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Case Report

Primary ovarian carcinoid: A report of two cases and a decade registry

Islam H. Metwally [a,*], **Amr F. Elalfy** [a], **Shadi Awny** [a], **Islam A. Elzahaby** [a], **Reham M. Abdelghani** [b]

[a] *Surgical Oncology Unit, Oncology Center Mansoura University (OCMU), Mansoura, Egypt*
[b] *Pathology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt*

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KEYWORDS

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Carcinoid syndrome;
Registry;
Carcinoid heart

Abstract *Objectives:* This study aims at reporting 2 cases of primary ovarian carcinoid tumor, and providing an adequate registry of such cases and how they were managed.
Methods: 2 female patients with primary ovarian carcinoid were diagnosed and treated in our center. Discussion of their presentation, pathology and treatment is entitled. Also a thorough search of all published registries and case reports of ovarian carcinoid was done with analysis of reported data.
Results: 164 cases of primary ovarian carcinoid tumor were detected since 2005 with the predominance of the insular variant. Carcinoid syndrome occurs in nearly 14% of these cases. Most of the cases were treated with hysterectomy. Unfortunately, the prognosis was not documented in most series.
Conclusion: Primary ovarian carcinoid is a relatively rare disease with an indolent course and excellent outcome. Carcinoid syndrome, especially carcinoid heart disease may worsen the prognosis. Total abdominal hysterectomy with bilateral salpingo-oophorectomy has been commonly used as the treatment of choice of primary ovarian carcinoid tumors.

Background

Ovarian carcinoid tumors may be primary or metastatic (mostly from GIT origin). Differentiation is usually difficult, but bilaterality, peritoneal deposits, absence of teratomatous element, and lymphovascular invasion are signs of metastatic carcinoid [1]; more recent studies suggested that immunohistochemistry with CDX2 may be of value in differentiating carcinoids of GIT origin [2]. Primary carcinoid tumor of the ovary represents less than 1% of all carcinoid tumors and less than 0.1% of all ovarian neoplasms. Two thirds of these tumors manifest as a localized lesion, while about one third presents with distant spread [3]. Most tumors are seen in perimenopausal women, commonly presenting with ovarian heterogeneous mass, or as an incidental finding in abdominal

* Corresponding author at: Surgical Oncology Unit, Oncology Center Mansoura University, Geehan Street, Mansoura City, Dakahlia Governorate, Egypt.
E-mail address: drislamhany@mans.edu.eg (I.H. Metwally).
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radiology done for other purpose. Histologically, according to WHO, there are four major variants of primary ovarian carcinoid: insular, trabecular, strumal, mucinous and mixed (insular and trabecular) [4]. 30% of patients with carcinoids have symptoms of the carcinoid syndrome, mainly affecting patients with insular type, while it rarely occurs with trabecular type. Extremely rare cases presented with an intractable constipation mainly due to peptide YY which inhibits intestinal motility [5,6]. Primary ovarian carcinoid may occur on top of teratoma or in an otherwise normal ovary. Surgery remains the cornerstone for treatment of localized cases with excellent prognosis.

Methods

This study reports 2 different cases of primary ovarian carcinoid who attended the Oncology Center Mansoura University (OCMU) in 2014, and aims to review and register all published cases since 2005 till March 2016.

Case report one

Malignant ovarian carcinoid on top of teratoma.

Female patient 59 years old, postmenopausal with 5 offspring, hypertensive and hepatic (HCV + ve) with no surgical history, presented with abdominal pain, enlargement and bloating to her gynecologist, who recommended computerized tomography. CT revealed right ovarian mass $9 \times 11 \times 7.3$ cm mostly cystic with irregular outline with omental metastasis and moderate ascites.

The patient was referred to our center (OCMU) where revision of CT suggested ovarian cancer, and after multidisciplinary panel discussion the decision was exploration.

Exploration was done on March 2014 under general anesthesia with a midline incision where about one liter of ascites was aspirated and sent for cytology, followed by right salpingo-oophrectomy and frozen section. The frozen pathology revealed malignant ovarian neoplasm, so complete staging laparotomy in the form of total abdominal hysterectomy, contralateral salpingo-oophrectomy, omentectomy, bilateral iliac lymphadenectomy and random peritoneal biopsies was done.

Postoperative pathology showed a malignant carcinoid tumor of the right ovary mostly on top of teratoma (insular variant) with no lymphovascular emboli with Ki67 $<2\%$ (Fig. 1). Left ovary, omentum and peritoneal biopsies were free with reactive hyperplasia of 14 dissected lymph nodes.

Patient was sent home at 4th day postoperative with drain output of 300c.c serous discharge.

The patient was readmitted one week later to the ICU with wound infection, low grade fever and disturbed conscious level. Investigations showed mildly elevated liver enzymes (SGOT = 65), mild deterioration of renal function (Cr = 2.3), leucocytosis (20,000) mainly neutrophilia, thrombocytosis (620), hyperbilirubinemia (1.5), respiratory alkalosis (PH = 7.42, CO_2 = 35 and HCO_3 = 21), hypernatremia (160), hypocalcemia (Ca = 6.5) and normal potassium (K = 5). The condition was recognized as severe sepsis leading to hepatic pre-coma and unusual electrolyte disturbances. The patient was managed by wound drainage, liver supports, IV fluids and electrolyte replacement.

The patient was re-discharged 5 days latter with good general status.

No chemotherapy was given and patient was scheduled for follow up every 6 months in 1st two years. No evidence of recurrence was detected in radiology after two years of follow up.

Case report two

Pure ovarian carcinoid tumor.

Female patient was aged 48 years with liver cirrhosis and surgical history of splenectomy followed by hernioplasty for incisional hernia one year later. CT (pre-excision) was done revealing large, well defined, bilobed solid and cystic mass in the right adenexal region with multiple areas of calcifications contacting and compressing right psoas muscle 6×11 cm suggestive of dermoid cyst. Left simple ovarian cyst 3 cm was also detected.

