

OVARIAN TERATOMA IN ROUTINE BIOPSY MATERIAL DURING A FIVE-YEAR PERIOD

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SUMMARY – Teratomas are tumors derived from germ cells, most frequently arising in the gonads. The aim of this study was to determine the number of ovarian teratomas diagnosed in the routine biopsy material at Ljudevit Jurak Clinical Department of Pathology, Sestre milosrdnice University Hospital Center during a 5-year period, as well as their clinical, gross and microscopic characteristics. Teratomas accounted for 48.6% (n=166) of primary ovarian tumors. The patient mean age was 34.74±12.37 years. Difference in the incidence of teratoma between the left and right ovary was not significant; bilateral teratoma was found in 13 patients. Teratomas were detected by ultrasonography in 115 (69.27%) cases and the rest were found during surgery performed for other indications. Most teratomas (n=161; 96.9%) were mature and cystic (dermoid cysts). Mature and solid teratomas were diagnosed in 5 (3.01%), ovarian struma in 2 (1.8%) cases and strumal carcinoid in 1 (1.2%) case. Mature cystic teratomas contained sebaceous material in 123 (76.8%) cases, and a total of 16 teeth were found; 157 (94.5%) teratomas measured <10 cm in largest diameter. Microscopically, mature cystic teratomas most frequently contained ectodermal (skin with appendages, mature glia and nerve ganglia) and mesodermal (fibrous, fat tissue, cartilage and bone) tissues. Frequently found tissues of endodermal origin were respiratory and intestinal epithelia. Small foci of thyroid tissue were found in 20 (12%) teratomas. Chronic granulomatous foreign body reaction in the wall of mature cystic teratomas was found in 11 (6.8%) tumors.

Key words: *Teratoma – diagnosis; Struma ovarii – diagnosis; Carcinoid tumor*

Introduction

Teratomas are fascinating, most frequently benign tumors, derived from germ cells and commonly arising in the gonads. They can also develop along the body midline (base of the skull, mediastinum, sacrococcygeal region), which is a migratory pathway of the primordial germ cells from the yolk sac^{1,2}. In the sacrococcygeal area, teratomas arise as congenital tumors; in the testicles teratomas usually develop in childhood, but ovarian teratomas can arise throughout the lifespan, being most frequent in the reproductive period^{1,3,4}.

The most common symptoms of ovarian teratomas are pressure, pelvic pain and irregular bleeding, but the symptoms can also result from complications such as torsion, rupture, peritonitis and autoimmune hemolytic anemia²⁻⁴. Most ovarian teratomas are grossly cystic, but they can also be solid. Microscopically, they can be composed of tissues derived from all three embryonic layers, i.e. ectoderm, mesoderm and endoderm. The tissues in teratomas are usually well differentiated (i.e. mature), but they can also remain at the fetal stage of development (i.e. immature). The most common immature tissue found in teratomas is neuroectodermal tissue, and such tumors are considered malignant. Mature teratoma can undergo malignant transformation in 2% of cases (the malignant component being most frequently squamous cell carcinoma). The treatment of teratomas is surgical (salpingo-oophorectomy

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or resection of the ovary), and depends upon the age of the patient and the volume of the tumor. Immature teratomas are treated by a combination of surgery and multimodal chemotherapy^{3,5,6}. The aim of this study was to determine the number of ovarian teratomas in the routine biopsy material received and diagnosed at Ljudevit Jurak Clinical Department of Pathology, Sestre milosrdnice University Hospital Center during a 5-year period, as well as their clinical, gross and microscopic characteristics.

