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Case report

Dedifferentiated endometrioid adenocarcinoma with trophoblastic components: Prolonged remission after treatment with bleomycin, etoposide, and cisplatin

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ABSTRACT

Dedifferentiated endometrial adenocarcinoma (DEAC) with trophoblastic components is a rare neoplasm with an aggressive behavior and a poor prognosis. Only seven cases have been reported in the literature. We present a 61-year-old patient who was diagnosed with Stage IB dedifferentiated endometrioid adenocarcinoma with trophoblastic elements. A post-operative β-hCG was elevated at 1877 mIU/mL. The patient received 6 cycles of carboplatin and paclitaxel with normalization of β-hCG; however, three months after completion of chemotherapy, her β-hCG increased to 39 mIU/mL and a mass overlaying the psoas muscle was noted on imaging. The mass was resected and confirmed to be recurrent disease. Four cycles of bleomycin, etoposide, and cisplatin were administered, and the patient remains without evidence of disease 3 years after completing treatment. Due to the small number of reported cases of DEAC with trophoblastic components, there is limited information regarding the appropriate first-line adjuvant chemotherapy regimen.

1. Introduction

Dedifferentiated endometrial adenocarcinoma with trophoblastic components is a rare entity, with only seven cases reported in the literature. Dedifferentiated endometrioid adenocarcinoma (DEAC) is described by the World Health Organization as a "malignant tumor with an epithelial structure that is too poorly differentiated to be placed in any other category of carcinomas" (Cai, 2018). DEAC is thought to account for 2–9% of endometrial adenocarcinomas (Hamza, 2018). Trophoblastic components have been reported only rarely in cases of DEAC.

Choriocarcinoma can be divided into two types, gestational and non-gestational. Choriocarcinomas are characterized microscopically by the distinctive presence of cytotrophoblasts, intermediate trophoblasts and syncytiotrophoblasts. Syncytiotrophoblasts account for the abnormally elevated β-hCG levels that are present in all cases (1). In most cases, the elevated β-hCG will decrease or normalize after initial surgical and medical treatment. Fluctuations in β-hCG, however, can signify recurrence. The reported cases of DEAC with trophoblastic components have been associated with non-gestational choriocarcinoma, often in postmenopausal patients. These neoplasms appear to be aggressive and hold a poor prognosis overall. On review of the literature, most cases are treated with adjuvant combination chemotherapy, with various regimens reported (Cai, 2018; Rawish, 2017). In particular, the use of bleomycin, etoposide, and cisplatin (BEP) for treatment of DEAC with trophoblastic components has been reported in two cases in the literature (Pesce et al., 1991). We present a case of prolonged remission after treatment with BEP in a patient diagnosed with recurrent dedifferentiated endometrioid adenocarcinoma with trophoblastic elements.

Case. A 61-year-old female presented with a one-month history of postmenopausal bleeding. Her evaluation included an endometrial biopsy that revealed uterine carcinosarcoma and CT scan of the abdomen and pelvis that showed an endometrial mass, but no lymphadenopathy.

The patient underwent a robotic total hysterectomy with bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy. Final pathology showed stage IB dedifferentiated endometrioid adenocarcinoma with trophoblastic elements (50% undifferentiated adenocarcinoma, 40% choriocarcinoma, 10% low to intermediate grade endometrioid adenocarcinoma) (See Fig. 1). There was also lymphovascular space invasion with trophoblastic and undifferentiated elements. Immunohistochemical analysis was done to confirm the histologic diagnosis. Trophoblastic elements were immunoreactive for cytokeratin (CK7), CKAB 1/3, GATA3, CAM 5.2, pancytokeratin, E-

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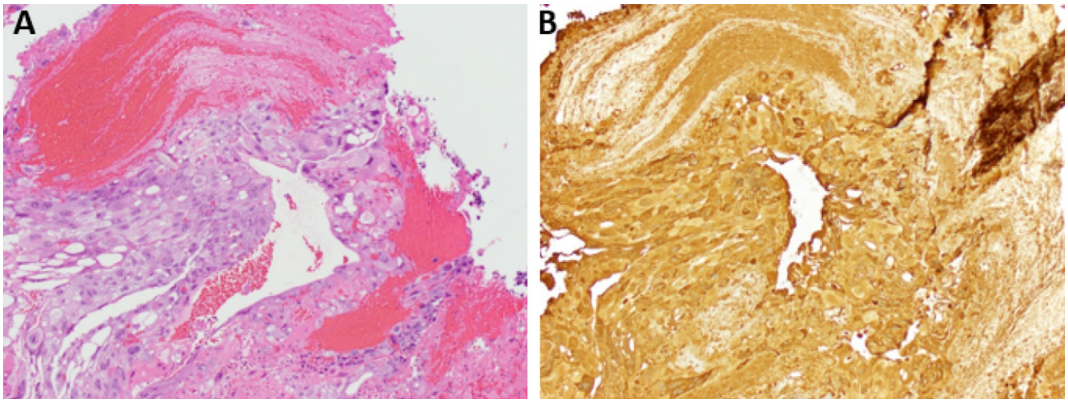

Fig. 1. Primary endometrial tumor. A: Focus of trophoblast-like elements within the primary endometrial tumor, hematoxylin and eosin stain (100× magnification). B: Same focus as in A, HCG immunohistochemical stain (100× magnification).

cadherin, p40, p63 and human placental lactogen (hPL), and negative for ER, PR, PAX8.