Unilateral right salpingo-oophrectomy was done outside our center. Postoperative pathology revealed a carcinoid tumor (trabecular variant) with positive chromogranin and synaptophysin, and Ki67 $<2\%$ (Fig. 2). CT after the operation was free. Serum 5-HIAA = 8.9.

Multidisciplinary panel at OCMU decision was completion hysterectomy, omentectomy and appendectomy which was done at November 2014 with postoperative pathology free of tumor tissue. Patient remains disease free after one and half year of follow up.

Registry

Although population based registries of primary ovarian carcinoid tumors are deficient, multiple researchers had made efforts on registering and analyzing reported cases of these tumors. The last of this published registry up to our knowledge was Modlin et al. [3] at 2003. A thorough search on pubmed, medline and google was done with headings (primary ovarian carcinoid, carcinoid on top of teratoma and malignant transformation of teratoma) and all reported cases since 2005 till March 2016 were registered (Table 1).

From the collected data we recognized 52 cases with insular variant (commonest pathology), 21 cases with trabecular variant, 20 cases with strumal variant, mixed variant in 4 cases and mucinous in 1 case with the remaining 66 case non-specified (Fig. 3). The mean age was 50 years. The average tumor size was about 11 cm. Most of the cases were pure carcinoid (68 cases) while carcinoid transformation of a benign teratoma occurs in 45 cases (51 cases were unreported) (Fig. 4).

Functioning ovarian carcinoid causing endocrine symptoms occurs rarely (only 25 cases). 14 cases manifested with carcinoid heart disease (2 of which were diagnosed in postmortem pathology). Another 9 cases manifested with constipation, which was related to polypeptide secretion. Only one case presented with Cushing syndrome and one with hyperinsulinemia (Fig. 5). More interestingly all cases documented with constipation were strumal variant and none of the cases with trabecular variant were functioning.

Associated tumors occur in only 16 cases (mucinous cystadenoma = 5, contra-lateral ovarian epithelial cancer = 1, liver metastasis = 2, strumal thyroid cancer + breast cancer = 1, endometrial cancer + gliomatosis peritonii = 1,

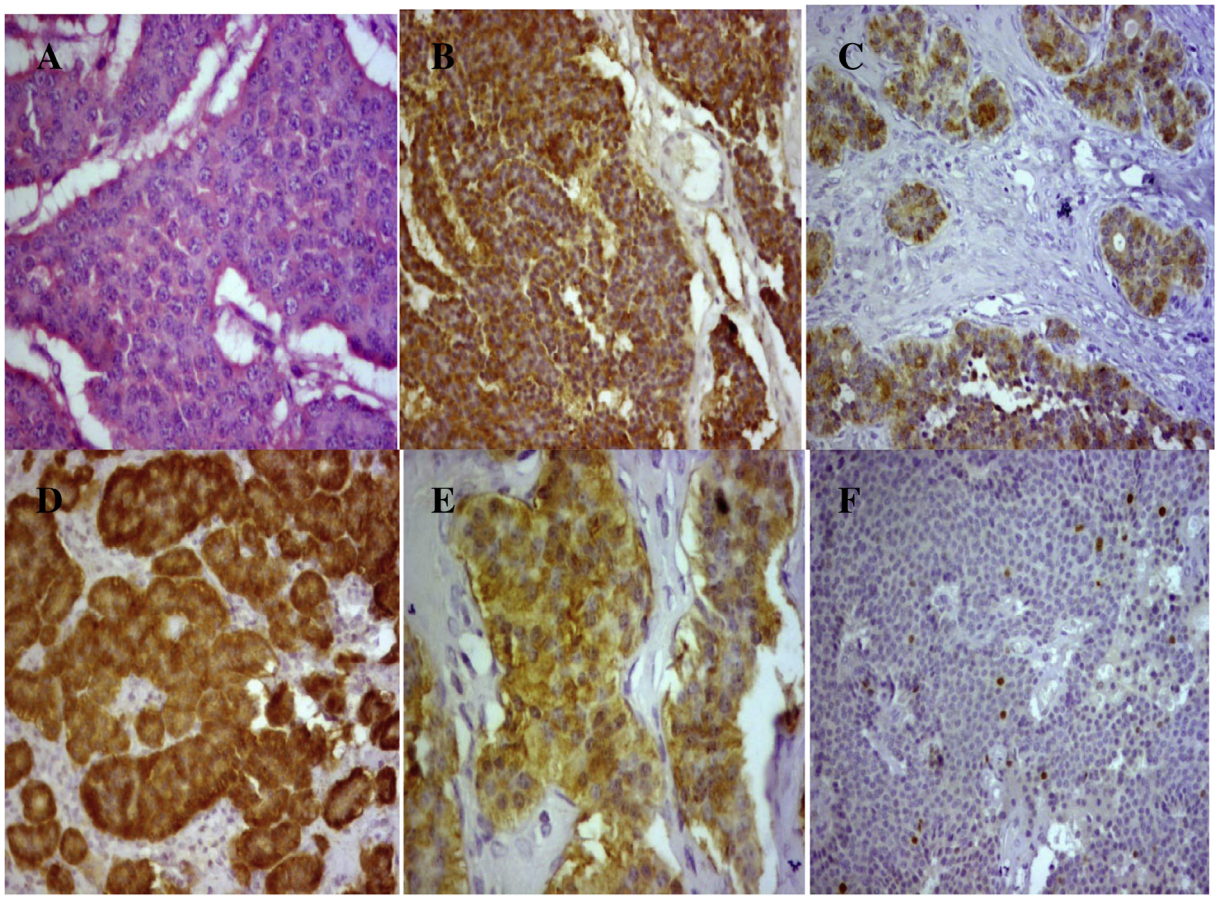

Figure 1 Case one insular carcinoid on top of teratoma. (A) monotonous cells with granular salt and pepper chromatin (H&E.×400). (B) Positive cytoplasmic reaction for chromogranin (×200). (C) Positive cytoplasmic reaction for CK (×200). (D) Strong reaction for synaptophysin (×200). (E) Cytoplasmic reaction for NSE (×400). (F) The only field showing scattered positive nuclei for Ki67, less than 2% of the tumor (×200).