Materials and Methods

Using the Thanatos computer program designed for routine pathologic sample description and documentation, data on the number of biopsy samples of the ovary received during the period from October 1, 2005 until September 30, 2010 were retrieved. Because the study period was relatively short, it was divided into one-year intervals, as follows: interval 1 starting on October 1, 2005 and ending on September 30, 2006; interval 2 starting on October 1, 2006 and ending on September 30, 2007; interval 3 starting on October 1, 2007 and ending on September 30, 2008; interval 4 starting on October 1, 2008 and ending on September 30, 2009; and interval 5 starting on October 1, 2009 and ending on September 30, 2010. The Thanatos program was searched for the following keywords: dermoid cystic, solid and immature teratoma (lat. *teratoma dermoides cysticum*, *teratoma solidum* and *teratoma immaturum*), struma of the ovary (lat. *struma ovarii*) and carcinoid of the ovary (lat. *carcinoides ovarii*). Diagnoses were made on the routine biopsy material of the ovary removed by laparoscopy or laparotomy, after routine fixation and paraffin embedding. The tissue was routinely cut at 5 μ m, stained with hematoxylin-eosin (H-E) and examined by light microscopy. When necessary, immunohistochemical analysis was done, using appropriate antibodies, most frequently against thyroglobulin, calcitonin, synaptophysin, chromogranin A, vimentin and desmin, according to the manufacturer's manual (Dako, Denmark). After the diagnoses that contained the keywords for the analyzed period were found, the age of patients, the way the tumor was clinically discovered, the laterality and size of the tumor, and the gross and microscopic features of the tumors were analyzed. Regarding the size, teratomas were divided into 4 groups: group 1 with

greatest diameter <5 cm, group 2 with greatest diameter 5.1-10 cm, group 3 with greatest diameter 10.1-15 cm, and group 4 with greatest diameter >15 cm.

Results

During the 5-year period analyzed, 1580 biopsy specimens of the ovary were received for histopathologic examination. In 370 (23.4%) cases, primary ovarian tumor was diagnosed. Teratomas were diagnosed in 153 patients, but in 13 cases the tumors were bilateral, so the total number of diagnosed teratomas was 166/370 cases (44.86%). Distribution according to one-year intervals showed that 46/166 (27.7%) teratomas were found in interval 3; 35/166 (21.1%) teratomas in interval 1; 29/166 (17.5%) teratomas in intervals 2 and 4 each; and the lowest number of cases, 27/166 (16.3%) in interval 5 (Fig. 1).

Difference in the incidence of teratomas diagnosed in one-year intervals was not significant. In 56/153 (36.6%) patients, teratoma arose in the left ovary and in 67/153 (43.8%) patients in the right ovary ($\chi^2=1.359$, $p<0.05$, NS). Bilateral teratomas were found in 13/153 (8.5%) patients. In 17/153 (11.1%) patients, the laterality of the ovary was not noted in pathologic report, presumably because the tumor was discovered incidentally, in the specimen from hystero-salpingo-oophorectomy, and the uterus was so deformed that it was not possible to determine which ovary was the left and the right one. In one case, the patient underwent surgery for teratoma of the left ovary in 2007 and for teratoma of the right ovary in 2008 (at the time of the first operation she was aged 40). One patient had first surgery for ovarian teratoma before 2005 and the diagnosis of that tumor was not included in the analysis. In

