CASE REPORT



Ovarian strumal carcinoid - case report

DELIA GABRIELA CIOBANU APOSTOL^{1,2)}, TUDOR ANDREI BUŢUREANU³⁾, DEMETRA GABRIELA SOCOLOV³⁾, DANIELA CLAUDIA SCRIPCARU⁴⁾, OANA LUMINIŢA ROSIN⁵⁾, LUDMILA LOZNEANU^{1,2)}

Abstract

Strumal carcinoid represents a rare form of ovarian teratoma, consisting of both thyroid tissue and carcinoid structures. The carcinoid component is a well-differentiated neuroendocrine tumor with excellent prognosis. Strumal carcinoid tumors are commonly found in perimenopausal women who are not usually interested in preserving their fertility and who are thus open to radical surgical treatment. In this report, we present a 24-year-old, nulliparous patient with strumal carcinoid, confirmed by histopathology and a large panel of immunohistochemistry (IHC) markers, who wished to preserve her fertility. In this case, a conservative surgical treatment (salpingo-oophorectomy) served to preserve vital and reproductive prognosis, and correct tumor classification was of extreme importance. The morphological examination of strumal carcinoid showed struma ovarii with a thyroid follicle-like structure [positive for thyroid transcription factor 1 (TTF1), thyroglobulin, CD56, cytokeratin (CK) 19, and negative for Hector Battifora and mesothelioma 1 (HBME1)], and a neuroendocrine cell component with a trabecular arrangement and island growth (positive for synaptophysin, chromogranin, CD56, and CK7 negative), which were interlocked and intimately associated. Papillary thyroid carcinoma of follicular type was ruled out by CD56 positivity and HBME1 negativity. Medullary thyroid carcinoma with strumal component was excluded by calcitonin negative staining. Solid rosette-like structures with negative glial fibrillary acidic protein (GFAP) staining ruled out a neuroectodermal component. A multilocular mucinous cystadenoma was identified without other teratoma components. Strumal carcinoid requires a meticulous examination to rule out other entities with malignant behavior and poor prognosis. In this case, a conservative treatment is sufficient to remove the tumor, preserving vital and reproductive prognosis.

Keywords: strumal carcinoid, struma ovarii, neuroendocrine tumor cells, ovarian teratoma.

→ Introduction

Strumal carcinoid is an ovarian teratoma composed of thyroid tissue of teratomatous origin and carcinoid structures. The carcinoid component is considered primary and not metastatic in terms of several criteria including unilaterality, uninodular growth, presence of mucinous cystic elements, and tumor size. Most of these tumors are found in pre- or postmenopausal women who are not interested in preserving their fertility [1]. In the ovary carcinoid tumors has an incidence of 0.8% to 1.2% of all carcinoid tumors [2, 3]. However, strumal carcinoid is a type of cancer with excellent prognosis when it is localized in the ovary. Although the carcinoid component of ovarian strumal carcinoid is considered a malignant transformation of teratoma, it is usually benign in evolution and a conservative surgical treatment (salpingo-oophorectomy, or even a simple oophorectomy), is usually sufficient [4].

Morphologically four patterns are described: insular, strumal, trabecular, and mucinous. Each architectural type can be mixed or can be pure histological type [5]. The data from the literature identifies about 100 cases of ovarian strumal carcinoid [6–8], but for Romania, this lesion is rarely reported, and presented in the context of a singular pathology [9], or in the context of other tumors outside ovary location [10].

Aim

Although the stromal ovarian carcinoid is generally identified at the end of reproductive life, in our study, we reported a case of a young patient who addressed for infertility without specific symptomatology regarding neuroendocrine symptoms. The treatment applied to the patient was conservative, so the need for accurate identification of biological tumor behavior required in complex immunohistochemical studies.