With the post-operative finding of dedifferentiated endometrioid adenocarcinoma with trophoblastic elements, a serum β-hCG was drawn 8 days after surgery and was elevated at 1877 mIU/mL. Six cycles of carboplatin with dose-dense paclitaxel were administered, with complete normalization of β-hCG after two cycles.

Three months after completing six cycles of chemotherapy with carboplatin and paclitaxel, her β-hCG was noted to be elevated at 39 mIU/mL. A PET scan revealed an isolated 2 cm left lateral psoas muscle hypermetabolic mass. On biopsy, this was proven to be dedifferentiated adenocarcinoma. The patient then underwent laparoscopic resection of the mass. Pathology of the mass demonstrated dedifferentiated malignant neoplasm that stained positive for β-hCG (See Fig. 2). One week after surgery the β-hCG normalized. Four cycles of bleomycin, etoposide, and cisplatin (BEP) were administered, and the β-hCG remained at undetectable levels. Now, three years later, the patient currently has no evidence of disease with normal β-hCG and PET scan.

2. Discussion

On review of the literature, dedifferentiated endometrioid adenocarcinoma with trophoblastic components has an aggressive and usually fatal course. DEAC is historically missed on endometrial biopsy because the dedifferentiated component is small and deep within the myometrium. The neoplasm often appears to be low grade on intraoperative frozen section pathology, so lymph node dissection may not be performed during surgery. Pathology of the dedifferentiated component usually contains "*solid growth pattern of pleomorphic epithelial cells with prominent nucleoli, brisk mitotic activity, and significant atypia*" (Hamza, 2018).

Gestational trophoblastic neoplasia (GTN), compared to what little we know about DEAC with trophoblastic components, is usually a curable gynecologic malignancy that is highly sensitive to chemotherapy. The cure rate of GTN is 98% with effective treatment (Aminimoghaddam, et al., 2018). EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) and EMA-EP (etoposide, methotrexate, actinomycin D, etoposide, and cisplatin) are the most widely used regimens for treatment of high risk gestational trophoblastic neoplasia. There are limited case reports which review EMA-CO as the combination regimen for initial treatment of non-gestational choriocarcinoma, including DEAC with trophoblastic components. There are too many confounding variables, including patient age, extent of disease, etc., and too few reported cases to adequately determine the chemosensitivity patterns among these neoplasms.

Our patient's disease recurred within three months after completing carboplatin and paclitaxel. She had no measurable disease until her recurrence. This very short disease-free interval reflects the typical aggressive nature of this disease. While there was an immediate normalization of the β-hCG following resection of the recurrent mass, she received additional chemotherapy with concern for residual microscopic disease.

There have been only 8 cases of DEAC with trophoblastic components reported in the literature, including the current case. Various chemotherapy regimens were used (Table 1). Of the cases reported, four patients died within the range of 47 days to 16 months after diagnosis. Only two other patients have been reported to have received BEP. One patient died 47 days after diagnosis but had widespread retroperitoneal disease. The other patient was still reported alive without disease

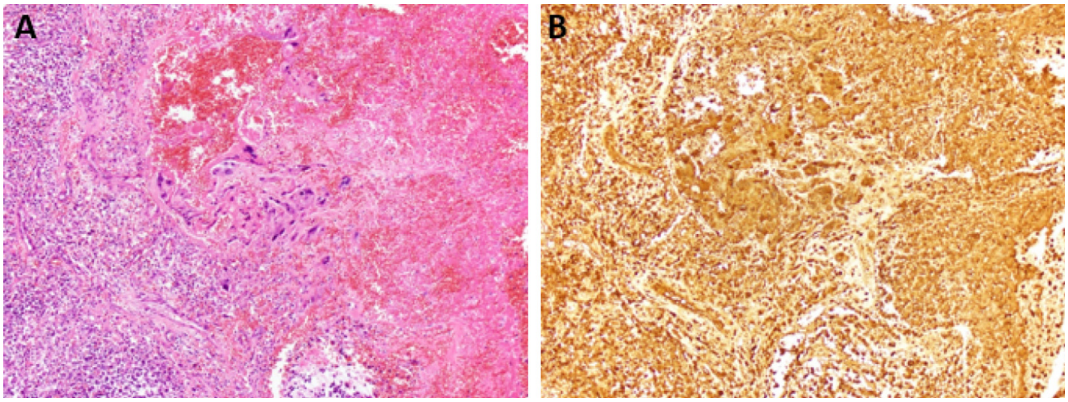

Fig. 2. Subsequent metastatic tumor. A. Focus of trophoblast-like elements within the subsequent metastatic lesion, hematoxylin and eosin stain (100× magnification). B. Same focus as in A, HCG immunohistochemical stain (100× magnification).

