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Case study

Ovarian neuroendocrine carcinoma of metastatic origin: clues for diagnosis☆

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Summary Neuroendocrine tumors of the ovary are rare and of uncertain histogenesis. They may be primary or metastatic. Pathogenesis of ovarian carcinomas remains unknown. We report the case of an ovarian large cell carcinoma expressing all neuroendocrine markers (CD56, chromogranin A, synaptophysin) that presented as a primary tumor and coexisted with a typical endometrial serous carcinoma also expressing one neuroendocrine marker (CD56). The 2 tumors had identical molecular mutational profiles as examined by next-generation sequencing. We propose that the ovarian neuroendocrine tumor was metastatic from an endometrial serous carcinoma with limited neuroendocrine differentiation.

1. Introduction

Neuroendocrine tumors of the ovary are very rare. They include *carcinoids,* which often originate from teratomas, mucinous, or Brenner tumors; small cell carcinomas of the pulmonary type, which arise in older women; and large cell neuroendocrine carcinomas, for which data are largely lacking [1]. Small cell carcinoma of the hypercalcemic type, a rare, highly aggressive malignancy in young women associated with an SMARCB4 mutation, has recently been reinterpreted as a different tumor, similar to rhabdoid tumors of other sites [2]. Primary small and large cell neuroendocrine carcinomas of the ovary are very rare, with few cases described in the literature. Excluding a pulmonary or other primary origin is necessary and usually based on clinical grounds, as morphology and immunophenotype are actually similar. Regarding their histogenesis, the cell of origin for these carcinomas is unknown; they may arise from rare resident neuroendocrine cells or other cells that can differentiate into neuroendocrine cells, as in the case of a teratoma, or may originate either from other epithelial tumors through a form of dedifferentiation/progression of a certain carcinoma or from the same single-cell precursor. The few cases of neuroendocrine carcinomas described in the literature are usually found within an otherwise typical mucinous borderline tumor or mucinous/endometrioid carcinoma of the ovary and very rarely (2 cases) as a component of an ovarian high-grade serous carcinoma.

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We present the case of an ovarian neuroendocrine carcinoma arising as a metastasis of a high-grade serous carcinoma of the uterus, a diagnosis made possible only after examining the endometrial component and comparing their molecular profiles.

2. Materials and methods

2.1. Case presentation

An 88-year-old woman presented with pain in the right iliac fossa. Clinical examination revealed ascites and edema of the right leg. Computed tomographic scan demonstrated a pelvic mass replacing the right adnexa. The uterus showed thickening of the endometrium and suspicious myometrial lesions. A coelioscopy was performed. There was less peritoneal carcinomatosis and fewer adhesions than expected for an advanced ovarian cancer. Hysterectomy with bilateral adnexectomy was performed. After surgery, chemotherapy was administered (6 cycles of carboplatin/taxol). Follow-up showed no disease 6 months later.

2.2. Histopathologic examination

Surgical specimen showed a unilateral right ovarian tumor, 10 cm at largest diameter, with solid and necrotic areas. The uterus showed a thickened endometrial surface, as well as several lesions in the uterine serosa. The ovarian tumor was composed of a population of medium-size to large cells intermixed with small cells (Fig. 1). Nuclei showed coarse chromatin with occasional visible nucleoli. Mitotic activity was very high. Large areas of necrosis were present. Typical glandular or papillary areas were not found, but perivascular pseudorosettes were occasionally seen. Immunohistochemical techniques demonstrated strong and diffuse expression of all neuroendocrine markers (CD56, chromogranin A, synaptophysin). Keratin expression was granular cytoplasmic and detected in most cells by KL1 antibody and in a few cells with AE1/AE3 antibody. WT1 was completely negative. P53 was strongly positive. All other markers studied (estrogen receptor, progesterone receptor, cytokeratin 7, cytokeratin 20, glypican, D2-40, CD117, α-fetoprotein, CD30) were negative. The contralateral ovary was unremarkable. The uterus contained a tumor that was morphologically different from the ovarian one. It showed a prominent papillary architecture and cytologic features typical of endometrial serous carcinoma. The tumor clearly originated from the endometrium and extensively invaded the myometrial wall. There were also several serosal tumor implants. The microscopic appearance was typical of a primary endometrial serous carcinoma. The uterine tumor showed positivity for p53 (mutation pattern) and positivity for CD56, but negativity for chromogranin A or synaptophysin (Fig. 2).

