Neuroendocrine Tumors Arising in a Mature Ovarian Cystic Teratoma: A Case Report

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Abstract
We describe a case of low-grade neuroendocrine tumor originating and recognized in the context of a mature cystic ovarian teratoma in a 41-year-old woman who did not present any symptoms. The patient underwent operative laparoscopy for the removal of a dermoid cyst of the right ovary, highlighted on vaginal ultrasound examination. The subsequent follow-up is now 6 years and the woman is in good health. In addition to the histopathological aspects that have suggested the diagnostic orientation, the prognostic factors of these rare tumours are also discussed.

Introduction
Neuroendocrine tumors have a very heterogeneous clinical behaviour; according to a recent classification system [1-3], it is possible that highly aggressive neoplasms (poorly differentiated) as well as neoplasms with a slow evolutionary clinical course (well differentiated or moderately differentiated forms) are identified in the context of the same organ at the same time. Neuroendocrine tumors can occur sporadically or less frequently (<10% of cases) in the context of inherited genetic syndromes with an autosomal dominant character.

Neuroendocrine tumors are a heterogeneous group of distinct clinical-pathological entities that have a characteristic expression, namely a common potential for endocrine differentiation. In the ovary, the term "neuroendocrine" refers mainly to carcinoids, but it can also be applied to non-small cell neuroendocrine carcinomas [4,5] and small lung-type carcinomas. Ovarian neuroendocrine tumors can develop in their pure form or in association with other cancers, mostly along with teratomas [6-11]. They come from endocrine cells, whether of teratomatous or ovarian origin. Ovarian neuroendocrine tumors are probably epithelial neoplasms expressing a differentiating endocrine pattern. Non-small cell type neuroendocrine tumors exhibit cell monomorphism and are characterized by the presence of islets, cords, and trabeculae separated by thin septiments of stromal tissue (organoid growth pattern). The presence of neuroendocrine differentiation is confirmed by the positive expression of at least two specific markers (chromogranin A and synaptophysin). Initial overviews suggest that the manifestation of neuroendocrine differentiation is indicative of a worse prognosis. We describe a case of low-grade neuroendocrine tumor originating and recognized in the context of a mature cystic ovarian. Neuroendocrine tumors are sporadic neoplasms; the incidence is 5 cases per 100000 inhabitants-year [1]. They originate from the cells of the neural crest and can be found in all organs and systems of the human body. The gastro-entero-pancreatic system represents the most frequent site of onset of neoplasms originating from these kinds of cells (about 70%) [2].

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Case Presentation

Clinical History

A 41-year-old woman goes to her gynecologist for a periodic check-up without reporting any symptoms and even without irregular menstrual cycles. The abdomen was soft and non-tender; no pain was evoked, even on deep palpation. The pelvic physical examination with bimanual palpation, but mostly the ultrasound examination with a vaginal probe, showed a suggestive right ovarian neoplasm given the ultrasound characteristics for a dermoid cyst of about 6 cm in maximum diameter. The patient underwent right adnexectomy. The histological examination, as discussed below, revealed a low-grade neuroendocrine tumor in the context of a mature cystic teratoma. The post-operative course was regular and the patient was discharged on the third day from surgery. Subsequently, she was followed by oncologists with the help of periodic abdominal-pelvic CT scan too. The follow-up has been going on for 6 years now and the woman's condition is good.

Anatomopathology Findings

The material received for histological examination was fixed in buffered 4% formalin and embedded in paraffin. Sections in hematoxylin-eosin were prepared and further sections of the most representative inclusion were set up for different immunohistochemical stains. Immunostaining were performed for: Pancitokeratin AE1/AE3, Synaptophysin, Chromogranin A, CD56, CD99, Vimentin, Smooth muscle actin, Specific muscle actin, Calretinin, Inhibin and Ki67, CK 5/6, CK 7, CK 20, CDX2, SATB2, TTF-1 [12].

Macroscopic Examination: the cystic lesion received for histopathological confirmation appeared round, 6x4x1 cm, with smooth walls; when cut it presented a single chamber containing poltaceous material mixed with hair and odontogenic formations.

