Thyroid Insular Carcinoma Arising from Ovarian Dermoid Cyst: Case Report

Ovarian Dermoid Kistten Gelişen Tiroid İnsular Karsinomu

M. Anıl ONAN, MD,[a]
Mertihan KURDOĞLU, MD,[b]
Mustafa GÜRELİ, MD,[c]
Ömer ULUOĞLU, MD,[c]
Haldun GÜNER, MD[a]

Departments of [a]Obstetrics and Gynecology, [c]Pathology,
Gazi University School of Medicine,
ANKARA
[b]Department of Obstetrics and Gynecology,
Yuzuncu Yıl University
School of Medicine, VAN

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Yazışma Adresi/*Correspondence:*
Mertihan KURDOĞLU, MD
Yüzüncü Yıl University
School of Medicine
Department of Obstetrics
and Gynecology, VAN
mkurdoglu@yyu.edu.tr

ABSTRACT Malignant transformation of the ectopic thyroid tissue of the ovarian dermoid cyst (mature cystic teratoma) is extremely rare. Poorly differentiated thyroid carcinoma (insular carcinoma) arising from ovarian dermoid cyst has not been reported previously. We report a poorly differentiated thyroid carcinoma of the ovarian dermoid cyst which was detected incidentally in the left ovary of a woman during cesarean section. The patient was managed with a complementary staging surgery including total abdominal hysterectomy, right salpingo-oophorectomy, pelvic washing, infracolic omentectomy and bilateral iliac and paraaortic lymphadenectomy, followed by total thyroidectomy and subsequent radioactive iodine treatment. Besides the other treatment modalities, radical surgery together with total thyroidectomy and subsequent radioactive iodine treatment may be a convenient option in the management of this kind of ovarian cancer. The number of available patients is not enough to draw the outlines of the optimum treatment strategies.

Key Words: Ovary, dermoid cyst, thyroid neoplasms

ÖZET Over kaynaklı dermoid kistlerin (matür kistik teratomların) ektopik tiroid dokusunun malign değişimi oldukça seyrektir. Ovarian dermoid kistten gelişen az diferansiye tiroid karsinomu (insular karsinom), daha önceden bildirilmemiştir. Bir olguda, sezaryen esnasında sol overde tesadüfen saptanan ovarian dermoid kistin az diferansiye tiroid karsinomunu sunuyoruz. Hasta; total abdominal histerektomi, sağ salfingoooferektomi, pelvik yıkama, infrakolik omentektomi ve bilateral iliak ile paraaortik lenfadenektomiyi içeren tamamlayıcı evreleme cerrahisinin ardından total tiroidektomi ve takip eden radyoaktif iyot tedavisiyle yönetildi. Diğer tedavi şekilleri yanında, radikal cerrahiyle birlikte total tiroidektomi ve ardından radyoaktif iyot tedavisi, bu tip over kanserinin yönetiminde uygun bir seçenek olabilir. Mevcut hasta sayıları, en uygun tedavi stratejilerini şekillendirmek için yeterli değildir.

Anahtar Kelimeler Over, dermoid kist, tiroid neoplazileri

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Teratomas are tumors comprising more than a single cell type derived from more than one germ layer. They range from benign, well-differentiated (mature) cystic lesions to those that are solid and malignant (immature). Mature cystic teratomas, commonly referred to as dermoid cysts of the ovary are the most common type of ovarian teratoma and germ cell neoplasm comprising 10-20% of ovarian tumors. In its pure form, mature cystic teratoma of the ovary always is benign, but in some cases, it may undergo malignant transformation into one of its elements. Squamous cell carcinoma is the most common malignant tumor arising in dermoid cysts al-

though other neoplasms, including adenosquamous carcinomas, melanomas, sarcomas, basal cell carcinomas and thyroid carcinomas, have been reported.[1]

The ovarian thyroid is identical to cervical thyroid and may demonstrate all the pathological features observed in the thyroid gland. In the literature, there are few reports of thyroid carcinomas mostly papillary variant, arising in the dermoid cysts.[2-5] However, to best our knowledge, there is no previous report of poorly differentiated thyroid carcinoma (insular carcinoma) arising in an ovarian dermoid cyst. We present poorly differentiated thyroid carcinoma detected in a left ovarian dermoid cyst, incidentally during cesarean section.

