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Malignancy in cases with suspected mature cystic teratoma in the preoperative and intraoperative evaluations

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Summary

Objective: To report cases who were suspected to have mature cystic teratoma in the preoperative and intraoperative periods, but were found to have malignancy together with mature cystic teratoma in the final histopathological examination. *Materials and Methods:* The medical records of 148 cases were retrieved. The records were used to review the sociodemographic properties, histopathology, intraoperative tumor size, the surgical procedure, adjuvant therapy, and follow-up of the patients who were suspected to have mature cystic teratoma in the preoperative and intraoperative periods, but were found to have malignancy together with mature cystic teratoma in the frozen or final histopathological examination. *Results:* Of the patients, 8.2% were found to have malignancy arising in mature cystic teratoma. The median age of the patients was 32- (min:15, max: 66) years-old and the tumor size was 12.1 (min: 4, max: 25) cm. Six patients were established to have an immature teratoma, three had a carcinoid tumor, one had a primitive neuro-extrodermal tumor (PNET), one had serous borderline tumor, and one had a borderline mucinous tumor. *Conclusion:* Although a mature cystic teratoma is benign, since it may involve different degrees of malignancy, intraoperative attitudes and procedures should follow the rules that apply to the management of a complicated adnexal mass and the possibility of a malignant transformation should be in kept in mind when informing the patient in the preoperative period.

Key words: Mature cystic teratoma; Malignancy; Immature teratoma.

Introduction

The most common benign neoplasm originating from the ovary, teratoma constitutes 10% to 20% of all ovarian tumors [1]. It involves the three germ layers, namely, the endoderm, ectoderm, and mesoderm. Although it is usually identified in the reproductive period and incidentally, it may sometimes manifest itself with symptoms like pelvic pain, a feeling of pressure, and swelling. Frequently reported complications include torsion, rupture, and infection, but more importantly, the presence of major degeneration [2].

The rate of malignant degeneration in the dermoid cyst varies in the literature reports. Although the mean rate in the literature is roughly 2%, there are studies which report a rate around 5% to 6.6% [3]. The matter is further complicated by both the difficulty of diagnosing the malignant transformation preoperatively and intraoperatively and the lack of standard management guidelines in case of an unexpected situation.

The present study aims to present the experience gained and the methods used in the present clinic in relation to malignancies that arise in the teratomas.

Materials and Methods

Of the cases who presented at the Obstetrics and Gynecology Services at Seyhan Research and Application Hospital on the Adana Campus of Baskent University Medical School, this study retrospectively evaluated the cases who were thought to have a dermoid cyst in the preoperative and intraoperative periods, but whose final histopathological examination showed a malignant focus. For this purpose, the patient records were reviewed in terms of sociodemographic characteristics, age, preoperative ultrasonographic cyst size, levels of tumor markers, including CA-125, surgical operations, whether or not the cyst ruptured, intraoperative complications, if any, and definitive pathological diagnosis. Criteria defined for mature cystic teratoma in the preoperative and ultrasonographic evaluations and frozen examinations were assessed. These criteria include the appearance of an intensely echogenic mass with or without a cystic component, appearance of an echogenic thin band-like cystic mass, cystic echo containing fluid or appearance of a dense fluid containing intense echogenic tubercles, and cystic appearance with a fluid-fat level [4]. Intraoperative presence of hair, bone, cartilage, skin, and fat content is suggestive of a mature cystic teratoma diagnosis.

The histopathology, intraoperative tumor size, surgical procedure, adjuvant therapy, and follow-up of the patients who were found to have a malignant transformation were reviewed. The data were expressed in percentages (%).

