ANTICANCER RESEARCH *38*: 3669-3675 (2018)
doi:10.21873/anticanres.12644

Malignant Transformation in Mature Cystic Teratomas of the Ovary: Case Reports and Review of the Literature

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Abstract. *Malignant transformation occurs in 1.5-2% of mature cystic teratomas (MCT)s of the ovary and usually consists of squamous cell carcinoma, whereas other malignancies are less common. Diagnosis and treatment represent a challenge for gynecologic oncologists. The preoperative detection is very difficult and the diagnostic accuracy of imaging examinations is uncertain. The tumor is usually detected post-operatively based on histopathologic findings. This paper reviewed 206 consecutive patients who underwent surgery for a histologically-proven MCT of the ovary between 2010 and 2017. Malignant transformation occurred in 3 (1.5%) of them, and consisted of squamous cell carcinoma in one, type 2 papillary renal carcinoma in one, and papillary thyroid carcinoma in another one. The paper reported the clinical, radiological and histological features of these cases and reviewed the literature data on the treatment options.*

Mature cystic teratoma (MCT) of the ovary has an incidence of approximately 1.2-14.2 cases per 100,000 women per year and accounts for 10-20% of all ovarian tumors (1, 2). Laparoscopic salpingo-oophorectomy with an endoscopic retrieval bag is the standard treatment in postmenopausal women and in perimenopausal women with a large teratoma, whereas laparoscopic cystectomy can be a rational option in younger women (3). Malignant transformation occurs in 1.5-2% of the cases and usually consists of squamous cell carcinoma (4-8). Other less frequent malignancies include mucinous carcinoma (8-10), adenocarcinoma arising from the respiratory ciliated epithelium (11), melanoma (9), carcinoid (8), thyroid carcinoma (8, 10, 12-15), oligodendroglioma (10) and sarcoma (10).

The diameter of a squamous cell carcinoma arising in an ovarian MCT ranges from 9.7-15.6 cm (1, 4-8, 16, 17) and median age of patients is approximately 55 years (1, 16), whereas the size of thyroid carcinoma in an MCT ranges from 5 to 20 cm and the median age of patients is about 42-45 years (12, 15). The preoperative detection of malignant transformation is very difficult and the diagnostic accuracy of ultrasound, magnetic resonance imaging and computed tomography (CT) is uncertain (18-23). Malignancy is usually diagnosed post-operatively based on histopathologic findings (6, 8, 13, 15, 24).

The standard primary treatment of squamous cell carcinoma within an MCT of the ovary should consist of bilateral salpingo-oophorectomy, total hysterectomy and comprehensive surgical staging in early disease and optimal cytoreductive surgery in advanced disease (1, 6, 25). Patients with surgical stage Ia tumor can undergo observation alone, whereas chemotherapy is warranted for those with more advanced disease (4, 16, 17, 25, 26). The combination of paclitaxel and carboplatin is the most frequently used regimen, although chemotherapy seems to be less effective in this malignancy compared to the common epithelial ovarian cancers (16, 21, 25-27). The role of radiotherapy or chemoradiotherapy is debated (1, 5, 6, 16, 26-29).

Papillary and follicular carcinoma are the most frequent types of thyroid carcinoma occurring in an ovarian MCT (14). The diagnostic criteria for papillary carcinoma are similar to those of cervical thyroid gland carcinoma and are based primarily on nuclear and architectural features, whereas the diagnosis of follicular carcinoma is mainly based on infiltration into the surrounding ovarian tissues and vascular invasion besides detection of metastasis. Although

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Key Words: Teratoma of the ovary, squamous cell carcinoma, papillary renal cell cancer, thyroid carcinoma, *struma ovarii*, surgery.

the management of thyroid carcinoma in MCT is controversial, many authors have suggested that treatment should be similar to the one used for the differentiated carcinoma of the thyroid gland, and that, following surgical excision of the ovarian tumor, the patient should undergo thyroidectomy, iodine $[I]^{131}$ ablation, and levothyroxine suppressive therapy (12, 15, 30).

In this paper, 3 cases of malignant transformation in MCTs of the ovary are reported.

