Primary ovarian carcinoid arising in mature cystic teratoma: case study and brief literature review

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Abstract: - Carcinoid tumors are low-grade, well differentiated and slow-growing neuroendocrine neoplasms. Primary carcinoid tumors of the ovary are extremely rare, accounting for less than 5% of all carcinoid tumors and less than 0.1% of all ovarian malignancies. They represent the second most frequent type of monodermal teratoma and may occur in pure form (15%) or combined with other teratomatous elements (85%). Primary ovarian carcinoids are more common than metastatic ovarian carcinoids, which are mostly of gastrointestinal origin. The distinction between ovarian primary and metastatic carcinoid is crucial and has various clinical, therapeutic and prognostic implications. To date, there are no specific histopathological or immunohistochemical criteria for differentiating between primary ovarian carcinoids and metastatic tumors from the gastrointestinal tract. However, features like the association with ovarian teratoma, unilaterality and the absence of lymphovascular invasion are considered to be suggestive of a primary ovarian carcinoid, rather than a metastatic tumor. Some studies suggest that CDX-2 may be a useful marker to distinguish primary ovarian carcinoids from metastatic ovarian carcinoids of gastrointestinal origin, but there are multiple reports demonstrating that insular and mucinous carcinoids of either origin may express this marker with various intensity. The current consensus is that in the absence of other teratomatous elements, it may be difficult or even impossible to determine whether an ovarian carcinoid is primary or metastatic. Much more relevant to the diagnosis seems to be the interpretation of ancillary immunohistochemical tests, in each individual clinical context. The case presented in this paper attempts to explore the most important diagnostic and therapeutic challenges posed by primary ovarian carcinoid tumors.

Keywords: - Primary ovarian carcinoid arising in mature cystic teratoma: case study and brief literature review.

Introduction:

Carcinoid tumors are relatively rare, slow-growing neuroendocrine neoplasms arising from APUD cells of neuroectodermal origin (previously referred to as APUDomas). Although carcinoid tumors of gastrointestinal origin are rare, their background, pathophysiology and practice essentials are well documented. In contrast, those that arise from the female reproductive system are exceedingly rare and sparsely documented [1]. Due to being so infrequent, patients presenting with nonspecific symptoms may not be properly diagnosed preoperatively, leading to unexpected hemodynamic issues under general anesthesia.

Neuroendocrine tumors of the ovary comprise both poorly differentiated high-grade subtypes (small cell and large cell neuroendocrine tumors) as well-
differentiated, indolent subtypes known as carcinoids.

Primary carcinoid tumors of the ovary are exceedingly rare and account for less than 5% of all carcinoid tumors and less than 0.1% of all ovarian malignancies [2,3].

According to the WHO Classification of Tumours of Female Reproductive Organs, primary ovarian carcinoid tumors are well-differentiated neuroendocrine neoplasms that resemble carcinoids of the gastrointestinal tract [4]. When affecting the ovary, these tumors are typically unilateral. The women range in age from 14 to 79 years and the vast majority of patients are diagnosed incidentally [4]. However, up to one third of patients with insular carcinoid of the ovary may present with carcinoid syndrome, even in the absence of metastatic disease [4,5]. Women can have flushes, diarrhea and carcinoid heart disease due to increased secretion of serotonin and other compounds which are released directly into the systemic circulation. Contrarily, patients with gastrointestinal carcinoids do not present similar symptoms because the substances are inactivated in the liver and carcinoid syndrome is exceptionally rare, unless metastatic liver disease is present [6].

Primary ovarian carcinoids are the second most frequent type of monodermal teratoma. They may occur in pure form (15%) or, more frequently, combined with other teratomatous components (85%), such as a mature teratoma or a struma ovarii. They are more common than ovarian metastatic carcinoids, which are mostly of gastrointestinal origin [4]. Distinction between primary ovarian carcinoid and metastatic ovarian carcinoid is of paramount significance, having clinical and prognostic implications [7,8].

In the absence of other teratomatous elements, primary ovarian carcinoid may be extremely difficult to distinguish from a metastatic carcinoid [9,10]. Therefore, clinical history of carcinoid tumor in the gastrointestinal tract, lung or elsewhere is extremely useful. Additional evidence favoring a metastasis includes: bilateralness, multinodularity, the presence of peritoneal metastases and persistence of carcinoid syndrome or elevated 5-hydroxyindolacetic acid levels in the urine even after removal of the ovarian tumor [11,12]. On the other hand, features like unilaterality, association with ovarian teratomatous components and the absence of lympho-vascular space invasion are considered to be suggestive for primary ovarian carcinoids [13].

Ovarian carcinoids in young patients pose a challenging dilemma about the optimal therapeutic strategy in women willing to preserve their fertility [14].

