DOI: https://doi.org/10.5114/pm.2018.77304

Menopause Rev 2018; 17(2): 63-68

ORIGINAL PAPER

Malignant transformation in mature cystic teratoma of the ovary: a retrospective study of eight cases and review of literature

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Abstract

Introduction: Mature cystic teratoma (MCT) is the most common type of ovarian germ cell neoplasm, but occasionally it may undergo malignant change in any one of its elements. In this study, these rarely encountered tumors, occurring over a period of 25 years, were studied.

Material and methods: A retrospective, tertiary hospital-based study was carried out in all histopathologically diagnosed cases of MCT (230) of the ovary from January 1990 to December 2014. The clinicopathological features of malignant transformation (MT) in MCT of the ovary were retrieved from the archives of the Department of Pathology and were analyzed.

Results: Two hundred thirty (230) mature cystic teratomas of the ovary were found. MT was noted in eight of these cases, i.e. 3.5% of all the MCT. The mean age of the patients with MCT was 32.5 ±13.11 while the mean age of the patients with malignant transformation in MCT was 44.2 ±8.94 years. Grossly the mean size of the malignant teratoma was 11.7 ±2.7 cm, whereas it was 7.6 ±2.1 cm for mature cystic teratoma. Squamous cell carcinoma (SCC) was the most frequent MT seen in four out of eight cases, while one case showed an adenocarcinoma and the other a malignant melanoma, and two cases had transitional cell carcinoma.

Conclusions: The rate of malignant transformation in MCT increases with age and is much higher in the postmenopausal age group. Moreover, although SCC is still the commonest, transitional cell carcinoma (TCC) may also develop not infrequently as malignancy apart from other rare differentiations such as adenocarcinoma or malignant melanoma in an MCT.

Key words: ovarian tumor, teratoma, malignant transformation, squamous cell carcinoma, transitional cell carcinoma, malignant melanoma.

Introduction

Mature cystic teratoma (MCT) of the ovary, commonly known as dermoid cyst, has been known since antiquity. MCT is the most common type of ovarian germ cell neoplasm. It occurs relatively frequently and comprises approximately 20% of all ovarian neoplasms [1, 2]. In its pure form, mature cystic teratoma is always benign. Malignant transformation (MT) is an uncommon complication of a mature cystic teratoma. It occurs in approximately 1-3% of all MCT cases, although in one report the frequency was as high as 6.67% [3-5].

The lack of specific signs and symptoms indicating a malignant transformation, their similarity to MCT and their uncommon occurrence makes it difficult to diagnose such transformations pre-operatively [5]. Hence, MT arising in an MCT is currently diagnosed by post-operative pathological examination in most cases. In this study, these rarely encountered tumors, occurring over a period of 25 years were further studied.

Material and methods

A retrospective study was carried out in all histopathologically diagnosed cases of MCT (230) of the ovary from January 1990 to December 2014. Relevant data were retrieved from the archives of the Department of Pathology. Institutional Ethics committee approval was obtained before retrieving the data for this retrospective study. Eight cases of a malignant tumor arising in a teratoma were identified. The mean age and size of the tumors were noted in all the patients with MT in MCT and compared with those of MCT. The morphological and clinicopathological features of MT in MCT of the ovary were analyzed. Chi square test, using SPSS software version 22, was performed to find the association of age, size and laterality of these tumors with MT.

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Submitted: 17.04.2017
Accepted: 22.06.2018

Results

A total of 1102 ovarian tumors were diagnosed over a period of 25 years. 25.7% (284/1102) of all the ovarian tumors were germ cell tumors. Of the consecutive 242 cases of ovarian teratoma 231 (20.9%) were MCT and 11/242 cases of immature teratoma. For statistical purposes we took 230 cases of MCT in this study. Malignant transformation was noted in eight of these cases, i.e. 3.5% (8/230) of all the MCT.

