


Malignant Transformation of Mature Cystic Teratomas: A Retrospective Analysis of 181 Cases

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ABSTRACT

Objective: Mature cystic teratoma (MCT) constitutes 20% of all ovarian tumors and is the most prevalent ovarian germ cell tumor. Notably, any of its component tissues may undergo a malignant transformation (MT). This study aimed to retrospectively analyze the malignancies that arise from MCT of the ovary.

Methods: Data of histopathological analysis of ovarian masses resected from adult patients and diagnosed at our laboratory between January 2012 and December 2018 were reviewed.

Results: Of our 181 cases, 7 (3.86%) were detected to have MT. Among the MT cases, five had papillary thyroid carcinoma, one had squamous cell carcinoma, and one had a strumal carcinoid.

Conclusion: The diagnosis of malignancies arising from MCT is crucial to decide on the follow-up and treatment options for patients. Reporting data obtained from cases that demonstrate MT will aid in the pre- and postoperative management of patients.

Keywords: Malignancy, mature cystic teratoma, ovarian tumor

INTRODUCTION

Mature cystic teratoma (MCT) of the ovary is the most prevalent ovarian germ cell tumor and originates from two or three germ layers (ectoderm, mesoderm, and endoderm). It constitutes 20% of all ovarian tumors (1).

The prevalence rates of these tumors, encountered in patients of ages ranging from childhood to postmenopause, typically peak around ages 20–40 years (2). MCTs are generally clinically asymptomatic and are detected either incidentally or because of the pressure from the mass during gynecological examination. Transvaginal ultrasonography is the primary diagnostic tool used in the diagnosis of MCT (3). Notably, tumor markers have a limited role in diagnosis (4).

Mature cystic teratomas have a typical macroscopic appearance; most are cystic and contain sebaceous material. Tumor components include various tissues, including hair, fat, bone, cartilage, glial tissue, gastrointestinal epithelium, respiratory epithelium, and thyroid tissue (3).

Mature cystic teratoma is a benign tumor; however, it may rarely undergo a malignant transformation (MT) (at a rate of 1%–2%), typically encountered in more advanced ages (5). MT may arise

from any of the MCT tissue components. The most common MT reported in a case series is squamous cell carcinoma (SCC), and the literature contains reports of various types of sarcoma and adenocarcinoma, melanoma, and basal cell carcinoma arising from MCT (6–13).

This study aimed to retrospectively evaluate 181 adult patients with MCT who were analyzed and diagnosed by our laboratory between 2012 and 2018 concerning their histopathological findings and MT.

METHODS

Results of histopathological diagnoses of ovarian masses resected from adult patients between January 2012 and December 2018 were reviewed. Data of 181 patients who were diagnosed with MCT or dermoid cysts were evaluated in terms of patient age, tumor location, tumor diameter, macroscopic properties of the tumor, and MT observed after histopathological diagnosis. The evaluation was based on hospital file records, as well as pathology reports. Besides, archived pathology slides were re-evaluated where necessary.

RESULTS

The ages of our patients ranged from 17 to 72 years (mean: 30.47 years), and 62.43% of MCT patients were aged between

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Figure 1.a-c. Follicular architecture of thyrocytes with nuclear overlapping, crowding, and nuclear enlargement. Hematoxylin and Eosin (H&E) ×200, ×400 (a, b). Immunohistochemical membranous positivity with HBME-1, HBME-1 ×400 (c)