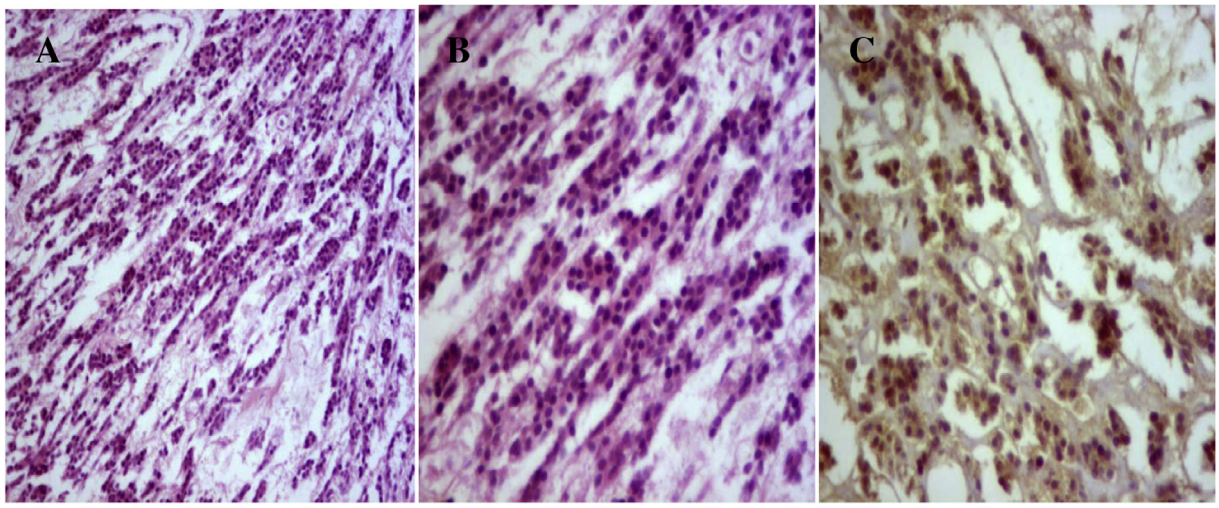

Figure 2 Case two pure ovarian carcinoid (trabecular variant). (A) Cords of monotonous cells separated by fibrovascular stroma (H. &E.×200). (B) Higher magnification showing moderate amount of eosinophilic cytoplasm hyperchromatic nuclei and inconspicuous nucleoli (H.&E.×400). (C) Positive IHC reaction for chromogranin in tumor cells (×400).

teratoma of contra-lateral ovary = 1, nodal recurrence = 1, + MEN1 = 1, pseudomyxoma peritonii = 1, colonic gall bladder carcinoid = 1, ovarian ependymoma lymphangiocele = 1).

Table 1 Show reported cases of ovarian carcinoid since 2005 with their full data.

	No.	Variant	Age	Size	Overlying teratoma	Functional presentation	Associated tumor	Treatment
Kopf et al. [7]	1 case	Insular	79	18 cm	No	No	No	BSO
DiazMontes et al. [8]	1 case	Insular	80	6 cm	Yes	Yes	No	TAHBSO + staging
Chatzipantelis et al. [9]	1 case	Insular	57	//	Yes (bilateral)	No	Mucinous cystadenoma	//
Zhao et al.* [10]	42 cases	//	//	//	//	//	//	//
Morken et al. [11]	1 case	//	//	//	No	Insulin secreting	No	//
Kawano et al. [12]	1 case	Strumal	//	//	No	Constipation	Contralateral ovarian epithelial cancer	Oophorectomy
Nyktari et al. [13]	1 case	//	66	//	Yes	Yes (CHD)	No	TAHBSO
Bonaros et al. [14]	1 case	//	//	//	//	Yes (CHD)	//	//
Djordjevic et al. [15]	1 case	Trabecular	//	//	Yes (recurrent)	No	Liver mets	Excision
Chargui et al. [16]	3 cases	//	50 23 28	//	No	No	No	SO followed by TAH
Somak et al. [17]	1 case	Mixed	55	11 cm	No	No	No	TAHBSO
Dotto et al. [1]	1 case	Insular	50	21.5 cm	No	No	No	//
Pelosi et al. [18]	1 case	Strumal	69	21 cm	Yes	No	Strumal thyroid cancer + breast cancer	CBS + Oophrectomy
Lagoudianakis et al. [19]	1 case	Insular	44	//	Yes	No	No	SO
Engohan-Aloghe et al. [20]	1 case	Insular	75	9 cm	No	No	No	TAHBSO + staging
Rabban et al. [21]	16 case	6insular + 6strumal + 3trabecular + 1mucinous	average 52	About 3.4 cm	Yes (10/16)	//	No	//
Takahashi et al. [22]	1 case	//	52	10 cm	No	Yes (CHD)	No	TAHBSO
Cheng et al. [23]	1 case	//	//	//	//	//	//	//
Guney et al. [24]	1 case	//	54	9 cm	Yes	No	No	TAHBSO
Gungor et al. [25]	1 case	//	47	4 cm	Yes	No	No	TAHBSO + staging + appendectomy
Tangour et al. [26]	1 case	//	//	//	//	//	//	//
Chen et al. [27]	1 case	Strumal	//	//	No	Constipation	No	Lap. oophrectomy
Kurabayashi et al. [28]	1 case	Strumal	34	//	No	No	No	//
Bai et al. [29]	1 case	Trabecular	55	6.2 cm	No	No	No	TAHBSO
Aggeli et al. [30]	1 case	//	60	//	No	Yes (CHD)	No	//
Alexander et al. [31]	1 case	//	//	//	Yes (recurrent)	No	Endometrial cancer + gliomatosis peritonii	TAHBSO
Roberts et al. [32]	1 case	//	53	//	No	Yes (CHD)	liver mets	//
Levin et al. [33]	1 case	//	//	//	//	//	//	//

