



Case report

Aggressive neuroendocrine tumor of the ovary with multiple metastases treated with everolimus: A case report

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1. Background

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms, ranging from aggressive small cell cancers to the relatively slow-growing, well-differentiated carcinoid tumors. It is uncommon for an NET to occur in the gynecologic tract; they are usually seen in the lungs or the gastrointestinal tract. Ovarian NETs account for 0.5% of all carcinoid tumors (Modlin et al., 2003) and 0.1% of all ovarian cancers (Talerman, 1997). One-third of patients with ovarian NETs show clinical neuroendocrine symptoms such as facial flushing, diarrhea, and abdominal cramping (Robboy et al., 1975). The differential diagnosis of NET in the ovary includes germ cell tumors, sex-cord and granulosa cell cancers, other gynecologic cancers, and metastatic neoplasms (Reed et al., 2014). The accurate classification and grading of NETs is generally difficult because the characteristics of the tumor differ depending on the tissue subtype and the site of origin. Ovarian NETs are managed using surgical resection, ideally with negative margins. The Society of Gynecologic Oncology (Gardner et al., 2011) and the Gynecologic Cancer InterGroup (Reed et al., 2014) have published documents covering the diagnosis and management of gynecologic NETs. Most primary ovarian carcinoids are International Federation of Gynecology and Obstetrics (FIGO) stage I, often very slow growing and infrequently associated with metastatic disease.

There are only a few case reports describing primary ovarian

carcinoid tumors with aggressive histology such as a loss of the neuroendocrine growth pattern, frequent mitotic figures, and foci of coagulative tumor necrosis (Kim et al., 2015) (Vora et al., 2016). A new targeting agent that affects the mammalian target of rapamycin (mTOR) pathway has been used to treat advanced NETs (Chan and Kulke, 2014) (Cives and Strosberg, 2017). We describe a patient with an aggressive primary ovarian NET, successfully treated with everolimus (an mTOR inhibitor). We describe the histomorphology and clinical behavior of this rare disease.

2. Case presentation

2.1. Presentation and course

A 54-year-old woman, gravida 2 para 2, with lower abdominal distension but no other gastrointestinal symptoms consulted a nearby gynecologist's office. She was referred to our hospital when ultrasonography revealed an ovarian mass. Physical examination demonstrated a solid tumor, 20 cm in diameter, with a large amount of ascites in the pelvis. Magnetic resonance imaging of the pelvis showed a solid ovarian mass with a low signal on T2-weighted imaging and significant enhancement with gadolinium contrast (Fig. 1A). There was massive ascites present in the pelvis, and T1-weighted imaging showed a mixed signal consistent with bleeding inside the tumor and significant

Abbreviations: NETs, neuroendocrine tumors; FIGO, International Federation of Gynecology and Obstetrics; mTOR, mammalian target of rapamycin; MRI, magnetic resonance imaging; CT, computed tomography; CA-125, carbohydrate antigen 125; BEP, bleomycin, etoposide, and cisplatin; CD56, cluster of differentiation 56; EMA, epithelial membrane antigen; CDX2, caudal-type homeobox transcription factor 2

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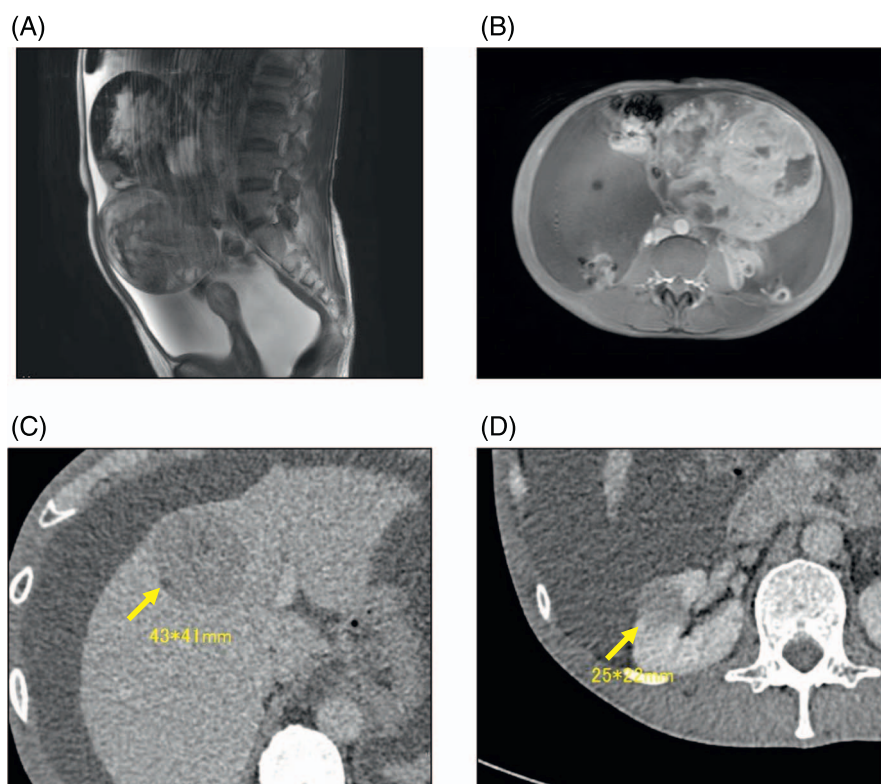


Fig. 1. Imaging studies.