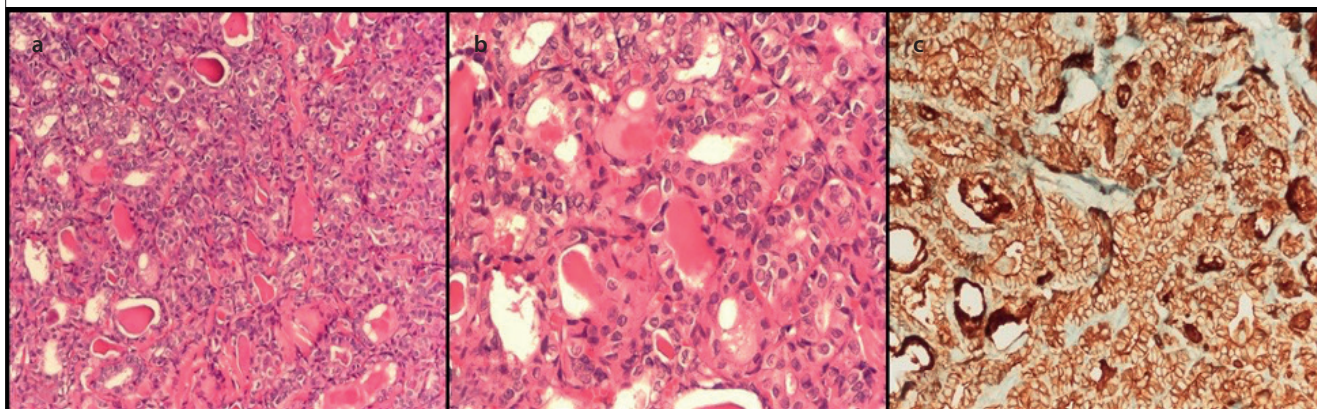


Figure 2. a-d. Solid nests composed of small uniform cells with round hyperchromatic nuclei, H&E ×40 (a, b). Tumorous area (left side) adjacent to the ovarian stroma (right side), H&E ×200 (c). Increased mitotic figures, H&E ×400 (d)

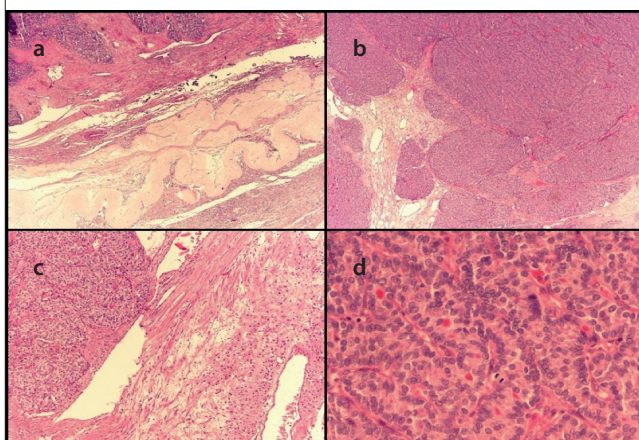
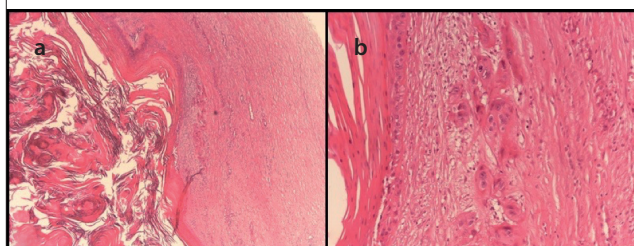


Figure 3. a, b. Squamous lining epithelium with prominent keratin, H&E ×40 (a). Irregular and atypical squamous islands in the stroma, H&E×400 (b)



20–40 years. The tumor was localized in the right ovary in 85 cases (46.96%), left ovary in 77 cases (42.54%), and bilateral in 19 cases (10.49%). Evaluation of macroscopic tumor characteristics revealed that the diameter of the tumor was smaller than 10 cm in 124 cases (68.5%), between 10 and 20 cm in 53 cases (29.28%), and greater than 20 cm in 4 cases (2.2%). Macroscopi-

cally, the surface of the section was cystic in 68 cases, solid in 41, and solid-cystic in 72. Macroscopically, the solid component was observed to increase at greater tumor diameters.

