

Case Report

# Ovarian Teratoid Carcinosarcoma Is an Aggressive Tumor of Probable Mullerian Derivation with a Carcinosarcomatous and Mixed Germ-Cell Morphology

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## Keywords

Chemotherapy · Drug Therapy · Gynecological Cancer · Molecular Pathology · Ovarian Carcinoma · Pathology · Targeted Therapy

## Abstract

Ovarian carcinosarcoma is also referred to as malignant mixed Mullerian tumor (MMMT). It is a rare neoplasm, and although it represents less than 5% of malignant ovarian tumors, it remains generally well-known among clinicians and pathologists. Rarer yet is ovarian teratoid carcinosarcoma, defined as carcinosarcoma with the added feature of immature neuroectodermal tissue, with or without elements of primitive germ cell tumor. To our knowledge, six ovarian teratoid carcinosarcomas have been reported in the literature [Matsuura et al. *J Obstet Gynaecol Res.* 2010 Aug;36(4):907–11]. These tumors resemble nasopharyngeal tumors of the same name. We report a 55-year-old woman seen at Orlando Health's division of gynecological oncology whose pathology showed ovarian teratoid carcinosarcoma, and present what we believe to be a seventh report of this entity.

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## Introduction

Teratoid carcinosarcoma was first described in the nasopharynx [1] and ovarian teratoid carcinosarcoma, described in 1989 [2], closely resembles its nasopharyngeal counterpart. Teratoid carcinosarcomas are biologically aggressive tumors. All previously reported cases of ovarian teratoid carcinosarcoma occurred in post-menopausal women and were discovered in advanced clinical stages. As with their nasopharyngeal counterparts, all ovarian teratoid carcinosarcomas behaved in a highly aggressive manner [3]. Histologically, teratoid carcinosarcomas show an admixture of carcinosarcoma, primitive neural tissue (a component whose overall proportion has been associated with progressively worse prognosis in immature teratomas [4]), and other components of mixed germ cell tumor. Normally, mixed germ cell tumor of ovary is a tumor of children and young adults and is uncommon in postmenopausal women.

## Case Report

A 55-year-old Caucasian woman presented to Orlando Health's gynecologic oncology division with complaints of increasing abdominal pain, low-grade fevers, and early satiety of approximately two months. Computed tomography showed ascites and a 13 cm in greatest dimension mixed cystic and solid mass in the central portion of her pelvis, without radiographic evidence of extra pelvic masses. Serum tumor markers were: increased quantitative HCG, 126 mIU/mL (reference range:  $\leq 8$  mIU/mL); increased  $\alpha$ -1-Fetoprotein, 5.0 ng/mL (reference range: 0.0–0.9 ng/mL); increased Lactate Dehydrogenase, 406 U/L (reference range: 140–271 U/L); and increased CA-125, 599 U/mL (reference range: 0–35 U/mL). Following exploratory laparotomy, optimal tumor-reductive surgery was performed along with total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and omentectomy, leaving only microscopic residual disease.

Surgical findings encompassed a 16.8 cm in greatest diameter left ovarian cystic, necrotic mass that had ruptured prior to surgery and in which there was pre-operative abdominal cavity spillage. The mass was uniformly soft, necrotic and approximately 50% attached to the cyst wall of the ovary. Pre-procedural pelvic washings were positive for malignant cells. Remaining surgical-pathology specimens were negative for malignancy; however, the opposite ovary showed clustered benign epithelial inclusions resembling a small adenofibroma that was WT1-negative, ER-positive and PAX8-positive and was consistent with endometrioid adenofibroma, generally considered a product of remote endometriosis. This observation is noteworthy, because the presentation of an aggressive tumor, for example clear cell carcinoma, as stage I disease is not an uncommon finding among endometriosis-associated malignancies; although, carcinosarcoma associated endometriosis is extremely rare [5].

Specimen microscopy showed assorted tumor components that comprised: (1) carcinosarcoma with EMA (epithelial membrane antigen) positive and PAX-8 positive glands that were present in a CD10 positive stroma; (2) immature teratoma with neuroepithelial, blastemal and primitive cartilage tissue; (3) immature embryonic elements including embryoid bodies that showed well-defined inner cell mass, trophoderm and yolk-sac; (4) an isolated focus resembling embryonal carcinoma; and, (5) an isolated focus of CD117 positive cells resembling dysgerminoma. Stage IC teratoid carcinosarcoma was diagnosed; and, an extramural expert consultant confirmed the diagnosis. Salient histopathological findings are highlighted in Figure 1.

