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Original Articles

Primary ovarian carcinoid tumors: our experience and review of the literature

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Summary

Primary ovarian carcinoid tumors are rare neuroendocrine tumors representing a small percentage of malignant ovarian germ cell tumors, accounting for less than 0.1% of all ovarian carcinomas and 5% of all carcinoid tumors. These tumors arise in the intestine, with the appendix most frequently involved, and more rarely from the thymus, bronchus, stomach or pancreas. Because of their rarity, the diagnosis is often difficult until the patient undergoes an intraoperative histopathologic sample examination. During the surgery procedure of excision of the lesion, some hemodynamic instability could occur. The different type of carcinoid tumors of the ovary are the insular, trabecular, strumal or mucinous type (goblet cell). Despite imagery with CT and MRI preoperatively which recognizes solid characterisitics, the differential diagnosis with other ovary malignancies is very difficult. In cases of suspicion of a carcinoid, the perioperative management and diagnostic testing are crucial to delay the surgery. Better knowledge of this rare disease and its clinical manifestations may improve preoperative evaluation, minimize the pitfalls of management, and enable the surgery and anesthesiology team to take appropriate precautions for optimal surgical management. The authors present eight cases with ovarian tumors, which underwent a radical hysterectomy with bilateral adnexectomy and regional and para-aortical lymph node clearance. The histological examination revealed primary ovarian carcinoid tumors.

Key words: Ovarian tumor; Carcinoid tumor; Neuroendocrine; Rare ovarian tumor.

Introduction

The embryologic origin of neuroendocrine tumors arise from neuroendocrine cells (NECs), which have the followed characteristics: the ability to produce neuromodulators neurotransmitters or neuropeptide hormones, the NECs contain dense core secretory granules, but lack axons and synapses [1]. They could be present in all solid organs, skin, and mucosa. As a result, neuroendocrine tumors can begin from almost every location [2]. The incidence of these tumors in the general population is about five cases per 100,000 per year [3] and actually this rate is probably underestimated.

The most common location of neuroendocrine tumors is in the gastrointestinal tract (about 70% of cases), followed by the respiratory tract (about 25%), with other locations being rare as breast. Neuroendocrine tumors occurring in the male genital tract, however are more common in the female. Specifically, a broad array of neuroendocrine tumors and tumors with neuroendocrine elements have been recognized in all parts of the female genital tract and breast

Table 1. — *Description of our series of carcinoid tumors of the ovary.*

Case number	1	2	3	4	5	6	7	8
FIGO Stage	Ia	Ia	Ia	Ia	Ia	Ia	Ia	Ia
Lymph node removal								
Para-aortal	19	16	17	18	16	18	15	14
Iliacal	48	42	39	41	44	40	45	42
Complications	No	No	No	No	No	No	No	No
Recurrence	No	No	No	No	No	No	No	No
Follow-up (months)	yes	yes	yes	yes	yes	yes	yes	yes
Adjuvant	No	No	No	No	No	No	No	No

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(Tables 1 and 2) [4, 5]. Some of these tumors cause clinical syndromes owing to their endocrine production of a secretory substance, because carcinoid tumors secrete a wide variety of neurohumoral substances such as serotonin, histamine, tachykinin, bradykinin, kallikrein, corticotropin, substance P, motilin, and prostaglandins.

Regarding neuroendocrine tumors of the ovary, carcinoid tumor represent the most important and its origin is teratomatous. Frequently clinical diagnosis is done as metastatic disease and less as primary ovarian neoplasm. Primary carcinoid tumors of the ovary represent less than 5% of all carcinoid tumors and less than 1/1,000 of all ovarian tumors [6]. The median age at the time of diagnosis is 55 (range 17-83) years [7]. These tumors have a low but definitely malignant potential (1.4 ± 2%) [8]. Immunochemical identification of these tumors is mandatory for the histopathological differentiation. This technique assess chromogranin A granules, enterochromatin, argyrophilia, and/or argentaffinity in the cells.