Whereas the mean age of the patients with MCT was 32.5 ±13.11 years, ranging from 8 years to 70 years, the mean age of the patients with malignant transformation in MCT was 44.2 ±8.94 (mean ± standard deviation) years, ranging from 33 years to 56 years. Considering the fact that MCT are a rare occurrence in the postmenopausal age group, in our study 19/223 cases, i.e. 8.2% of all the MCT, were seen in postmenopausal females, and 4 of these 19 cases had developed malignant transformation. The association of age of the patients and malignancy status was found to be statistically significant (p value = 0.035), indicating that the chances of a tumor being malignant were higher as the age increased. The most common symptom of presentation was painful abdomen (5/8) followed by lump in the abdomen (Table 1).

Duration of symptoms ranged from 3 to 6 months except in one patient, who presented with a short history of 3 days as acute pain of the abdomen due to torsion. Owing to the lack of specific symptoms suggestive of a malignant transformation in a teratoma, these cases are often missed. In this study only one case of adenocarcinoma with metastasis, presenting with ascites and pleural effusion, was clinically suspected to have malignancy. Considering the laterality of this transformation, it was found that while 4 cases were right sided the other 4 were left sided. The association of laterality with malignancy was not found to be statistically significant (p = 0.241).

In all the cases where radiological investigations were available, it was found that although malignancy was suspected in 25% (2/8) of cases none of the cases were diagnosed as MT in these investigations. One of the cases was diagnosed as mature cystic teratoma on contrast enhancing computed tomography (CECT)

Table 1. Clinicopathological features of all eight cases of malignant transformation arising in mature cystic teratoma

No.	Age (years)	Laterality	Symptoms	Investigations	Tumor gross	Clinical diagnosis	Histopathological diagnosis
1	35	Left	Pain × 6 months	USG: cystic mass with few solid areas	Solid cystic ovarian mass 12 × 8.5 × 6 cm C/s variegated	Dermoid cyst ovary	SCC in teratoma
2	42	Left	Lump × 5 months Pain × 3 months	CECT: mature cystic teratoma left ovary	15 cm diameter predominantly cystic mass with tiny solid areas	Malignant ovarian tumor	SCC in teratoma
3	56	Right	Pain × 4 months Post-menopausal bleeding × 3 months	USG: cystic ovarian mass with few solid areas	14 × 10 × 3.5 cm solid cystic mass	Malignant tumor ovary	Teratoma with TCC
4	50	Right	Pain × 6 months	USG: possibly malignant ovarian tumor	12 × 7 × 5 cm bosselated solid cystic ovarian mass	Malignant ovarian tumor	Teratoma with malignant melanoma
5	55	Right	Lump × 4 months	USG: solid cystic ovarian mass	10 × 7 × 6 cm well-circumscribed solid cystic with areas of hemorrhage and necrosis	Dermoid? Malignancy?	Teratoma with grade III TCC
6	33	Left	Lump × 4 months	NA	12 cm diameter cystic mass with one polypoidal solid area	Dermoid cyst	SCC in teratoma
7	37	Left	Acute pain × 3 days	NA	13 × 10 × 7 cm solid cystic ovarian mass	Solid cystic ovarian mass? Dermoid?	SCC in teratoma
8	46	Right	Abdominal distention × 1 month, ascites and pleural effusion	USG: ovarian malignancy	6 cm diameter predominantly solid mass with hair and pultaceous material inside	Malignant ovarian tumor	SCC Adenocarcinoma in teratoma metastatic to omentum

NA – not available, SCC – squamous cell carcinoma, TCC – transitional cell carcinoma

