication. Preoperative diagnosis is difficult because of the lack of specific symptoms and signs indicating malignancy. Thus, we retrospectively analyzed the clinical characteristics of patients and the role of surgery in their management.

Material and Methods: During a 9-year period (2002–2010), six patients with malignant transformation arising from ovarian MCT were treated at the Gynecologic Oncology Unit of Bakirkoy Woman and Children's Training and Research Hospital. A retrospective chart review and analysis of the patients' data were conducted.

Results: Malignant transformation arising from ovarian MCT accounted for 1.9% of all ovarian MCT (6/321). Three cases were stage IA and the other three were stage IC. Histologically, three of six cases had squamous cell carcinoma (50%), two had a carcinoid tumor (33%), and one had mucinous adenocarcinoma (17%). All patients underwent comprehensive surgical staging. Two patients received adjuvant chemotherapy and one received adjuvant chemoradiation. Five of six patients were observed for 16–104 months and no recurrence was detected. One patient with a carcinoid tumor in stage IC died of disease within 34 months following the surgery.

Conclusion: Early detection of malignant transformation arising from MCT is mandatory for treating patients, but in most patients malignancy was detected intraoperatively. Surgical cytoreduction with a complete staging procedure and adjuvant treatment may be reasonable for stage IC. Additionally, prognosis is better when the tumor is completely excised and does not extend beyond the capsule.

Key words: malignant transformation, mature cystic teratoma.

Introduction

Teratomas, most of which consist of mature cystic teratomas (MCT), are the most common germ cell tumor of the ovary and comprise 10–20% of all ovarian tumors. Any of the mature tissue elements of MCT have the potential to undergo malignant transformation, which occurs in approximately 1–3% of cases.[1] Not surprisingly, the most common malignant tumor arising from teratomas is squamous cell carcinoma (SCC) derived from ectoderm, which accounts for most of these tumors. However, various adenocarcinomas, carcinoid tumors, melanomas, and various soft tissue sarcomas have also been reported.[2–5]

Although a preoperative diagnosis of MCT is relatively easy, determination of malignant transformation is actually very difficult and is rarely diagnosed preoperatively. Thus, malignant transformation is currently diagnosed only by postoperative histopathologic examination in most cases.

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The prognosis for these tumors has been reported to be very poor when disease has spread beyond the ovary.[6] Because these tumors are rare, few studies have been published concerning the clinical pathology of MCT with malignant transformation and no consensus exists regarding optimal management. We retrospectively analyzed six patients with malignant transformation arising from MCT of the ovary to evaluate clinicopathologic features and prognosis.

Material and Methods

From January 2002 to December 2010, six cases with malignant transformation arising from MCT of the ovary were identified at Bakirkoy Woman and Children's Training and Research Hospital. The available clinical records of patients with malignant transformation arising from MCT were reviewed for age, parity, presenting symptoms, serum tumor markers, intraoperative findings, adjuvant treatment, and survival in months. Surgical staging was performed using the International Federation of Gynaecology and Obstetrics (FIGO) system. Regular physical examination, serum tumor marker analysis, gynecological sonography, chest X-ray, and magnetic resonance imaging (MRI) were performed at the postoperative follow-up. All intervals were determined from the date of surgery.

