

CASE REPORT

The dedifferentiation of neuroendocrine tumor metastases: myth or reality?

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Abstract

Dedifferentiation is a process that may be found in metastasis from the neuroendocrine tumors. We present the case of a female within the seventh decade of life incidentally diagnosed with a mature teratoma with element of cartilages, bronchia, mucinous glands, and a poorly differentiated neuroendocrine carcinoma (Ki67 of 30%). After six months of chemotherapy and another six months of disease free interval, a metastasis of the great omentum was removed. The dedifferentiation was diagnosed based on much higher Ki67 (of 70%). The loss of estrogen receptor of 40% from the initial site to 3% into metastasis indicates an exclusive neuroendocrine aggressive pattern. The ovarian carcinooid is a rare situation, and metastasis to the great omentum with dedifferentiation is even seldom.

Keywords: teratoma, neuroendocrine, carcinooid, dedifferentiation.

Introduction

The carcinooid elements in ovarian teratomas, regardless of insular, trabecular, or mucinous type, are exceptional [1–3]. Unlike the mature teratomas, the neuroendocrine elements are found in older women, especially in post-menopause [1].

The neuroendocrine tumor may progress on its own, including distant metastasis, without teratoma elements, and associating aggressive behavior as dedifferentiation.

Patient, Methods and Results

62-year-old female patient, with negative family history, had a previous medical history of arterial hypertension and osteoporosis since the last decade, both under adequate therapy. She is in menopause since the age of 49 years. One year later, she accused non-specific abdominal symptoms, and a right ovarian tumor was diagnosed. The Magnetic Resonance Imaging (MRI) scan pointed a 7/8/7.5 cm tumor with a cystic and solid aspect (Figure 1).

Total hysterectomy associated with bilateral salpingo-oophorectomy was performed. The pathological exam showed a mature ovarian teratoma with elements of cartilages, bronchia, mucinous glands and a neuroendocrine component of poorly differentiated neuroendocrine carcinoma (Figure 2A). The immunohistochemistry of the tumor showed: neuroendocrine elements indicated by positive CROMO (Figure 2B), SYNAPTO, positive reaction for estrogen receptor of 35–40% (Figure 2C), positive WT1, Vim, TTF1, Cytokeratin (CK)

20, pointing different tissue types. Negative reaction was for progesterone receptor, CK7, and Inhibin. The high aggressive profile was indicated by Ki67 of 25–30% (Figure 2D).

After surgery, the serum tumor markers CA125 and carcinoembryonic antigen were normal, as well as neuroendocrine markers serum Serotonin and urinary 5-Hydroxyindolacetic acid (5-HIAA), except for serum Chromogranin A of 263 mg/dL (normal levels between 19.4 and 98.1 mg/dL) and serum neuron-specific Enolase of 19 ng/mL (normal levels <17 ng/mL). The whole-body positron emission tomography – computed tomography (PET-CT) was negative, except for metabolic active mediastinal lymph nodes. After six months of chemotherapy with Cisplatin and Etoposide, the neuroendocrine markers normalized. After other six months of disease-free interval, a tumor at the level of great omentum was newly found. The computed tomography (CT) scan indicated a tumor of 4.2/6/6.6 cm that was removed (Figure 3). Carcinomatous metastases were confirmed and the immunohistochemistry revealed positive reaction for estrogen receptor but only of 1–3%, and the neuroendocrine component was suggested by CROMO and SYNAPTO positive. Higher Ki67, up to 65–70%, indicates a more aggressive profile. The progesterone receptor was negative, as well as CK7.

The Vimentin (Vim) expression became negative, revealing that the metastases were correlated only with the neuroendocrine part of the initial teratoma (Figure 4, A–D). The increased proliferation index indicates a dedifferentiation process in neuroendocrine metastasis.