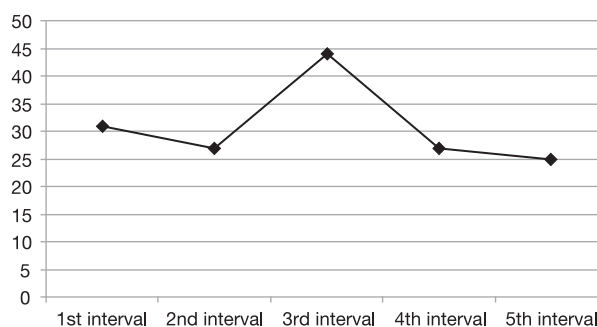
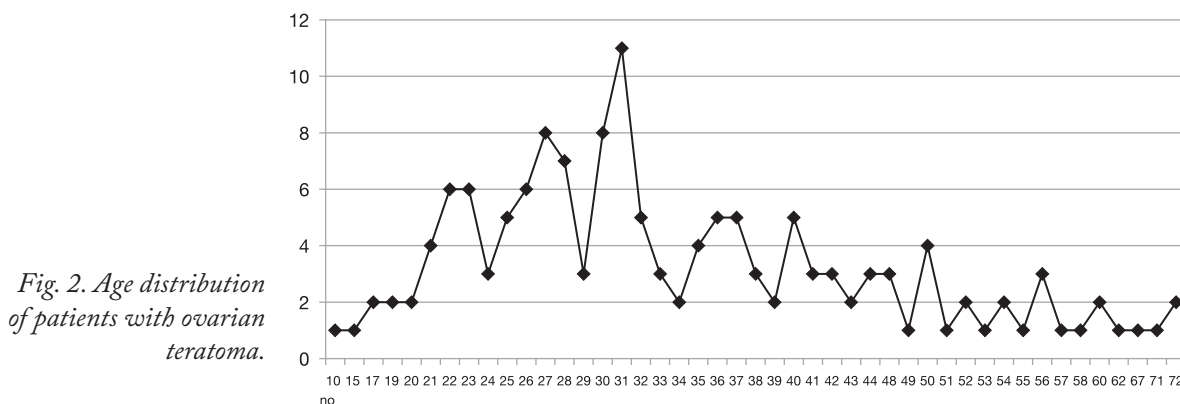


Fig. 1. Number of ovarian teratoma cases diagnosed in 1-year intervals during the 5-year study period (NS).



all other bilateral cases, both teratomas were diagnosed simultaneously. In 6/153 (3.9%) patients, age was not noted in the form requesting pathologic examination, and the mean age of the remaining patients was 34.7 ± 12.4 years. Age distribution showed that most teratomas occurred and were diagnosed during the reproductive period, but they can also appear in young girls and postmenopausal women (Fig. 2).

Most teratomas, 115/166 (69.27%), were diagnosed ultrasonographically. On ultrasonography, the examiner made clinical diagnosis of teratoma in 21/153 (13.7%) cases, while in the remaining patients clinical diagnosis was unspecified cystic ovarian tumor. In 14/166 (8.43%) cases, teratoma was discovered incidentally, during surgery for another indication: in four patients during cesarean section, in three patients during myomectomy, in two patients during salpingo-oophorectomy for ovarian abscess, in one patient during hystero-salpingo-oophorectomy for endometrial carcinoma, in one patient during surgery for uterine prolapse, in two patients during surgery for suspected tumor of the pouch of Douglas, and in one patient during surgery for ovarian torsion. In 37/166 (22.28%) cases, information on the way of making clinical diagnosis was not available. Regarding tumor volume, the largest (mature cystic) teratoma measured 20x12.5x7 cm. In 157 (94.5%) teratomas, the largest diameter was <10 cm.

Mature cystic teratoma was diagnosed in 161/166 (96.9%) cases. In 124/161 (77%) teratomas, the cystic part of the tumor contained sebaceous material and hair, in 14/161 (8.7%) tumors the content was necrotic, in 13/161 (8.07%) mucinous, and in 10/161 (6.2%) the content of the cyst was not described in the pathologic report.

Mature solid teratomas were diagnosed in 5/166 (3.01%) cases, 3 of them (1.8%) being ovarian struma (Fig. 3), while in 2 cases (1.2%) strumal carcinoid was diagnosed. On gross examination, 16 well formed teeth were discovered protruding into the cystic cavity of the tumor, 4 of them from Rokitansky's protuberance. In most teeth containing tumors, only one tooth was found, while 2 teeth were found in 2 cases.



Fig. 3. Solid teratoma grossly resembling thyroid tissue. Histopathologic diagnosis was ovarian struma.