Results

During the 9-year period, six cases of malignant transformation and 315 cases of uncomplicated ovarian MCT were resected and histopathologically identified at our institution. According to these data, malignant transformation comprised 1.9% (6/321) of all MCT. The median age was 43 years (range, 38–55 years), which was much older than the 32.6 years of patients with uncomplicated ovarian MCT. The mean diameter of the tumor was 11.5 cm (range 9–16 cm) and all patients with malignant transformation had unilateral ovarian tumor. In patients with uncomplicated ovarian MCT the mean cyst size was 6.4 cm (3.3–17 cm) and bilaterality was 4%. Clinical presentation was abdominal/pelvic pain or discomfort in four patients. Additionally, two of six patients were associated with pregnancy. One of these patients was ascertained incidentally at the time of the cesarean section, and the other was referred to our clinic due to bilateral adnexal mass in the postpartum period that had been detected in the third trimester of pregnancy. FIGO stage was determined in all patients: three were staged as IA and the other three as IC. SCC was the most frequent malignant transformation (Fig. 1a), occurring in three patients (50%), followed by a mucinous adenocarcinoma in one patient (17%; Figs 1b,2a), and carcinoid tumor (Fig. 2b) in two patients (one insular and one trabecular carcinoid tumor; 33%). Preoperative CA-125 and CA-19-9 were extensively used as tumor markers in patients. While CA-125 was elevated in two patients with SCC (89 U/mL and 65 U/mL) and one patient with an insular carcinoid tumor (737 U/mL), CA-19-9 was elevated in only one patient with an insular carcinoid tumor (65 U/mL). Frozen sections were evaluated in five of six patients. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO), omentectomy, and bilateral pelvic ± paraaortic lymph node dissection were performed in four patients. Unilateral salpingo-oophorectomy with staging biopsy in the remaining two patients was performed at initial surgery. The patient, who underwent

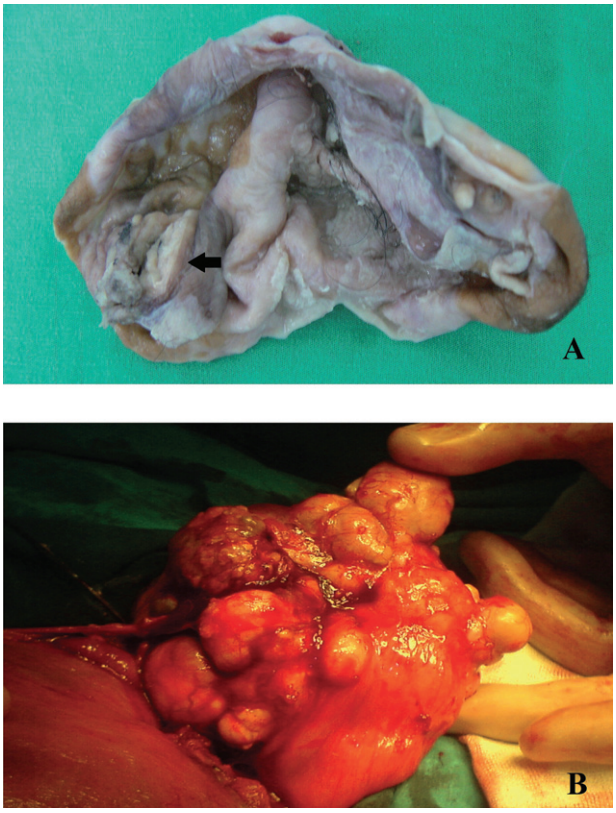

Figure 1 (a) Gross appearance of mature cystic teratoma with squamous cell carcinoma. The focal solid area (arrow) was approximately 3 × 2 × 2 cm in size in the wall of the cyst. (b) Intraoperative view of mucinous adenocarcinoma arising in ovarian mature cystic teratoma in a pregnant woman.

