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(CASE REPORT)

Management of a rare and aggressive primary ovarian large cell neuroendocrine carcinoma with multiple metastases using sunitinib: A case report

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Abstract

Ovarian neuroendocrine tumors (oNETs) are a rare and aggressive subtype of epithelial ovarian cancer with poor long-term survival. They rarely occur at all sites in the female genital system accounting for about 2% of all gynecologic malignancies.

We report the case of a 70-year-old multiporous woman who presented with a 13-cm abdominopelvic mass with peritoneal, hepatic, and bone metastasis. A lump in her left breast was also found during a physical examination. She underwent an exploratory laparotomy whereby the pelvic mass was resected and a trucut biopsy of the breast lesion. A stage IVb non-small cell neuroendocrine carcinoma diagnosis was rendered after pathological and immunohistochemistry (IHC) examination. She was subsequently treated with sunitinib and hormonotherapy for her stage I breast ductal carcinoma. She died within 6 months of her adjuvant chemotherapy.

This is a report of a rare and aggressive primary ovarian large cell neuroendocrine carcinoma. In the majority of presentations, the tumor is metastatic with a poor prognosis.

Keywords: Ovarian cancer; Neuroendocrine; Metastasis; surgery; Sunitinib; Case report

1. Introduction

Neuroendocrine tumors (NETs) are heterogeneous group of tumors, mostly seen in the lungs or gastrointestinal (GI) tract, accounting for 0.5% of all carcinoids and 0.1% of all ovarian cancers[1,2]. They rarely occur in the gynecological tract. The cervix is the most common site of high-grade NET in the female reproductive system. When NETs occur in the ovary, they can appear as small-cell carcinomas, large cell variants, and clinically benign, well-differentiated carcinoid tumors that arises in dermoid cysts[3].

The main differential diagnosis includes germ cell tumors, sex-cord and granulosa cell cancers, other gynecologic cancers, and metastatic neoplasms[3,4].

Since oNETs are rare, there are no clear recommendations regarding the treatment. The most current National Comprehensive Cancer Network guidelines for neuroendocrine tumor (Version 2.2021) do not include ovarian carcinoids or any oNETs[5]. A report on a new agent such as sunitinib targeting the mammalian target of rapamycin (mTOR) pathway has been used to treat advanced NETs and is recommended for patients with progressive tumors that are locoregional, unresectable and/or metastatic [5,6]. However, surgery still remains the cornerstone of management and should be considered in all cases especially in for localized disease [7,8].

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We report the case of and aggressive oNET in a 70year old woman with multple metastasis diagnosed with concomitant breast cancer discussing the clinicopathological study, management modalities.

2. Case report

A 70 year old female patient, gravida 6 para 6, with history of mild hypertension under calcium channel blockers, was admitted in our departement for worsening chronic pelvic pain (for over 5 months). She complained of spotting with metrorrhagia, bone and joint pains, vomiting, diarrhea, non-productive cough and dyspnea.

Physical examination revealed a distended abdomen with large amounts of ascitic fluid. In addition, we noticed a 2cm lump in the left breast. A recent abdomino-pelvic ultrasound test revealed a solid cystic right latero-uterine mass occupying the entire abdomino-pelvic cavity.

Computed tomography (CT) scan objectified the large right pelvic mass, measuring 133x105mm axially and 144mm in height with multiple hepatic, bone metastasis and peritoneal carcinosis (Fig. 1 and 2) with a diffused skin thickening of the left breast englobing a 16mm lump in the supra areolar quadrant stage 4 according to American Classification of Radiology (ACR) classification system.

Her cancer antigen 125 (Ca-125) level was relatively high at 348.90 U/ml. All other gynecologic tumor markers were within normal limits.

We decided to remove the pelvic tumor to establish a histological diagnosis and to alleviate the worsening compression symptoms caused by the tumor and ascites. So an exploratory laparotomy was carried out where a 5000mL of ascitic fluid was drained. During the procedure, we found an enormous pelvic mass mesuring about 13cm with smooth surface, which was in contact with the uterus, intestinal bowel and parietal pelvic wall. A right salpingo-oophorectomy resecting the tumor was performed (Fig. 3).