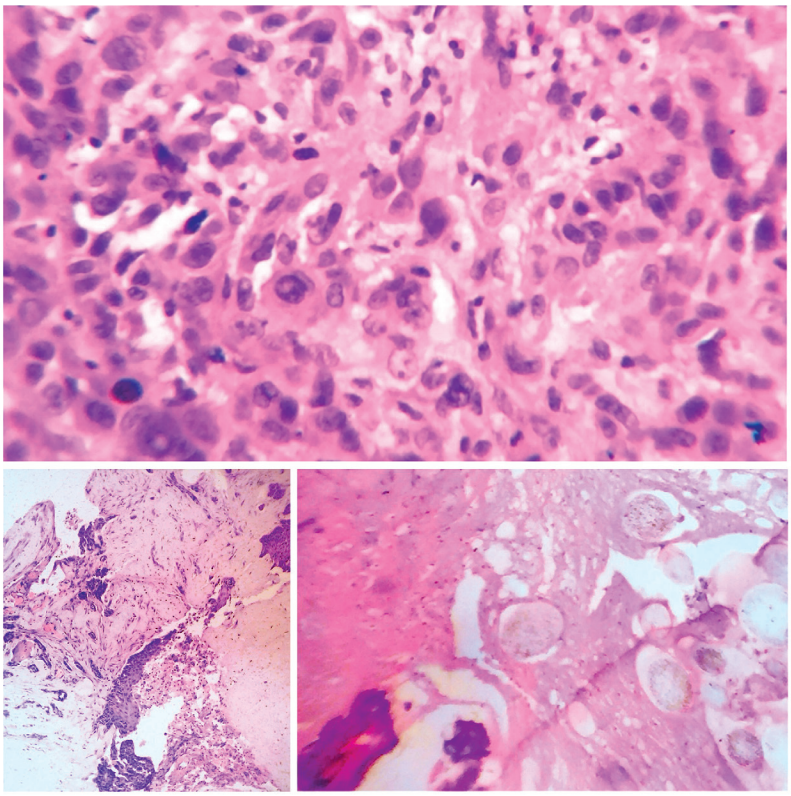

Fig. 1. Areas with malignant transformation into squamous cell carcinoma, nests of malignant squamous cells infiltrating the stroma with entrapped hair follicles (H&E ×40)

of the abdomen but turned out to be a squamous cell carcinoma developing in a mature cystic teratoma on histopathology sections. Clinical and radiological details of patients and histopathological diagnosis are summarized in Table 1.

Pathological findings

Gross examination

Grossly the mean size of MT in MCT was 11.7 ±2.7 cm, whereas it was 7.6 ±2.1 cm for mature cystic teratoma. The cut surface for all MT in MCT was predominantly solid cystic with only two of eight cases having a variegated appearance. The tumors were predominantly cystic, filled with pultaceous material and hair. Foci of solid areas were identified in all the cases. In one case, the tumor had undergone partial necrosis and hemorrhage, presumably due to torsion. The association of size of the tumor with malignancy status was found to be statistically significant (p = 0.00) in this study.

Microscopic examination

All the tumors showed keratinized stratified squamous epithelium, hair follicles, sebaceous glands, lobules of mature cartilage, glands lined by respiratory mucosa, skeletal muscle and adipocytes. Digestive tract mucosa was also identified in one case. No immature elements were identified in any of the cases. Squamous

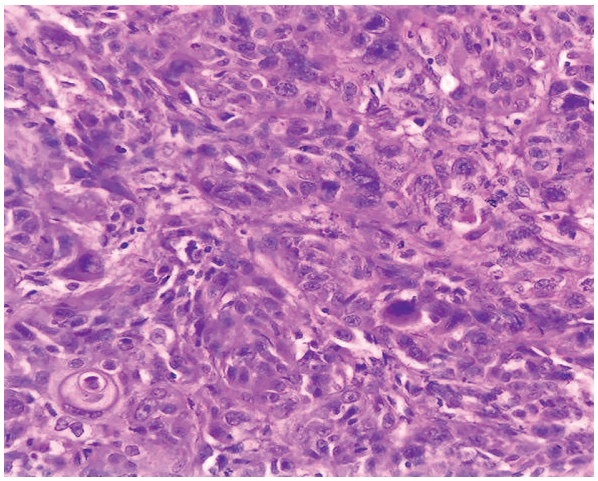

Fig. 2. Squamous cell carcinoma with atypical mitotic figures (H&E ×400)

cell carcinoma (SCC) was the most frequent MT (Figs. 1 and 2), seen in four out of eight cases (50%), while one case showed an adenocarcinoma and the other a malignant melanoma, and two cases (25%) had malignant transformation in the form of transitional cell carcinoma (Figs. 3-5). The only case where the suspicion of malignancy was high and the patient presented with ascites had adenocarcinoma in the peritoneum (Fig. 3). While 5/8 cases were treated with a total abdominal hysterectomy with bilateral salpingo-oophorectomy, in