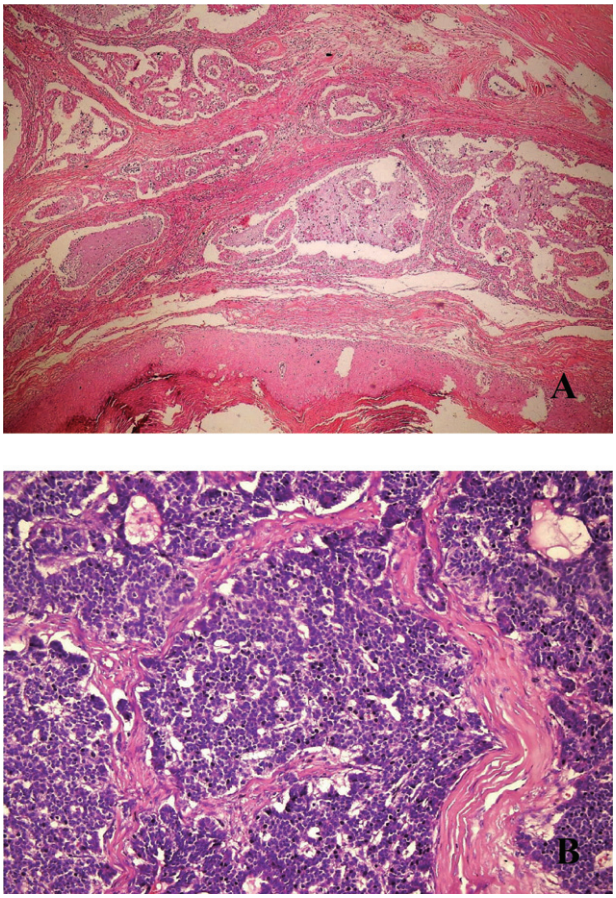

Figure 2 (a) Cyst lining composed of keratinized benign mature squamous epithelium and malignant component displaying well to moderately differentiated glandular structures (HE, ×40). (b) The tumor was composed of islands of cells with closely packed small acini at the periphery, was diagnosed as insular carcinoid.

unilateral salpingo-oophorectomy with staging biopsy during the cesarean section, demonstrated capsular invasion and, afterwards, she underwent a second staging laparotomy including TAH+USO omentectomy, appendectomy, and pelvic and para-aortic lymph node dissection. While one patient with SCC received adjuvant chemotherapy and radiotherapy, one patient with an insular carcinoid tumor and another with mucinous adenocarcinoma received only adjuvant chemotherapy with six cycles of paclitaxel + cisplatin/carboplatin for 3-week intervals. Currently, five of six cases have been observed for 16–104 months and no recurrence has been detected. One case with an insular carcinoid tumor in stage IC died of disease within 34 months following the surgery. The demographics and clinical and pathological features of the six cases are given in Table 1.

Discussion

Preoperative determination of malignant transformation arising from MCT is actually very difficult and characteristics belonging to malignant transformation from ultrasound examination, generally, may not differ from uncomplicated MCT. Gross changes that suggest malignant transformation vary from adherence to surrounding pelvic structures and a large tumor measuring in excess of 15–20 cm in the largest diameter to plaque, nodule, or thickening in the cyst wall. In some cases, the diagnosis is not suspected until microscopic examination has been completed. Thus, a definitive diagnosis in such cases is most often rendered postoperatively. Although magnetic resonance imaging and computed tomography can be useful to determine malignant transformation, clinical use of these imaging tools in preoperative diagnosis remains unclear.[7]

Patient age, tumor size, imaging characteristics, and serum tumor markers are risk factors for malignancy arising from MCT.[8] Although malignancy occurs at any age, most patients are postmenopausal, and the median age of the patients is 45–60 years.[9] Rim *et al*. reported 11 cases of malignant transformation arising from MCT with a mean age of 50.6 years, which was much higher than the median age of 35 years in patients with MCT.[10] In our series, the median age was 43 years which is slightly lower than other reports. Five of six patients (83%) were premenopausal and two of them were under 40 years of age. Compared to previous reports, the small number of patients with malignant transformation and their low median age in our study may not accurately reflect the full age spectrum of these tumors. Tumor size has also been found to predict malignant transformation. Kikkawa *et al*. demonstrated that tumors in most cases with SCC arising from MCT are >9.9 cm and commonly contain areas of hemorrhage and necrosis.[11]

The use of tumor markers has been investigated in multiple series. SCC antigen appears to be most relevant, although it is elevated in some benign MCT and may not be sensitive in early stage malignancy.[8] Mori *et al*. reported that the combination of the patient's age (>40 years) and serum SCC antigen level (>2.5 ng/mL) was 77% sensitive and 96% specific for malignant transformation.[12] In our series, 66% (2/3) of patients with SCC had elevated CA-125 levels. CA-125 was also elevated during the follow-up period in patients with