General observation of the samples displayed a right ovarian tumor measuring 10.5x10x7cm, a fallopian tube measuring 7x1cm. It's cut section showed a solid-cystic appearance, with the discharge of a haemorrhagic fluid with vegetations within the cyst. The initial histopathological diagnosis was an ovarian tumour with proliferation of nests, cords and trabeculae, surrounded by a fine vascular stroma. The tumour cells are rounded, monotonous, with abundant eosinophilic cytoplasm, and nuclei of nearly inverted polarity, with coarse chromatin with clear cyto-nuclear atypia. The number of mitoses was estimated at 9mitoses/10 fields, at high magnification, this proliferation remains limited to the ovary without tumour necrosis. Hematoxylin and eosin staining showing abundant nuclear and eosinophilic cytoplasm (Fig. 4). Immunohistochemistry (IHC) was performed in order to confirm the ultimate histological diagnosis. The tumour cells express chromogranin, cluster of differentiation (CD) 56, CDX2, and did not express CK7 or CK20. The proliferation index assessed by Ki67 was estimated at 4%.

A definite diagnosis of a well-differentiated ovarian large cell neuroendocrine carcinoma (grade 2 according to the gastrointestinal neuroendocrine tumor criteria) (International Federation of Gynecology and Obstetrics stage IVb; American Joint Committee on Cancer staging T3cN0M1) was made based on the clinical presentation, histopathological features, and IHC profiles.

A simultaneous biopsy of the lump in the left breast was performed and the pathological results were in favor of a grade 1 infiltrating ductal carcinoma (estrogen receptors, progesterone receptors, and herceptine 2 receptor were positive, with low Ki67 of 8%).

We administered chemotherapy regiment consisting of sunitinib 37,5mg/day en continue (two weeks on and 1 week off) with hormonotherapy for the breast cancer. The evolution was marked by slight clinical improvement with repeat CT examination after two months of treatment revealing a stability in all aspect of the disease. Unfortunately, the patient died six months into her adjuvant chemotherapy regiment.

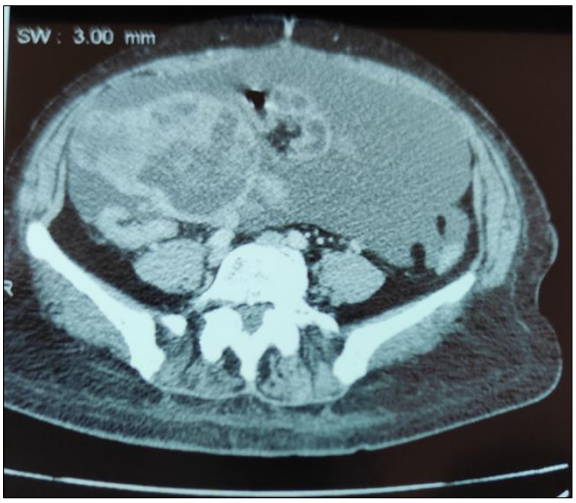

Figure 1 CT scan showing the large abdominopelvic mass

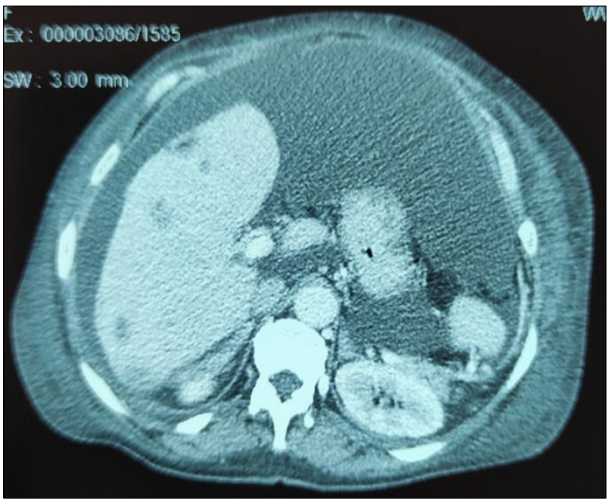

Figure 2 CT scan showing ascitic fluid with multiple metastatic lesion in the liver.