Ovarian carcinoid tumors are divided into four subtypes, i.e. insular, trabecular, strumal or mucinous type (goblet cell) (Table 3). The first two subtypes are close to intestinal carcinoid tumors arising from midgut or hindgut origins, respectively, while the latter two categories also contain non-carcinoid epithelial structures (thyroid follicles and mucinous epithelium). Moreover mixed type tumors could be found but, in general, a predominant pattern is recognized for the subclassification of the carcinoid tumor. Ovarian carcinoid tumors have the characteristics of a solid ovarian tumor which make them almost indistinguishable from other solid malignancies of the ovary like teratoma, seminoma even using more than transvaginal ultrasound, CT and MRI.The prognosis depends on the histologic subtype and the site of origin. The well-differentiated neoplasms (i.e. carcinoid and atypical carcinoid) are clinically and morphologically distinct from high-grade neuroendocrine carcinoma (i.e. small cell and large cell).

The aim of this article was to present several clinical cases of ovarian neuroendocrine tumors and to provide a comprehensive review on these tumors. Additionally, the authors present a platform from which they could evaluate the available treatment options for these challenging cases.

Materials and Methods

Case report 1

A 63-year-old woman presented with diarrhea and abdominal swelling the last 6 weeks. The presence of a tumor of the right ovary was revealed after the physical abdominal and pelvic examination and was confirmed by MRI. CA-125 blood concentrations were within normal ranges and preoperative staging (CT, ultrasound, chest scan) was non-suspicious for distant metastasis.

A staging mid-line laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and pelvic and para-aortic lymphadenectomy were carried out for a right-sided ovarian cyst tumor measuring 2 cm at its largest diameter. Peritoneal implants of 0.4 cm, non-invasive, of borderline type were identified and removed. None of them showed invasion of the stroma and were characterized by typically non-aggressive behavior. There were no ascites or spread of the tumor beyond the right ovary. Histopathology showed a 2-cm trabecular tumor of the right ovary; the unilateral tumor was associated with a small area of borderline tumor, which was estrogen receptor positive. The tumor cells were surrounded by fibrous stroma, but no mitoses or necrosis were identified. Histologic grading was 1. Immunohistochemistry showed expression of synaptophysin and chromogranin; cytokeratin 7, and cytokeratin 20. Proliferation rate was MIB1-AG<3%. All lymph nodes removed were negative of metastasis.

Case reports 2 and 3

Two women, 49- and 71-years-old, presented with a two-month history of pain like a cramp in the lower abdomen in addition to constipation. Upon physical examination and MRI, the diagnosis of an ovarian tumor was made, while intrasurgical frozen section analysis laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and pelvic and para-aortic lymphadenectomy were carried out.

Histopathology showed a 0.5-cm insular tumor of the right ovary incidental finding in the dominating dermoid structures because of its smaller size associated with a solid dermoid cyst 4 cm. Grade was 1. Immunohistochemistry showed expression of the markers synaptophysin and chromogranin, cytokeratin 7, cytokeratin 20. Proliferation rate was MIB 1-AG<3% (MIB-1 is an monoclonal antibody used to investigate the Ki67 antigen and is a valuable marker for tumor cell proliferation). All lymph nodes removed were negative.

Case report 4

A 37-year-old woman presented with a three-week abdominal pain. Abdominal and pelvic examination and an MRI confirmed the presence of a mass both of the right ovary and the appendix. Preoperative investigations and CA-125 were within normal limits. A staging laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy infracolic omentectomy, and pelvic and para-aortic lymphadenectomy were carried out for a right-sided ovarian tumor. Histopathology showed a 1-cm trabecular tumor of the right ovary. Grade was 1 and was estrogen receptor positive, Immunohistochemistry showed expression of the markers synaptophysin and chromogranin, cytokeratin 7, and cytokeratin 20. Proliferation rate was MIB-1-AG<3%. Proliferations rate MIB 1 showed antibodies cells

Case reports 5, 6, and 7

Three women, 52-, 61-, and 65-years-old, presented the first two with a two-month history diabetes mellitus and constipation and the third with a one-month history of diarrhea. The presence of an ovarian tumor was confirmed by an MRI. A laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy infracolic omentectomy, and pelvic and para-aortic lymphadenectomy were carried out. Histopathology showed a tumor of 1.2 cm and 1.5 cm, 1.2 cm, and 1.5 cm neuroendocrine tumor of mixed type, respectively. Grade was 1. Immunohistochemistry showed expression of the markers synaptophysin and chromogranin, cytokeratin 7, cytokeratin 20. Proliferation rate wasMIB 1-AG<3%

Case report 8

A 59-year-old woman presented with a five-week history of diarrhea and abdominal swelling and pain. Abdominal and pelvic examination and an MRI of the pelvis confirmed the presence of a mass of ovarian origin. Preoperative investigations and CA-125 were within normal limits. A staging laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and pelvic and para-aortic lymphadenectomy were carried out. Histopathology showed a 1-cm insular tumor of the left ovary. Grade was 1. Immunohistochemistry showed expression of the markers synaptophysin and chromogranin, cytokeratin 7, and cytokeratin 20. Proliferation rate was NIB1-AG<3%. All lymph nodes removed were negative.