Microscopic Examination: the sections examined showed normal ovarian structures along with histological patterns of mature cystic teratoma. A circumscribed formation was found in the context of the teratoma, 1.1 cm in maximum diameter, consisting of monomorphic elements, with large eosinophilic and granular cytoplasm, gathered in trabeculae with adequate vascularization (Figure 1).

No areas of necrosis and the presence of rare mitosis were appreciated.

At the immunohistochemical investigation, the cellular elements described above showed: positivity for Pancitokeratin AE1/AE3, Synaptophysin (Figure 2), CD56, CD99, Vimentin and SATB2 (Figure 3); focal positivity for Chromogranin A (Figure 4) and CDX2; negativity for smooth muscle actin, specific muscle actin, calretinin and inhibin, TTF-1, CK 5/6, CK 7, CK 20.

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At the immunohistochemical investigation, the cellular elements described above showed: positivity for Pancitokeratin AE1/AE3, Synaptophysin (Figure 2), CD56, CD99, Vimentin and SATB2 (Figure 3); focal positivity for Chromogranin A

The mitotic proliferative index of the neoplastic elements, measured with the immunohistochemical staining of Ki67, was less than 3% (Figure 5).
The histological diagnosis was low grade neuroendocrine tumour (G1) arising from mature cystic teratoma.

Discussion

Diffuse neuroendocrine system tumors (DNETS) can arise in any area of the gynecological tract: vulva, vagina, cervix, endometrium and ovary. Generally speaking, these tumors are very seldom scored in the female reproductive tract, making up only 2% of utero-adnexal cancers [13-16]. These neoplasms have a variable biological potential and, due to the rarerness of these tumors, histological diagnoses are closely related to the pathologist's experience. The classification system currently in use for neuroendocrine tumors is the WHO 2017 one, based both on morphological criteria and on the tumor growth fraction. The morphological criteria, related to the pattern, are: trabecular, glandular, insular, undifferentiated and mixed.

Histological grading, mitotic count and tumor growth fraction divide neuroendocrine tumors into groups: G1 neuroendocrine tumors (NET), with mitosis <2x10HPF, Ki67 <2%; neuroendocrine tumors (NET) G2, with mitosis 2-20x10HPF, Ki67 3-20%; neuroendocrine carcinomas (NEC) G3, with mitosis> 20x10HPF, Ki67> 20%.

The criteria listed above are supported by the following specific immunohistochemical determinations for neuroendocrine cells: synaptophysin (38,000 kD membrane glycoprotein); chromogranin (soluble protein present in the matrix of secretory granules of neuroendocrine cells); CD56 (surface glycoprotein involved in the cell adhesion process); TTF-1 (nuclear protein of 38 kd expressed by neuroendocrine neoplasms of the lung and not by those of the gastrointestinal tract); CDX2 and SATB2 (expressed in tumors of the gastrointestinal tract); NSE (present in secretory granules of cells but also expressed by non-neuroendocrine cells); somatostatin receptors.

Primary neuroendocrine tumors of the ovary are rare and consist of a group of heterogeneous neoplasms that express similar immunohistochemical markers. Primary neuroendocrine tumors confined to the ovarian parenchyma often result from ovarian stroma and teratoma and are carcinoid tumors with a good prognosis. Neuroendocrine tumors arising from the superficial epithelium or dedifferentiated de novo from carcinoma often involve both the ovarian stroma and the superficial epithelium and clinically present as aggressive malignant tumors with poor prognosis. The histopathological diagnosis of ovarian neuroendocrine tumour is a fairly rare finding and therefore requires good experience on the part of the pathologist. Generally speaking, this is an occasional finding, and in the present case it was a low-grade tumour, identified in the context of a mature cystic teratoma of the ovary.

Patients with neuroendocrine ovarian cancer have significantly worse survival rate than most epithelial ovarian cancer subtypes’ one (including serous, endometrioid, mucinous and clear cell) and similar to ovarian carcinosarcoma survival rate. However, women with low-grade neuroendocrine ovarian carcinoma have longer average survival times than those with high-grade neuroendocrine ovarian cancer. This case described a low-grade tumour confined in the context of a mature ovarian teratoma. In this case, surgery was - we believe - decisive and, together with the other prognostic factors described above, it certainly contributes to a good prognosis.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