Chemotherapeutic options were discussed with the patient; and proposed agents included carboplatin, paclitaxel and ifosfamide [6–8]. Also considered were bevacizumab and Herceptin. At the time of the first patient encounter, there were phase 1 and phase 2 randomized clinical trials for ovarian carcinosarcoma without extant phase 3 trials. The patient was made aware of the gravity of her disease and offered chemotherapy.

The patient elected to defer chemotherapy until disease recurrence. A month later, she presented with increasing abdominal girth, early satiety and abdominal discomfort. Computed tomography showed significant ascites, carcinomatosis, an 8 cm right pelvic sidewall mass, an abdominal wall nodule and an enlarged left internal iliac lymph node.

She underwent therapeutic paracentesis and chemotherapy port placement. Her initial chemotherapy included six cycles of ifosfamide and paclitaxel. She then received 3 cycles of carboplatin, gemzar (Gemcitabine, an antimetabolite used to treat a variety of cancers) and bevacizumab. Follow up computed tomography showed disease progression and chemotherapy was discontinued. She then received two cycles of nivolumab (Opdivo®, a PD-1 protein inhibitor used for platinum resistant tumors) but, again, showed disease progression. FoundationOne CDx™ Testing (Foundation Medicine, Cambridge, MA, USA; FDA approved as companion diagnostic in solid tumors, 2017) was performed on her tumor and the outcome revealed: PIK3CA E545K-subclonal, MSI-stable and Tumor Mutation Burden (TMB)–low, with 3 mutations per megabase. In this context, the Analysis of Tumor mutational burden (TMB) and Microsatellite Instability (MSI) serves as the basis for therapeutic decisions on cancer immunotherapies.

Because of the PIK3CA-E545K mutation, it was concluded that therapies that would potentially benefit this patient included the mTOR (mammalian target of rapamycin) inhibitors, Everolimus and Temsirolimus. The PIK3CA-E545K occurs within the highly conserved helical domain. Mutated PIK3CA proteins have increased catalytic activity resulting in enhanced downstream signaling and oncogenic transformation in vitro [9]. Alterations in the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway are common in endometrial cancers. PIK3CA mutations promote cell growth and invasion, are oncogenic both in vitro and in vivo, and have been associated with response to PI3K/AKT/mTOR signaling pathway inhibitors [9–12].

The patient declined other chemotherapy or radiation therapy options and decided on going to University of Texas MD Anderson Cancer Center in Houston, Texas, USA, for further intervention. She was admitted to the hospital directly after her initial consultation. She was found to be in renal failure. She had bilateral percutaneous nephrostomy tubes placed and her renal function normalized. She was then given “BEP” as one 5-day cycle of Bleomycin, Etoposide, and Cisplatin [13]. She developed a neutropenic fever one week later, was hospitalized for another week, and died prior to being able to receive cycle 2. Her death occurred 14 months from the time of her initial surgery.

## Discussion

A malignant ovarian tumor composed of Mullerian epithelial tumor and malignant germ cell tumor is rare, with most cases composed of endometrioid adenocarcinoma and yolk sac tumor [14]. Ovarian carcinosarcoma with malignant neuroectodermal components resembling immature teratoma is extremely rare; and, to our knowledge, this is the seventh case of ovarian teratoid carcinosarcoma to be reported in the literature. It is uncertain whether this and other tumors of similar kind develop from arrested primitive embryonic tissues or from

somatically derived pluripotential cells arising in the course of epithelial tumor dedifferentiation or in the course of epithelial to mesenchymal transition with the acquisition cellular stemness.

Teratoid carcinosarcomas show significant tumor heterogeneity; and, we argue that, in this case, tumor heterogeneity is linked to carcinoma dedifferentiation followed by stable epithelial to mesenchymal transition (i.e., carcinosarcoma) with increased stemness leading to fetal-like stem cell emergence and the appearance of differentiated germ tumor end-products. Cellular differentiation is a process eventuating in cellular change, generally to a more specialized type. Ontogenetic differentiation happens when a multicellular organism changes from a simple zygote, for example, an embryo or embryoid body to a complex system of tissues and cell types. Cellular differentiation does not involve a change in the cells' DNA sequence. Tissue stem cells are a self-renewing population of cells that undergo divisions to self-renew or differentiate into multiple kinds of differentiated progeny. Stem cells have prolonged self-renewal ability, can repopulate the bone marrow in transplant paradigms, and can produce multiple phenotypes in colony assays [15–17].