Histologically, primary carcinoid tumors can be classified into four distinct subtypes: insular, trabecular, mucinous and mixed. The insular type is the commonest variant of primary ovarian carcinoid (26-53%), followed by the strumal (26-44%) and trabecular (23-29%) types [4]. Mucinous primary ovarian carcinoids are the least common [14,15].

Similar to other well-differentiated neuroendocrine tumors, primary ovarian carcinoids are immunoreactive in variable extent and intensity for one or more neuroendocrine markers, such as chromogranin, synaptophysin, CD56 and NSE. However, whether the tumor is primary to the ovary or metastatic from the gastrointestinal tract remains a difficult problem in daily clinical practice.

The case presented in this paper highlights our personal experience regarding this uncommon histological subtype of ovarian tumor and explores the most important diagnostic and therapeutic challenges posed by carcinoid tumors involving the ovary.

Upon microscopic examination, gastrointestinal carcinoid tumors metastatic to the ovary have similar cyto-architectural features with primary ovarian carcinoids and distinction is practically impossible by cytometric features alone. Immunohistochemistry is not decisive either, since most immunohistochemical markers have either high sensitivity and low specificity or vice-versa [16,17]. Current guidelines suggest that differentiation between these entities should involve extensive clinical correlation, but there are some tumor-related features which are much more frequently associated with one of the two.

Our case report explores the main clinicopathological features of primary ovarian carcinoids in the attempt to create a detailed etiopathogenic framework of this rare entity.

**Body Text:**

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We report the case of a 64-year-old woman presenting to the Department of General Surgery of the Emergency University Hospital Bucharest Romania for localized abdominal pain. Physical examination revealed no other specific signs or symptoms. Upon ultrasound investigation, she was found with a right adnexal tumor and she was referred to the Department of Obstetrics and Gynecology in the same clinic, for therapeutic management. No carcinoid syndrome was present.

Ultrasonography showed a right ovarian mass measuring 4.7/5.6 cm, with prominent peripheral vascularity, showing both arterial and venous waveforms. No abnormalities were found in the left adnexa, uterus or abdominal cavity. A full-body CT scan revealed an expansive tumor process involving the right adnexa, with well-defined margins and mixed components: an intensely iodophile mass with cystic areas, measuring 66/57/58 mm. Left adnexa and the uterine corpus appeared normal. No ascites, abdominal or pelvic lymphadenopathies were detected. Magnetic resonance imaging (MRI) of the abdomen revealed a right ovarian mass measuring 49/55/62 mm which was hypointense on T1 and T2. T1 postcontrast (gadolinium) axial scan showed an enhanced right ovarian mass. Results of routine blood tests, including complete blood count, electrolyte, liver function test, renal function test and thyroid function test were normal. Serum tumor markers, such as cancer antigen-125, b-HCG, human epididymis protein 4, and carcinoembryonic antigen were within normal limits.

Exploratory laparotomy and right salpingo-oophorectomy was performed. Intraoperative frozen section examination was suggestive for the diagnosis of ovarian teratoma, which was quite unusual, since most of these tumors occur during reproductive years. The surgically resected specimen was submitted to the Department of Pathology in the same clinic, for histopathological evaluation. Postoperative course was uneventful.

Upon gross examination, the right ovary measured 57/67/52 mm and featured smooth and lobulated external surface. Serial sectioning revealed a unilocular cystic space filled with sebaceous material and a solid, firm, yellow-colored nodule with hemorrhagic areas, measuring 2/1.5cm.

Tissue samples underwent fixation with 10% buffered formalin and were processed by conventional histopathological methods, using inclusion in paraffin and Hematoxylin–Eosin (HE) staining. Subsequent histopathological examination of paraffin-embedded samples confirmed the diagnosis established on frozen sections, but the nodule identified within the wall of the mature teratoma (Figure 1-2) proved to be an incidental focus of carcinoid tumor. The tumor was composed mostly of islands and nests (Figure 3) but also trabeculae (Figure 4) of monotonous cells, separated by fibrovascular stroma. Some areas showed a slightly different architectural pattern, composed of ribbons, cords and parallel trabecular structures. The neoplastic cells were polygonal, featuring moderate or abundant eosinophilic cytoplasm and granular salt and pepper chromatin. Mitotic figures were extremely rare, with less than 1 mitosis per 10 HPF. The tumor was limited to the left ovary, without rupturing the cyst wall (T1a).
Figure 2 – Histopathological aspect of the primary ovarian carcinoid demonstrating development from a mature cystic teratoma, seen on the lower left side of the picture (HE staining, 400x).