Table 1 Clinical characteristics of patients with malignant transformation arising from mature cystic teratoma of the ovary

Patient	Age (years)	Mean diameter of mass (cm)	Treatment	Histology	Stage	Adjuvant therapy	Follow-up (months)
1	55	12 cm	TAH+BSO+oment+pelvic LND	Carcinoid tm (insular)	IC	TC	DWD, 34 m
2	47	10 cm	TAH+BSO+oment+BPPLND	SCC	IA	–	NED, 16 m
3	39	11 cm	LSO	Carcinoid tm (trabecular)	IA	–	NED, 104 m
4†	43	16 cm	TAH+BSO+oment+BPPLND	SCC	IC	RT/TCA	NED, 46 m
5†	38	9 cm	LSO/TAH+USO+oment+BPPLND	Adenoca (mucinous)	IC	TCA	NED, 60 m
6	43	13 cm	TAH+BSO+oment+pelvic LND	SCC	IA	–	NED, 44 m

†Associated with pregnancy. BPPLND, bilateral pelvic and para-aortic lymph node dissection; BSO, bilateral salpingo-oophorectomy; DWD died with disease; LND, lymph node dissection; LSO, left salpingo-oophorectomy; NED, no evidence of disease; oment., omentectomy; RT, radiotherapy; SCC, squamous cell carcinoma; TAH, hysterectomy; TC, paclitaxel, cisplatin; TCA, paclitaxel, carboplatin; tm, tumor.

an insular carcinoid tumor and suggested tumor recurrence prior to occurrence of metastatic lesions radiologically. However, SCC antigen was not analyzed in any of these cases preoperatively due to an expensive marker for routine clinical practice.

The most common malignancy is SCC, which represents about 75% of malignant transformation.[13] Other neoplasms, including adenocarcinoma, neuroendodermal tumors, sarcoma, and malignant melanoma have also been reported. In our study, SCC was the most frequently identified malignant transformation found in three cases (50%). Additionally, two carcinoid tumor cases existed. While one of these cases showed an insular pattern, the other case demonstrated a trabecular pattern.

The prognosis heavily depends on the extent of the disease, biologic aggressiveness of the tumor, and presence of a complete surgical resection similar to epithelial ovarian cancer. However, conservative treatment with unilateral salpingo-oophorectomy and surgical staging for early-stage tumors in younger patients and pregnant women needs to be considered. Tseng *et al*. reported a 2-year disease-free survival of 100% in four stage IA patients treated with this approach.[14] Peterson *et al*. showed a 75% 5-year survival rate in cases of unruptured stage I tumors.[2] Because of the rarity of this tumor, adjuvant treatment has not been prospectively evaluated. According to Sakuma *et al*. stage IA disease after surgical staging does not require adjuvant chemotherapy.[15] For stage IC and more advanced disease, different adjuvant regimens have been described in individual cases with variable outcomes. For stage IIB-IIIC disease, Tseng *et al*. advocated multimodality therapy, including cytoreduction, followed by platinum-based multi-agent chemotherapy with or without pelvic radiation and demonstrated that the overall 2-year disease-free survival was 69%, which is considerably higher than in prior series.[14] In our series, the median follow-up was 45 months and five of six patients survived at 16–104 months of follow-up with no detectable recurrence.

Because of the relative rarity of these tumors, the literature is limited to descriptive case series. Our study and other recent studies, including patients with complete surgical staging, support the idea that malignant transformation arising from MCT presents at earlier stages. Rim *et al*. reported that eight of 11 patients with malignant transformation were in stage IA.[10] Additionally, Dos Santos *et al*. reported 17 cases of SCC arising from MCT, in which stage I–II tumors accounted for 75% of all malignant transformation.[8] Symptoms such as abdominal or pelvic pain and discomfort caused by MCT, followed by surgery without delay, may be the reason for early detection of developing cancer in the wall of the cyst.