It has become apparent that cancers are not composed of a group of near-homogenous, ectopically growing cells. Rather, cancer cells are heterogeneous, including in terms of their malignant potential to metastasize and to cause relapse. Phenotypic and functional heterogeneity arises among cancer cells within the same tumor because of genetic change, micro-environmental differences and reversible changes in cell properties. Cancers may contain a hierarchy of cells in which tumorigenic cancer stem cells may even differentiate into non-tumorigenic end-organ progeny [18]. Intra-tumor heterogeneity impedes the investigation and treatment of cancer since individual tumor-tissue samples may not be representative of the whole tumor. Cancer stem cells are the only cells within a tumor that possess indefinite self-renewal abilities and whose differentiation leads to the emergence of all cell types in the tumor [19–23].

Epithelial to mesenchymal transitions (EMT) are transdifferentiation programs required for tissue morphogenesis during embryonic development (ontogenesis) and these programs reemerge during tissue repair and in tissue neoplasms. The EMT process is regulated by a diverse array of cytokines and growth factors that can be dysregulated during malignant tumor progression. EMT induction in cancer cells results in the acquisition of invasiveness, metastasis and drug resistance. Recent reports indicate that the emergence of stem cell-like features occurs as a result of EMT, for example, via cues from tumor stromal components [24]. Investigators from the Cancer Genome Atlas project identified a strong EMT gene signature in a subset of endometrial cancer cases that was attributable to epigenetic alterations at microRNA promoters; and, the range of EMT scores in uterine carcinosarcomas was the largest among all tumor types studied [25]. Dedifferentiation through aberrant activation of embryonic EMT enhances cancer cell motility and dissemination [26]; and, gene expression patterns in human cancers indicate that cancer cells combine EMT properties with a stem-cell phenotype that leads to cell migration and metastasis [27].

Teratoid carcinosarcoma is a study in multipart tumor heterogeneity. Although it is uncertain whether this or other similar tumors develop from arrested primitive embryonic tissues or from somatically derived pluripotential cells arising in the course of epithelial tumor dedifferentiation or in the course of epithelial to mesenchymal transition, there is good data to favor a tumor's ability to eventuate in a complex, albeit disorganized, "organ system". We speculate that this tumor may have arisen in the context of an endometriosis-associated malignancy, become a carcinosarcoma through EMT with stabilization of its stromal component and to have acquired stemness, also through EMT, allowing it to mimic the action of primitive

stem cells and to exhibit multilineage differentiation. A Mullerian “endometrioid” underpinning of this lesion is proposed because: (1) there is morphological evidence of a contralateral endometriosis-associated benign lesion, (2) the tumor was confined to a large cyst of one ovary (stage I) – a typical finding of endometriosis associated neoplasms, (3) there was subclonal mutation of the PIK3CA-pathway – a common finding in endometriosis associated ovarian neoplasms, and (4) the carcinosarcoma’s glands and stroma morphologically and immunohistochemically resembled those of homologous endometrial carcinosarcoma.

The EMT process and stemness may explain this tumor’s ultimate resistance to any chemotherapy, as it appears that tumors presenting as heterogeneous tumor-tissue end products are highly resilient and can resist a variety of therapeutic assaults. Cancer metastasis and cancer drug resistance are two complex and poorly understood processes, which often co-exist clinically. EMT generates cancer stem cells that afford tumor heterogeneity and contributes to both metastasis and therapy resistance. EMT should be of therapeutic interest in the treatment of cancer and attempts should be made to target its pathways, either to prevent tumor dissemination in patients at high risk of developing metastatic lesions or to eradicate metastatic cancer cells in patients with advanced disease [28–30]. Being mindful of the above observations and recognizing the value of next generation sequence testing of tumor tissue could lead us to discover better treatment options with improved patient survival, especially for women with aggressive cancer subtypes.

### Statement of Ethics

The authors have no ethical conflicts to disclose.