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Table1. — *Tumor characteristics and surgical operations.*

Patient number	Age (years)	Histopathology	Tumor diameter (cm)	Grade	Primary surgery	Staging surgery	Adjuvant therapy
1	66	Carcinoid	6		TAH+BSO¶	-	-
2	16	Immature	25	2	L/S Cystectomy©	-	3 cycles BEP◊
3	20	Immature	12	1	USO+BPPLND ∞	+	No
4	19	Immature	7	1	L/S Cystectomy	-	- No
5	22	Immature	20	1	L/S Cystectomy	-	No
6	15	PNET*	10	No	L/S Cystectomy	-	3 cycles BEP
7	47	Carcinoid	4	No	L/S Cystectomy	-	No
8	37	Borderline mucinous	30	No	USO+Om+AppΩ	+	No
9	48	Carcinoid	9	No	L/S Hys.+BSO ▲	-	No
10	22	Immature	15	1	L/S Cystectomy	-	No
11	36	Immature	4	1	L/S Cystectomy	+	No
12	37	Borderline serous	4		L/S Cystectomy	+	No

*cm: centimeter * Primitive neuro-extrodermal tumor. ¶ Total abdominal hysterectomy, bilateral salpingo-oophorectomy.*
© Laparoscopic cystectomy ∞ unilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy.
Ω: Unilateral salpingo-oophorectomy, omentectomy, appendectomy. ▲ Laparoskopic hysterectomy, bilateral salpingo-oophorectomy.
◊: Bleomisin, etoposide, platin. + Yes, - No.

Results

The tumor characteristics of and surgical operations performed on the cases who were found to have mature cystic teratoma are presented in Table 1. Six patients were established to have an immature teratoma, three had a carcinoid tumor, one had a primitive neuro-extrodermal tumor (PNET), one had serous borderline tumor, and one had a borderline mucinous tumor.

All patients, but one, were surgically treated for adnexal masses. One case was already known to have an adnexal mass during pregnancy and a cystectomy was performed on her and was sent as frozen sectioin. When the cyst was reported to be an immature teratoma, a staging operation was performed. Five cases (one PNET, two immature teratoma, one serous borderline tumor, and one carcinoid) were found to have a malignancy arising in the mature cystic teratoma in the final histopathological examination and were restaged. One case was put on three courses of bleomycin, etoposide, and cisplatin (BEP) treatment due to an intraoperative rupture before staging surgery; one patient was given BEP for PNET and one was administered BEP as she had an advanced stage disease.

Discussion

The rate of a malignant focus in mature cystic teratoma was found to be 8.2% in the present study. The rates reported in the literature are around 2% to 3% and was reported to stand at 6% in a single study. The rate found in the present study is considerably higher than those in the literature. This high rate can be explained in several ways. One explanation is that immature teratoma cases were classified as immature teratoma, rather than as a malignant tumor arising in a mature cystic teratoma. In fact, immature teratoma involves all three germ layers, like mature teratoma, but unlike mature teratoma, immature teratoma also includes immature or embryonic elements, which are diagnostic. As it is known, immature teratoma was previously called solid teratoma, malignant teratoma, teratoblastoma, and teratocarcinoma [5], and these multiple designations have caused some confusion. When the present rates are re-evaluated by leaving six immature teratoma cases aside, the rate of malignancy drops to 4%. The fact that the present rate is still closer to the highest rate in literature seems to be associated with being a referral gynecological oncology center. Actually, it is known that the risk of malignancy in mature cystic teratoma is directly correlated with patient age and tumor diameter, and 40% of the present cases have tumor diameters larger than 10 cm, and half of them are older than 30 years [6]. These cases were referred to the present center due to the increased risk of malignancy. In this respect, it seems reasonable to expect malignancy rates higher than the mean rates in the general literature in gynecological oncology centers.

Another significant aspect of the present study is the rate of immature teratoma cases among the suspected mature cystic teratoma cases is 5%. It is reported in the literature that the immature teratomas constitute 1% of all teratomas [7]. Still another different and interesting finding of the present study is that squamous cell carcinoma, which is reported to be the most common malignancy arising in the teratoma at a rate of 85%, was not seen in any of the present cases [8]. This difference can also be attributed to regional differences, as well as the present being a referral center. The rates of immature teratoma were reported to be higher in the Mediterranean region [9]. As the present study explanations show, of the six immature teratoma cases, five had grade 1 tumors and two had immature foci at the millimetric level. These findings may be explained by the detailed examination performed in the study. As a matter of fact, the examination of mature cystic teratoma to identify