In our series, 7 (3.86%) of the 181 patients manifested MT. Of these, five had papillary thyroid carcinoma (PTC), one had SCC, and one had a strumal carcinoid (Figures 1-4). Three of the PTC cases had microcarcinomas (<1 cm). Clinical complaints included pelvic pain in five cases, pelvic tenderness in one case, and a clinically asymptomatic mass that was incidentally detected during a routine check-up. We could access the tumor marker levels of only two cases, and both these cases were determined to have high CA 125 levels. Three cases were operated for a malignant preliminary diagnosis, whereas the rest were operated for a preliminary diagnosis of a dermoid cyst. The majority of cases demonstrated unilateral localizations and solid cut surfaces. The clinicopathological findings of our MT cases are presented in Table 1.

Main Points:

- Although MCT is a benign tumor, it may rarely undergo a malignant transformation from any of the tissue components. Macroscopically, the ovarian mass with increased solid component and tumor diameter must be examined carefully for MT.
- The diagnosis of malignancies that arise from mature cystic teratomas is important for the follow-up and treatment options of the patients.
- Reporting the data obtained from cases of MT will be informative for the pre/postoperative management of the patients.

DISCUSSION

Mature cystic teratoma is the most prevalent ovarian germ cell tumor and constitutes 20% of all ovarian tumors (1). The most common complications associated with it include torsion, infection, and rupture. MT of the MCT is a rare (1%–2%) but serious complication (5, 14). Per the literature, a 35-year study by Ayhan et al. (14) determined an MT rate of 1.4% among their 501 study patients. Rathore et al. (15) determined this rate to be 3.5% in

their 230-patient series, whereas Bal et al. (16) identified an MT rate of 6.6% in their 75-patient series. In our series, 7 of the 181 cases were observed to have MT, and the MT rate was 3.8%.

Nevertheless, the clinical prediction of MT is difficult. Studies have not observed a correlation between MT and serum tumor markers; however, more than 70% of cases were reported to have high CA 125 or CA 19-9 levels (4). In our case series, of the three cases suspected of having malignancies, tumor marker levels of only two could be accessed, and both these cases were determined to have high CA 125 levels.

Most often MTs of the MCT are unilateral (16). In our series, three cases underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy, whereas others underwent unilateral excision for the unilateral masses. Notably, patients who under-

went bilateral salpingo-oophorectomy also had unilateral tumors.

Notably, SCC is the most common MT of MCT. However, among the seven MT cases in our series, only one had SCC (0.55%). Nonetheless, the most common MT was PTC arising from struma ovarii, as observed in five cases (2.76%). One of our cases (0.55%) had a strumal carcinoid.

Struma ovarii is a monodermal teratoma of the ovary and constitutes 2% of all germ cell tumors. Notably, 5%–10% of struma ovarii cases are malignant, and typically manifest as unilateral masses during the reproductive period. However, their incidence increases with age. The most prevalent MT in struma ovarii is PTC, followed by follicular carcinoma and follicular variant of papillary carcinoma (17). Five of our cases were noted to have a follicular

Figure 4. a-f. Monomorphic cells growing in solid nests and trabeculae admixed with thyroid microfollicles containing colloid, H&E×40, ×100 (a, b). Solid islands of cells forming rosettes, H&E×40 (c). Follicular nuclear TTF-1 positivity in the thyroid component, TTF-1×100 (d). Low proliferation index with Ki 67, Ki67×100 (e). Inhibin negativity of the tumor, Inhibin×100 (f)