The neuroendocrine biomarkers indicated high serum Chromogranin A of 294 ng/mL (normal ranges between 27 and 94 ng/mL), that increased up to 554 ng/mL within two months, and a mildly elevated level of 5-HIAA of 9.3 mg/24 h (normal ranges between 2 and

9 mg/24 h). A typical carcinoid syndrome was not present. Chemotherapy with Paclitaxel and Carboplatin was initiated, associated with monthly Octreotidum LAR. Close follow-up is necessary. Poor prognosis is considered.

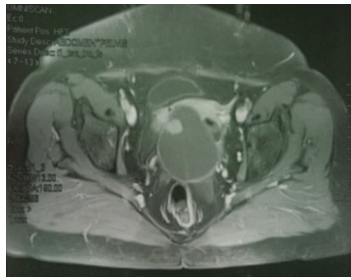
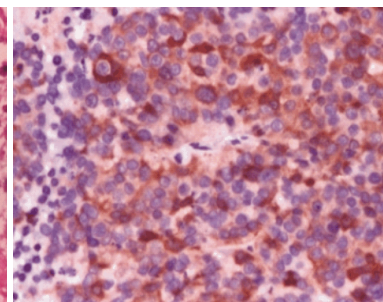
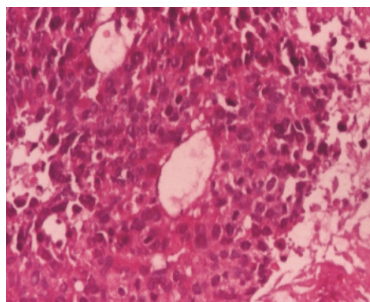
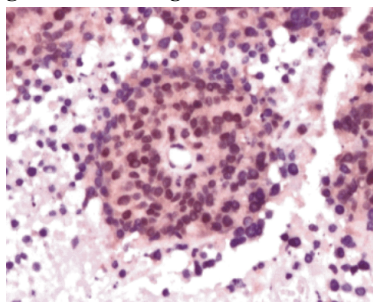


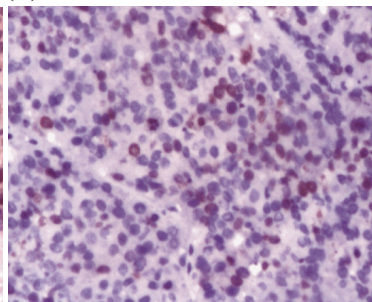
Figure 1 – MRI: right ovarian tumor. (A)



(B)

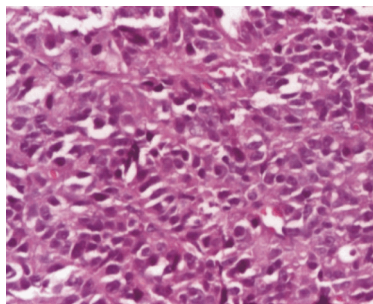


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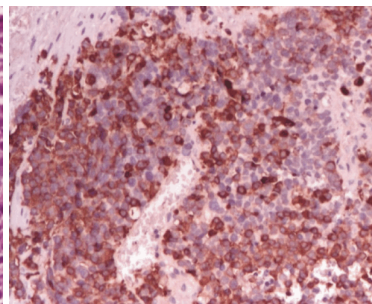


(D)

Figure 2 – Ovarian teratoma: (A) Histological report, HE stain, ob. 20x; (B) IHC: CROMO+ve, ob. 20x; (C) IHC: Estrogen Receptor+ve, ob. 20x; (D) IHC: Ki67 of 30%, ob. 20x.



(A)

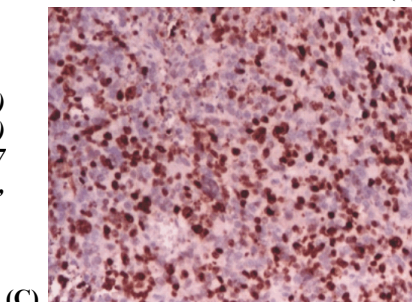


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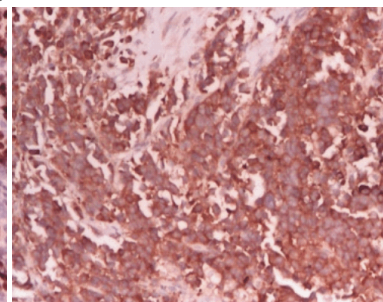


Figure 3 – CT: metastasis of the great omentum.