Figure 3 – Histopathological aspect of the ovarian carcinoid showing readily identifiable neuroendocrine architecture, with trabecular growth pattern and dense fibrous strands (HE staining, 400x).

Figure 4 – Histopathological aspect of ovarian carcinoid featuring trabecular architecture with thin strands of polygonal cells lacking marked atypia, with vesicular nuclei and abundant granular cytoplasm (HE staining, x100).

Ancillary immunohistochemical (IHC) tests were performed, using the following antibodies: Chromogranin A (mouse monoclonal, clone LK2H10 + PHE5, ready-to-use), Synaptophysin (mouse monoclonal, clone 27G12, ready-to-use), CD56 (mouse monoclonal, clone BC56C04, 1:100 dilution), EMA (mouse monoclonal, clone E29, 1:100 dilution), Pan-cytokeratin (mouse monoclonal, clone AE1/AE3, 1:100 dilution), CK7 (mouse monoclonal, clone OV-TL 12/30, 1:200 dilution), CK20 (mouse monoclonal, clone Ks20.8, dilution 1:100), ER (mouse monoclonal, clone E29, 1:100 dilution), PR (mouse monoclonal, clone 16, 1:100 dilution), Inhibin (mouse monoclonal, clone BC/R1, 1:100 dilution), CDX2 (rabbit monoclonal, clone EP25, dilution 1:100) and Ki-67 (mouse monoclonal, clone MIB-1, ready-to-use).

Immunostaining for Chromogranin-A (Figure 5), Synaptophysin (Figure 6) and CD56 revealed diffuse cytoplasmic positivity within almost all tumor cells, confirming the neuroendocrine lineage. Interestingly, immunostaining for CDX2 (Figure 7) revealed diffuse nuclear positivity in all tumor cells. Ki-67 proliferation index was less than 1% (Figure 8), which correlated with the lack of prominent mitotic figures, as evaluated on standard H.E. staining. AE1/AE3 was diffusely positive within the tumor, as well as epithelial membrane antigen. Both CK7 and CK20 were negative across the specimen and immunostaining for ER, PR and inhibin was also negative.

Figure 5 – Immunostaining for Chromogranin-A revealed diffuse cytoplasmic positivity in all tumoral cells, characteristic for neuroendocrine tumors (DAB chromogen staining, x100).
Figure 6 – Immunostaining for Synaptophysin revealed diffuse cytoplasmic positivity in all tumoral cells (DAB chromogen staining, x100).

Figure 7 – Immunostaining for CDX2 revealed weak but diffuse nuclear positivity in all tumoral cells (DAB chromogen staining, x100).

Result and Discussion:

Carcinoids are rare neuroendocrine tumors with an incidence of 1 to 2 cases per 100,000 patients. Primary ovarian carcinoids account for less than 1% of all carcinoid tumors and less than 0.1% of all ovarian neoplasms [18], being so rare that a clinician may not encounter even one during his or her entire medical career [19].

Primary ovarian carcinoid tumors are thought to be derived from the neuroendocrine component found in the respiratory and gastrointestinal epithelium of ovarian teratomas. Solid ovarian carcinoids without a discernable teratomatous component are considered to appear from a one-sided teratomatous element [20].

The current WHO Classification of Tumours of Female Reproductive Organs recognizes four different histologic subtypes of ovarian carcinoids: insular (midgut derivation), trabecular (foregut or hindgut derivation), strumal and mucinous (goblet or adenocarcinoid). Mixed architectural patterns can be observed as well and any histologic subtype may be associated with mature cystic teratoma [21]. Among all variants, insular carcinoid is the most common type of primary ovarian carcinoid, followed by trabecular and mucinous subtypes.

Patients range in age from 14 to 79 years old, with an average age of 53 years. Most women are either perimenopausal or postmenopausal [4]. On a thorough literature review, we found one case reported during pregnancy and another associated with a primary bronchial carcinoid [22,23]. We also noted that bilateral presentation appears to be exceptional [24].

Primary ovarian carcinoids are frequently unilateral. As in our case, the tumor usually appears as a firm, yellow-brown nodule within the wall of a dermoid cyst. Rarely, the tumor may be uniformly solid, with necrotic and hemorrhagic areas.
In daily practice of the pathologist, the major problem with ovarian carcinoid tumors is discerning between primary ovarian and metastatic carcinoids, because the current guidelines provide limited histopathologic criteria and are dependent upon clinical data. Usually, an immunohistochemical panel composed of CK7 and CK20 can be used for the diagnostic work-up for carcinoma of unknown primary, due to differences in immunopositivity for these two keratins based on the location of the primary tumor. In carcinoid tumors, immunoeexpression of those cytokeratins is even more variable and does not correlate with tumor origin. Insular and trabecular ovarian carcinoids tend to be CK7 positive and CK20 negative, while mucinous carcinoids usually show an opposite pattern of immunohistochemical expression. However, some cases, ours included, can be negative for both CK7 and CK20.