Case Description

This paper reviewed 206 consecutive patients who underwent surgery for a histologically proven MCT of the ovary between 2010 and 2017. The median age of patients was 39 years (range=9-83 years). Malignant transformation occurred in 3 (1.5%) of them and consisted of squamous cell carcinoma in one (a), type 2 papillary renal carcinoma in one (b), and papillary thyroid carcinoma in another one (c).

a) A 55-year-old, postmenopausal, gravida 4, para 2 woman was admitted to the hospital for the onset of abdominal swelling. She took levothyroxine for hypothyroidism and valproic acid for depression. Gynecological examination revealed a huge, mobile pelvic mass, and abdominal-pelvic CT scan showed an 18×11 cm complex ovarian mass which had no apparent cleavage plan with the uterus and which displaced adjacent organs. Its content was mainly fluid, with a small solid area in the lower part and some vascularized papillary projections. There were no enlarged retroperitoneal nodes, no peritoneal implants, and no suspected lesions in the liver, pancreas, spleen, and kidneys. Chest X-ray was unremarkable and serum CA 125 was 19 U/ml. Laparoscopy detected a large, rounded, smooth mass involving left ovary, whereas uterus and right ovary were grossly normal and pelvic peritoneum, para-colic gutters, small and large bowel, mesentery, liver, spleen, and diaphragmatic surfaces were free of macroscopic lesions. Left salpingo-oophorectomy was performed, and the adnexum was recovered with an endoscopic retrieval bag and sent for frozen sections which showed a squamous cell carcinoma within an MCT. Then, the patient underwent peritoneal washing, total hysterectomy, right salpingo-oophorectomy, infra-colic omentectomy, and systematic pelvic and aortic lymphadenectomy. Macroscopically, the left ovarian tumor measured 19×17×7 cm, with whitish, smooth external surface, widely necrotic wall with hair, and inner yellowish content. The definitive histopathological examination revealed an invasive poorly differentiated, keratinizing squamous cell carcinoma arising in an MCT and approaching to the external ovarian surface (Figure 1). Immunostaining for p16 was negative. Adjacent areas of squamous cell carcinoma in situ were detected, whereas there was neither lymph vascular space involvement nor perineural invasion. The left fallopian tube, right ovary, right fallopian tube, omentum and pelvic and para-aortic nodes as well as peritoneal cytology were negative. FIGO stage was Ia. The patient is currently undergoing adjuvant chemotherapy with paclitaxel 175 mg/m^2 plus carboplatin area under the curve (AUC) 5 every 3 weeks. Clinical and ultrasound evaluation after the fifth cycle of chemotherapy showed no evidence of disease.

b) A 48-year-old, premenopausal, gravida 1, para 0 woman presented with a history of abdominal pain. She had undergone myomectomy for a uterine fibroid one year before. She took levothyroxine for Hashimoto's thyroiditis, venlafaxine for depression, and noretisterone acetate for abnormal uterine bleeding. Gynecological examination detected a small, tense elastic cyst in the left ovary, and pelvic and transvaginal ultrasound showed that this lesion was multilocular solid with International Ovarian Tumor Analysis (IOTA) color score 3-4. Right ovary contained a corpus luteum, uterine body and cervix were normal, and endometrial lining was thin. Chest X-ray and cervical smear were normal and serum CA 125 was 42.8 U/ml.

Laparoscopy evidenced a 3-4 cm smooth cyst of the left ovary, whereas uterus and right ovary were grossly normal and pelvic peritoneum, para-colic gutters, small and large bowel, mesentery, liver, spleen, and diaphragmatic surfaces were free of macroscopic lesions. Left salpingo-oophorectomy was performed, the adnexum was removed with an endoscopic retrieval bag, and the definitive histological examination revealed a type 2 papillary renal carcinoma with neuroendocrine features within an MCT (Figure 2). The neoplasia, measuring 1.5 cm in the largest diameter, presented tubular-papillary architecture, severe atypia, mitotic count=5/10 High Power Field (HPF), subepithelial deposits and foamy macrophages. Immunostaining was positive for CK7, CAM5.2, Ber-EP4, EMA, CD56, NSE and estrogen receptor (ER) (focal) and negative for CK20, thyroglobulin, TTF-1, CA19.9, S-100, GCDFP-15, calretinin, WT-1 and progesterone receptor (PR). No tumor was present on ovarian surface as well as in fallopian tube. A positron emission tomography (PET)/CT scan performed 3 months after surgery was negative. The patient, who refused total hysterectomy and right salpingo-oophorectomy, is currently undergoing periodical follow-up and is free of disease 16 months after surgery.