Figure 4 – Carcinomatous metastasis: (A) Pathologic report, HE stain, ob. 10x; (B) IHC: CROMO+ve, ob. 10x; (C) IHC: Ki67 of 70%, ob. 10x; (D) IHC: SYNAPTO+ve, ob. 10x.



(C)



(D)

Discussion

The ovarian teratomas vary from frequent types as mature (of ectodermal origin as skin, brain; mesodermal origin as muscle, fat; endodermal origin as mucinous epithelium) to less frequent groups as immature teratomas (with pluripotential origin of either mentioned before), and extremely rare tumors as monodermal teratomas, for example struma ovarii, or teratomas with neuroendocrine or neural component [4]. Usually, the immature tumors do not originate from mature teratomas, thus the malignant type is a malignant tumor from very beginning, but it may arise in a mature teratoma. This finding is reported in 1–2% of the mature teratomas in some studies, and it is typically seen in patients much older than those with completely benign tumors are (in the 6th or 7th

decade of life) [4, 5]. Also, as found in the present case, the median age at diagnosis is higher if the teratoma associates ovarian carcinoid [1]. The ovarian carcinoid usually is associated with mature rather than immature teratomas, as seen here, and it has a solid aspect [1–3]. It typically embraces a relatively benign clinical course, but the potential for malignancy and rapid evolution with poor prognosis is present in rare situations [1, 3]. This aggressive exceptional phenotype was found in the reported case. Two similar cases published in 2009, reported death within one year [6]. The carcinoid syndrome is not usual in ovarian carcinoid, and we did not find it either. The site of the metastasis in our case at the great omentum level is unusual. Extremely atypical metastases in neuroendocrine tumors were reported as orbital or thyroid metastasis [7, 8].

A process of retroconversion may take place under chemotherapy: the reduction of the malignant component of the teratoma and a consecutive more stable behavior having a mature appearance was registered in association with the possibility of long-term remission of the retro-converted tumor [9, 10]. Another almost bizarre behavior, that might take place regardless chemotherapy, is considered the dedifferentiation process, meaning the increased aggressive profile in metastasis, especially related to the neuroendocrine tumors or sarcomas. As seen in our case, the carcinoid component is the only one that suffered this process, even the teratoma included different other tissues.

Various mechanisms are underlying dedifferentiation. For example, IL-6 induces cell proliferation and down-regulates the expression of neuron-specific enolase, and it may stimulate a higher tyrosine kinase phosphorylation of STAT3 signaling pathway in non-small cell lung carcinomas that exhibit neuroendocrine properties [1]. Aberrant or lack of E-cadherin expression or catenin complex is also related with dedifferentiation, based on different studies, for example in liver metastasis of neuroendocrine tumors of gastrointestinal type or not [12, 13]. Hypoxia may activate a dedifferentiated phenotype, based on observations in ductal breast carcinoma or neuroblastoma [14]. High bombesin/gastrin releasing peptide receptor mRNA levels were correlated in a study with dedifferentiation of the neoplasia and lymph vessels invasion, but not with proliferation [15]. A positive correlation was found between Chromogranin A and tumor dedifferentiation in prostatic cancer [16].

✉ Conclusions

The mature teratoma with neuroendocrine elements is a rare event and this may have a bizarre behavior with dedifferentiation in distant metastases only for the carcinoid component. This is usually an event seen in older women, and the prognosis is poor, regardless chemotherapy.

Various mechanisms underline dedifferentiation as aberrant cadherin/catenin complex expression, IL-6 effects on neuron-specific enolase, chromogranin production.

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