Results

In the Gynecologic Oncologic database of the Department of Obstretics and Gynecology of Aschaffenburg, Germany, University Hospital during the period from January 1, 1991 to December 31, 2011, a total of eight patients with neuroendocrine ovarian tumors were consecutively registered. Four of them had trabecular tumors, two of them with a solid mature teratoma. One patient had insular tumor, while the remaining three patients had mixed type tumors with a solid mature teratoma having been diagnosed. All patients had a history of hypertension. All tumors were unilateral and pelvic, and para-aortic lymph node dissection revealed negative histological findings.

A short description of a few selected cases confirmed histopathologically follows. No intraoperative complications or recurrences were noted (Tables 1 and 2). Their follow-up included measurement of blood levels of serotonin, gonadotrophins, carcino-embryonic antigen (CEA), CA-125 and alpha-fetoprotein (αFP). Moreover, clinical examination and ultrasonography every three months during the first year, every six months in the second year, and yearly thereafter were performed.

Discussion

In the majority of women, primary ovarian carcinoid tumors are found incidentally on cross-sectional CT or ultrasound imaging. Aside from the standard ultrasound modalities applied, 3D/4D ultrasound can also be used in the preoperative evaluation of ovarian tumors by adding 3D morphological and Doppler technology to assess the vascularisation, this facilitating the final preoperative approach [8].

These tumors are considered to be of germ cell origin with teratomatous elements, e.g. a dermoid cyst in up to 90% of cases [9, 10]. In some cases, the carcinoid tumor is seen macroscopically as a solid nodule of yellowish tanned tissue adjacent to or protruding into a cyst, while in other cases mural thickening may be evident. Rarely, the sectioned surface is cystic [11]. A few ovarian carcinoid tumors have been reported to be associated with otherwise typical pure mucinous cystic tumors, usually as a minor component but rarely as a major one [12, 13].

The majority of primary ovarian carcinoid tumors remain clinically asymptomatic. Unfortunately in many cases metastasis reveals the disease. The commonly reported symptoms are diarrhea and flushing. These symptoms are linked to their endocrine capacity and to the release from these tumors of 5-hydroxytryptamine (5-HT) metabolites, kinins, and prostaglandins. In one case series [14], major clinical manifestation of carcinoid syndrome was diarrhea, flushing, and less commonly, wheezing, while heart-valve dysfunction and pellagra was the most frequently reported symptom complex in 13% (21/157) of women [7]. Metastatic disease could be present in uncommon sites as carcinoid heart disease [15]. Right-sided heart failure could occur during anesthetic procedures and also requires life-saving heart surgery as valve replacement in some cases [16]. An acute carcinoid crisis may be activated by the release of chemically active molecules from the tumor, particularly after hepatic artery embolization of liver metastases or after an anesthetic for surgery. Dyschezia, constipation due to inhibition of intestinal motility by the tumor-producing gut hormone peptide-YY, and hirsutism has also been reported [17, 18]. This gastrointestinal peptide called PYY presents mainly in the endocrine cells of the distal intestine has a function to inhibit the bowel motility [18, 19].

Soga *et al.* published a large series (329 cases) [20] which comprised cases described in 273 articles. These authors separated the carcinoids into those with an associated dermoid (group A: n=189) and those without (group B: n=140). The tumors in group B were larger (89 mm *vs.* 45 mm), were associated with a higher rate of overall (22.1% *vs.* 5.8%) and hepatic (15.0% *vs.* 2.1%) metastases and had a higher rate of carcinoid syndrome (22.9% *vs.* 13.8%) and poorer five-year survival (84% *vs.* 93.7%), thus providing some prognostic information [20].