Several authors demonstrated that CDX2 may be a useful marker to distinguish primary ovarian carcinoid tumors from gastrointestinal carcinoids metastatic to the ovary [25]. However, our case of primary ovarian carcinoid was diffusely positive for CDX2 and after a thorough literature review we observed that this is not an isolated case. Other authors also reported that CDX2 immunoeexpression alone cannot be reliably used to determine whether a carcinoid is primary in the ovary or metastatic from the intestine, as insular and mucinous types of either origin may express this marker [26]. Current guidelines suggest that unilateral localization, lack of multinodular growth, early stage, presence of teratomatous elements, and size 3 cm or smaller are the most helpful criteria for suggesting a primary origin for an ovarian carcinoid.

When dealing with an ovarian tumor which histologically appears to be a trabecular carcinoid, the main differential diagnoses to be considered are metastatic carcinoids, strumal carcinoids, Sertoli-Leydig’s tumors with trabecular pattern and poorly differentiated carcinomas.

Unlike metastatic ovarian carcinoids, primary ovarian carcinoids are usually unilateral and present with grossly visible teratomatous components. In our case, the tumor was unilateral and appeared to develop from a mature cystic teratoma. Strumal carcinoids tend to be entirely solid, feature distinctive morphology and stain positively for thyroglobulin. Sex cord tumors lack epithelial differentiation and are immunoreactive for inhibin and calretinin. Poorly differentiated carcinomas tend to have prominent cellular atypia and increased mitotic rate and are always negative for neuroendocrine markers.

While certain subtypes of carcinoid tumors with aggressive behavior, such as mucinous or undifferentiated variants are able to metastasize, trabecular carcinoid has a favorable course.

Carcinoid tumors generate an extensive range of neurohumoral products, such as serotonin, histamine, tachykinin, bradykinin, kallikrein, corticotropin, P substance, motilin, and prostaglandins [27,28]. Increased and prolonged systemic exposure to these compounds may lead to carcinoid syndrome, characterized by flushing of the upper extremities and face, wheezing and diarrhea. In most cases of intestinal carcinoid, systemic exposure to these products does not occur before the tumor metastasizes. This is due to effective hepatic metabolism of the secreted products. Unlike intestinal carcinoids, primary ovarian carcinoids may trigger these symptoms before they metastasize, because the venous drainage of the ovary bypasses the portal system [29]. Interestingly, our patient did not show any clinical signs of carcinoid syndrome, probably due to the small size and incipient stage of the tumor. Another interesting fact is that, to our knowledge, trabecular carcinoid subtype was never reported to be associated with carcinoid syndrome. However, there are case reports in the scientific literature of patients initially misdiagnosed with rosacea or other pathologies, due to unawareness of carcinoid syndrome produced by a primary ovarian carcinoid [30].

A challenging aspect in treating patients with primary ovarian carcinoid tumors is the anesthetic management when the underlying pathology is unknown. It is well known that these patients may exhibit extreme hemodynamic lability and exaggerated physiologic responses to apparently mild stimuli. Therefore, careful dosage of anesthesia is advisable in order to avoid major hemodynamic surges, as is avoidance of catecholamines and sympathomimetics, because drugs like epinephrine, norepinephrine [31], dopamine and beta-agonists have been reported to unleash carcinoid crisis, which can be fatal. Moreover, the anesthesiologist should also avoid histamine-releasing drugs, due to the risk of bronchospasm [32-34].
Conclusion:

Primary ovarian carcinoid tumors are uncommon entities which are usually diagnosed only after the patient has been anesthetized and an intraoperative frozen section has been performed. The final diagnosis relies not only on careful histopathological evaluation, but also on immunohistochemical techniques, which are required in order to confirm neuroendocrine differentiation. Distinction between primary and metastatic carcinoid is difficult and relies on association with ovarian teratoma, unilaterality, absence of lymphovascular invasion as well as clinical information. The majority of patients are FIGO stage I and have good prognosis, chemotherapy and radiotherapy being unnecessary. However, due to the products it secretes, anesthesia and tumor manipulation during surgery can cause extreme hemodynamic instability, with a fatal risk for the patient. We strongly believe that increased awareness for all possible clinical manifestations of these tumors may improve the quality and thoroughness of preoperative evaluation, enabling the anesthesiologist to take precautions for a suspected ovarian carcinoid.

Conflict of interests:

The authors declare that they have no conflict of interests.

Compliance with ethical standards:

We undersign, certificate that the procedures and the experiments we have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000 (5), as well as the national law.

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