c) A 44-year-old, premenopausal, gravida 0, para 0 woman had previously undergone thyroidectomy followed by I^{131} ablation and levothyroxine suppressive therapy for a papillary carcinoma of the thyroid gland. Six months later routine serum thyroglobulin assay showed raised antigen levels (674 ng/ml). Whole-body radioiodine scintigraphy evidenced a focal, intense I^{131} uptake in the right pelvis suggestive of the presence of ectopic thyroidal tissue, and a transvaginal ultrasound detected a 7×3 cm, multilocular solid, vascularized round mass in the right ovary, a 1.5 cm

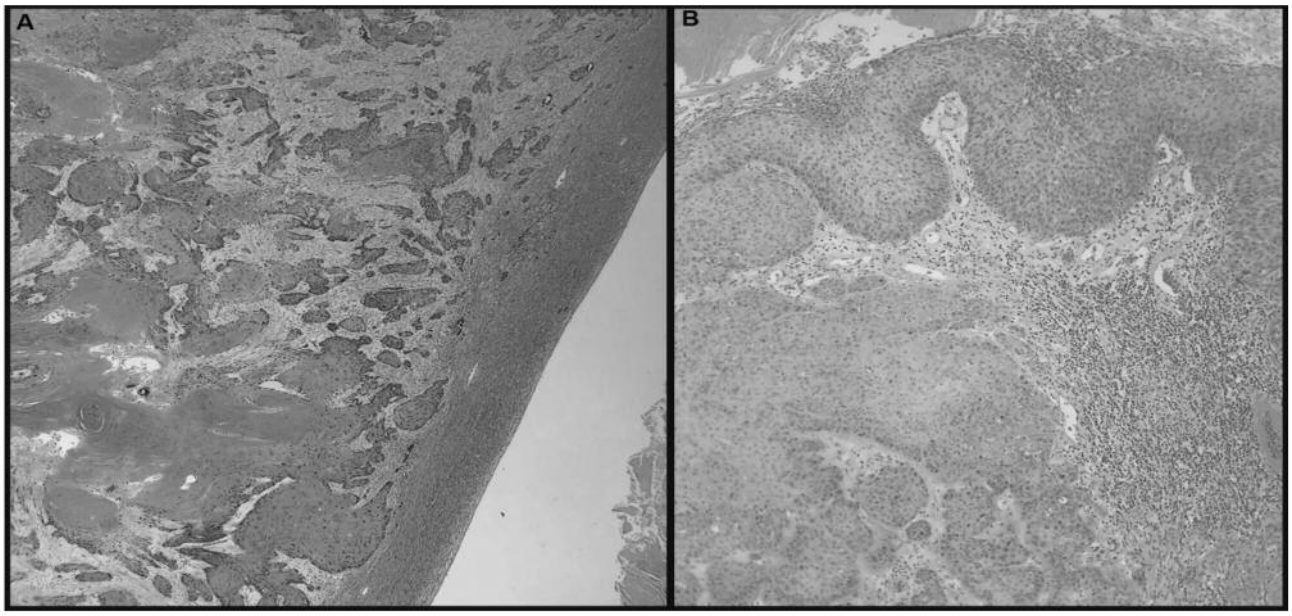

Figure 1. *Squamous cell carcinoma within a mature cystic teratoma of the ovary. A: Squamous cell carcinoma arising in a mature cystic teratoma of the ovary. Invasive squamous cell nests are surrounded by ovarian stroma; keratin formation is detectable in some nests. B: Features similar to a squamous cell carcinoma in situ are present in the epithelium near the invasive component.*

intramural myoma in the uterine fundus, and a normal left ovary. CT scan revealed a 7×5×6 cm multilocular, complex mass with a solid portion and internal calcification in the right ovary, whereas peritoneal surfaces, retroperitoneal lymph nodes, and upper abdomen organs were unremarkable. Radioiodine scintigraphy and CT findings suggested the presence of a *struma ovarii*. Chest X-ray and cervical smear were normal. Laparoscopy detected a 5-cm mixed cystic and solid mass of the right ovary, where uterus and left ovary were apparently normal. The inspection of pelvic and abdominal peritoneum, ileum, colon, liver, spleen, and diaphragmatic surfaces failed to detect any macroscopic lesions. Right salpingo-oophorectomy was performed and the surgical sample was recovered with an endoscopic retrieval bag. The definitive histological examination showed a 0.7 cm, well differentiated papillary thyroid carcinoma within a *struma ovarii* (Figure 3). The residual ovarian parenchyma contained a necrotic nodule with calcification and *corpora albicans*. The patient, who underwent periodical serological, clinical and ultrasound examinations, is currently free of disease 52 months after surgery.