At the moment the surgical management of ovarian carcinoids or ovarian neuroendocrine tumors (NETs) is not well clarified and there are no international guidelines. The classical procedure of complete excision remains. National Comprehensive Cancer Network (NCCN) guidelines recommend that the tumor should be removed completely with negative margins, while extrapolating from the more common gastrointestinal neuroendocrine tumors; the typical management is surgical large resection [21, 22]. Moreover if the diagnosis is done preoperatively, it is recommended to inject octreotide (100-500 mcg SC/IV every 6-12 hours) immediately prior to and during the resection of the tumor to prevent the rare complication of carcinoid crisis [23] which can occur during induction of anesthesia.).Octreotide is an eight-amino acid synthetic analog of somatostatin which was designed to bind with the somatostatin receptor. In case of young patients, fertility sparing surgery is possible, as these tumors are generally unilateral and associated with a good prognosis. Thus, the surgical approach

can preserve an ovary. Many surgical procedures including everything from fertility sparing surgery to radical debulking are options depending on patient age and disease distribution [23-27].

The most common sites of metastatic disease include regional lymph nodes, liver, omentum, peritoneum, fallopian tubes, and contralateral ovary. Some patients present distant metastases to the lungs, bone, brain, liver, and mesenteric surfaces of the spleen and diaphragm. Liver lesions should be considered for resection to control tumor burden, as most carcinoid tumors demonstrate a remarkable tropism for the liver: if those lesions are not resectable, they should be considered for cryotherapy, radiofrequency ablation [28, 29] or regional embolization [30-32] upon progression, as recommended by the NCCN guidelines. However, metastases to the regional lymph nodes or distant metastases may be present at the time of surgery. They are found in about 10% of patients with gall bladder NETs, in up to 70% with laryngeal NETs and in up to 30% with ovarian NETs [33]. However at the time of surgery, proximal or distant lymph nodes metastasis may be present. They are detected in almost 10% of patients diagnosed with gall bladder NETs, in up to 70% with laryngeal NETs, and in up to 30% diagnosed with ovarian NETs [33]. In general, radiotherapy with or without medical treatment with biphosphonates is the "gold standard" method for the management of the bone metastasis.

Regarding adjuvant therapy, there is no evidence to support that either hormonal, chemotherapy or radiation therapy could be useful for gynecologic carcinoid tumors, and also for gastrointestinal and pancreatic carcinoid tumors**.** Various combinations of chemotherapy have been used. Doxorubicin, 5-flourouracil, dacarbazine, actinomycin-D, cisplatin, cyclophosphamide, etoposide or carboplatin, and paclitaxel protocols are chemotherapies which have been administered in the setting of recurrent or unresectable disease. All of these agents have a true objective response rate from 10-15% [34-39]. A radionuclide therapy (90Yttrium or 177Lutetium-labelled analogs, 131I-MIBG) may also be considered as palliative treatment [39]. Due to the paucity of relevant literature and the heterogeneity in presentation and response to surgery, chemotherapy, and radiation, it is not possible to predict the efficacy of surgical debulking, chemotherapy and radiation protocols. There is hence a need for prospective clinical studies for more optimal modalities of treatment.

Recurrent disease may remain silent for many years and there is no reliable tumor marker to help early detection or provide a preoperative diagnosis in these cases. With regard to advanced-stage and recurrent disease, although NCCN guidelines do not include rare (<5%) tumors and thus do not include ovarian carcinoid and NETs, the data presented is more rigorous, and some early and late phase clinical trials have been completed. At this time, the NCCN panel recommends that patients with recurrent or unresectable carcinoid tumors who have no signs of carcinoid syndrome and are asymptomatic be observed until the disease becomes symptomatic. Practically speaking, the majority of regimens follow those recommended for germ cell tumors, with many reports also advocating radiotherapy. However, it is difficult to estimate response rates and thus difficult to recommend one treatment strategy over another. Consideration is needed for those who participate in a clinical trial or for octreotide therapy. A depot long-acting release preparation of a once-monthly intramuscular injection of octreotide or a similar drug, lanreotide, can stabilize disease. One report showed a doubling of progression-free survival when octreotide was compared to placebo in metastatic midgut carcinoid tumors [39-40]. These drugs are also highly effective in treating hormonally-induced NET symptoms [41-48]. The dose and frequency can be slowly titrated until the patient's symptoms are controlled [45, 49]. Radio-labelled somatostatin analogs have been reported to result in tumor shrinkage in metastatic bowel related carcinoids in a small number of patients [50, 51]. Further trials are required to establish the role of these treatments and their long-term benefits. Moreover, it seems that alpha-interferon alone improves hormonal symptoms and induces tumor stabilization in up to 70% of NET patients and achieves an objective tumor response in 10% of patients [46]. However, due to its side effect profile (anorexia, weight loss, fatigue), alpha-interferon is rarely utilized [49, 50]. Many data reported that as for endometrial cancer [52], molecular pathways may reveal possible therapeutic targets for adjuvant therapy thus improving overall survival. The same mechanisms may also be involved in ovarian carcinogenesis and may respectively reveal future molecular targeted therapies.