The presence of the 2 tumors in 2 different locations, right ovary and uterus, could be explained by 1 of 2 hypotheses: (1)

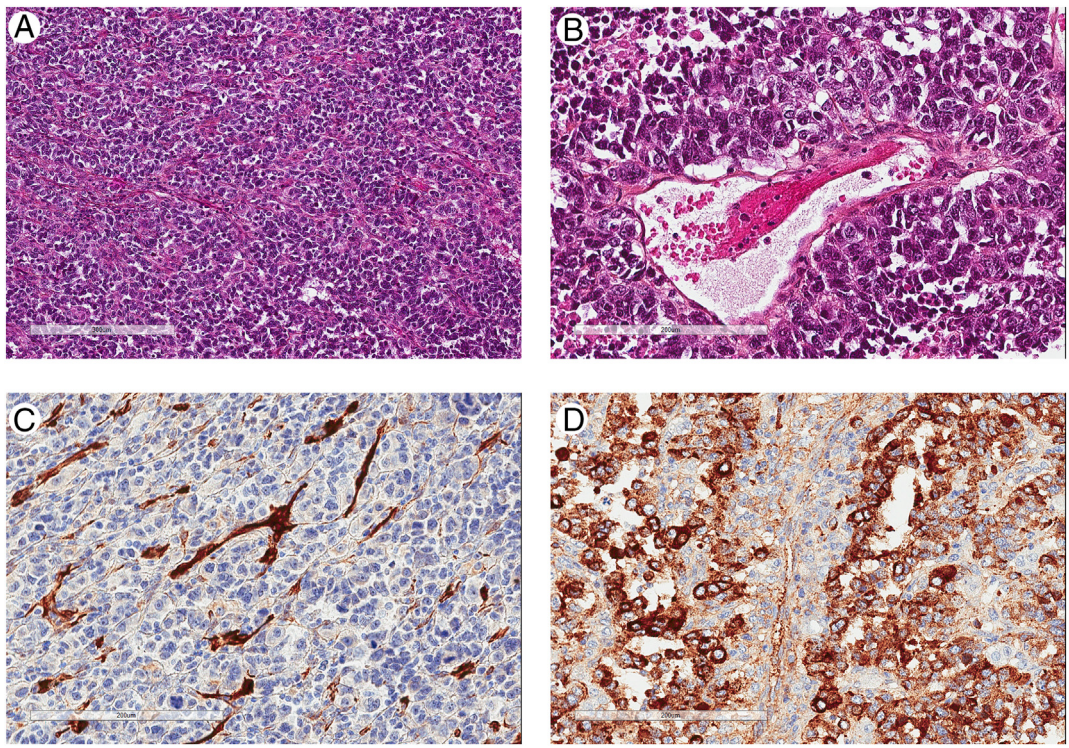

Fig. 1 Ovarian tumor. Tumor cells are small to large and have coarse chromatin and often visible nucleoli (A, original magnifications ×100; B, ×200). They are diffusely developed (A) or form perivascular pseudorosettes (B). They do not express WT1 (C, ×200; vessels serve as internal positive control). Chromogranin A expression is strong (D, ×200).

they could represent 2 different primary tumors, or (2) one tumor was metastatic from the other.

Based on microscopic analysis, it was clear that the uterine serous carcinoma was a primary tumor. It was not clear, however, if the ovarian tumor was a second primary or was metastatic from the endometrial carcinoma, but exhibiting a prominent neuroendocrine differentiation.

