Risk factors for malignant transformation of mature cystic teratoma

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Objective

The aim of this study was to investigate the preoperative characteristics of benign mature cystic teratoma (MCT) and struma ovarii and their risk factors associated malignancies, and determine the appropriate treatment options for these tumors.

Methods

This was a retrospective study on 248 patients who were pathologically diagnosed with ovarian MCT, struma ovarii, or malignant transformations of these tumors at Inje University Haeundae Paik Hospital from March 2010 to January 2015. Routinely evaluated results of adnexal masses before surgery were compared.

Results

A total of six patients (2.4%) were confirmed to have malignant tumors. Of the struma ovarii patients, two out of five patients (40%) were confirmed to have malignancy. The mean age at the diagnosis of patients with malignant transformation of teratomas was 43.0 years (range, 27 to 67 years), which was higher than that of patients with benign teratomas (36.5 years). The mean diameter of the tumor before surgery in the malignant tumor group was 11.4 cm and larger than 6.5 cm of benign group (P=0.003). The mean CA-125 level in the malignant tumor group was higher than that in the benign tumor group (P=0.01).

Conclusion

Risk factors for malignant transformation of MCT include elevated CA-125 levels, older age, large tumor masses, and postmenopausal status.

Keywords: Malignant transformation; Mature cystic teratoma; Struma ovarii

Introduction

Mature cystic teratoma (MCT) was first described 300 years ago, and is the most common ovarian tumor in both adolescents and women of reproductive age. Most MCTs are benign, and are typically treated by laparoscopic gynecologic surgery. However, malignant transformation has been reported in 0.17% to 3% of cases [1-4]. In such cases, different management is needed compared to in benign cases.

Struma ovarii is a rare ovarian tumor, reportedly accounting for 0.5% to 1% of all ovarian masses. It is the most common type of monodermal teratoma. In benign cases, laparoscopic operation (cystectomy or unilateral salpingoopherectomy) is the standard treatment option. However, some tumors are histologically identical to differentiated thyroid cancer and are defined as malignant struma ovarii by the World Health Organization, and, in such cases, extensive management may be needed. Since struma ovarii patients do not present with definite symptoms or signs that distinguish them from other

diseases, or with specific radiologic findings, it is difficult to diagnose these advanced ovarian tumors and to establish the appropriate type of surgery required prior to the operation. Therefore, in some cases that are misdiagnosed preoperatively, complete surgical resection is not performed, thereby harming the prognosis and the quality of patient care.

With this in mind, the aim of this study was to investigate the preoperative characteristics of benign MCT and struma ovarii and their associated malignancies, and to report our experience in managing these diseases in our hospital. Finally, we hope that this study might help in determining the appropriate treatment options for these rare tumors.

Materials and methods

This was a retrospective study on patients who were pathologically diagnosed with ovarian MCT, struma ovarii, or malignant transformations of these tumors at Inje University Haeundae Paik Hospital from March 2010 to January 2015. Clinical information was gathered from the electronic medical records and pathologic examination notes.

In our hospital, routine evaluation of adnexal masses does not always include tumor marker detection, except for CA-125, or imaging studies such as computed tomography (CT) and magnetic resonance imaging, although performing these tests is acceptable for excluding the possibility of malignancy. Two gynecologic surgeons performed all operations. In addition, two experienced pathologists reviewed every biopsy sample obtained during the operations. If a malignant tumor was diagnosed, tumor staging surgery was performed according to the FIGO (International Federation of Gynecology and Obstetrics) surgical system. Generally, following the surgery, ovarian cancer tumor markers, including serum CA-125 levels, were routinely measured before every cycle of chemotherapy. CT or positron emission tomography/CT was used to evaluate the response to treatment. The response was assessed according to the RECIST (Response Evaluation Criteria in Solid Tumours) criteria. After the end of treatment, pelvic exams and CA-125 level detection were performed every three months.

We used SAS ver. 9.1 (SAS Institute, Cary, NC, USA) for data management and statistical analysis. Categorical variables were assessed with the Fisher exact test or χ^2 test based on category size. All statistical tests were 2-sided, and differences were considered statistically significance at a probability value

of <0.5, and if it was available, odds ratio was calculated, too.