☐ Case presentation

Herein, we present the case of a 24-year-old woman, gravida 0, para 0, incidentally diagnosed with a tumor of the right ovary during a gynecological exam performed one year ago, for primary infertility of three years duration. She denied any history of chronic constipation or symptoms of carcinoid syndrome (like diarrhea, facial flushing, wheezing, carcinoid heart disease, abdominal cramps), but she did complain of 3–4 months of mild diffuse pelvic pain. No signs of androgen production with virilism were noted. The patient had a past medical history of congenital scoliosis, surgically treated with metal rod, and a history of smoking. The transvaginal ultrasound showed an ovarian tumor of echo mixed structure with solid and cystic areas, well defined, of 61.2/50.8/52.9 mm with Doppler signal

¹⁾Department of Morpho-Functional Sciences I, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania

²⁾Laboratory of Pathology, "St. Spiridon" Emergency County Hospital, Iaşi, Romania

³⁾Department of Obstetrics and Gynecology, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania

⁴⁾Department of Pathology, "Cuza Vodă" Obstetrics and Gynecology Hospital, Iași, Romania

⁵⁾Department of Obstetrics and Gynecology, "Cuza Vodă" Obstetrics and Gynecology Hospital, Iași, Romania

in the solid portion with resistive index (RI) <0.5. The uterus and the contralateral ovary were normal and there was no free liquid in the Douglas sac. Abdominal ultrasound confirmed that there were no liver nodules or ascites.

The patient's cancer antigen-125 (CA-125) was in normal ranges (15 mIU/mL). Consent was obtained for a laparotomy with right ovariectomy and intraoperatory frozen section exam. Intraoperatively, a large right ovarian mass of 8 cm was seen, while the uterus, Fallopian tubes and left ovary were normal. There was neither ascites nor pelvic lymphadenopathy.

The diagnostic at frozen sections examination was mucinous cystadenoma associated with adenofibroma with borderline foci. Because of the presence of borderline compound, right salpingo-ovariectomy was performed. Gross examination revealed an 8 cm diameter tumor of the right ovary with a smooth surface and intact capsule. On cut sections, we identified a well-circumscribed, yellowish white in color, solid nodule with few mucinous cystic spaces and without areas of hemorrhage or necrosis. Tissue samples were fixed in 10% formalin and embedded in paraffin blocks, sectioned at 4-µm thickness, and routinely stained with Hematoxylin–Eosin (HE), at the

Department of Pathology, "Cuza Vodă" Obstetrics and Gynecology Hospital, Iași, Romania.

Microscopically, the ovarian parenchyma showed two cell populations with different architecture, which were interlocked and intimately associated. The first category, representing about two-thirds of the tumor mass, consisted of medium size thyroid follicle-like structure with lowcuboidal cells, rotund nuclei and central colloid material (struma ovarii) (Figure 1); the second category was represented by a cellular population in a trabecular arrangement and focal island area consisting of polygonal cells with round uniform nuclei, coarse chromatin in a "salt and pepper" pattern, and acidophilic cytoplasm (the carcinoid cell component) (Figure 2). The struma component showed a focal area with a solid pattern of small follicles without colloid material mixed with carcinoid structures (Figure 3). Fibrous stroma, a low mitotic rate and a mild inflammatory infiltrate were also identified. Aspects of cellular atypia and tumor necrosis were not found. In addition, the tumor had multilocular mucinous cystadenoma cells, lined by simple columnar mucinous epithelial cells (Figures 4 and 5). The tumor was limited to the ovarian parenchyma, without the involvement of the ovarian capsule (stage IA). No other teratoma component was identified.

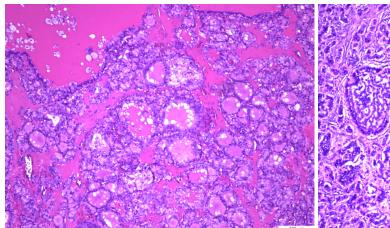


Figure 1 – Struma ovarii component (HE staining, ×100).

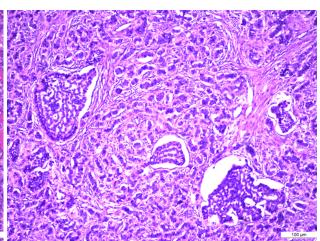


Figure 2 – Carcinoid component showed trabecular pattern and insular growth (HE staining, ×100).

