Malign Transformation in the Mature Cystic Teratoma of the Ovary: Presentation of 9 Case Studies

Overin Matür Kistik Teratomunda Malign Transformasyon: 9 Olgu Sunumu

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ABSTRACT Objective: Mature cystic teratoma (MCT) is the most frequently observed ovarian germ cell tumor. It constitutes up to 10-20% of the ovarian tumors. The incidence rate of malign transformation in ovarian mature cystic teratoma is approximately 2%. Clinical presentation of malignant MCT depends on the extension and histological type of the secondary malignancy. Squamous cell carcinoma is the most common secondary tumor seen in malignantly-transformed MCT cases. The prognosis of patients with malignant transformation in teratoma is very poor and most patients die within 1 year. However, the prognosis is better if the tumor is limited to one ovary, with an intact capsule not adhered to adjacent structure and with a uniform thickness of the cyst wall. In this study, the incidence, histologic types, and prognosis of the malign transformed MCT were assessed. **Material and Methods:** Six hundred seventy-six cases were diagnosed as mature cystic teratoma of the ovary between January 2000 and December 2010 in our Pathology Laboratory, Tepecik Obstetrics and Gynecology Hospital. Malignant transformation was determined in 9 of these patients (1.48%) of whom operative data, histopathologic findings, and postoperative follow-up data were evaluated in light of the literature. **Results:** Out of 676 mature cystic teratoma cases, malignant transformation was determined in nine of them (1.48%). Six out of nine patients were in the postmenopausal period while two were in perimenopausal period and one was premenopausal period. Median age was found to be 45.7 (34-71 years). The average diameter of the ovarian tumor was 9.5 (7-15) cm. The tumor settled on the left in five cases, whereas it settled on the right in four cases. Squamous cell carcinoma was found in three cases, mucinous cystadenocarcinoma was found in two cases, thyroid papillary carcinoma was found in two cases, carcinoid tumor was found in one case and signet ring cell carcinoma was found in one case. According to surgical FIGO staging, four cases were classified as stage IA, three cases were classified as stage IC, one case was classified as stage II B and one case was classified as stage II C. Average follow-up period was 71 months (5-126 months). **Conclusion:** In cases preliminary diagnosed as mature cystic teratoma, malign transformation possibility should be considered especially in women in postmenopausal period and in those with large-size tumors. Frozen section examination plays an important role in identifying both the method of surgical treatment and the patient prognosis.

Key Words: Ovarian neoplasms; teratoma; carcinoma; cell transformation, neoplastic

ÖZET Amaç: Matür kistik teratom (MKT) en sık görülen ovarian germ hücreli tümördür. Over tümörlerinin %10-20 kadarını oluşturur. Overin matür kistik teratomlarının malign transformasyon insidensi yaklaşık %2 civarındadır. Malign değişim gösteren MKT'nin klinikte belirtileri sekonder malignitenin yayılımı ve histolojik tipine bağlıdır. Skuamöz hücreli karsinom malign değişim gösteren MKT olgularında en sık görülen sekonder tümördür. Malign transformasyon gösteren matür kistik teratomlu hastalarda prognoz oldukça kötüdür, çoğu hasta 1 yıl içinde ölür. Ancak tümör bir overe sınırlıysa, kist duvar kalınlığı üniform ve kapsül intakt, çevre dokulara yapışıklık göstermiyorsa prognoz daha iyidir. Bu çalışmada malign transformasyonun insidensi, histolojik tipleri ve prognozu değerlendirildi. **Gereç ve Yöntemler:** Ocak 2000 ile aralık 2010 tarihleri arasında Tepecik Kadın Hastalıkları ve Doğum Hastanesi Patoloji Laboratuvarında 676 olgu overin matür kistik teratomu tanısı almıştır. Bu hastaların dokuzunda (%1,48) malign transformasyon saptanmıştır. Bu 9 olguya ait operasyon verileri, histopatolojik bulgular, postoperatif takip verileri literatür bilgileri ışığında değerlendirilmiştir. **Bulgular:** Serimizde incelenen 676 matür kistik teratom olgusunun 9 (%1,48)'unda malign transformasyon saptandı. Bu dokuz hastanın altısı postmenopozal, ikisi perimenopozal ve biri de premenopozal dönemde idi. Yaş ortalaması 45,7 (34-71) yıl idi. Tümörün ortalama çapı 9,5 (7-15) cm idi. Tümör 5 hastada sol tarafta 4 hastada ise sağ tarafta yerleşmişti. Skuamöz hücreli karsinom 3 hastada, müsinöz kistadenokarsinom 2 hastada, tiroid papiller karsinom 2 hastada, karsinoid tümör 1 hastada ve taşlı yüzük hücreli karsinom 1 hastada bulundu. Ortalama takip süresi 71 aydı (5-126 ay). Cerrahi FIGO sınıflandırmasına göre, 4 hasta evre 1A, 3 hasta evre 1C, 1 hasta evre 2B ve 1 hasta evre 2C olarak sınıflandırıldı. **Sonuç:** Matür kistik teratom düşünülen olgularda özellikle postmenopozal kadınlarda ve büyük tümör boyutu varlığında malign transformasyon olasılığı akla getirilmelidir. Frozen inceleme cerrahi tedavinin şeklini ve hastanın prognozunu saptamada önemli bir rol oynamaktadır.