### Disclosure Statement

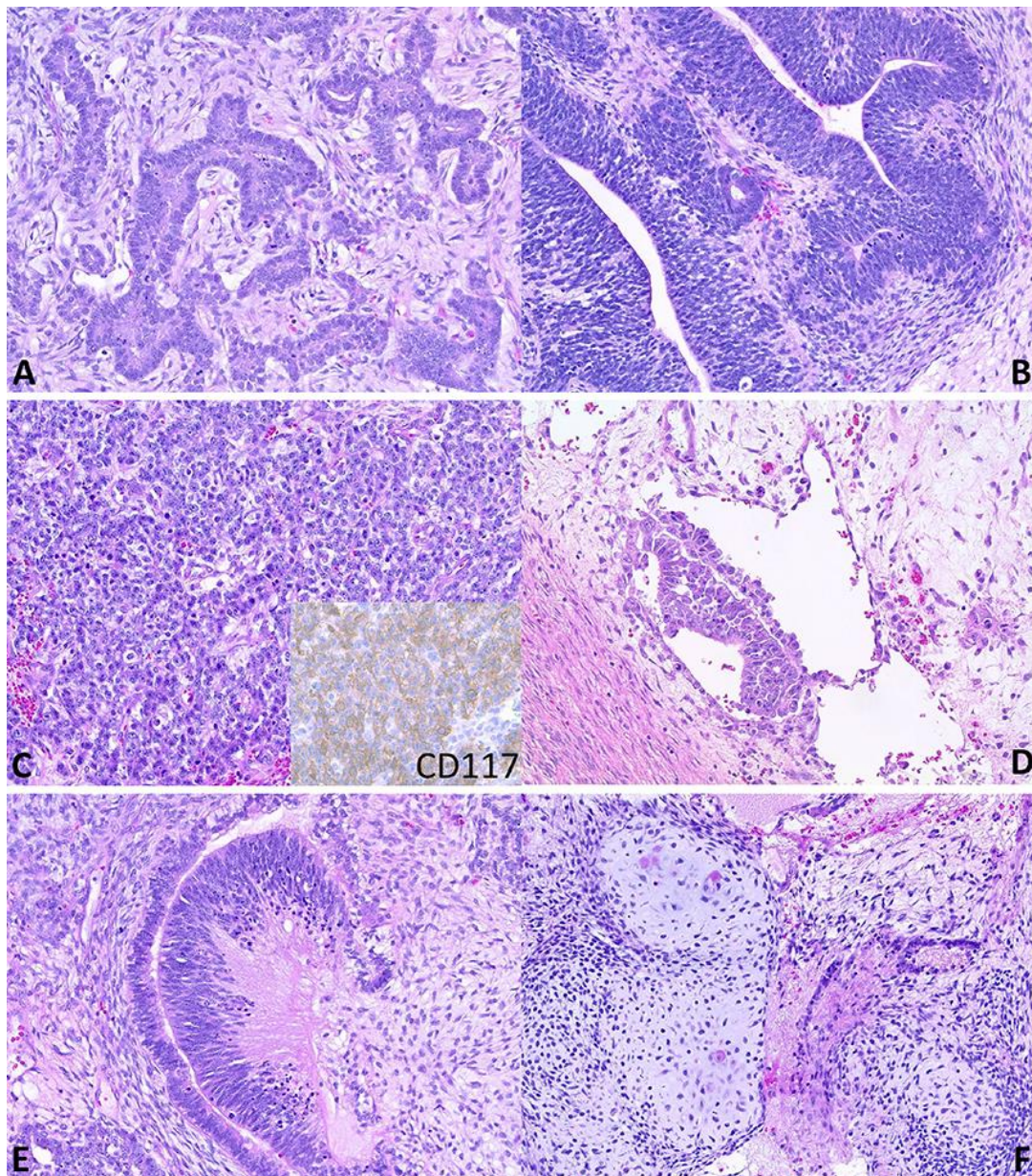
The authors have no conflicts of interest to declare.

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**Fig. 1.** A. Homologous carcinosarcoma with endometrioid gland morphology and nonspecific fibrous stroma. B. Primitive neuroepithelial tissue. C. CD117 positive cells (*inset*) resembling dysgerminoma. D. Embryoid body showing trophoderm, amniotic cavity, inner cell mass (ectoderm and endoderm), and yolk sac cavity. E. Primitive retinal tissue. F. Fetal cartilage.