Shin et al. [34]	1 case	//	60	12 cm	No	Yes (CHD)	//	Oophrectomy + chemotherapy
Djurovic et al. [35]	1 case	//	49	//	No	Yes	No	TAHBSO
Matsunami et al. [36]	1 case	Strumal	45	//	No	Constipation	Teratoma of contralateral ovary	BSO
Takeuchi et al. [37]	2 cases	Strumal Insular	72 77	// 10 cm	No	No	Mucinous cystadenoma	//
Hinshaw et al. [38]	1 case	Strumal	74	8.5 cm	Yes	No	Adenocarcinoma + strumal thyroid cancer	Robotic assisted Lap. TAHBSO + staging
Buda et al. [39]	1 case	Insular	78	13 cm	Yes	Yes (CHD)	//	TAHBSO + staging
Takatori et al. [40]	1 case	Strumal	48	6 cm	No	Constipation	No	Adenexectomy
Lenicek et al. [4]	2 cases	Strumal	//	//	//	//	//	//
Ulker et al. [41]	2 cases	Insular Trabecular	55 39	12 11	No	No	No	TAHBSO + staging SO
Yamaguchi et al. [42]	1 case	Strumal	24	12 cm	No	Constipation	Mucinous cystadenoma	Oophrectomy
Hayashi et al. [43]	1 case	Strumal	45	//	//	//	//	//
Ouyang et al. [44]	1 case	//	//	//	//	Constipation	//	//
Amano et al. [45]	1 case	//	67	7 cm	No	Yes (CHD)	Nodal recurrence	Excision
Bassi et al. [46]	1 case	//	45	20rt + 15lt	No	No	Gall bladder carcinoid	TAHBSO + staging + Radical cholecystectomy
Petousis et al. [47]	1 case	Trabecular	28	10.5 cm	Yes	N0	No	Lap. Excision
Desouki et al. [2]	46 case	35insular + 11trabecular	//	//	30 No 16 Yes	//	//	//
Ting et al. [48]	1 case	Insular	//	//	Yes	No	No	BSO
Horikawa et al. [49]	1 case	Trabecular	57	//	Yes	//	//	//
Huang et al. [50]	1 case	//	46	//	Yes (bilateral)	Cushing	No	BSO
Spaulding et al. [51]	1 case	Trabecular	51	5.5 cm	Yes	No	Ovarian ependymoma + MEN1	Robotic TAHBSO
Tome et al. [52]	1 case	//	//	//	//	//	//	//
Sharma et al. [53]	1 case	Trabecular	50	8 cm	Yes	No	No	TAHBSO
Muller et al. [54]	1 case	strumal	34	//	No	Constipation	No	//
Dessauvagie et al. [55]	1 case	//	69	//	No	Yes (CHD)	No	//
Quiñonez et al. [56]	1 case	Mixed		//	Yes	No	Pseudomyxoma peritonii	//
Agarwal et al. [57]	1 case	//	75	//	No	Yes (CHD)	No	SO
Erdinbatar et al. [58]	1 case	Mixed	70	6 cm	No	Constipation	No	TAHBSO + staging
Tarcoveanu et al. [59]	1 case	Strumal	55	7 cm	No	No	Colonic lymphangioma	Laparoscopic SO
Kolouch et al. [60]	1 case	Insular	77	//	No	Yes (CHD)	No	TAHBSO
Kim et al. [61]	1 case	Mixed	39	9 cm	Yes	NO	No	SO

CHD = carcinoid heart disease, TAHBSO = total abdominal hysterectomy and bilateral salpingo-oophrectomy, Lap. = laparoscopic, // = unmentioned.

* Zhao et al. 40 cases were registered by armed forces institute of pathology before 2005 but were not published till 2007 and were included in previous registry so included.

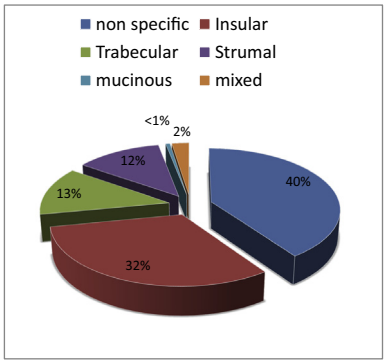

Figure 3 Incidence of different pathological variants of ovarian carcinoid.

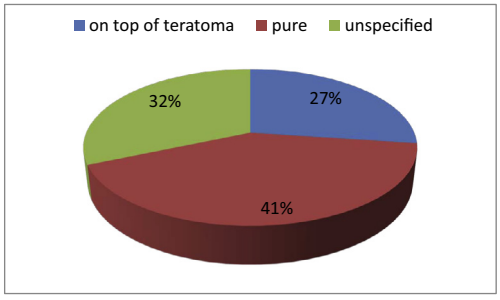

Figure 4 Relation of ovarian carcinoid to Teratoma.

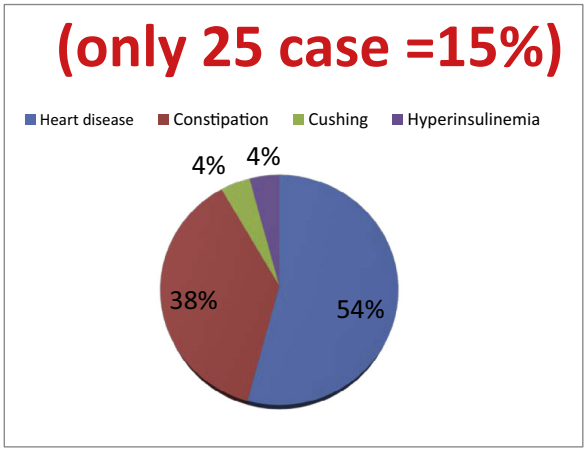

Figure 5 Hormonal presentation of ovarian carcinoid tumors.