CASE REPORT

A 38-year-old, Turkish, white female, gravida 6, para 3 was admitted to the Department of Obstetrics and Gynecology of Gazi University in November 2004. Six weeks prior to referral, she had undergone a cesarean section in another hospital. In surgical exploration on that occasion, an irregular cystic mass in left ovary had been noticed and removed through a salpingo-oophorectomy. When the nature of the tumor was known from the pathology report to include strumal carcinoid component, the patient was then referred to our clinic for confirmation of the diagnosis and further management. Review of the outside pathology showed a focus of insular carcinoma in an ovarian dermoid cyst.

Grossly, the tumor was multicystic and capsulated measuring 9x 7x 4 cm. Sectioning revealed homogeneous, glistening hair including tissue with multiple tan-yellow areas averaging between 0.5-3.5 cm in diameter. Within the wall of the cyst, a solid white-tan area measuring 6 x 6x 5 cm which is diffusely heterogeneous and nodular in appearance including a focal hemorrhagic site was noticed.

Microscopically, on prepared sections, tumor composed of cystic and solid areas and a small region of normal ovarian stroma were identified. Cystic regions of the tumor were composed of mature tissues consisted of squamous and intestinal type epithelium (Figure 1), bronchial wall at one site together with transitional cell fields, thyroid, glial tissue and smooth musculature (Figure 2). These findings were compatible with mature teratoma. Next to the teratoma which forms a big region of ovarian mass, malignant tumor development in trabecular and solid pattern was collected of atypical cells characterized by hyperchromatic and vesicular nuclei with indistinct nucleoli (Figure 3, 4). With these features, it resembled to the trabecular (insular) carcinoma of the thyroid.

Immunohistochemistry stains for thyroglobulin were diffusely positive in tumor cells (Figure 5); immunohistochemical studies for keratin and synaptophysin were also positive (Figure 6) while

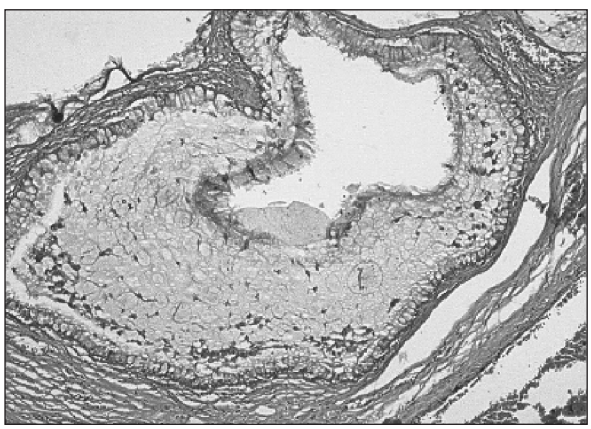

Figure 1. Cystic region of teratoma lined by intestinal type epithelium (H&E, X100).

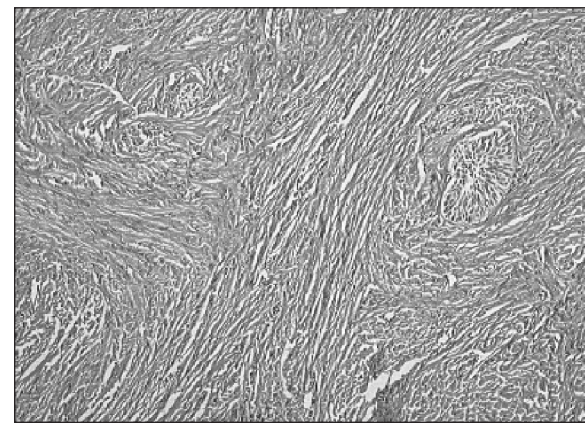

Figure 2. Areas belonging to the smooth muscle component of teratoma (H&E, X40).