immature areas was performed thoroughly and by pathologists who are experienced in gyno-oncology [10], as was suggested previously [10]. Identification of a grade 1 area at the millimeter level requires obtaining cross-sections from a very high number of areas [11]. The literature studies reporting rates do not specify how the examination was performed and thus, some immature areas may have been missed, as was the case in previous studies [12]. Furthermore, it does not seem possible to reach a conclusion through the preoperative and intraoperative evaluations of immature teratomas. Levels of alpha-fetoprotein, one of the most valuable markers in differentiation, may remain normal in some early-stage cases [11]. None of the present patients, except one, was found to have an extra-ovarian intraperitoneal disease. Although the retroperitoneal area was not assessed, these are the cases who were accepted to be in the early stage. Some MRI findings were identified in the preoperative imaging of immature teratomas, but these are not diagnostic and only elevate suspicion scores. There is no test or imaging method that can decisively predict malignancy in the preoperative period [13]. Malignancy risk increases with increasing tumor size and in the perimenopausal period, but these are not diagnostic either [14-17]. Furthermore, tumor diameter renders frozen examination difficult. Although three of the present cases had tumors with diameters larger than 10 cm, the diagnosis could be given on the basis of millimetric foci in the postoperative examination. These tumors, except for the ones with higher grades, can suggest mature cystic teratoma due to their content in the macroscopic examination. In all the cases in this study, the cyst content was opened intraoperatively, examined, and still only a grade 2 could be diagnosed as immature teratoma in the frozen examination.

Another group of malignant cases in the present study comprises the cases with a carcinoid in the teratoma. As it is reported in the literature, all such cases are seen at old age. These cases did not show any difference from mature cystic teratoma in the preoperative and intraoperative examinations. The mean age of the cases was advanced and tumor size was among the large-diameter mature cystic teratomas, as noted in the literature [5]. Neither of the present carcinoid cases had postoperative high 5-hydroxy indole acetic acid levels, carcinoid syndrome signs or metastasis.

Laparoscopy was performed in all the present cases, except for two of patients. One of them was examined during cesarean. The other one treated with mini-laparotomy which was due to mass size and to prevent from rupture of cyst. Due to the lack of any radiological, biological or clinical sign predictive of malignant transformation in the preoperative period, laparoscopy is preferred as a less invasive method in the surgical management of mature teratomas. However, a rupture that can occur during the surgery of teratomas which can be diagnosed to have malignant degeneration only in the postoperative period may elevate the grade of the disease from FIGO IA to IC1. Mayer *et al.* reported that the dissemination of the tumor as a result of an intraoperative capsule rupture causes both an increase in grade and additional morbidity and strongly suggested starting aggressive adjuvant therapy in such cases [18]. It was reported in another study that invasion on the cyst wall, rupture, tumor dissemination, acid, presence of adhesion, and tumor types other than squamous cell carcinoma were poor prognostic factors in the malignant degeneration arising in teratoma [19, 20].

Conclusion

In conclusion, although mature cystic teratoma has a benign character, it may contain malignant components. Therefore, the risk of malignancy should always be kept in mind both in the preoperative evaluation and intraoperative management of mature cystic teratoma. As is done in the management of adnexal masses, care should be taken in the management of mature cystic teratoma to avoid tumor rupture and the resulting upstage.

References

[1] Ayhan A., Bukulmez O., Genc C., Karamursel B.S.: "Mature cystic teratomas of the ovary: case series from one institution over 34 years". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2000, *88*, 153.

[2] Ulbright T.M.: "Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues". *Mod. Pathol*., 2005, *18*, 61.

[3] Bal A., Mohan H., Singh S.B., Sehgal A.: "Malignant transformation in mature cystic teratoma of the ovary: report of five cases and review of the literature". *Arch. Gynecol. Obstet.*, 2007, *275*, 179

[4] Caspi B., Appelman Z., Rabinerson D., Elchalal U., Zalel Y., Katz Z.: "Pathognomonic echo patterns of benign cystic teratomas of the ovary: classification, incidence and accuracy rate of sonographic diagnosis". *Ultrasound Obstet. Gynecol*., 1996, *7*, 275.