Discussion

Malignant transformation occurs in 1.5-2% of the MCTs of the ovary, and usually consists of squamous cell carcinoma (4-8). Regarding the patient with such malignancy in our series, age (55 years) and tumor diameter (19×17 cm) matched with the median values reported in the literature (1, 4-8, 16, 17). The preoperative evaluation was not exhaustive and the squamous cell carcinoma was first detected at intraoperative frozen sections. Immunostaining for p16 was negative, which did not support the hypothesis that human papillomavirus (HPV) is a risk factor for this malignancy. Very few and conflicting data are available in the literature as regarding HPV detection and p16 expression in squamous cell carcinoma arising in MCTs of the ovary (31-34). In agreement with most authors (1, 6, 25), the patient underwent bilateral salpingo-oophorectomy, total hysterectomy and comprehensive surgical peritoneal and retroperitoneal staging, and the definitive histological examination of surgical specimens revealed that FIGO stage was Ia. Although some authors (26, 27) suggest observation alone in this clinical setting, we chose to give adjuvant paclitaxel/ carboplatin-based chemotherapy, after exhaustive discussion with the patient herself who preferred to receive a prophylactic treatment.

Papillary renal cell carcinomas account for 10-20% of all renal cell cancers (35). Based on cytologic and histologic criteria, Delahunt *et al*. (36) divided these tumors into two morphologic groups, type 1 and type 2, differing in stage, grade and prognosis. Type 2 tumors have a more aggressive biological behavior (37). In any case, patients with stage I papillary renal cell carcinoma do not need adjuvant treatment (38).