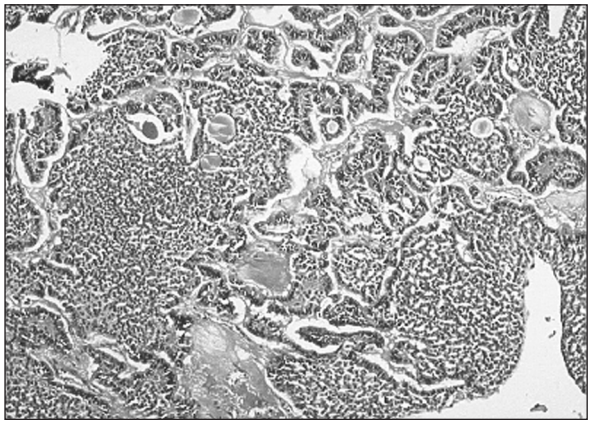

Figure 3. Regions developed in solid pattern (H&E, X40).).

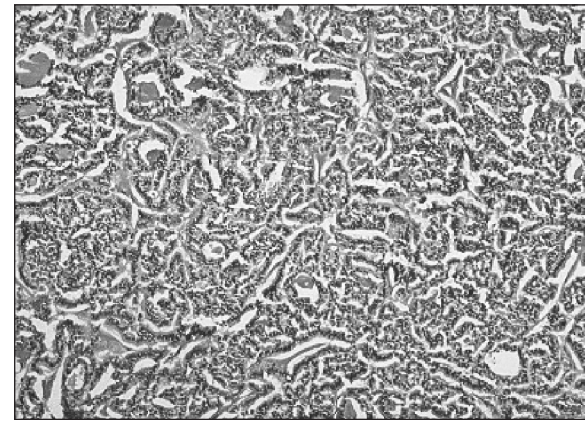

Figure 4. Insular carcinoma composed of follicules with insular pattern including colloid in between (H&E, X40).

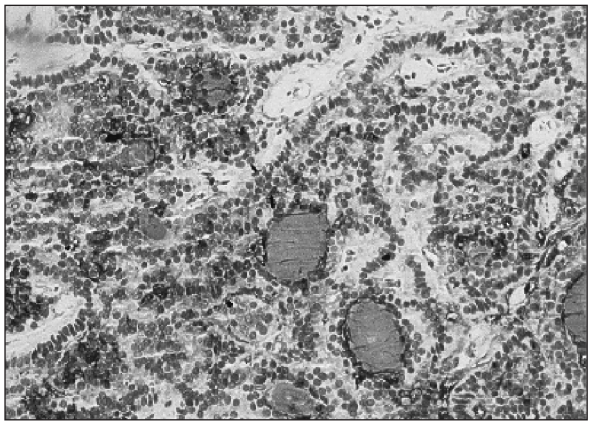

Figure 5. Cytoplasmic positivity with thyroglobulin (Thyroglobulin, X100).

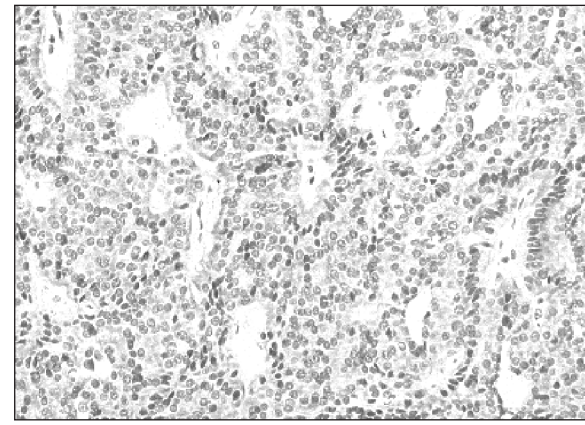

Figure 6. Diffuse cytoplasmic staining with synaptophysin (X100).

studies for calcitonin, neuron-specific enolase, chromogranin, thyroid transcription factor (TTF)-1 and bcl-2 were negative. The small ovarian tissue was found to be normal on histology.

It was realized that the histological and cytological features of the solid area in the wall of the cyst which was reported previously to be carcinoid tumor were most consistent with the poorly differentiated insular variant of thyroid carcinoma.

The serum thyroglobulin level was 79.2 (normal range 0.73-84) ng/ml. Thyroid-stimulating hormone 1.261 (normal range 0.35-5) mIU/ml, free thyroxine 1.09 (normal range 0.7-1.9) ng/dl and free triiodothyronine was 3.18 (normal range 1.57-4.71) pg/ml. An ultrasound of the thyroid was obtained and both thyroid lobes were found to be minimally heterogeneous and bigger than normal (the diameter of right and left lobes were 25x18x67 mm and 23x18x62 mm respectively). Positron emission tomography (PET) revealed normal physiological distribution of ^{18}F-FDG in thyroid gland and the other body areas.