Anahtar Kelimeler: Over tümörleri; teratom; karsinom; hücre dönüşümü, neoplastik

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Mature cystic teratoma is the most frequently observed ovarian germ cell tumor. It constitutes up to 10-20% of the ovarian tumors.[1,2] Incidence rate of malign transformation in ovarian mature cystic teratoma is approximately 2%.[3-5] The most frequently observed malign transformation in mature cystic teratoma is the squamous cell carcinoma, which constitutes up to 75-80% of the cases.[4] Cases of adenocarcinoma and carcinoid may be observed with a lower rate of frequency.[5] Depending on age, malign transformation is frequently observed in 5th to 6th decades. It is difficult to identify during the pre-operative stage since it is rare and resembles mature cystic teratoma.[6] It is usually diagnosed through post-operative pathological examination.[2]

MATERIAL AND METHODS

Between January 2000 and December 2010, in a series of 676 cases diagnosed as mature cystic teratoma in our unit, 9 cases were identified as having malign transformation. Clinic data were gathered from patient files and pathology reports. Surgical staging was conducted in line with FIGO system. The patients' ages, complaints, stages, tumor diameter, treatment applied and follow-up results were recorded. In pre-operative stage routine biochemical tests, CA 125 test, chest radiography, ultrasonography, CT or MRI imaging results have been taken. Since there were no patients requiring fertility protection, all patients were applied hysterectomy, bilateral salpingooophorectomy, omentectomy, appendectomy, peritoneal cytology, multiple peritoneal biopsy and cytoreductive surgery involving pelvic/paraaortic lymph sampling steps.

Post-operative adjuvant treatment was personalized according to surgical stage and thereby added. In addition to chemotherapeutic regimes such as NP (navelbine, Cisplatin) and TK (paclitaxel, carboplatin), radiochemotherapy (weekly Cisplatin 40 mg/m²) administration was added. The cases were followed up by taking into consideration their CA 125 measurements, gynecologic examination, gynecologic sonography and CT results after the therapy ended. Average follow-up period was 71 months (5-126 months) (Table 1).

RESULTS

The rate of malign transformation in ovarian mature cystic teratoma cases in our unit was found to be 1,48%. Six of these patients were in postmenopausal period while two were in perimenopausal period and one was premenopausal period. Median age was found to be 45.7 (34-71) years. Total abdominal hysterectomy and bilateral salpingooophorectomy, abdomen cleansing sampling, omentectomy, appendectomy, pelvic/paraaortic lymph adenectomy operations were applied on all advanced age patients who had completed child breeding period. Materials were sent

TABLE 1: Clinical and pathological findings of the cases.

Case	Age (year)	Tumor Diameter (cm)	Stage	Histopathological Diagnosis	Monitoring Period
1	71	15	IA	Thyroid papillary carcinoma in teratoma	126 months, disease free survival
2	46	7	IA	Mucinous cystadenocarcinoma in teratoma	94 months, disease free survival
3	62	12	IC	Signet ring cell carcinoma in teratoma	5 months exitus
4	59	15	IA	Mucinous cystadenocarcinoma in teratoma	53 months, disease free survival
5	51	10	IC	Carcinoid tumor in teratoma	53 months, disease free survival
6	61	8	IIC	Squamous cell carcinoma in teratoma	122 months, disease free survival
7	63	12	IC	Thyroid papillary carcinoma in teratoma	99 months, disease free survival
8	47	10	IIB	Squamous cell carcinoma in teratoma	16 months exitus
9	34	8	IA	Squamous cell carcinoma in teratoma	54 months disease free survival

to the pathology laboratory for intraoperative frozen section examination.

The average diameter of the ovarian tumor was 9.5 (7-15) cm. The tumor settled on the left in five cases whereas it settled at the right in four cases. When tumor section was taken in all cases, cystic structure full of sebaceous material and hair formations was found in addition to solid areas in the form of irregular thickening on the cystic wall as well as necrotic change in some of the cases.

In microscopical examination, again in all cases, keratinized squamous epithelium, hair follicles, sebaceous glands, glands fitted with adipocyts and respiratory mucosa were observed. Nerve tissue, skeletal muscle and hyaline cartilage were observed though in fewer amounts. Squamous cell carcinoma was found in three cases, mucinous cystadenocarcinoma was found in two cases, thyroid papillary carcinoma was found in two cases, carcinoid tumor was found in one case and signet ring cell carcinoma was found in one case (Figures 1-5).