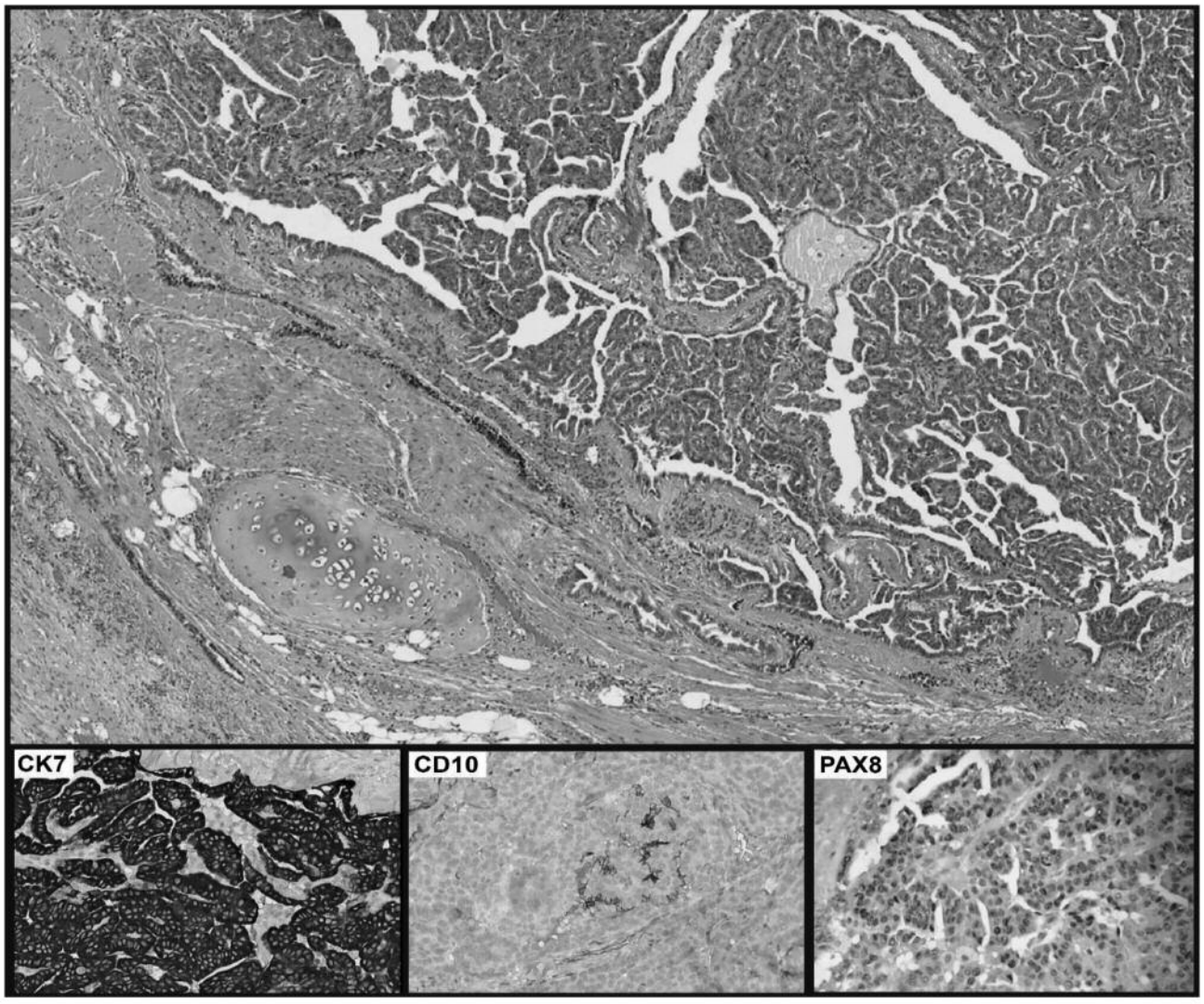

Figure 2. *Type 2 papillary renal cell carcinoma within a mature cystic teratoma of the ovary. A type 2 papillary renal cell carcinoma arising in a mature cystic teratoma: papillary projections occupy the lumen of the cyst cavity, while fragments of cartilage are present inside the cyst wall. Immunohistochemical analysis showed strong positivity for CK7 and mild positivity for CD10 and PAX8, suggesting a renal lineage.*

Our patient with type 2 papillary renal carcinoma within an MCT of the ovary is free of disease 16 months after unilateral salpingo-oophorectomy. To our best knowledge, this is the first case of such malignancy reported in the literature.

About 15% of MCTs contain thyroid tissue, but the term *struma ovarii* must be used only when thyroid tissue is the predominant element (39). *Struma ovarii* accounts for 2-5% of all MCTs, malignant transformation occurs in 5-10% of *struma ovarii*, and metastases develop in 5-23% of malignant *struma ovarii* (12, 13, 15, 39-41). Clinical hyperthyroidism has been observed in 5- 8% of the cases (12, 13, 39).

The surgical management ranges from bilateral salpingo-oophorectomy with total hysterectomy, omentectomy and retroperitoneal node dissection to unilateral salpingo-oophorectomy especially in patients who have no evidence of extra-ovarian disease and who wish to preserve fertility (12, 15, 42, 43). Abdominal surgery should be followed by thyroidectomy and I^{131} ablation, since thyroidectomy can enable follow-up with serum thyroglobulin assay and radioiodine scintigraphy and I^{131} treatment can prevent local and distant recurrence (12, 15, 44). Thyroidectomy and I^{131} ablation are strictly recommended as first-line treatment in cases with extra-ovarian spread of disease (12, 15, 45).

Our patient with papillary thyroid carcinoma within a *struma ovarii* had previously undergone thyroidectomy followed by I^{131} ablation for a papillary carcinoma of the