Histogenetically, teratomas most commonly contained tissues of ectodermal origin. Skin with appendages was found in 155/161 (96.3%) cases, followed by mature glia in 50/161 (3.1%), well formed ganglion(s) in 27/161 (16.3%) and choroid plexus in 6/161 (3.3%) cases (Fig. 4).

Among mesodermally derived tissues, connective tissue was found in 149/161 (92.5%), adipose tissue in 130/161 (80.7%), hyaline cartilage in 56/161 (34.7%),

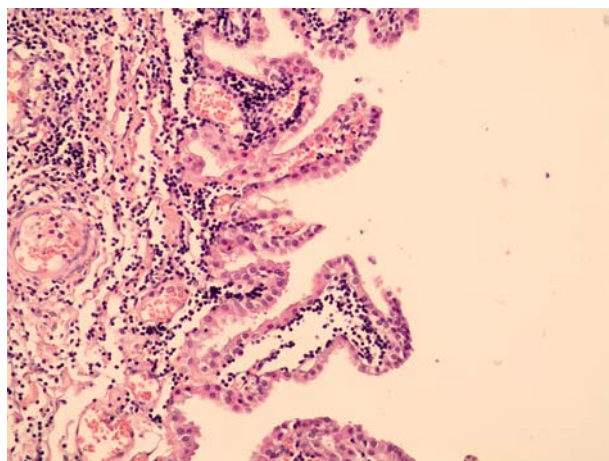


Fig. 4. Choroid plexus in one of the cystic spaces in the wall of cystic teratoma. It was surrounded by mature glial tissue (HE, X200).

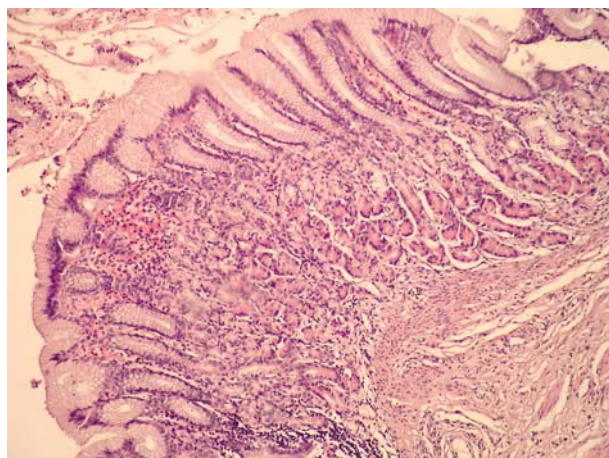


Fig. 5. Well differentiated gastric mucosa covering a part of the cystic cavity in a mature cystic teratoma (HE, X100).

bone in 41/161 (25.4%), smooth muscle in 20/161 (12.4%) and skeletal muscle in 6/161 (3.7%) teratomas. Ectodermal derivatives were the rarest finding, the most frequent of them being respiratory epithelium in 52/161 (32.3%), different types of gastrointestinal tract epithelia ranging from gastric to colonic epithelium in 13/161 (8.1%) (Fig. 5), ependyma in 8/161 (4.9%) and transitional epithelium in 6/161 (3.7%) teratomas.

According to histogenesis, the tissues found in teratomas are summarized in Table 1. The most frequently found glandular tissue in mature cystic teratomas

was thyroid tissue in 20/161 (12.4%), small mucous glands in 15/161 (9.3%), and salivary gland tissue in 10/161 (6.2%) cases. Adrenal and breast tissue was found in 1/161 (0.6%) case each. In 1/161 (0.6%) case, the tissue of pigmented nevus was also found. In 11/161 (6.8%) cases of cystic teratoma, the wall contained a conspicuous chronic foreign body inflammatory reaction with numerous lipid laden macrophages, probably due to destruction of the lining epithelium and leakage of sebaceous cyst contents into the wall. In 7/161 (4.3%) cases, abundant clusters of lymphocytes without germinal centers were found. The diagnosis of ovarian struma was made in 3/166 (1.8%) and the diagnosis of strumal carcinoid in 2/166 (1.2%) teratomas. In all 3 cases of ovarian struma, thyroid tissue was well differentiated, whereas in strumal carcinoid, carcinoid tumor confirmed by immunohistochemical methods was found besides thyroid tissue.