In immunohistochemical examination, thyroglobulin (+) was found in two cases with thyroid papillary carcinoma, pancytokeratin (+) and p63 was found in three cases with squamous cell carcinoma, cytokeratin 7(-), cytokeratin 20 (+) were found in two cases with mucinous cystadenocarcinoma and signet ring cell carcinoma and kromogranin (+), Neuronspecific enolase (+), synaphtophysin were found in one case with carcinoid tumor.

As a result of surgical FIGO staging of the cases, four cases were classified as stage IA, three cases were classified as stage IC, one case was classified as stage II B and one case was classified as stage II C. Malign cells were found during abdomen cleansing in three cases. One of these cases was

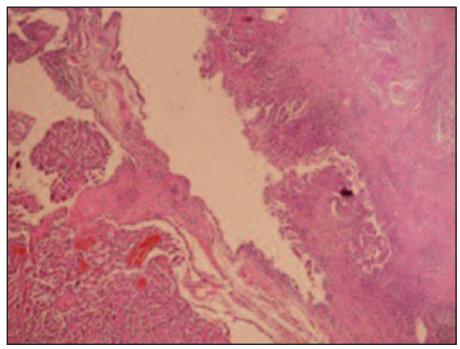

FIGURE 1: Thyroid papillary carcinoma in teratoma (HxE,x40).

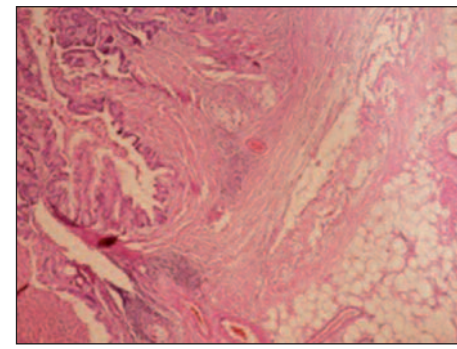

FIGURE 2: Mucinous cystadenocarcinoma in teratoma (HxE,x40).

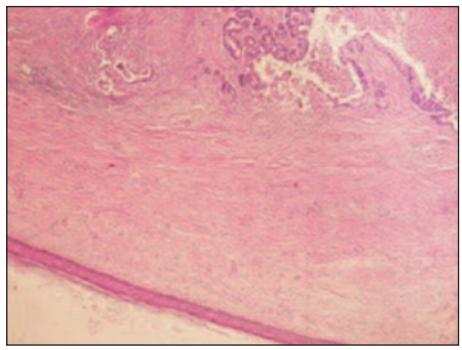

FIGURE 3: Signet ring cell carcinoma in teratoma (HxE,x40).

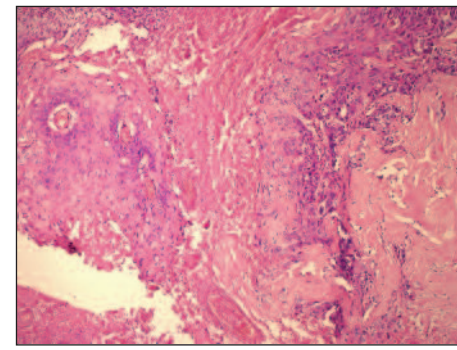

FIGURE 4: Squamous cell carcinoma in teratoma (HxE,x40).

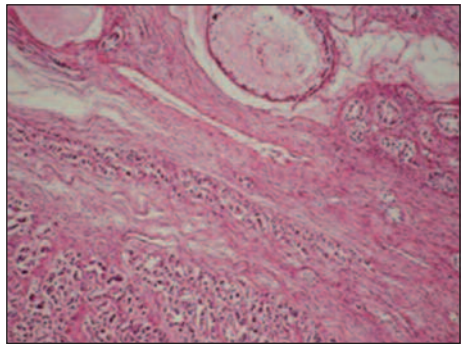

FIGURE 5: Carcinoid tumor in teratoma (HxE,x40).

found to have metastatic tumor in the omentum. The case diagnosed as having signet ring cell carcinoma (case 3) developed lung metastasis after a short period of time. After two cures of chemotherapy exitus occurred on the 5th month.

On one of the cases with squamous cell carcinoma diagnosis (case 8) radiochemotherapy was administered after a metastatic tumor was discovered in the abdomen; however, patient was lost 16 months later. The other patient with squamous cell carcinoma diagnosis was administered radiochemotherapy after the operation. This case is followed as a disease-free survival in the 122nd month. The other seven cases were taken under the scope of clinical follow up without any adjuvant therapies after the operation.