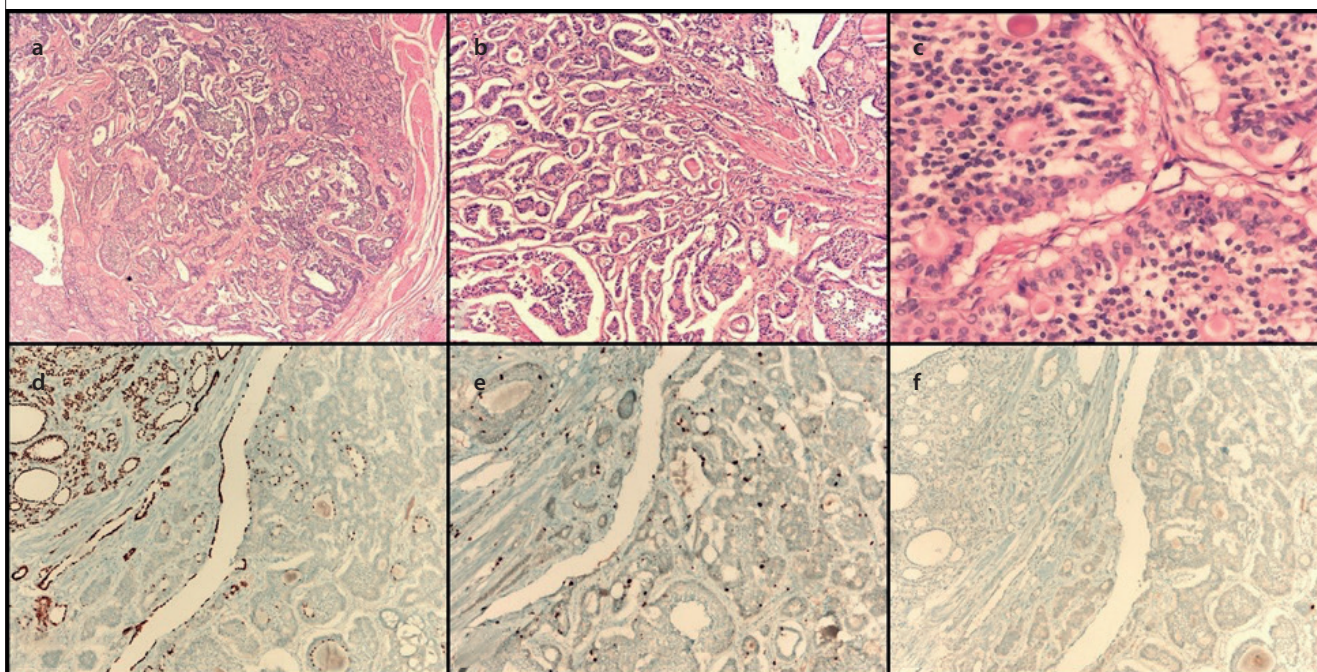


Table 1. Clinicopathologic parameters of 7 cases with malignant transformation

Case	Age	Localization	Symptom	Tm marker	Clinical diagnosis	Macroscopy	Histopathologic Diagnosis
1	47	R	Pelvic pain	None	Malignant	11 cm	SCC
2	27	R	Control	None	DC	3 cm	PMC
3	20	R	Pelvic pain	None	DC	4.5 cm	PMC
4	47	L	Pelvic pain	None	DC	7.2 cm	PMC
5	62	R	Pelvic tenderness	CA 125:80.6 U/ml	Malignant	7.5 cm	PDTC
6	72	L	Pelvic pain	CA 125:3648 U/ml	Malignant	10 cm	PTC
7	24	R	Pelvic pain	None	DC	9 cm	Strumal Carcinoid

R: right; L: left; DC: dermoid cyst; SCC: squamous cell carcinoma; PMC: papillary microcarcinoma; PDTC: poorly differentiated thyroid carcinoma; PTC: papillary thyroid carcinoma

variant of papillary carcinoma, whereas one case had a poorly differentiated thyroid carcinoma arising from PTC. All these cases were unilateral, with two in the second decade, one in the fourth decade, and the other two in the sixth and seventh decades. Two cases of advanced age were detected to have PTC and poorly differentiated thyroid carcinomas arising from PTC, whereas three cases had tumors in the form of a microcarcinoma. The presence of microcarcinoma led to PTC being the most prevalent MT in our series, contradicting the literature and our expectations. We reasoned that the detection of microcarcinoma cases was probably linked to the high number of macroscopic samples.