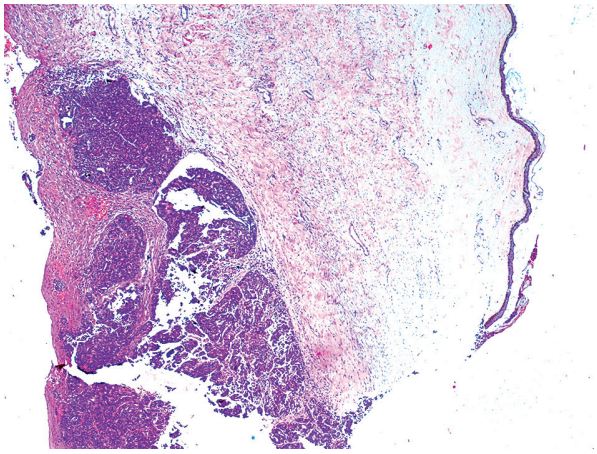

Fig. 3. Adenocarcinoma with glands and numerous mitotic figures (arrows) (H&E ×40)

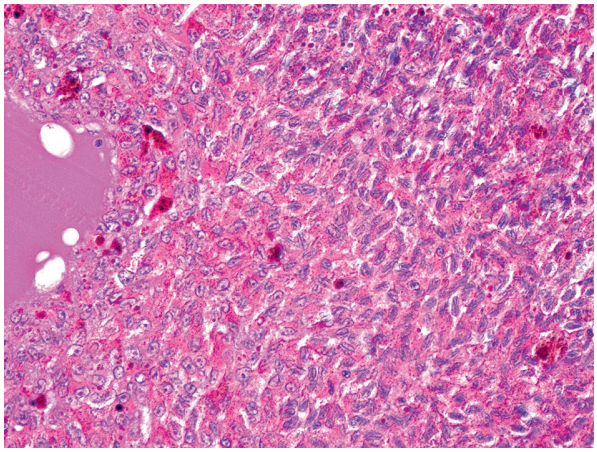

Fig. 4. Malignant melanoma arising in mature cystic teratoma showing sheets of epithelioid cells with vesicular nuclei, prominent eosinophilic nucleoli and melanin (H&E ×400)

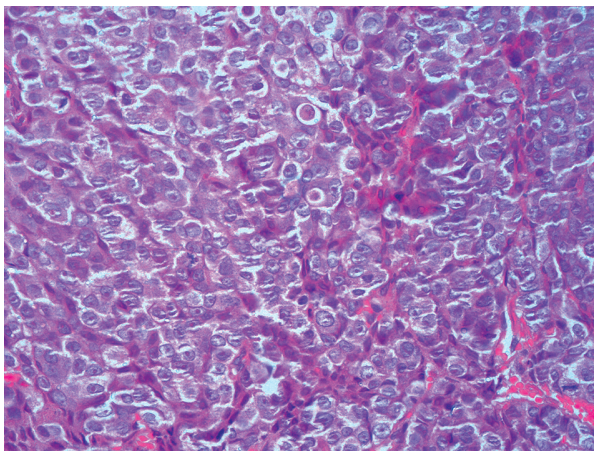

Fig. 5. Transitional cell carcinoma arising in mature cystic teratoma (H&E ×400)

3/8 cases unilateral salpingo-oophorectomy was performed. A peritoneal biopsy was also taken along with the removal of tumor in one case where the suspicion of metastasis was high.

Discussion

Malignant transformation of a mature cystic teratoma is exceedingly rare and occurs in only 1-3% of cases [3, 5]. However, there are two studies where the frequency of such malignant transformation was as high as 6.67% and 5% respectively [4, 6]. The frequency in our study is higher than the reported literature, at 3.5%.