Prognosis of Stage I disease is excellent. In a study reviewing 11 patients, five-year survival was 100% [7]. Prognosis and long-term survival are related to the histopathological typing, the staging at the time of the diagnosis and the type and completeness of the intervention. For localized and well-differentiated tumors treated with complete surgical resection, five-year survival approaches 90% for ovary NETs [6].

Among ovarian carcinoid tumors, those containing thyroid tissue or epidermal differentiation were associated with better prognosis and with few recurrences. Measuring peptide YY could be a reliable way in monitoring tumor status, since recurrence often manifested as severe constipation. Matsuda *et al.* [18] reported that a 50-year-old woman experienced constipation again ten months after resection of a Stage Ia stromal carcinoid tumor. She had lived with a recurrent tumor in the liver during the 27-month follow-up. In contrast to primary ovarian carcinoids, metastatic carcinoids are more aggressive, with one-third of the patients dying within one year and three fourths dying within five years after initial diagnosis [52-54]. Survival decreases in patients with larger tumor size and in patients with initially

Table 2. — *Female genital tract neoplasms with neuroendocrine differentiation [4].*

Location	Neoplasm type
Fallopian tube, breast	Carcinoid tumor. Small cell undifferentiated carcinoma
Uterine cervix	Adenocarcinoma and adenosquamous carcinomas with neuroendocrine cells. Small cell undifferentiated carcinoma, large cell neuroendocrine carcinoma, atypical carcinoid tumor, typical carcinoid tumor
Uterine corpus	Endometrial adenocarcinoma with neuroendocrine cells. Small cell undifferentiated carcinoma
Vagina	Small cell undifferentiated carcinoma
Vulva	Small cell undifferentiated carcinoma of Bartholin gland. Merkel cell tumor

Table 3. — *Primary ovarian carcinoid tumor (POCT) [4].*

Ovary	Surface epithelial tumors with neuroendocrine cells (mucinous, Brenner, endometrioid, serous). Sertoli-Leydig cell tumors with heterologous elements containing neuroendocrine cells, with or without carcinoid tumorlets
Histological differentiation	Teratomas with neuroendocrine cells. Insular carcinoid tumor. Trabecular carcinoid tumor. Strumal carcinoid tumor. Mucinous (goblet-cell) carcinoid tumor. Mixed or heterogeneous carcinoid tumors. Small cell carcinoma, pulmonary type. Undifferentiated carcinoma, non-small cell neuroendocrine type
Trabecular subtype [51]	The most rare. Excellent prognosis. Absence of a clinical carcinoid syndrome
Hormonal neuropeptide occurrence in carcinoid tumors [51]	Serotonin glucagon encephalin gastrin ACTH, calcitonin ectopic Insulin peptide YY
Carcinoid syndrome [52]	The majority of POCT are asymptomatic. In cases of carcinoid syndrome, carcinoid heart disease, anesthetic complications referred to
Survival rate ***[18]***	Excellent prognosis associated with dermoid cyst. Improved of association with carcinoid syndrome without dermoid cyst. High rate in liver metastasis without dermoid cyst. Reduced five-year rate 84% without dermoid cyst

higher levels of 5-hydroxyindoleacetic qcid [7, 13].

Conclusion

In conclusion, primary ovarian carcinoids are special type ovarian tumors. The prognosis is related to tumor grading, local invasion, presence of metastases, and time of the diagnosis. The basic treatment of these tumors remains surgical. Radical surgery is an effective treatment, with an excellent prognosis in the early stage of the disease. Surgery remains the main treatment for these tumors. In the cases of early stage of the disease, the prognosis is excellent after radical surgical treatment.The management of advanced disease may be a combination of optimal debulking and adjuvant chemotherapy, while use of radiation when appropriate may improve the progression-free, long-term palliation, and survival rates of these rare tumors. Main prognostic factors are: tumor grading, local invasion, presence of metastasis, and time of the diagnosis. In all cases a close follow-up of the patients is mandatory to detect the possible recurrences. Although carcinoid ovarian tumors are rare, they should be well known by gynecologists to offer to the patients with a solid ovarian tumor the better management.

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