Malignant struma ovarii cases may clinically manifest thyrotoxicosis, and studies have reported cases of hypothyroidism after resection (17). The clinical data of our cases were inspected concerning their thyroid states, and it was observed that none had a history of any thyroid-related clinical complaints.

Nevertheless, there is no consensus regarding the clinical approach for malignant struma ovarii cases. According to various approaches in the literature that have been described for cases and case series, patients must be screened for metastasis after diagnosis, and their serum thyroglobulin and iodine 131 levels must be monitored. Notably, thyroidectomy has been reported in some cases (17, 18). We could access the postoperative follow-up data of three cases (cases 5 and 6), and thyroid examinations of these cases did not indicate any pathologies.

The second most prevalent MT in our series was SCC, which is the most common MT of MCT (19). In a study by Kikkawa et al. (20) that investigated a series of 37 patients with SCC arising from MCT over 17 years, the mean age was determined as 55.2 years. Notably, our case was 47 years old. Regarding the epidermal component, MT may arise from squamous, ciliated, and non-ciliated columnar epithelia. When dealing with ovarian SCC, metastatic carcinomas must certainly be eliminated. Notably, the most common primary cancers are cervical or vaginal SCC in ovarian metastases. Immunohistochemically, SCC arising from MCTs were reported to show HPV and strong P16 positivity. Based on these findings, HPV was thought to be a risk factor for this malignancy (19). Upon gynecological examination, our case did not have any cervical or vaginal pathologies. Our patient was not immunohistochemically evaluated for HPV and P16 expression. The conventional treatment for SCC arising from MCTs is total hysterectomy, bilateral salpingo-oophorectomy, surgical staging (omentectomy, appendectomy, peritoneal biopsies, pelvic and paraaortic lymphadenectomy) in early-stage cases, and optimal cytoreductive surgery in advanced stage cases. Chemotherapy is recommended for those with more advanced disease, but the efficacy of radiotherapy is uncorroborated. Notably, the prognosis is poor in cases with extra-ovarian spread (19).

Strumal carcinoid tumor of the ovary is a rare form of ovarian teratoma composed of carcinoid and thyroid tissue (21). Strumal carcinoid was first described in 1970 by Robboy et al. (22). Clinically, the symptoms associated with the mass may be accompanied by symptoms of carcinoid syndrome. Our case did not clinically manifest symptoms of carcinoid syndrome. Strumal car-

cinoids can present an admixture of thyroid tissue and the carcinoid tumor component. The thyroid component is composed of micro and macrofollicles containing colloid. The carcinoid component demonstrates a pure trabecular or a mixed trabecular-insular pattern in most cases. Notably, the thyroid and carcinoid components can be differentiated based on immunohistochemical markers, as well as cellular properties (21). Our case showed an admixture of thyroid tissue and the carcinoid component presenting trabecular and solid patterns. Furthermore, in our case, the carcinoid component exhibited synaptophysin and chromogranin positivity, and the thyroid component exhibited follicular nuclear TTF-1, cytoplasmic and colloidal thyroglobulin positivity. When diagnosing ovarian stromal carcinoid tumors, the following differential diagnoses must be excluded: thyroid carcinomas, ovarian granulosa, and Sertoli Leydig cell tumors arising from stromal carcinoids. Strumal carcinoids almost always have a benign manifestation (23). Kurabayashi et al. (24) reported detecting bone and breast metastases in cases who had shown marked cellular atypia, high mitotic activity, and focal necrosis 3.5 years earlier. Nevertheless, our case did not have cellular atypia, high mitotic activity, or necrosis, and is currently undergoing the first year of postoperative follow-up.

CONCLUSION

The diagnosis of malignancies that arise from MCT is crucial in deciding the follow-up and treatment options of patients. MCTs are encountered quite frequently in the pathological routine and must be inspected thoroughly for MT. Reporting data obtained from cases with MT can aid in the pre- and postoperative management of patients.

Ethics Committee Approval: Ethical committee approval was obtained from Gaziantep University School of Medicine ethical board (Approval No: 2019/323).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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