2.3. Molecular analysis

To further investigate this hypothesis, we performed a molecular analysis; briefly, DNA was extracted from formalin-fixed, paraffin-embedded tissue from both ovarian and uterine tumors. DNA was obtained using the Qiamp FFPE Kit (Qiagen, Courtaboeuf, France) according to the manufacturer's instructions. A total of 10 ng of DNA was used to prepare the sequencing libraries with the Ion AmpliSeq colon and lung CE-IVD Panel (Thermo Fisher, Waltham, MA). In total, 192 amplicons were generated and 22 genes were analyzed (AKT1 [NM_05163), ALK [NM_004304], BRAF [NM_004333], CTNNB1 [NM_001904], DDR2 [NM_001014796], EGFR [NM_005228], ERBB2 [NM_004448], ERBB4 [NM_005235], FBXW7 [NM_033632], FGFR1 [NM_023110], FGFR2 [NM_022970], FGFR3 [NM_000142], KRAS [NM_033360], MAP2K1 [NM_002755], MET [NM_001127500], NOTCH1 [NM_017617], NRAS [NM_002524], PIK3CA [NM_006218], PTEN [NM_000314], SMAD4 [NM_005359], STK11 [NM_000455], TP53 [NM_000546]). Sequencing was carried out using Ion 316 chips on the Ion Personal Genome Machine System (PGM; Thermo Fisher Scientific). For data analysis, Torrent Suite (Thermo Fisher, USA, 5.2), Ion Reporter (Thermo Fisher, USA. 5.10), and Alamut software (Interactive Biosoftware, France, 1.9) were used. The 2 tumors had the following identical molecular abnormalities: *PIK3CA* exon 10 c.1635G > C, *FBXW7* exon 8 c.1200C > A, and *TP53* splicing mutation in exon 5. No other abnormalities were detected. The identical molecular mutational profiles confirmed the common origin of the 2 tumors. Interestingly, coexistence of *PIK3CA*, *FBXW7*, and *TP53* mutations is not infrequently seen in serous carcinoma of the endometrium.

In conclusion, molecular results confirmed that the ovarian tumor was a metastasis from the endometrial serous carcinoma but exhibited a prominent neuroendocrine differentiation, only detected in the primary tumor by CD56 expression.

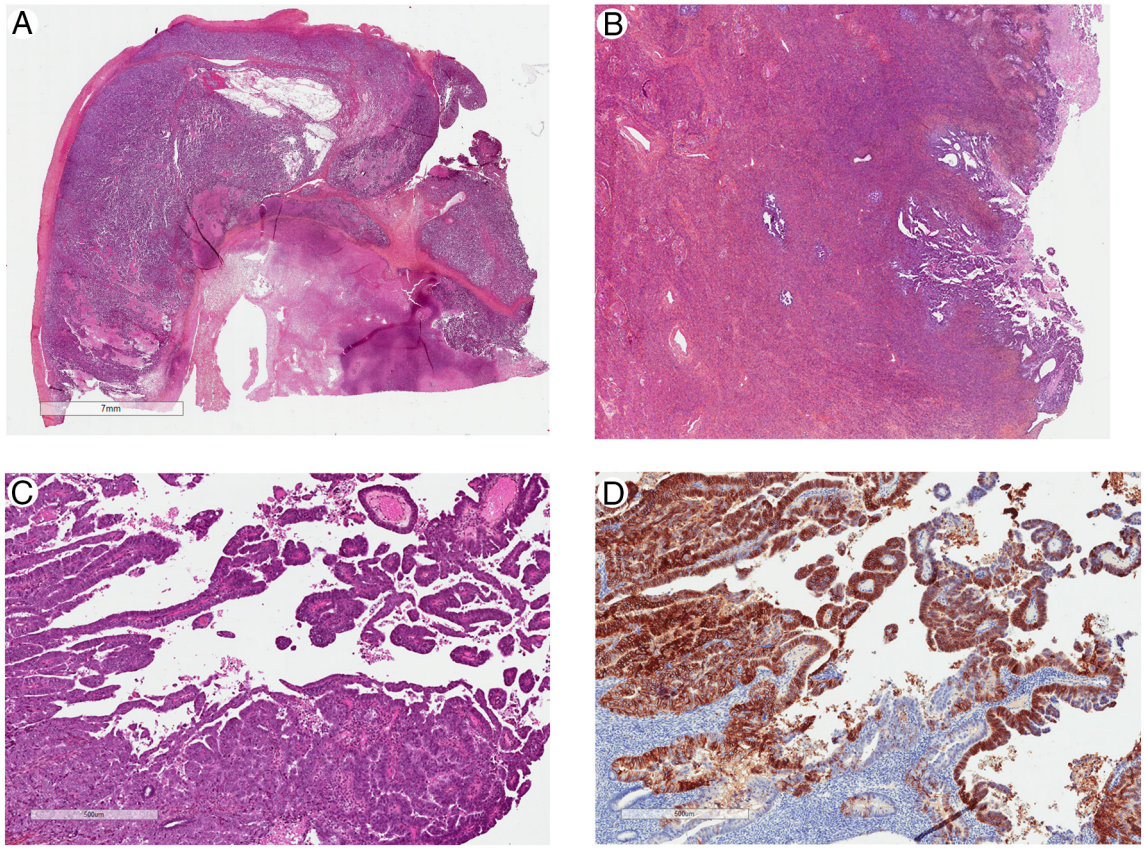

Fig. 2 Even at this magnification, the difference in morphology between the ovarian (A, original magnification ×3) and uterine lesions (B, ×3) is obvious. The former shows a diffuse pattern with large areas of necrosis, whereas the latter has a papillary/glandular architecture of a tumor invading endometrium and myometrium. Prominent papillary architecture (C, ×50) of the endometrial tumor, which also shows strong CD56 expression (D, ×50).