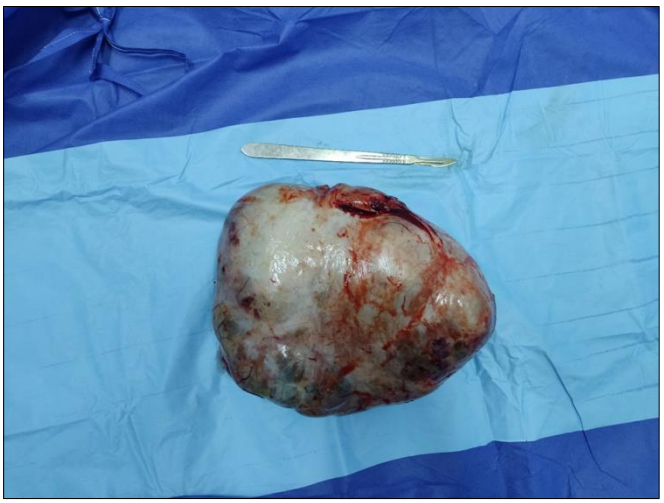

Figure 3 Surgical specimen of right salpingo-oophorectomy

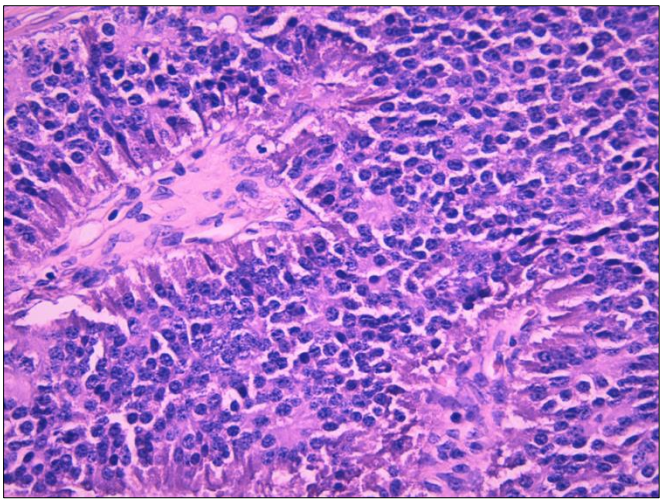

Figure 4a Microscopic analysis of the specimen showing rounded and monotonous tumor cells, with abundant eosinophilic cytoplasm, and with coarse chromatin without clear cytonuclear atypia. (HE x400 magnification).

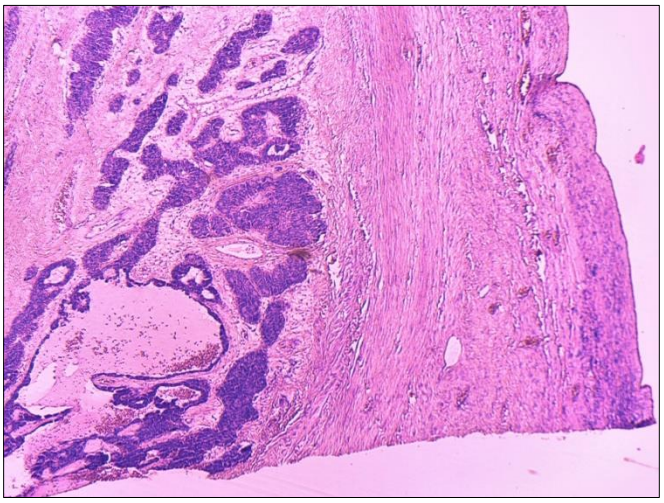

Figure 4b Tumor cells showing positivity for chromogranin immunostain (400x magnification)