Treatment was extremely variable, most cases underwent total abdominal hysterectomy and bilateral salpingo-oophrectomy (13 cases); three of them completed surgery after initial oophrectomy and paraffin section. Other surgeons preferred complete staging laparotomy with lymphadenectomy as for epithelial ovarian cancer (8 cases). Bilateral salpingo-oophrectomy was done in 6 cases; while fertility sparing surgery (unilateral salpingo-oophrectomy) was done in 10 cases with no documentation of long term follow up except one case with 2 year disease free survival. In the remaining 127 cases treatment was not reported.

From the collected data there were 164 cases of primary ovarian carcinoid reported since the beginning of 2005 till March 2016 adding to this our 2 case reports, making a total of 658 cases of primary ovarian carcinoid reported since first diagnosed at 1939 till now.

Is there a rule for appendectomy in treatment of primary ovarian carcinoid

Although it is a commonly performed practice aiming to exclude appendiceal origin, there is no consensus on it and all cases were negative in our review and in our case report. In spite of this some experts prefer doing appendectomy in the mucinous variant of carcinoid.

Discussion

Neuroendocrine tumors are relatively rare tumors arising from APUD cells of neuroectodermal origin (previously called APUDomas); they include Medullary thyroid cancer, Merkel cell carcinoma, pheochromocytoma, pancreatic islet cell tumors, carcinoid tumors (bronchopulmonary, GIT and thymus) and neuroendocrine tumors of the gynecological tract. Neuroendocrine tumors are usually sporadic, but may arise in the context of syndromes as MEN, Von Hippel Lindau and neurofibromatosis [62]. Neuroendocrine tumors of the ovary include: poorly differentiated high grade variants (small cell & large cell NETs) and well differentiated indolent variants known as carcinoids [63].

Ovarian carcinoid tumors were first described in 1939 by Stewart et al. [64]. Since then, multiple case reports were published. At 2000 Soja et al. published an important analysis of ovarian carcinoid tumors registered worldwide [65]. In his paper 329 cases of primary ovarian carcinoid were analyzed with 57% occurring on top of teratoma and 47% occurring as pure form. He concluded that pure forms were larger in size (average 8.9 cm), had higher rates of metastases (22%) and a higher incidence of carcinoid syndrome (22.9%) [57]. The second large registry of primary ovarian carcinoid was Modlin et al. [3] at 2003 in which 492 cases were described. Approximately 66% of them were localized lesions, while about 31% present with distant spread. Unfortunately, in his paper Modlin did not differentiate cases occurring as pure form from those occurring on top of teratoma.

Mature teratoma of the ovary is known to be the most common ovarian tumor, representing 20% of all ovarian neoplasms. Malignant transformation of teratoma was described, although rare. The commonest overlying malignancy was squamous cell carcinoma [66], followed by adenocarcinoma then carcinoid tumor.

Carcinoid tumors secrete a great variety of neurohumoral substances including; serotonin, histamine, tachykinin, bradykinin, kallikrein, corticotrophin, substance P, motilin, and prostaglandins [67]. Persistent body exposure to large quantities of these hormones and amines result in carcinoid syndrome with the classic triad of; flushing of arms and face, wheezes, and diarrhea. Normally, carcinoid syndrome does not occur with an intestinal carcinoid until it has metastasized or in the presence of hepatic dysfunction or hepatic shunts (as TIPS), because of the efficient hepatic detoxification of secreted substances. However, functioning primary ovarian

carcinoid tumors can cause these symptoms directly, because their venous drainage bypasses the portal venous system [68]. Trabecular carcinoid variant was never associated with carcinoid syndrome. Carcinoid syndrome was absent in both cases in our report.

The insular type is the commonest variant of primary ovarian carcinoid, followed by the strumal and trabecular types; while mucinous carcinoids are the least common. Bearing in mind that metastatic carcinoids in the ovary are mostly of insular type, the diagnostic problem is in these cases, and are only occasionally with trabecular or mucinous types [21].

Immunohistochemistry is crucial in the diagnosis of primary carcinoid tumors of the ovary. Synaptophysin and chromogranin are the classic markers. CD56 may be used, but is nonspecific. Estrogen and progesterone receptors are always negative, in contrast to adenocarcinoma. TTF1 and CDX2 may be used to differentiate primary from secondary carcinoid tumors [10]. Most primary ovarian carcinoids are stage I on FIGO system with tumor confined to one ovary, while few cases with advanced disease were reported [7].

Clinical and pathological prognostic factors of the neoplasm are the basic determinants of the therapeutic strategy in these rare cases, because of the absence of evidence-based guidelines. Cyst wall invasion, intra-operative rupture of the ovarian tumor and disseminated tumor are considered unfavorable prognostic factors [69].

Premenopausal women with tumors confined to the ovary may be treated with fertility-sparing surgery, as tumors are usually unilateral and carry a good prognosis, but careful staging to exclude occult metastases is important. However, in the absence of controlled trials to validate this approach, hysterectomy with bilateral salpingo-oophrectomy and surgical debulking of extra-ovarian spread and/or metastases is the treatment of choice [47], using the commonly taught dictum "diagnose as rare and treat as common". In rare patients with mucinous variant of ovarian carcinoid, omentectomy and para-aortic lymph node dissection may also be needed because these tumors spread mainly through lymphatics [63].

Anesthesia of those patients with carcinoid syndrome can be challenging due to extreme hemodynamic lability and exaggerated physiologic responses to trivial stimuli. Recommendations include: titrated induction of anesthesia and avoidance of catecholamines and sympathomimetic drugs because these drugs may trigger a carcinoid crisis. In addition perioperative cover with an Octreotide infusion reduces the risks [70–74].