The patient underwent a staging surgery with total abdominal hysterectomy, right salpingo-oophorectomy, pelvic washings, infracolic omentectomy and bilateral iliac and para-aortic lymphadenectomy, followed by total thyroidectomy. Histopathological study of all surgical specimens did not reveal any malignancy in these tissues. Postoperative course of the patient was

complicated by hypocalcaemia and treated with electrolyte replacement. I^{131} was performed according to the advices of the gynecologic and endocrine oncologists.

The patient is currently receiving thyroid hormone and calcium replacement and free of disease 2 year from diagnosis.

DISCUSSION

Mature cystic teratoma of the ovary or dermoid cyst is composed of well-differentiated derivatives of the three germ layers: ectoderm, mesoderm, and endoderm while ectodermal elements usually predominate. Additionally, teratomas may be monodermal and highly specialized like struma ovarii which contains thyroid tissue as the predominant cell type.[1]

Rarely within some mature teratomas, certain elements (most commonly squamous components) may undergo malignant transformation representing only 1-2 % of mature cystic teratomas and 1% of all ovarian carcinomas. Approximately 15% of teratomas have a small, nonsignificant focus of thyroid tissue while 0.8-3% of teratomas contain functional thyroid tissue or thyroid tissue occupying most of the mass classified as a struma ovarii.[1] Thyroidal elements of both of these tumors can show malignant transformation with a possibility of seeing every type of carcinoma.[2-5] However, most of the cases were defined as arising in struma ovarii.

In 1984, Carcangiu et al. established diagnostic criteria for a distinctive type of thyroid cancer with solid clusters of cells or "insulae" and a propensity to metastasize to regional lymph nodes and distant sites: insular thyroid carcinoma.[6] With the experience of many years, it is suggested that, this neoplasm may not be morphologically intermediate between typical follicular or papillary carcinomas, and undifferentiated carcinoma, but may also be a distinctly independent tumor entity. Since the formal characterization of this tumor type by Carcangiu et al. over 200 cases of insular thyroid cancer have been described in the literature. However, we came across with only a single article related to its arise from the thyroidal tissue in a struma ovarii[7] but none in a mature cystic teratoma of the ovary.

Insular carcinomas represent 2-6% of all thyroid cancers and are seen mostly in women (female to male ratio of greater than 2:1) in their mid fifties. Our case was diagnosed with such a tumor in her left ovary at the age of 38.

Exclusion of a primary lesion of the cervical thyroid is also important because of the minor possibility of metastasis to the ovary. This is particularly significant in cases where the primary tumor is a pure struma ovarii. We also performed a specific cervical thyroid gland and whole body survey. Our results showed that left ovary was the primary site of the malignant lesion.

The microscopic features as described by Carcangiu et al.[6] are guidelines used by most pathologist and they were also the mainstay in our diagnosis. The important features are formation of solid clusters of tumor cells containing a variable number of small follicles; small size and uniformity of tumor cells; a variable but consistently present mitotic activity; capsular and blood vessel invasion; and frequent necrotic foci, sometimes leading to the formation of "perithelomatous (relative sparing of insulae sitting around large blood vessels from necrosis)" structures. In the present case, each microscopic feature of the tumor was compatible with most of these characteristics.

Microscopically, solid and microfollicular areas of the struma ovarii must be differentiated from carcinoid tumors. It has been reported that some cases defined as malignant struma ovarii can be reclassified as stromal carcinoid from immunohistochemistry for neuroendocrine markers. In addition, Ljungberg et al. discussed intermediate thyroid carcinoma consisting of solid and/or cribriform structures like insulae associated with neoplastic follicles, and immunohistochemically showing positive reactions with antibodies to neurohormonal peptides as well as thyroglobulin.[8] So we performed the immunoreaction to distinguish these clinical entities and immunoreactivity was observed only for antisynaptophysin antibody. Fu-