3. Discussion

Given the rare incidence of oNETs, most of the published literature consists of case reports and small case series with a few numbers of oNET being reported [3,7,10]. The reported age range is 22-76 years, in perimenopausal women. The histogenesis is currently unclear. Several hypotheses have been put forward. Firstly, neuroendocrine cells are present in the epithelium of benign, borderline, and malignant tumors of the female genital tract. Secondly, primitive endocrine cells can differentiate into endocrine and other cells. Thirdly, ovarian neuroendocrine tumors can develop from non-neuroendocrine cells, which activate genes that promote neuroendocrine differentiation. These cells can produce biologically active amines and peptides that act as neurotransmitters, hormones, or paracrine regulators [11].

The most common chief complaints are pelvic pains followed by abdominal distension, and postmenopausal bleeding [12]. One-third of ovarian NET patients present with clinical neuroendocrine symptoms such as flushing, diarrhoea and abdominal cramps [13]. Preoperative diagnosis of oNET is rarely possible. CA-125 is a tumour antigen present in 75% to 83% of epithelial ovarian cancers and is rarely elevated in oNET [14]. CT and MRI are not useful for differential diagnosis with other ovarian tumours and usually show non-specific results [7]. They may appear as a solid mass or often combined with benign teratomas or mucinous tumors. It is important to exclude a primary NET cancer from another site causing metastasis to the ovary; these are more usually bilateral [3,11].

IHC is important for the diagnosis of neuroendocrine carcinoma. The most commonly used immunohistochemical markers are chromogranin A, synaptophysin, cytokeratin, and CD56 [3]. To diagnose a neuroendocrine tumour of the

female gynaecological tract, there must be at least two positive neuroendocrine markers which was present in our case. IHC may also be used to differentiate a primary oNET from a metastatic gastrointestinal carcinoid in order to select appropriate therapy. In our patient, the primary tumor was aggressive due to high mitotic proliferation activity, as she had metastases to the liver, the peritoneum and to the bone. Kurabayashi et al. [16] reported that the proliferation activity of a primary ovarian carcinoid can be a prognostic factor.

There is no standard management protocols for oNET. Some studies suggest that the management of NETs of the ovary is similar to that of epithelial cancers and consists of complete surgical resection of the tumour followed by adjuvant chemotherapy[6,13].The main controversy with chemotherapy remains the benefit of adjuvant chemotherapy. Some treatment options exist for metastatic or advanced ovarian carcinoids, such as streptozocin, 5-fluorouracil, capecitabine, and cisplatin-containing regimen based on previous reports[4]. Recently, altered expression in the mTOR signaling pathway has been used in NETs, and molecular-targeted mTOR inhibitors have shown promise in treating gastrointestinal carcinoid. Patients with advanced pancreatic NET, treatment with biologic targeted mTOR inhibitor, sunitinib was associated with improved progression-free survival [6]. Based on these results, sunitinib was administrated to our patient, and a good follow-up for 6 months without serious side effects. In addition to sunitinib, everolimus, a multi-targeted recepteur tyrosine kinase inhibitor, has recently been used for pancreatic NET with good overall follow-up. This could be another treatment option if sunitinib fails to treat this patient's tumour. Further multicentric studies are needed to determine the best management this rare tumour entity. The prognosis of NETs of the ovary is difficult to determine due to the rarity of the disease. The prognosis is excellent for patients with stage I primary oNET, with more than 90% survival, however patients with more advanced stages, such as our patient, have a poor prognosis. [8,9].

4. Conclusion

Ovarian cancer is among the most lethal malignant tumors and is the most common cause of mortality from gynecologic cancer. Early stage and low tumor grade independently predict improved survival for neuroendocrine carcinoma of the ovary. The association of NET of the ovary and ductal carcinoma of the breast remains unknown, further studies are desirable to establish a link between the two eventualities.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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