Results

During the study, 248 patients underwent surgery for ovarian MCT or struma ovarii at Inje University Haeundae Paik Hospital. From these, a total of six patients (2.4%) were confirmed to have malignant tumors. These results correspond to those obtained in other studies [1-4]. Of the struma ovarii patients, two out of five patients (40%) were confirmed to have malignancy. Differentiating between MCT, struma ovarii, and their malignant forms is necessary for choosing appropriate treatment option.

The mean age at the diagnosis of patients with malignant transformation of teratomas was 43.0 years (range, 27 to 67 years), which was higher than that of patients with benign teratomas (36.5 years). In contrast, the proportion of postmenopausal women with a benign tumor was 20.0% (n=49). The mean diameter of the largest tumor before surgery was 11.4 cm (range, 3.5 to 19 cm) in the malignancy group, which was significantly larger compared to in the benign group ($P<0.05$).

To evaluate the biological markers, the levels of CA-125 and other tumor markers were acquired preoperatively. CA-125 levels were higher than normal in four patients with malignancy and in 33 patients (16.4%) with benign tumors. The mean CA-125 level in the malignant tumor group was higher than that in the benign tumor group ($P<0.05$). In the benign MCT group, 37 patients (27%) had higher CA-19-9 levels than normal. The carcinoembryonic antigen and squamous cell carcinoma antigen (SCCAg) levels were collected in some patients with malignancy, and the results were all within the normal ranges (Table 1).

The malignant struma ovarii patients (cases 5 and 6) were 35 and 27 years old, respectively (Table 2). In the malignancy, three patients (60%) visited for a palpable abdominal mass. Two (40%) presented with abdominal pain, one patient complained about dyspepsia and anorexia with a palpable mass, and one patient who was asymptomatic visited our hospital following abnormal ultrasonographic findings. Two of the six patients with malignancy had tumors in the contralateral ovaries. One displayed tumor invasion (case 4) and the other a hemorrhagic corpus luteum (case 5). Most patients underwent a staging operation that included total abdominal hysterec-

Table 1. Preoperative characteristics of benign and malignant teratomas

	Benign (n=242)	Malignant (n=6)	Odds ratio	P-value
Age (yr)[a]	36.5	43.0	26	0.36
Menopausal (n, %)	49 (20.2)	3 (50.0)	3.5	0.13
Tumor size (cm)[b] (>8)	6.5 (n=54)	11.4 (n=5)	17.4	0.003
CA-125 (U/mL)[a] (>35)	27.7 (n=33)	218.4 (n=4)	10.2	0.01
SCCAg (ng/mL)[a]	0.4	0.8 (n=1)	-	1.0
CA-19-9 (U/mL)[a]	97.8	201.7	1.8	0.62
CEA (ng/mL)[a]	3.0	1.2	-	1.0

SCCAg, squamous cell carcinoma antigen; CEA, carcinoembryonic antigen.
[a]Data are presented as the mean value; [b]Mean largest diameter of the mass before surgery as detected by ultrasonography (if there were bilateral tumors, the larger mass was chosen).

Table 2. Characteristics of mature cystic teratoma malignant transformation

Malignancy	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (yr)	33	48	67	48	35	27
Menopause	No	Yes	Yes	Yes	No	No
Parity	0	2	4	2	1	0
Symptoms	Mass	Mass,dyspepsia	Abdominal pain	Mass	Abdominal pain	Asymptomatic
CA-125 (U/mL)	41.2	866.7	20.4	294.0	70.0	18.5
SCCAg (ng/mL)	NA	0.8	0.8	NA	NA	NA
CA-19-9 (U/mL)	76.4	887.0	16.7	NA	25.8	2.8
CEA (ng/mL)	0.5	NA	NA	NA	0.6	2.6
Tumor site (ovary)	Right	Left	Left	Both	Right	Right
Size (cm)	19	17	8	12 (Right)	9	3.5
Diagnosis	Sebaceous carcinoma	SCC	SCC	Mucinous adenocarcinoma and carcinoid	Multifocal carcinoma	Struma carcinoid
FIGO stage	IA	IIIC	IIB	IV	IC	IA