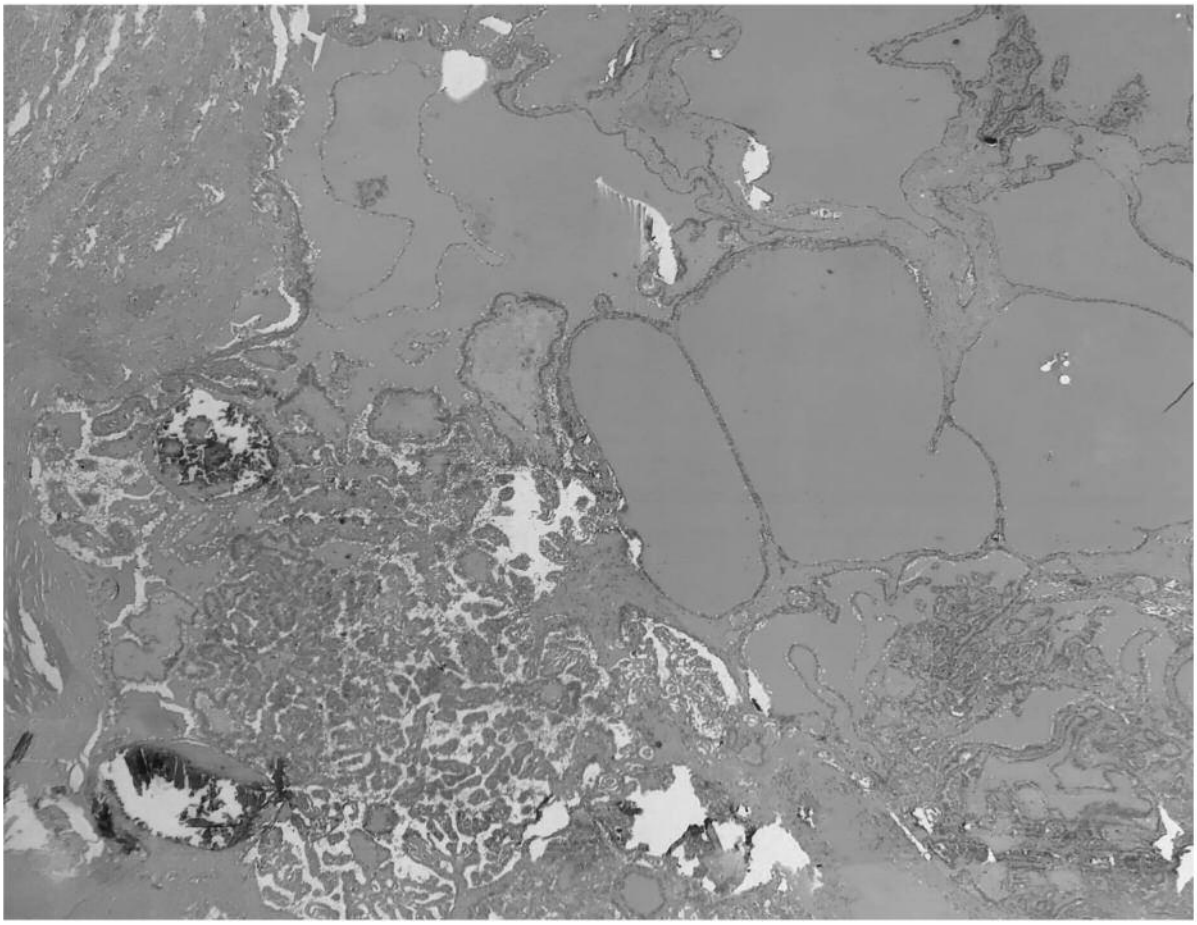

Figure 3. *Papillary thyroid carcinoma within a struma ovarii. Papillary thyroid carcinoma arising in a struma ovarii; the carcinoma is located in the lower left of the image, and it is surrounded by apparently normal thyroid follicles.*

thyroid gland. Radioiodine scintigraphy, performed for the detection of elevated serum thyroglobulin levels, showed an intense I^{131} uptake in the right pelvis and CT scan revealed a complex mass involving the right ovary. The patient underwent right salpingo-oophorectomy and the definitive histologic examination showed a small papillary thyroid carcinoma within a *struma ovarii*. The presence of the latter excluded the hypothesis of an ovarian metastasis from the primary thyroid neoplasia. The patient is free of disease 52 months after surgery.

Malignant transformation of an MCT of the ovary is a rare, but not exceptional event, which usually presents like an incidental pathologic finding. Prospective randomized trials on the surgical and postoperative treatment cannot be planned because of the rarity of these malignancies. However, a large international centralized database could maximize clinicians' knowledge in order to better define treatment guidelines (1, 39).

Conflicts of Interest

The Authors have no conflicts of interest regarding this study.

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Received April 5, 2018
Revised May 8, 2018
Accepted May 9, 2018