[5] Bidus A.M.,Elkas J.C., Rose G.S.: "Germ cell, stromal, and other ovarian tumors". *In:* DiSaia P.J., Creasman W.T. (eds). *Clinical gynecologic oncology*. 8th ed. Philadelphia: Elsevier Saunders, 2012, 342.

[6] Yamanaka Y., Tateiwa Y., Miyamoto H., Umemoto Y., Takeuchi Y., Katayama K., *et al.*: "Preoperative diagnosis of malignant transformation in mature cystic teratoma of the ovary". *Eur. J. Gynaecol. Oncol.*, 2005, *26*, 391

[7] Talerman A.: "Germ cell tumours of the ovary". *In:* Kurman, R.J. *Blaustein's pathology of the female genital tract*. 3rd ed. New York (NY): Springer-Verlag, 1987, 659

[8] Pins M.R., Young R.H., Daly W.J., Scully R.E.: "Primary squamous cell carcinoma of the ovary. Report of 37 cases". *Am. J. Surg. Pathol*., 1996, *20*, 823.

[9] Ozgur T., Atik E., Silfeler D.B., Toprak S.: "Mature cystic teratomas in our series with review of the literature and retrospective analysis". *Arch. Gynecol. Obstet.*, 2012, *285*, 1099.

[10] Norris H.J., Zirkin H.J., Benson W.L.: "Immature (malignant) teratoma of the ovary: a clinical and pathologic study of 58 cases". *Cancer*, 1976, *37*, 2359

[11] Scully R.E., Young R.H., Clement P.B.: "Surface epithelial stromal tumors. Serous tumors". *In:* Scully RE, Young RH, Clement PB (eds). *Atlas of the ovary, maldeveloped gonads, fallopian tube, and broad ligament.* Washington, D.C.: Armed Forces Institute of Pathology, 1998, 51.

[12] Yamaoka T., Togashi K., Koyama T., Fujiwara T., Higuchi T., Iwasa Y., *et al.*: "Immature teratoma of the ovary: correlation of MR im-

aging and pathologic findings". *Eur. Radiol.*, 2003, *13*, 313.

[13] Park J.Y., Kim D.Y., Kim J.H., Kim Y.M., Kim Y.T,. Nam J.H.: "Malignant transformation of mature cystic teratoma of the ovary: experience at a single institution". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2008, *141*, 173.

[14] Hackethal A., Brueggmann D., Bohlmann M.K., Franke F.E., Tinneberg H.R., Münstedt K.: "Squamous-cell carcinoma in mature cystic teratoma of the ovary: systematic review and analysis of published data". *Lancet Oncol.*, 2008, *9*, 1173.

[15] Kikkawa F., Nawa A., Tamakoshi K., Ishikawa H., Kuzuya K., Suganuma N., *et al.*: "Diagnosis of squamous cell carcinoma arising from mature cystic teratoma of the ovary". *Cancer*, 1998, *82*, 2249.

[16] Oranratanaphan S., Khemapech N.: "Characteristics and treatment outcomes of patients with malignant transformation arising from mature cystic teratoma of the ovary: experience at a single institution". *Asian Pac J Cancer Prev*.2013;14:4693

[17] Tseng C.J., Chou H.H., Huang K.G., Chang T.C., Liang C.C., Lai C.H., *et al.*: "Squamous cell carcinoma arising in mature cystic teratoma of the ovary". *Gynecol. Oncol.*, 1996, *63*, 364.

[18] Mayer C., Miller D.M., Ehlen T.G.: "Peritoneal implantation of squamous cell carcinoma following rupture of a dermoid cyst during laparoscopic removal". *Gynecol. Oncol.*, 2002, *84*, 180.

[19] Stamp G.W., McConnell E.M.: "Malignancy arising in cystic ovarian teratomas. A report of 24 cases". *Br. J. Obstet. Gynaecol.*, 1983, *90*, 671.

[20] Kikkawa F., Ishikawa H., Tamakoshi K., Nawa A., Suganuma N., Tomoda Y.: "Squamous cell carcinoma arising from mature cystic teratoma of the ovary: a clinicopathologic analysis". *Obstet. Gynecol.*, 1997, *89*, 1017

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