Kikkawa *et al*. studied 37 cases of SCC arising from MCT in a 17-year period [7]. In their study the mean age of patients with SCC of the ovary was 55.2 years as against 37.5 years in patients with MCT. The mean age of patients with MT in our series was however slightly earlier, being 44 years as against 32.5 years for MCT. The rarity of this malignant transformation is generally true for all age groups, but the chances of any of the components becoming malignant is higher in perimenopausal and older women, as is seen in this study. Described uncommonly in postmenopausal women, we had 8.2% (19/230) cases of MCT, of which 21% (4/19) had MT, i.e. of all the 8 cases of MT 50% (4/8) belonged to the postmenopausal age group (45-55 years). Wei *et al*. analyzed mature cystic teratomas in postmenopausal women and found that 7.6% of the total number of patients with benign ovarian teratomas had MT [8]. The incidence of malignant change in the postmenopausal age group in their study was 15% as against 21% in this study. The mean size of a malignant ovarian dermoid as studied by Kikkawa *et al*. Was 15.2 cm, compared to 8.8 cm in benign dermoid tumor [7]. However, in our study the mean sizes of both MCT and MCT with MT were smaller, being 7.6 cm for MCT and 11.7 cm for MT.

MT arising from MCT is diagnosed with difficulty in the preoperative period. Quite often, although the patients present with a painful abdomen or a lump in the abdomen, the possibility of MT in MCT is still missed owing to the lack of any specific signs and symptoms. Moreover, the preoperative radiological findings also in these patients may not differ much from those seen in uncomplicated MCT. Only a high index of suspicion based on history and examination of the patient may give a clue towards the diagnosis. Patients with MT of MCTs may sometimes present with a rapidly enlarging tumor or may present with systemic symptoms suggestive of malignancy in an advanced stage of the disease, as seen in one of our cases with a positive peritoneal biopsy. Most of our patients presented with abdominal pain and a history of lump in the abdomen, except one where the presentation was acute due to torsion of the tumor. The radiological investigations suspected a malignancy in only 2/8 cases. The diagnosis of MT in MCT was suspected in none of the cases radiologically.

The role of serum markers such as SCC antigen is also questionable in such cases since MT in MCT is a very rare occurrence, and is often not suspected on radiological or clinical examination. Mori *et al*. found

Table 2. Comparison of our study with other studies

Study No.	Author (year)	Duration of study (years)	Percentage	MT	Mean age (years)	Mean size (cm)	CL/F	Types of carcinoma	Most common
1	Ulker *et al.* (2012) [3]	9	1.9	6	43	11.5	Pain	SCC, Cd, M Aca	SCC
2	Harshmohan *et al.* (2007) [4]	6	6.67	5	46	11.6	Pain	SCC, PTC	SCC
3	Rim *et al.* (2006) [13]	20	1.7	11	50.6	NA	Lump	SCC, Aca	SCC
4	Present study	25	3.5	8	44	11.7	Pain	SCC, TCC, MM, Aca	SCC
5	Sakuma *et al.* (2010) [18]	18	NA	37	52.5	8.8	NA	SCC, Aca, ASca, MM	
6	Araujo *et al.* (2015) [19]	5	5.5	10	36	NA	NA	SCC, PTC ASca, Aca, WD NE Ca	SCC
7	Oranratanaphan *et al.* (2013) [20]	10	1.46	11	41.2	14.1	Lump	SCC, M Aca, Aca	SCC=M Aca
8	Fu Fan *et al.* (2013) [21]	48	8	3	48	16	NA	SCC	SCC
9	Futagami *et al.* (2012) [22]	7	2.6	2	42.5	10	Lump	SCC	SCC
10	Black *et al.* (2015) [23]	8	1.2	7	53.7	18	Bloating, pain	M Aca, MM, SCC, PD Aca	M Aca

MT – malignant transformation, CL/F – clinical features, NA – not available, SCC – squamous cell carcinoma, Cd – carcinoid, M Aca – mucinous adenocarcinoma, Aca – adenocarcinoma, PTC – papillary thyroid carcinoma, ASca – adenosquamous carcinoma, WD NE Ca – well-differentiated neuroendocrine carcinoma

that a combination of patient's age (above 40 years) with serum SCC antigen level (> 2.5 ng/ml) may be considered as a suitable marker for diagnosis [9]. Some studies including those of Suzuki *et al*. [10] and Mayazaki *et al*. [11] concluded that SCC antigen alone or in combination with other markers, such as macrophage-colony stimulating factor (M-CSF) and carcino-embryonic antigen (CEA), may be considered as suitable markers for a preoperative diagnosis of MT in MCT. But since the serum level of SCC antigen depends on the tumor volume, early detection of small tumors becomes difficult. However, in the present study serum SCC levels were not determined in any of the cases, possibly due to the lack of a strong clinical and radiological suspicion of a malignant change and the poor economic status of the patients.