3. Discussion

Ovarian neuroendocrine carcinomas are rare and of uncertain histogenesis. Although sometimes primary, they can also be metastatic. When they are primary, they usually occur in combination with other histologic types. A second component was seen in 13 of 16 cases in 2 main series of large cell neuroendocrine carcinomas of the ovary [3,4]. The case presented in this report shows an endometrial serous carcinoma with limited neuroendocrine differentiation and metastatic spread to the ovary, exhibiting a pure neuroendocrine phenotype, mimicking a primary neuroendocrine carcinoma of the ovary. Despite extensive sampling, typical areas of serous carcinoma were not found in the ovarian mass.

There are examples of neuroendocrine carcinomas arising from ovarian high-grade serous carcinomas. In a previously reported case, the neuroendocrine component was seen in a peritoneal recurrence of an ovarian high-grade serous carcinoma, which led to a retrospective reevaluation of the primary tumor that revealed a tumor cell component with expression of neuroendocrine markers but absence of morphologic features of neuroendocrine differentiation [5]. In another reported case, the 2 components (serous and neuroendocrine) were both morphologically identified in the same tumor [6].

Neuroendocrine differentiation may also occur in endometrial serous carcinoma [7,8]. Our case is particularly unusual because the neuroendocrine component was particularly dominant in the metastatic tumor. Actually, in our case, a diagnosis could not have been reached in the absence of the uterine tumor, which was a typical serous carcinoma. The classical criteria for diagnosing ovarian metastasis from an endometrial tumor are small ovaries bilaterally involved by a multinodular pattern, large endometrial tumor with deep myometrial invasion and vascular invasion or tubal lumen involvement, and if the tumor is of the endometrioid type, atypical endometrial hyperplasia, and absent ovarian endometriosis [9]. However, molecular analysis of simultaneous endometrial and ovarian cancers has shown that the vast majority have a common ancestral clone and are therefore ovarian metastases of endometrial tumors, with the exception of Lynch syndrome patients, where independent primary tumors can be seen [10]. In the current case, there were no classical pathologic criteria to support the metastatic origin, as the ovarian tumor was unilateral, large, and of a different morphologic type. In this case, only the common molecular profile could delineate their common origin, whereas the better differentiated component, the endometrial serous tumor, should be the primary tumor.

Neuroendocrine differentiation in the form of chromogranin or synaptophysin expression is found in 6.7% and 20.7%, respectively, of ovarian high-grade serous carcinoma without any morphologic features of neuroendocrine differentiation [5], as what happens with many carcinomas. Pulmonary carcinomas can, for example, show neuroendocrine marker expression without morphologic evidence of such a differentiation and with uncertain importance [11]. Furthermore, the transformation of a pulmonary adenocarcinoma into small cell carcinoma after targeted therapy has been well described, and it is considered a resistance mechanism [12]. We propose that a similar progression/transformation progress can account for some of the ovarian neuroendocrine carcinomas, even in cases where the original component is no longer recognizable. This highlights that caution should be used when interpreting immunostaining results of poorly differentiated carcinomas because neuroendocrine marker expression does not necessarily indicate that the tumor has a neuroendocrine cell of origin; rather, it can represent a form of tumor progression, as shown in the current case.

To conclude, we present a very rare case of ovarian large cell neuroendocrine carcinoma arising as a metastasis of a uterine serous carcinoma, an origin that was recognized only after studying the endometrial tumor. Molecular analysis confirmed the clonal nature of both the ovarian and endometrial tumors. Because these primary neuroendocrine carcinomas are unusual in the ovaries, it is recommended to rule out a metastatic origin, particularly when the tumor does not have a non-neuroendocrine component, regardless of the fact that the clinical presentation suggests a primary tumor.

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