Conclusion

Primary ovarian carcinoid is a rare tumor with only 658 cases reported worldwide up-to-date. Diagnosis should be confirmed by immunohistochemistry, and secondary carcinoid should be excluded. Extensive sampling of any solid part within a mature teratoma is emphasized not to miss a focus of carcinoid. Adequate treatment is not well defined, but surgery still the main line with chemotherapy reserved for those with high proliferative index as measured by Ki67. Somatostatin analog is only used for those with functioning tumors as confirmed by urine 5-HIAA and/or serum chromogranin.

Conflict of interest

We have no conflict of interest to declare.

References

[1] Dotto J, Mezzetti T, Hui P. Primary or secondary? Genotyping confirmation of an ovarian primary carcinoid tumor. Int J Gynecol Pathol 2008;27(1):33–6.
[2] Desouki MM, Lioyd J, Xu H, Cao D, Barner R, Zhao C. CDX2 may be a useful marker to distinguish primary ovarian carcinoid from gastrointestinal metastatic carcinoids to the ovary. Hum Pathol 2013;44(11):2536–41.
[3] Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97(4):934–59.
[4] Lenicek T, Tomas D, Soljacić-Vranes H, Kraljević Z, Klarić P, Kos M. Strumal carcinoid of the ovary: report of two cases. Acta Clin Croat 2012;51(4):649–53.
[5] Motoyama T, Katayama Y, Watanabe H, Okazaki E, Shibuya H. Functioning ovarian carcinoids induce severe constipation. Cancer 1992;70:513–8.
[6] Matsuda K, Maehama T, Kanazawa K. Strumal carcinoid tumor of the ovary: a case exhibiting severe constipation associated with PYY. Gynecol Oncol 2002;87:143–5.
[7] Kopf B, Rosti G, Lanzanova G, Marangolo M. Locally advanced ovarian carcinoid. J Exp Clin Cancer Res 2005;24(2):313–6.
[8] Díaz-Montes TP, Rosenthal LE, Bristow RE, Grumbine FC. Primary insular carcinoid of the ovary. Gynecol Oncol 2006;101(1):175–8.
[9] Chatzipantelis P, Mavrogiorgis A, Kairi-Vassilatou E, Pafiti A. Ovarian neoplasm composed of an insular carcinoid tumor and a borderline mucinous cystadenoma arising in a mature cystic teratoma: a case report. Eur J Gynaecol Oncol 2006;27(6):636–7.
[10] Zhao C, Bratthauer GL, Barner R, Vang R. Comparative analysis of alternative and traditional immunohistochemical markers for the distinction of ovarian sertoli cell tumor from endometrioid tumors and carcinoid tumor: a study of 160 cases. Am J Surg Pathol 2007;31(2):255–66.
[11] Morken NH, Majak B, Kahn JA. Insulin producing primary ovarian carcinoid tumor. Acta Obstet Gynecol Scand 2007;86(4):500–1.
[12] Kawano K, Ushijima K, Fujimoto T, Komai K, Kamura T. Peptide YY producing strumal carcinoid of the ovary as the cause of severe constipation with contralateral epithelial ovarian cancer. J Obstet Gynaecol Res 2007;33(3):392–6.
[13] Nyktari E, Patrianakos AP, Parthenakis FI, Koutsopoulous A, Vardas PE. Carcinoid heart disease in a patient with primary ovarian carcinoid tumour. Hellenic J Cardiol 2007;48(4):234–5.
[14] Bonaros N, Müller S, Bonatti J, Kafka R, Tzankov A, Bale R, et al. Primary ovarian carcinoid heart disease curatively treated with a two-stage procedure. Thorac Cardiovasc Surg 2007;55(7):467–9.
[15] Djordjevic B, Euscher ED, Malpica A. Growing teratoma syndrome of the ovary: review of literature and first report of a carcinoid tumor arising in a growing teratoma of the ovary. Am J Surg Pathol 2007;31(12):1913–8.
[16] Chargui R, Bouzid T, Khomsi F, Damak T, Ben Hassouna J, Mtaallah M, et al. Primary carcinoid tumors of the ovary: report of three cases. Tunis Med 2007;85(7):604–6.
[17] Somak R, Shramana M, Vijay S, Nita K. Primary carcinoid tumor of the ovary: a case report. Arch Gynecol Obstet 2008;277(1):79–82.
[18] Pelosi G, Sonzogni A, Rosai J. Thyroid-type papillary microcarcinoma in ovarian strumal carcinoid. Int J Surg Pathol 2008;16(4):435–7.