Table 1. Tissues found in cystic ovarian teratomas (N=161) according to their histogenesis

Origin/type of tissue	n	%
Ectoderm		
Skin with appendages	155	96.3
Glia	50	31
Ganglions	27	16.8
Choroid plexus	6	3.7
Mesoderm		
Connective tissue	149	92.5
Adipose tissue	130	80.7
Hyaline cartilage	56	34.8
Bone tissue	41	25.4
Smooth muscle	20	12.4
Skeletal muscle	6	3.7
Endoderm		
Respiratory epithelium	52	32.3
Intestinal epithelium	13	8.1
Ependyma	8	4.9
Transitional epithelium	6	3.7

Discussion

According to the literature, mature cystic ovarian teratomas are the most common ovarian germ cell tumors, accounting for around 20% of all ovarian tu-

mors⁹. In our research, teratomas comprised 166 (44.9%) of all ovarian tumors during the 5-year study period. The reason for this discrepancy is hard to explain. One of the reasons could be that literature data on the incidence of ovarian teratoma are relatively outdated and that the incidence of these tumors has, in the past sixty years, increased under the influence of various environmental factors generally connected with increased tumor incidence. The difference (although not statistically significant) in the number of teratomas diagnosed in particular years during the 5-year study period is unexplainable. As nowadays ovarian tumors are most commonly discovered ultrasonically, these differences might possibly be explained by individual history and clinical data. In our study, teratomas were diagnosed ultrasonically in 69.3% of patients, but in 9.2% of cases teratoma was detected incidentally during surgical procedure for another indication. The information on the way in which the remaining 22.3% of teratomas were discovered could not be confirmed with certainty. Data on patient age were consistent with literature data, since most of the patients in this study were in the reproductive age, although the age range was from 10 to 72 years¹⁰. Although teratomas were found more frequently in the right than in the left ovary, the difference was not significant. In 8.5% of cases, teratomas were bilateral, which confirmed the results of other studies⁹. Although teratomas can reach huge proportions, in this study the largest diameter was up to 5 cm in 106 (63.9%) and up to 10 cm in 157 (94.6%) cases, confirming again the results of other studies^{9,11}. Grossly, most teratomas in this study were mature cystic (dermoid cysts), containing sebaceous, necrotic and mucinous material in 96.9%, while in 4.7% the content was not precisely described. In comparison to 31% of cases in which well formed teeth were grossly found, in this study, only 9.5% of mature cystic teratomas contained teeth¹². On microscopic examination, all mature cystic teratomas contained tissues of ectodermal origin, mostly skin with appendages and mature glia. Of tissues of mesodermal origin, connective and mature adipose tissues were most commonly found, followed by hyaline cartilage and well formed bone fragments. Of tissues of endodermal origin, respiratory epithelium and epithelium of different levels of the digestive tract were most frequent. Thyroid tissue was found in smaller foci in 12.5% of mature cystic and/or solid terato-