SCCAg, squamous cell carcinoma antigen; NA, not applicable; CEA, carcinoembryonic antigen; FIGO, International Federation of Gynecology and Obstetrics.

tomy, bilateral salpingoopherectomy, bilateral pelvic lymph node dissection, paraaortic lymph node dissection, appendectomy, omentectomy, and mass excision (if a mass was seen). However, in two cases, only a right salpingoopherectomy (case 1) and a laparoscopic right ovarian cystectomy (case 6) were performed. In case 1, the patient was unmarried and the malignant transformation was only focal and confined within the solid portion of the ovarian cyst. We therefore presumed that that the tumor was stage IA, and decided not to perform additional staging operations following several consultations with the patient. In case 6, the woman was also unmarried

and she had already undergone a left salpingoopherectomy due to a very large teratoma in 2000. The cyst was removed by laparoscopic surgery without spillage, and following the biopsy results, we performed chest, abdomen, and pelvic CTs and detected tumor markers consecutively. We also consulted with her several times. Three patients (cases 3 to 5) had specific findings of presumed malignancy, namely adhesion to the pelvic wall, peritoneum, and ascites. Two patients (cases 5 and 6) had stage I tumors, one (case 3) had stage II tumors, and the other cases (cases 2 and 4) had advanced-stage tumors with peritoneal carcinomatosis. The pathologic results were

two squamous cell carcinomas (SCCs) (cases 2 and 3), one sebaceous carcinoma (case 1), one combined mucinous adenocarcinoma with a carcinoid component (case 4), one multifocal carcinoma arising in struma ovarii (case 5), and one struma carcinoid (case 6). The first-line chemotherapeutic agents used were paclitaxel-carboplatin for adjuvant treatment in cases 2, 3, and 5 and palliative chemotherapy in case 4. Recurrence occurred in one patient (case 2) and death of disease. At the latest follow-ups, three patients (cases 1, 3 and 5) were in complete remission and were free from disease since their staging operation and chemotherapy (Table 2). On the other hand, patient 6 was free from disease since operation. Follow-up period was 41, 5 (death of disease), 8, 8 (death of disease), 24, 6 months each.

Discussion

MCT, better known as dermoid cyst, is part of a subclass of ovarian germ cell tumors believed to arise from the primordial germ cells [5,6]. MCT is the most common ovarian tumor in both adolescents and women of reproductive age, and constitutes 10% to 20% of all ovarian tumors [7]. MCT might arise from germ cells by failure of meiosis II or from a premeiotic cell in which meiosis I has failed [8]. While most patients with MCT show no signs or symptoms, abdominal discomfort, a palpable mass, and pain can occur [9].

MCT is composed of tissue originating from all germ cell layers, and, therefore, various malignancies can arise from any one of the germ cell layers. Malignant transformation has been reported to occur in only 0.17% to 3% of MCTs [1-4]. In previous studies, more than 80% of the malignant tumors were SCCs, which are derived from the ectoderm. Cutaneous-type adnexal tumors, including basal cell carcinomas, sebaceous tumors, malignant melanomas, adenocarcinomas, sarcomas, and neuroendodermal tumors, have also been reported [10,11]. Most MCTs may be detected 15 to 20 years prior to malignant transformation, and it is possible that prolonged exposure to various carcinogens in the pelvic cavity might lead to malignant transformation [12]. Therefore, malignant transformation typically occurs in postmenopausal women [3,4,13]. In our study, three out of six patients with malignancy (cases 2, 3, and 4) were post-menopausal.

On the other hand, struma ovarii is a dermoid cyst variant and is defined as monodermal teratoma predominantly composed of thyroid tissue (over 50%) or of macroscopically recognizable MCT components [14,15]. It accounts for 2.7% of all ovarian teratomas, and very rarely becomes malignant; malignant transformation occurs only in 0.3% to 10% of all struma ovarii tumors [16,17]. The higher proportion observed in our study may result from the small sample size. Most patients with struma ovarii have clinical manifestations similar to those of MCT, while some patients may be asymptomatic or have a palpable mass and lower abdominal pain. However, ascites, hydrothorax, elevated thyroid function test, and, in rare cases, thyroid tumors, can be observed [17,18].