[19] Lagoudianakis EE, Markogiannakis H, Karantzikos G, Papadima A, Alevizos L, Manouras A. Primary insular carcinoid of the ovary. Eur J Gynaecol Oncol 2008;29(5):554–5.
[20] Engohan-Aloghe C, Buxant F, Noel JC. Primary ovarian carcinoid tumor with luteinized stromal cells. Arch Gynecol Obstet 2009;280(1):119–21.
[21] Rabban JT, Lerwill MF, McCluggage WG, Grenert JP, Zaloudek CJ. Primary ovarian carcinoid tumors may express CDX-2: a potential pitfall in distinction from metastatic intestinal carcinoid tumors involving the ovary. Int J Gynecol Pathol 2009;28(1):41–8.
[22] Takahashi H, Okada K, Asano M, Matsumori M, Morimoto Y, Okita Y. Bioprosthetic pulmonary and tricuspid valve replacement in carcinoid heart disease from ovarian primary cancer. Circ J 2009;73(8):1554–6.
[23] Cheng NH, Huang HF, Lian LJ, Wu Y. Ovarian growing teratoma syndrome clinical study of 22 cases. Zhonghua Fu Chan Ke Za Zhi 2009;44(6):426–30.
[24] Guney N, Sayilgan T, Derin D, Ozcan D. Primary carcinoid tumor arising in a mature cystic teratoma of the ovary: a case report. Eur J Gynaecol Oncol 2009;30(2):223–5.
[25] Gungor T, Altinkaya O, Ozat M, Sirvan L, Yalcin H, Mollamahmutoglu L. Primary adenocarcinoid tumor of the ovary arising in mature cystic teratoma. A case report. Eur J Gynaecol Oncol 2009;30(1):110–2.
[26] Tangour-Bouaïcha M, Ben Brahim E, Bel Haj Salah M, Zidi Y, Kraiem J, Aziz Falfoul A, et al. Primary ovarian carcinoid tumor arising in teratoma. Tunis Med 2009;87(8):546–7.
[27] Chen CW, Chang WC, Chang DY. Laparoscopic resection of an ovarian strumal carcinoid tumor with dramatic relief of severe constipation. J Minim Invasive Gynecol 2010;17(2):242–5.
[28] Kurabayashi T, Minamikawa T, Nishijima S, Tsuneki I, Tamura M, Yanase T, et al. Primary strumal carcinoid tumor of the ovary with multiple bone and breast metastases. J Obstet Gynaecol Res 2010;36(3):567–71.
[29] Bai X, Li N, Wang F, Li S, Yu Q. Primary ovarian trabecular carcinoid tumor: a case report and literature review. Arch Gynecol Obstet 2010;282(4):407–11.
[30] Aggeli C, Felekos I, Kazazaki C, Giannopoulos D, Kartalis A, Pitsavos C, et al. Echocardiographic imaging of tricuspid and pulmonary valve abnormalities in primary ovarian carcinoid tumor. Cardiovasc Ultrasound 2010;8:37.
[31] Alexander M, Cope N, Renninson J, Hong A, Simpson RH, Hirschowitz L. Relationship between endometriosis, endometrioid adenocarcinoma, gliomatosis peritonei and carcinoid tumor in a patient with recurrent ovarian teratoma. Int J Gynecol Pathol 2011;30(2):151–7.
[32] Roberts WC, Varughese CA, Ko JM, Grayburn PA, Hebeler RF, Burton EC. Carcinoid heart disease without the carcinoid syndrome but with quadrivalvular regurgitation and unsuccessful operative intervention. Am J Cardiol 2011;107(5):788–92.
[33] Levin MA, Flynn BC. Case report: primary ovarian carcinoid: a rare tumor causing unexpected manifestations in a previously undiagnosed woman. Anesth Analg 2011;112(5):1158–60.
[34] Shin HW, Kim H, Yoon HJ, Park HS, Cho YK, Nam CW, et al. Ovarian tumor-associated carcinoid heart disease presenting as severe tricuspid regurgitation. J Cardiovasc Ultrasound 2011;19(1):45–9.
[35] Djurović M, Damjanović S, Tatić S, Micev M, Cetković A, Petakov M, et al. Primary carcinoid of the ovary. Vojnosanit Pregl 2011;68(3):274–6.
[36] Matsunami K, Takagi H, Ichigo S, Murase T, Ikeda T, Imai A. Peptide YY producing strumal carcinoid tumor of the ovary. Eur J Gynaecol Oncol 2011;32(2):201–2.
[37] Takeuchi M, Matsuzaki K, Uehara H. Primary carcinoid tumor of the ovary: MR imaging characteristics with pathologic correlation. Magn Reson Med Sci 2011;10(3):205–9.
[38] Hinshaw HD, Smith AL, Desouki MM, Olawaiye AB. Malignant transformation of a mature cystic ovarian teratoma into thyroid carcinoma, mucinous adenocarcinoma, and strumal carcinoid: a case report and literature review. Case Rep Obstet Gynecol 2012;2012:269489.
[39] Buda A, Giuliani D, Montano N, Perego P, Milani R. Primary insular carcinoid of the ovary with carcinoid heart disease: unfavourable outcome of a case. Int J Surg Case Rep 2012;3(2):59–61.
[40] Takatori E, Shoji T, Miura J, Takeuchi S, Yoshizaki A, Sugiyama T. Case of peptide-YY-producing strumal carcinoid of the ovary: a case report and review. J Obstet Gynaecol Res 2012;38(10):1266–70.
[41] Ulker V, Numanoglu C, Akbayir O, Akyol A, Tuncel A, Akca A, et al. Malignant transformation arising from mature cystic teratoma of the ovary: a report of six cases. J Obstet Gynaecol Res 2012;38(5):849–53.
[42] Yamaguchi M, Tashiro H, Motohara K, Ohba T, Katabuchi H. Primary strumal carcinoid tumor of the ovary: a pregnant patient exhibiting severe constipation and CEA elevation. Gynecol Oncol Case Rep 2012;4:9–12.
[43] Hayashi T, Haba R, Kushida Y, Kadota K, Katsuki N, Miyai Y, et al. Cytopathologic characteristics of the primary strumal carcinoid tumor of the ovary: a case report with emphasis on differential diagnostic considerations. Diagn Cytopathol 2013;41(9):812–6.
[44] Ouyang M, Zeng F. Primary ovarian carcinoid clinically manifested by intractable constipation: a case report. Nan Fang Yi Ke Da Xue Xue Bao 2013;33(2):312–3.
[45] Amano Y, Mandai M, Baba T, Hamanishi J, Yoshioka Y, Matsumura N, et al. Recurrence of a carcinoid tumor of the ovary 13 years after the primary surgery: a case report. Oncol Lett 2013;6(5):1241–4.
[46] Bassi R, Arora R, Bhasin S, Khurana N. An unusual case of synchronous carcinoid of ovary and gall bladder. Case Rep Obstet Gynecol 2013;2013:737016.
[47] Petousis S, Kalogiannidis I, Margioula-Siarkou C, Traianos A, Miliaras D, Kamparoudis A, et al. Mature ovarian teratoma with carcinoid tumor in a 28-year-old patient. Case Rep Obstet Gynecol 2013;2013:108582.
[48] Ting WH, Hsiao SM, Lin HH, Wei MC. Primary carcinoid tumor of the ovary arising in a mature cystic teratoma: a case report. Eur J Gynaecol Oncol 2014;35(1):100–2.
[49] Horikawa M, Shinmoto H, Soga S, Miyai K, Kaji T. 18F-FDG PET/CT and MR findings of ovarian carcinoid within a dermoid cyst. Clin Nucl Med 2014;39(9):e392–4.
[50] Huang B, Wu X, Zhou Q, Hu Y, Zhao H, Zhu H, et al. Cushing's syndrome secondary to ectopic ACTH secretion from carcinoid tumor within an ovarian mature teratoma: a case report and review of the literature. Gynecol Endocrinol 2014;30(3):192–6.
[51] Spaulding R, Alatassi H, Stewart Metzinger D, Moghadamfalahi M. Ependymoma and carcinoid tumor associated with ovarian mature cystic teratoma in a patient with multiple endocrine neoplasia I. Case Rep Obstet Gynecol 2014;2014:712657.
[52] Tomé Fernández-Ladreda M, Martínez de Pinillos Gordillo G, Pichardo López de Haro F, Cózar León MV. Carcinoid tumor on cystic ovarian teratoma. Endocrinol Nutr 2014;61(8):434–6.
[53] Sharma R, Biswas B, Puri Wahal S, Sharma N, Kaushal V. Primary ovarian carcinoid in mature cystic teratoma: a rare entity. Clin Cancer Investig J 2014;3(1):80–2.
[54] Muller KE, Tafe LJ, Gonzalez JL, West LA, Schned AR. Ovarian strumal carcinoid producing peptide YY associated with severe constipation: a case report and review of the literature. Int J Gynecol Pathol 2015;34(1):30–5.
[55] Dessauvagie BF, Lai PH, Oost E, Thomas A, Stewart CJ. Medial hypertrophy of the ovarian vein: a novel type of vascular