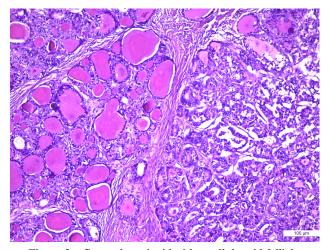


Figure 3 – Strumal carcinoid with small thyroid follicles with colloid-like material mixed with carcinoid structures (HE staining, $\times 100$).

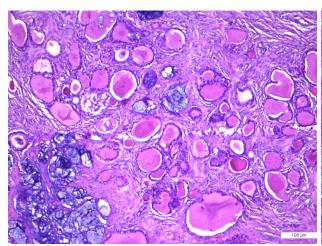


Figure 4 – Mucinous cystadenoma mixed with strumal elements of the tumor proliferation (HE staining, ×100).

Morphological aspects described above correspond to a strumal carcinoid. In order to confirm this diagnosis, immunohistochemically assessment was performed for cellular phenotyping of strumal and carcinoid areas at the Department of Pathology, "St. Spiridon" Emergency County Hospital, Iaşi, using monoclonal antibodies against synaptophysin (clone 27G12, Novocastra, 1:300 dilution), chromogranin (clone 5H7, Novocastra, 1:400 dilution), CD56 – also called neural cell adhesion molecule (NCAM, clone 123C3, Dako, 1:100 dilution), cytokeratin (CK) 19 (clone b170, Novocastra, 1:150 dilution), Hector Battifora and mesothelioma 1 (HBME1, clone HBME1, Dako, 1:100 dilution), thyroid transcription factor 1 (TTF1, clone SPT24, Novocastra, 1:200 dilution), thyroglobulin (clone 1D4, Novocastra, 1:70 dilution), CK7 (clone OV-TL12/30, Dako, 1:200 dilution), Ki67 (clone SP6, Thermo Scientific, 1:200 dilution), calcitonin (clone CL 1948, Novocastra, 1:200 dilution) and glial fibrillary acidic protein (GFAP, clone GFAP, Dako, RTU – ready to use). Internal positive control for neuroendocrine cells was medullary thyroid tumor cells on histological sections.

The neuroendocrine tumor cells were diffuse and immunopositive for synaptophysin (Figure 6), chromogranin (Figure 7), CD56 (Figure 8), and negative for CK7 (Figure 9). The struma ovarii structures were positive

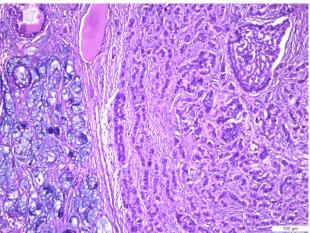


Figure 5 – Trabecular pattern of carcinoid proliferation, associated with the presence of a mucinous cystadenoma (HE staining, ×100).

for TTF1 (Figure 10), thyroglobulin (Figure 11), CD56 (Figure 8), CK7 (Figure 9), CK19 (Figure 12) but did not stain for HBME1 (Figure 13), which excluded malignant behavior of a thyroid component. Calcitonin (Figure 14) and GFAP staining (Figure 15) were negative in both components.

Final histopathology examination and immunohistochemistry confirmed a primary strumal carcinoid tumor of the right ovary (well-differentiated neuroendocrine tumor with Ki67 labeling index less than 1%), without the involvement of ovarian capsule, low-grade (G1) corresponding to *Federation of Gynecology and Obstetrics* (FIGO) stage IA, with mucinous components.

The case was presented to the multidisciplinary cancer team of the Regional Oncological Hospital, Iaşi, and a consensus was reached to monitor the patient closely, every six months, with an abdominal-pelvic computed tomography (CT) and repeated ultrasound, and ovarian tumor markers, for at least five years. Six months later, all these tests were normal. In this case, magnetic resonance imaging (MRI) investigation could not be performed due to the presence of metallic spinal rod. One year after the conservative surgery, the patient obtained spontaneous pregnancy and gave birth to a healthy eutrophic newborn.