The preoperative diagnosis of malignant MCT transformation is difficult, and the definitive diagnosis should be rendered postoperatively. Advanced age and larger tumor size due to areas of hemorrhage and necrosis could be helpful in anticipating malignant transformation [19]. The usefulness of tumor markers in MCT malignant transformation is not clearly understood [19]. However, SCCAg has been reported to be useful to diagnose SCCs arising in MCT of the ovary [4,20-22]. Tseng et al. [22] reported that 16 out of 24 (67%) patients with SCC arising in MCT had elevated SCCAg levels, and that all patients with recurrent lesions had increased SCCAg levels in serial SCC monitoring. Accordingly, the authors suggested that serum SCC antigen level monitoring could be helpful for early detection of cancer recurrence. In our study, we could not assess this parameter because of lack of data. On the other hand, the CA-125 levels were not elevated in any case in this previous study. High concentrations of tumor markers such as CA19-9 and CA-125 have been reported in patients with benign tumors, and therefore do not allow distinction between malignant and benign MCT [23,24]. Furthermore, Mori et al. [25] reported that the possibility of MCT malignant transformation was quite high in patients aged over 40 years and in cases of serum SCCAg exceeding 2.5 ng/mL. However, as germ cell tumors cannot be definitely discriminated from epithelial tumors preoperatively, tumor markers such as CA-125 should be included in the preoperative evaluation [12].

The standard therapeutic option for ovarian MCT with malignant transformation is surgery. Some operative findings such as nodular, papillary, or cauliflower-like growths protruding into the cyst cavities or nodules or plaques within the cyst walls; adhesion to pelvic walls; presence of ascites; areas of necrosis; and hemorrhage suggest malignancy [1,26,27]. However, in one study, malignancy was detected in frozen sections in only 50% of cases, with inappropriate treatment performed

Obstetrics & Gynecology Science

Chan-Hong Park, et al. Factors for malignant transformation

in two patients [28]. Tseng et al. [22] suggested that only unilateral oophorectomy might be justified for early stage IA tumors, especially in nulliparous and young patients. However, in postmenopausal women, complete cytoreduction surgery, including hysterectomy, bilateral salpingoopherectomy, and lymphadenectomy, improves the treatment outcome [22,29]. Iatrogenic rupture or spillage of tumor should be avoided. Furthermore, there are remarkable differences in the prognosis between stage I tumor and all other stages, but only mild differences between stages II, III, and IV [8,12].

Due to the rarity of malignant struma ovarii, there is a lack of data on the optimal treatment option. For nulliparous and young women, unilateral salpingoopherectomy can be considered in the absence of capsular invasion or distant metastasis, and there have been some reports of pregnancy following conservative operation due to malignancy [30]. Conversely, for advanced disease, the surgical protocol is similar to that for epithelial ovarian cancer.

Similarly, the appropriate adjuvant therapy for malignancies arising in MCT has not been systemically assessed. Some reports suggest that paclitaxel is an effective drug for advanced ovarian cancer and SCC of the cervix. Therefore, paclitaxel has been used increasingly for the management of SCC arising in ovarian MCTs. However, chemotherapy might lead to a greater morbidity, as well as numerous adverse effects [3,31,32]. Meanwhile, the use of iodine-131 as an adjuvant treatment modality in malignant struma ovarii remains controversial due to the paucity of studies.

In conclusion, most MCTs are detected during the reproductive age, whereas malignant transformation is generally detected in older patients. Risk factors for malignant transformation of MCT include elevated CA-125 levels, older age, large tumor masses, and postmenopausal status. Additionally, it seems to be related to the long-term presence of MCT in the pelvic cavity and exposure to carcinogens. If cancer arising in MCTs or malignant struma ovarii is detected early, ovary-conserving surgery is possible, and may contribute to enhancing the quality of life of the patients. For early detection and prevention of MCT malignant transformation, regular pelvic examinations by sonography are needed. When MCT is diagnosed during the childbearing years, operation should not be delayed.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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