All the tumors in our study showed keratinized stratified squamous epithelium, hair follicles, sebaceous glands, lobules of mature cartilage, glands lined by respiratory mucosa, skeletal muscle and adipocytes, but no immature elements were identified in any of these cases. Mature thyroid tissue along with other derivatives was seen in one of the cases. Struma ovarii was seen in 6/230 cases and neural differentiation was seen in 3/230 cases. 11/230 (5.2%) cases of immature teratoma were identified in the study over a period of 25 years, but none of these had evidence of MT as is found in MCT.

The most common MT reported in the literature is SCC, as is also seen in the present study [3]. Hirakawa *et al*. studied the clinical and pathological features of 28 patients with SCC arising in MCT of the ovary [12]. In 11 tumors, SCC was considered to have originated from a columnar epithelium (ciliated or non-ciliated) or from a metaplastic squamous epithelium. But in none of the cases was SCC a direct transition from the ordinary epidermis of the teratomatous skin tissue. However, in the present series, although the carcinoma arising from keratinized squamous epithelium was documented in one out of the four cases, the origin from columnar or metaplastic epithelium was seen in none. The comparison of our study with other studies on MT is shown in Table 2.

The pathogenesis of MT in MCT is still not clear. Rim *et al*. [13] studied 11 cases of MT in MCT and hypothesized that since 80% of MCTs are diagnosed during reproductive age, MT may develop due to the long-term presence of non-removed MCT. Though the reason for this is not clear, it is postulated by some authors that the long-term presence of mature cystic ovarian teratoma and squamous metaplasia of the columnar epithelium may be followed by such malignant change. Molecular studies conducted so far on these cases do show some evidence of p53 overexpression as a causative factor [14].

Though the most common malignancy seen in an MCT is SCC, which represents about 75% of malignant transformation, other neoplasms, including adenocarcinoma, neuroectodermal tumors, sarcoma, and malignant melanoma, have also been reported [15-21]. In

our study also SCC was the most frequently identified malignant transformation, found in four out of eight cases (50%). There was one case of adenocarcinoma and malignant melanoma each. The fact that although SCC was still the commonest tumor to be found, two cases of transitional cell carcinoma (TCC) (25%) were found in our study is unlike any other study reported so far. Malignant melanoma arising within a mature cystic teratoma is also extremely rare, with an estimated incidence of 0.2 to 0.8% [16]. In our study, out of the 230 cases of MCT, we had only one case of malignant melanoma, giving an incidence of 0.4%.

SCC arising in MCT of the ovary have been associated with a very poor prognosis in various studies [17]. Age, tumor size, clinical stage, histologic differentiation, capsular invasion and the presence of vascular invasion may predict the survival of patients with SCC arising from MCT [7, 12]. Unlike other tumors of the ovary, SCC of the ovary spreads transmurally with extensive local invasion. Hirakawa *et al*. reported an overall 5-year survival rate of 52% in their series of 28 patients [12]. Since ours was a retrospective study, a comment on prognosis cannot be made due to the unfortunate lack of complete follow-up of these patients.

Conclusions

We conclude that although rare, the rate of malignant transformation in MCT increases with age and is much higher in the postmenopausal age group, as compared to younger women, possibly due to the longer duration of MCT found in these women. A higher index of suspicion must be maintained for MCT occurring in the postmenopausal age group. Moreover, although SCC is still the commonest, TCC may also develop not infrequently as malignancy apart from other rare differentiations such as adenocarcinoma or malignant melanoma in an MCT.

Disclosure

The authors report no conflict of interest.

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