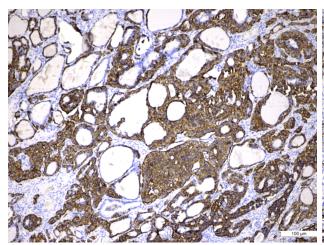


Figure 6 – Positive synaptophysin in carcinoid tumor (Anti-synaptophysin antibody immunostaining, ×100).

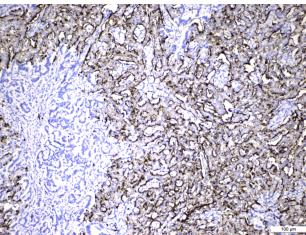


Figure 7 – Positive chromogranin in carcinoid tumor (Anti-chromogranin antibody immunostaining, ×100).

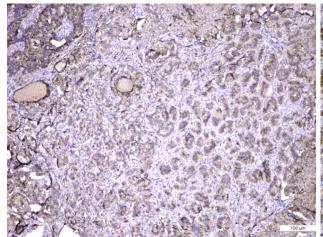


Figure 8 – Positive CD56 in both (strumal and carcinoid) components (Anti-CD56 antibody immunostaining, ×100).

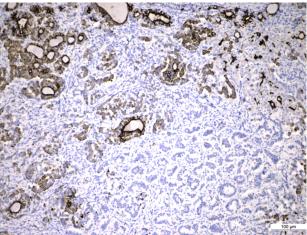


Figure 9 – Positive CK7 expression in strumal component, negative in carcinoid area (Anti-CK7 antibody immunostaining, ×100).

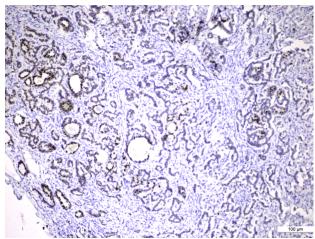


Figure 10 – Positive TTF1 in strumal component (Anti-TTF1 antibody immunostaining, ×100).

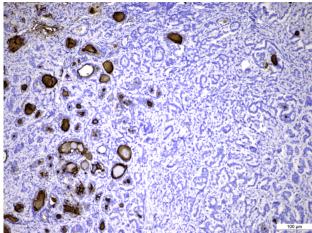


Figure 11 – Positive thyroglobulin in strumal component: follicles including the central colloid (Anti-thyroglobulin antibody immunostaining, ×100).

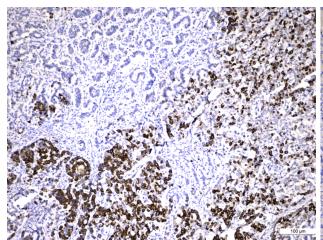


Figure 12 – Focal positive CK19 in strumal and carcinoid areas (Anti-CK19 antibody immunostaining, ×100).

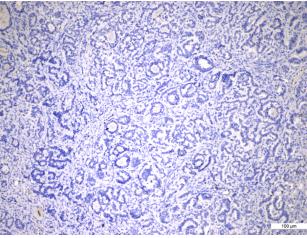


Figure 13 – Negative HBME1 in strumal and carcinoid areas (Anti-HBME1 antibody immunostaining, ×100).

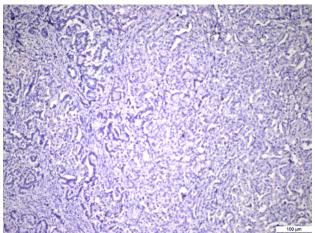


Figure 14 – Negative calcitonin in strumal and carcinoid areas (Anti-calcitonin antibody immunostaining, ×100).

. 100 µm

Figure 15 – Negative GFAP in strumal and carcinoid areas (Anti-GFAP antibody immunostaining, ×100).