(A) T2-weighted magnetic resonance imaging (MRI), sagittal section. (B) T1-weighted, enhanced MRI, horizontal section. (C) Computed tomography (CT) showing metastasis to the liver; (D) CT showing metastasis to the right kidney.

enhancement with gadolinium contrast (Fig. 1B). Computed tomography (CT) revealed multiple hepatic masses with a mottled contrast effect (Fig. 1C) and a marginally irregular tumor in the right kidney (Fig. 1D). There was also a shadow on the dorsal side of the right adrenal gland and swelling in the peripheral and para-aortic and left superior supraclavicular lymph nodes. These findings were suspicious for the presence of multiple metastases in the liver, right kidney, right adrenal gland, and multiple lymph nodes.

Testing for serum tumor markers revealed that the carbohydrate antigen (CA)-125 level was increased to 348 U/mL. A slight increase in hormone levels was observed: the testosterone level was 90 ng/dL and estradiol was 24.1 pg/mL. All other gynecologic tumor markers were within normal limits. We decided to remove the pelvic tumor to make a histological diagnosis and relieve the worsening compression symptoms caused by the tumor and ascites.

On laparotomy, we observed a right ovarian tumor along with 4700 mL of ascitic fluid. The surface of the tumor was smooth (Fig. 2A) and there was no adhesion. The tumor was mainly solid, with some cystic components that were bleeding (Fig. 2B). There was no macroscopic evidence of dissemination in the peritoneal cavity. We performed total hysterectomy with bilateral salpingo-oophorectomy and partial resection of the omentum. After surgery was completed, upper and lower gastrointestinal endoscopy and an ultrasound-guided liver biopsy were performed. No neoplastic lesions were detected. The initial histopathological diagnosis was a Sertoli-Leydig cell tumor of the ovary. We administered chemotherapy consisting of bleomycin, etoposide, and cisplatin (BEP). After 3 courses of BEP, repeat CT examination revealed that the liver metastasis was increasing in size; suspected bone metastases were also seen. We performed an ultrasound-guided liver biopsy that revealed small tumor cells exhibiting a cord-like sequence, similar to the ovarian tumor. The ovarian mass was then pathologically re-examined with the addition of immunohistochemical staining. The final diagnosis was an atypical carcinoid of the ovary, according to the pulmonary carcinoid criteria, and a NET (grade G2) according to the gastrointestinal neuroendocrine tumor criteria. We administered everolimus according to the chemotherapy for an advanced pancreatic

NETs. The patient's disease has been stable for more than 7 months.

2.2. Histopathological findings

The main part of the ovarian tumor specimen consisted of ribbon, cord-like tissue and formed a solid alveolar pattern of atypical cells, with hematoxylin and eosin staining showing abundant nuclear and eosinophilic cytoplasm (Fig. 2C). Tumor cells with fine granular cytoplasm proliferated in a cord shape between the abundant vascular networks that were composed of sinusoidal vessels (Fig. 2D). The differential diagnosis at this point included a Sertoli-Leydig cell tumor, endometrioid adenocarcinoma, and NET. Immunohistochemical staining was positive for synaptophysin (Fig. 3A), chromogranin A (Fig. 3B), cluster of differentiation (CD) 56, cytokeratin AE1/AE3, and epithelial membrane antigen (EMA). Staining for inhibin α (Fig. 3C) and WT-1 was negative. We suspected that the proliferative capacity of this mass was higher than that of a usual carcinoid tumor because nuclear mitosis was recognized in 3 of 10 high power fields and the Ki-67 index was high at 17% (Fig. 3D).

3. Discussion

When NETs occur in the ovary, they may present as small cell carcinomas, large cell variants, and well-differentiated carcinoid tumors (Reed et al., 2014). Primary ovarian carcinoid is subdivided into 4 categories: insular, trabecular, mucinous, and stromal (Vora et al., 2016). Since carcinoid tumor often shows a cord or tubular structure, differential diagnosis with Sertoli-Leydig tumor may be a problem in only morphological evaluation. Immunohistochemistry can be useful in the diagnosis, as synaptophysin, chromogranin, and CD56 are markers of ovarian carcinoid tumors (Reed et al., 2014). Carcinoid tumors are usually negative for EMA, estrogen receptors, progesterone receptors, and sex-cord stromal markers such as inhibin and calretinin (Reed et al., 2014). The use of immunohistochemistry is recommended if frequently observed finding in NETs, such as interposed abundant blood vessels between the cord like sequences, was seen in the tumor. It is also

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