pathology associated with a primary ovarian carcinoid tumor. Int J Gynecol Pathol 2015;34(1):36–9.
[56] Quiñonez E, Schuldt M, Retamero JA, Nogales FF. Ovarian strumal carcinoid containing appendiceal-type mucinous tumor patterns presenting as pseudomyxoma peritonei. Int J Gynecol Pathol 2015;34(3):293–7.
[57] Agarwal C, Goel S, Stern E, Warner R, Castillo J, Croft L, et al. Carcinoid heart disease without liver involvement caused by a primary ovarian carcinoid tumour. Heart Lung Circ 2015;24(7):e97–e100.
[58] Erdenebaatar C, Yamaguchi M, Saito F, Motooka C, Tashiro H, Katabuchi H. An ovarian carcinoid tumor with peptide YY-positive insular component: a case report and review of the literature. Int J Gynecol Pathol 2015. http://dx.doi.org/10.1097/pgp.0000000000000242.
[59] Tarcoveanu E, Vasilescu A, Fotea V, Ciobanu D, Crumpei F, Bradea C. Rare tumors, rare association: ovarian strumal carcinoid – retroperitoneal cystic lymphangioma. Chirurgia (Bucur) 2015;110(3):294–9.
[60] Kolouch T, Linkova H, Lang O, Ciprova V, Brunerova L. Carcinoid heart disease in a primary ovarian carcinoid. Acta Cardiol Sin 2016;32:112–5.
[61] Kim NR, Ha SY, Shin JW, Lim S, Park CY, Cho HY. Primary ovarian mixed strumal and mucinous carcinoid arising in an ovarian mature cystic teratoma. J Obstet Gynaecol Res 2016;42(2):211–6.
[62] Anluf M, Garbrecht N, Baeuesfeld J, Schmitt A, Henopp T, Komminoth P, et al. Hereditary neuroendocrine tumors of the gatroenteropancreatic system. Virchows Arch 2007;451(Suppl. 1):S29–38.
[63] Reed NS, Gomez-Garcia E, Gallardo-Rincon D, Barrette B, Baumann K, Friedlander M, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for carcinoid tumors of the ovary. Int J Gynecol Cancer 2014;24(9 Suppl. 3):S35–41.
[64] Stewart MJ, Willis RA, De Saram GSW. Argentaffine carcinoma (carcinoid tumour) arising in ovarian teratomas; a report of two cases. J Pathol Bacteriol 1939;49:207–12.
[65] Soga J, Osaka M, Yakuwa Y. Carcinoids of the ovary: an analysis of 329 reported cases. J Exp Clin Cancer Res 2000;19(3):271–80.
[66] Ueda G, Fujita M, Ogawa H, Sawada M, Inoue M, Tanizawa O. Adenocarcinoma in a benign cystic teratoma of the ovary: report of a case with a long survival period. Gynecol Oncol 1993;48:259–63.
[67] Sporrong B, Falkmer S, Robboy SJ, Alumets J, Håkanson R, Ljungberg O, et al. Neurohormonal peptides in ovarian carcinoids: an immunohistochemical study of 81 primary carcinoids and of intraovarian metastases from six mid-gut carcinoids. Cancer 1982;49:68–74.
[68] Robboy SJ, Norris HJ, Scully RE. Insular carcinoid primary in the ovary. A clinicopathologic analysis of 48 cases. Cancer 1975;36:404–18.
[69] Arora DS, Haldane S. Carcinosarcoma arising in a dermoid cyst of the ovary. J Clin Pathol 1996;49(6):519–21.
[70] Caplin ME, Buscombe JR, Hilson AJ, Jones AL, Watkinson AF, Burroughs AK. Carcinoid tumour. Lancet 1998;352:799–805.
[71] Kulke MH, Mayer RJ. Carcinoid tumours. N Engl J Med 1999;340:858–68.
[72] Kuc-Rajca M, Dacska-Bidzicska A. Contemporary management of neuroendocrine neoplasms of the female genital organs. Ginekol Pol 2011;82:685–9.
[73] Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012;61:6–32.
[74] Rindi G, de Herder WW, O'Toole D, Wiedenmann B. Consensus guidelines for the management of patients with digestive neuroendocrine tumors: the second event and some final considerations. Neuroendocrinology 2008;87(1):5–7.