rihata et al. also reported a similar result in their article about immunohistochemical characterization of a case of insular thyroid carcinoma.[9] Synaptophysin is widely distributed in neuroendocrine cells and neoplasms and is a good broad-spectrum neuroendocrine marker. However, synaptophysin is not specific for neuroendocrine cells and tumors because normal adrenal cortical cells, adrenal cortical adenomas, and carcinomas (like in our case) may show immunopositivity for synaptophysin. Furthermore, anti-chromogranin, calcitonin and anti-neuron-specific enolase antibodies gave immunohistochemically negative results although thyroglobulin was positive. It is important to know that, with some exceptions; chromogranin remains one of the most useful markers of neuroendocrine cells and tumors and has been described as the single most specific generic marker of neuroendocrine differentiation in general. These findings would suggest that the present tumor is a different tumor entity from stromal carcinoid and that of the intermediate thyroid carcinoma reported by Ljungberg et al.[8]

When the other immunohistochemical features of this tumor were searched, thyroglobulin showed strong expression confirming the thyroid epithelial nature of the neoplasm. However, TTF-1 was not detected in tumor cells. Bejarano et al. reported negative immunoreaction with TTF-1 antibody in 14% of the cases with poorly differentiated carcinoma.[10] Beside these, we also showed immunoreactivity for keratin as it was stated that insular carcinomas are usually positive for keratin with a broad spectrum cocktail of keratin antibodies.

In insular thyroid carcinoma, staining for bcl-2 is much commoner (84.2%) than in anaplastic carcinoma (13.6 %) and this may aid in their distinction. But, bcl-2 was negative in our case. However, our case lacked the prominent nuclear pleomorphism and frequent mitoses of anaplastic carcinoma together with abortive follicles and thyroglobulin immunoreactivity which are not features of anaplastic carcinoma.

When we looked at the clinical behavior of insular carcinoma, it appears to be an aggressive subtype of thyroid cancer, which has been shown in a number of case series to have a high propensity for local recurrence, distant metastasis, and increased mortality (overall tumor related mortality of 32%). However, its nature is unknown when it arises in an ovarian dermoid cyst like in our case. The rarity of this tumor makes it difficult to draw conclusions from the literature as to the best treatment options for the forms developing in both a thyroid gland and an ovarian dermoid cyst.

Since there is no any previous report of poorly differentiated (insular) thyroid carcinoma arising in a mature cystic teratoma of the ovary in the literature, we followed the general treatment guidelines proposed for the other types of thyroid carcinomas arising in struma ovarii. It is known that, malignant struma behave more like thyroid carcinomas, demonstrating poor iodine uptake. Hence, the management should be similar to that of thyroid carcinoma. However, primary ovarian tumor as well as the thyroid gland should be removed to enable effective ^{131}I ablative treatment and to facilitate serial follow-up with serum thyroglobulin measurement and radioiodine whole body scans and to exclude a primary thyroidal lesion. Since the patient completed childbearing and the histological subtype of tumor seems to be aggressive, we performed a complementary surgery with total abdominal hysterectomy and right salpingo-oophorectomy, sampling of pelvic and paraaortic lymph nodes, peritoneal washings, partial omentectomy and total thyroidectomy. Pathological examination of all these materials was showed to be free of tumoral involvement and then we accepted the patient to have stage IA malignant struma ovarii. She was decided to be followed up with traditional diagnostic methodologies after giving ^{131}I therapy. The patient is in close follow-up and free of disease 2 year after the second surgery.

Sayhan et al. presented a case of stage IA papillary carcinoma of the thyroid in a mature cystic teratoma of the ovary and treated their patient with only surgery without lymph node sampling and total thyroidectomy.[2] They followed her with only physical examination, laboratory and scintigraphy. The patient was free of disease for 8 months.

Radiochemotherapy and laparoscopic staging with surgery can be the other treatment options in selected patients. Conservative surgery in younger patients with complementary surgery after completion of childbearing can also be an option.

In conclusion, we describe the first case of poorly differentiated (insular) thyroid carcinoma arising from the thyroidal tissue of an ovarian dermoid cyst. In our opinion, radical surgery together with total thyroidectomy followed by ^{131}I therapy may be convenient for this kind of ovarian cancer. Further follow-up of these patients are needed to delineate the widely acceptable treatment strategies.

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