→ Discussion

Strumal carcinoid occurs commonly in pre- or post-menopausal women, with an average age at incidence of 53 years [1]. In our case, the tumor occurred at a younger age (24 years), in a woman diagnosed with primary infertility of three years duration. Usually, these tumors are asymptomatic or associated with nonspecific symptoms such as diffuse abdominal pain, as in the current case, but in some cases, they can express a carcinoid syndrome induced by serotonin, chronic constipation induced by the peptide YY (an inhibitor of intestinal motility), or clinical signs of hyperandrogenia. Most of these tumors are cystic and solid masses of about 10 cm maximum diameter. They are almost always unilateral, but up to 15% of cases present a mature cystic teratoma or a mucinous tumor in the controlateral ovary [1].

In light microscopy, strumal carcinoid was first described by Scully, in 1970 [11]. Primary ovarian carcinoids account for 0.1% of all ovarian malignancies and 0.5–1.7% of all carcinoid tumors [12, 13]. Strumal carcinoid, a neoplasm localized uniquely to the ovary, is composed of both struma ovarii and carcinoid (secondary somatic tumor), with these two types of tissues often being admixed.

Ovarian carcinoid tumor cell populations can grow in four histological patterns: insular, trabecular, follicular and mucinous, and there are also mixed types, resulting from the combination of pure types. They are also frequently associated with mature cystic teratomas [14]. The thyroid component of strumal carcinoid can express thyroxine, TTF1, thyroglobulin and rarely, calcitonin, while the neuroendocrine component expresses chromogranin, synaptophysin and CD56 [15]. In our case, the neuroendocrine tumor cells were diffuse immunopositive for synaptophysin, chromogranin, and CD56, focal positive for CK19 and negative for CK7, TTF1, and thyroglobulin. Thyroid tissue morphology in the strumal component revealed TTF1, thyroglobulin, CD56 and CK19 positivity with no expression of HBME1, which excluded a malignant tumor as papillary thyroid carcinoma follicular variant.

Strumal carcinoid may be a source of misdiagnosis because microscopic examination may reveal similar histological features with other entities. Strumal solid areas can share some features with medullary carcinoma and may be confused with medullary-type thyroid carcinoma, which has an extremely aggressive course of disease progression [16]. The morphological appearance of medullary carcinoma is similar to that found in the thyroid gland, with nests of round cells, and close-packed and fibrous stroma. In this context, we analyzed the expression of calcitonin, whose negativity ruled out the origin of medullary carcinoma.

The carcinoid tumor component may show morphological characteristics of immature teratomas, and therefore can be confused with primitive neuroectodermal tumors of the ovary, which was excluded in this case by negativity of GFAP. There is little published data describing the existence of primitive neuroectodermal tumors with ovary localization [17–21]. Primitive neuroectodermal tumors are immature teratomas with malignant behavior and a poor prognosis. Histologically, primitive neuroectodermal tumors contain immature tissue elements, most often consisting of immature neural tissue, which can be identified as neurotubules or rosettes.

Strumal ovarian carcinoid prognosis is good, allowing a conservative surgical treatment, in our case right adnexectomy, as the patient wanted to preserve her fertility [4]. Currently, the patient is in good condition, without any evidence of tumor recurrence, six months after the operation. Another particularity of the case was that, because of the metallic spinal rod, we were not able to use monopolar surgery during the operation and the patient could not undergo MRI; thus, CT and ultrasound were performed instead. In very rare cases, ovarian strumal carcinoid can lead to metastasis [4, 22]. The rare reported cases of strumal carcinoid metastases were of both carcinoid and thyroidal type. The clinical course of mucinous carcinoids tends to be more aggressive than the others [23]. For this reason, even though in the case of our patient, the proliferation index was low (Ki67 less than 1%), we recommended long-term follow up, for at least five years.

→ Conclusions

In this case report, we discuss immunohistochemistry approaches for an accurate and definitive diagnosis of

ovarian stromal carcinoid. The use of a large panel of antibodies is crucial in identifying such rare tumors and differentiating them from malignant ones, which have different evolutions and prognoses.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author

Tudor Andrei Butureanu, MD, PhD Student, Department of Obstetrics and Gynecology, "Grigore T. Popa" University of Medicine and Pharmacy, 16 University Street, 700115 Iaşi, Romania; Phone +40723–979 929, e-mail: tudorandreib@gmail.com

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