In conclusion, malignant transformation arising from MCT presents a diagnostic and therapeutic dilemma. Surgical cytoreduction with thorough staging procedures and adjuvant treatment may be reasonable for stage IC. Additionally, prognosis is better when the tumor is completely excised and does not extend beyond the capsule.

Disclosure

None declared.

References

1. Curling ON, Potsides PN, Hudson CN. Malignant change in benign cystic teratoma of ovary. *Br J Obstet Gynecol* 1979; **86**: 399–402.

2. Peterson WF. Malign degeneration of benign cystic teratomas of the ovary. A collective review of the literature. *Obstet Gynecol Surv* 1957; **12**: 793–830.
3. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Malignant transformation of mature cystic teratoma of the ovary: Experience at a single institution. *Eur J Obstet Gynecol Reprod Biol* 2008; **141**: 173–178.
4. Hackethal A, Brueggmann D, Bohlmann MK, Franke FE, Tinneberg HR, Münstedt K. Squamous-cell carcinoma in mature cystic teratoma of the ovary: Systematic review and analysis of published data. *Lancet Oncol* 2008; **9**: 1173–1180.
5. Karateke A, Gurbuz A, Kir G *et al*. Mucoepidermoid variant of adenosquamous carcinoma arising in ovarian dermoid cyst: A case report and review of the literature. *Int J Gynecol Cancer* 2006; **16** (Suppl 1): 379–384.
6. Miyazaki K, Tokunaga T, Katabuchi H, Ohba T, Tashiro H, Okamura H. Clinical usefulness of serum squamous cell carcinoma antigen for early detection of squamous cell carcinoma arising in mature cystic teratoma of the ovary. *Obstet Gynecol* 1991; **78**: 562–566.
7. Park SB, Kim JK, Kim KR, Cho KS. Preoperative diagnosis of mature cystic teratoma with malignant transformation: Analysis of imaging findings and clinical and laboratory data. *Arch Gynecol Obstet* 2007; **275**: 25–31. Epub 2006 Aug 22.
8. Dos Santos L, Mok E, Iasonos A *et al*. Squamous cell carcinoma arising in mature cystic teratoma of the ovary: A case series and review of the literature. *Gynecol Oncol* 2007; **105**: 321–324. Epub 2007 Jan 22.
9. Tangjitgamol S, Manusirivithaya S, Sheanakul C, Leelahakorn S, Thawaramara T, Jesadapatarakul S. Squamous cell carcinoma arising from dermoid cyst: Case reports and review of literature. *Int J Gynecol Cancer* 2003; **13**: 558–563.
10. Rim SY, Kim SM, Choi HS. Malignant transformation of ovarian mature cystic teratoma. *Int J Gynecol Cancer* 2006; **16**: 140–144.
11. Kikkawa F, Nawa A, Tamakoshi K *et al*. Diagnosis of squamous cell carcinoma arising from mature cystic teratoma of the ovary. *Cancer* 1998; **82**: 2249–2255.
12. Mori Y, Nishii H, Takabe K *et al*. Preoperative diagnosis of malignant transformation arising from mature cystic teratoma of the ovary. *Gynecol Oncol* 2003; **90**: 338–341.
13. Ueda G, Fujita M, Ogawa H, Sawada M, Inoue M, Tanizawa O. Adenocarcinoma in a benign cystic teratoma of the ovary: Report of a case with a long survival period. *Gynecol Oncol* 1993; **48**: 259–263.
14. Tseng CJ, Chou HH, Huang KG *et al*. Squamous cell carcinoma arising in mature cystic teratoma of the ovary. *Gynecol Oncol* 1996; **63**: 364–370.
15. Sakuma M, Otsuki T, Yoshinaga K *et al*. Malignant transformation arising from mature cystic teratoma of the ovary: A retrospective study of 20 cases. *Int J Gynecol Cancer* 2010; **20**: 766–771.