Table 1
Cases of DEAC with trophoblastic components reported in the literature. BEP = bleomycin, etoposide, platinum, CT = computed tomography, DOD = dead of disease, TAH = total abdominal hysterectomy, TH-BSO = total hysterectomy, bilateral salpingo-oophorectomy, MTX = methotrexate, EMA-CO = VP-16, MTX, actinomycin D, vincristine, VP-16 = etoposide.

Case	Year	Age	HCG Level	Surgery	FIGO Stage	Chemotherapy	Radiotherapy	Sites of disease	Outcome
Civantos and Rywlin	1971	87	1000 IU/mL	None	Not reported	None	External radiotherapy with supplementary radium	None	Alive at time of article submission
Pesce et al.	1991	78	19,500 mIU/mL	None	Not reported	BEP	None	Diffuse retroperitoneal adenopathy on CT	DOD 47 days after diagnosis
Pesce et al.	1991	48	3050 mIU/mL	TAH (Not clearly defined)	Not reported	MTX; BEP	None	Pulmonary	Alive at time of article submission
Masuyama et al	2015	42	19.5 mIU/mL	Radical TH-BSO Pelvic Lymphadenectomy	IIIC1	Paclitaxel/Carboplatin; MTX	None	Left external iliac artery lymph nodes	Alive without disease at 12 mo. followup
Rawish et al	2017	72	41,848 mIU/mL	TH-BSO, pelvic and para-aortic lymphadenectomy, omentectomy	IIIA	EMA-CO; Cisplatin/ paclitaxel	None	Pelvic lymph nodes, brain, liver, and peritoneum	DOD 7 mo. after primary surgery
Rawish et al	2017	62	6840 mIU/mL	TH-BSO pelvic lymphadenectomy	IIIC1	EMA-CO; Taxol/cisplatin -> Taxol/VP-16	Yes	Adrenal, lungs, peritoneum, vertebral bone	DOD 16 mo. after primary surgery
Cai et al	2017	33	238,418.35 IU/mL	TH-BSO, pelvic lymphadenectomy, omentectomy	IIIA	Patient declined treatment	None	Lungs	DOD 5 mo. after primary surgery

12 months after treatment. Our patient's durable response with BEP highlights this as a regimen to consider for primary treatment for this rare disease.

We do not fully understand the molecular comparisons between the trophoblastic components of gestational choriocarcinoma and choriocarcinoma differentiation of somatic carcinomas, which could affect chemosensitivity. One of the reported cases of endometrial adenocarcinoma with choriocarcinoma differentiation was evaluated by whole genomic copy number analysis. The analysis showed changes in the trophoblastic components that differ from what is known to occur in gestational choriocarcinoma. Furthermore, it is unclear if the size of the trophoblastic component plays a role in the effectiveness of adjuvant chemotherapy on β-hCG monitoring, thus affecting prognosis overall (Rawish, 2017).

DEAC with trophoblastic components appears to have good response to the combination of bleomycin, etoposide, and cisplatin based on our case and one additional case reported in the literature by Pesce et al. (1991). BEP is most commonly used as the first line chemotherapy regimen in patients with malignant ovarian germ cell tumors. Malignant ovarian germ cell tumors (OGCTs) include nondysgerminoma tumors, which include non-gestational choriocarcinomas. Long-term survival rates with surgery and adjuvant BEP are 95 to 100 percent for early-stage nondysgerminoma tumors and 75 to 80 percent for those with advanced disease at presentation (Murugaesu, 2006). Furthermore, in patients with recurrent disease resistant to initial chemotherapy, there may be a role for high-dose chemotherapy with bone marrow transplant. Successful treatment of recurrent testicular and ovarian germ cell tumors, as well as metastatic gestational trophoblastic disease, using high-dose carboplatin and etoposide with bone marrow transplant has been reported in the literature (Sears, 2017; Lotz, 1994). To our knowledge, there are no reported cases of bone marrow transplant used in treatment of DEAC with trophoblastic components; however, given the possible similarities to other germ cell tumors, it may be beneficial in refractory cases. While the choriocarcinoma differentiation may be similar between DEAC with trophoblastic components and nondysgerminoma ovarian germ cell tumors, we do not know how the coexisting endometrial adenocarcinoma affects the treatment and prognosis. Due to the very limited number of case studies using BEP in DEAC with choriocarcinomatous differentiation, more research is needed to determine its effectiveness in treating this rare neoplasm.

3. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Alexa Martin, DO drafted manuscript, reviewed changes made by Dr. Michael Stany, formatted manuscript for submission, and submitted finalized version of manuscript.

Elizabeth Jackson, MD assisted in drafting the manuscript.

Henry Edwards, MD created pathology photographs and drafted photo descriptions for the manuscript.

Michael Stany, MD reviewed and edited the initial manuscript and approved the final version of the manuscript for submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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