mas, but because of its focality, the findings did not warrant the diagnosis of struma ovarii. Struma ovarii was diagnosed in 1.8% of all teratomas. Struma ovarii was, in this study, the only example of monodermal teratomas that are very rare and by definition have to contain only one type of tissue from one of the embryonic layers (mostly ectoderm or endoderm)^{4,7}. All the pathologic processes found in the thyroid gland of normal localization can also develop in an ovarian struma⁷. Carcinoid of the ovary is diagnosed on conventional, H-E stained slides, and the diagnosis is confirmed immunohistochemically using neuroendocrine markers such as chromogranin A, synaptophysin and neuron specific enolase in the cytoplasm of tumor cells⁸. In both cases of strumal carcinoid in this study, besides thyroid tissue, tumorous tissue showed a mixture of insular and trabecular growth of cells with at the most 2 and 4 mitoses/10 high power fields. Immunohistochemically, thyroid tissue showed positive reaction with thyroglobulin and thyroid transcription factor, while in carcinoid tissue the expression of these markers was negative. Conversely, the carcinoid tissue cells immunohistochemically showed expression of chromogranin A and synaptophysin. Patients with primary carcinoid of the ovary are most often perimenopausal or postmenopausal, and in this study one of the patients was 40 and the other 44 years of age. In both cases, the tumor was removed because of the diagnosis made by ultrasound. Although carcinoid syndrome can be present in 30% of patients with insular, 13% with trabecular and 3.2% with strumal carcinoid of the ovary, typically withdrawing after surgical removal of the tumor, the information whether the carcinoid patients in this study had some symptoms was not available. However, because of the rarity of carcinoid syndrome associated with strumal carcinoid of the ovary, it is supposed that it was not the case¹²⁻¹⁴.

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Sažetak

TERATOM JAJNIKA U RUTINSKOM BIOPTIČKOM MATERIJALU U PETOGODIŠNJEM RAZDOBLJU

M. Kos, J. Nikić i T. Leniček

Teratomi su tumori podrijetla zametnih stanica koji se najčešće razvijaju u gonadama. Cilj rada bio je utvrditi koliko je dijagnoza teratoma jajnika postavljeno na rutinskom bioptičkom materijalu Kliničkoga zavoda za patologiju „Ljudevit Jurak“ Kliničkoga bolničkog centra „Sestre milosrdnice“ u Zagrebu u petogodišnjem razdoblju, kao i koje su bile njihove kliničke, makroskopske i mikroskopske osobine. U analiziranom razdoblju teratomi su sačinjavali 166 (44,86%) primarnih tumora jajnika. Srednja dob bolesnica s teratomom jajnika bila je 35±12,37 godina. Nije pronađena statistički značajna razlika u učestalosti teratoma lijevog i desnog jajnika, a u 13 (7,8%) bolesnica teratom je bio obostran. Teratom je u 115 (69,3%) slučajeva otkriven ultrazvukom, u 21 (12,6%) je ultrazvukom postavljena dijagnoza nespecificiranog cističnog tumora, a u 16 (9,6%) slučajeva teratom je otkriven prilikom operacijskog zahvata učinjenog iz nekog drugog razloga. U 160 (96,4%) slučajeva radilo se o zrelim cističnim teratomima (dermoidnim cistama), od kojih je 123 (76,8%) bilo ispunjeno lojem i u kojima je pronađeno sveukupno 16 zuba. U 157 (94,6%) slučajeva najveći promjer teratoma iznosio je do 10 cm. Mikroskopski, zreli cistični teratomi najčešće su sadržavali tkiva ektodermalnog i mezodermalnog podrijetla i to u 154 (96,3%) slučaja kožu s kožnim adneksima, odnosno u 148 (92,54%) slučaja vezivo. Od drugih ektodermalnih tkiva po učestalosti su slijedili zrela gljiva i živčani gangliji, a od mezodermalnih tkiva zrelo masno tkivo, hrskavica i kost. Od tkiva endodermalnog podrijetla najčešće je pronađen respiracijski i crijevni epitel. Manja žarišta tkiva štitnjače pronađena su u 19 (12%) cističnih teratoma. U 11 (7%) cističnih teratoma u stijenci su pronađena žarišta kronične upale tipa stranog tijela. Solidne građe bilo je 5 (3%) teratoma, od čega u 3 (2%) slučaja struma jajnika, a u 2 (1%) slučaja strumalni karcinoid.

Ključne riječi: *Teratom – dijagnostika; Struma jajnika – dijagnostika; Karcinoidni tumor*