DISCUSSION

Mature cystic teratoma is the most frequently observed ovarian germ cell tumor. It is especially observed during adolescence and reproductive period. It was reported in literature that malign transformation was observed in approximately 2% of the mature cystic teratoma cases and can be observed at any age while most of the patients are at postmenopausal period.[1,2,4] In this study, malign transformation in ovarian mature cystic teratoma was observed in 9 (1,48 %) out of 676 patients, while the average age was calculated as 45,7. The calculated average age conforms to the previous studies.

Benign cystic teratoma involves mature elements differentiated in three embryonic germ leaves. Ectodermal layer is the most significant one. The carcinoma may form from any epithelial element of the mature cystic teratoma.[1,5,7] Squamous cell carcinoma make up almost 85% of the malign transformation cases in mature cystic teratoma.[1,2,7,8] Adenocarcinoma, carcinoid tumor, malign melanoma, sebaseous carcinoma, carcinosarcoma, small cell carcinoma, sarcoma (leiomyosarcoma, chondrosarcoma, osteosarcoma) have also been reported.[9-16] In this study incidence rates of the tumors are similar to the literature with the incidence rate of squamous cell carcinoma was found (33,3%). The articles have also reported that malign transformation of ectopic thyroid tissue is very rare, whereas two such cases were discovered in the series subject to this study.[2]

It is very difficult to diagnose malign tumors developed in mature cystic teratoma during the pre-operative period. Clinical significance of tumor indicators is not clear. It has been reported that squamous cell carcinoma antigen, which is a useful marker in diagnosing squamous cell carcinoma of cervix, may be used for diagnosing squamous cell carcinoma developing during mature cystic teratoma of the ovary. In a study by Tseng et al., levels of squamous cell carcinoma antigen was found to be low in 16 (67%) out of 24 patients, who have developed squamous cell carcinoma in ovarian mature cystic teratoma, and in all recurrent patients squamous cell carcinoma antigen was found to rise again.[1] Measuring squamous cell carcinoma antigen in combination with other indicators such as Macrophage-colony stimulating factor (M-CSF) and carcinoembryonic antigen (CEA) may be useful in the pre-operative diagnosis of the disease.[2] In cases found suspicious of malign transformation in mature cystic teratoma, frozen section examination with adequate sampling, carried out by an experienced pathologist is a guiding factor in identifying the method of surgical treatment.[5] Frozen section examinations were carried out on the cases suspicious of malignancy during pre-operative period. In this series, measuring of tumor markers were not performed. Contrary all cases with malignant transformation were diagnosed by intraoperative histopathological examination.

Resection of pelvic genital organs and lymph nodes were performed.

The main treatment is surgery in malign transformations of the mature cystic teratoma of the ovary. Tseng et al. suggested conservative unilateral oophorectomy without requiring post-operative treatment, at the early stage (stage I A) especially for young and nulliparous patients. In postmenopausal women staging laparotomy surgery is appropriate through the total removal of pelvic genital organs.[1]

Some articles report postsurgical chemotherapy or radiotherapy as having no effect on survival.[1,5] However, Tseng et al. suggest chemotherapy and/or radiotherapy after surgery in advanced stage malignancy.[1] In the series subject to this study, all stage I patients have survived except one. Stage I C patient (case 3) with signet ring cell carcinoma diagnosis, died 5 months later. Stage II B patient (case 8) with squamous cell carcinoma diagnosis was administered postoperative radiochemotherapy, the patient remained unresponsive to chemotherapy due to intraabdominal metastasis development in month 10 and consequently exitus occurred in month 16. The patient diagnosed as stage II C squamous cell carcinoma, who was expected to have a bad prognosis, received additional 6 cures of radiochemotherapy due to malignancy discovered through second look laparotomy after 6 cures of postoperative chemotherapy; the patient is a disease-free survival case followed for 122 months.

Poor prognostic factors identified by Stamp et. al. for malignancies developing in the mature cystic teratoma of the ovary, are the cystic wall invasion, rupture, acid and existence of adhesion.[1] Age, size of the tumor, clinical stage and existence of lymphovascular tumor invasion are useful factors to determine the life expectancy of the patient.[2] Furthermore, like epithelial ovarian tumors, early FIGO stage and appropriate surgical approach are good prognostic indicators except the signet ring carcinoma.[1]

Most mature cystic teratoma is diagnosed at reproductive period. Contrary malign transformation of the mature cystic teratoma is frequently identified at post-menopausal period. Mature cystic teratoma is observed 15 to 20 years earlier compared to malign transformation. It is considered that long term exposure of mature cystic teratoma in pelvic cavity to various carcinogens may lead to malign transformation. In cases thought to be mature cystic teratoma, malign transformation possibility should be considered especially in postmenopausal women and when there are large-size tumors. Frozen section examination plays an active role in identifying both the method of surgical treatment and the patient prognosis.

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