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Dedifferentiated endometrioid adenocarcinoma of the uterus: a case report

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Summary

Background: Dedifferentiated endometrioid adenocarcinoma (DEAC) of the uterus was first described by Silva *et al.* in 2006. The tumor has high-grade endometrial carcinoma component which abruptly emerged from low-grade areas. DEAC showed more aggressive phenotype than FIGO grade 3 endometrioid adenocarcinoma. However, there have been a few studies evaluating effectiveness of adjuvant therapy for the patients with DEC. *Case Report:* A 41-year-old case with Stage IVB DEAC that clinically showed resistance to several regimens of chemotherapy is reported. The uterine corpus tumor with size of 120 x 100 mm, and the metastases were found in lung, liver, and pelvic lymph nodes. She underwent supra-vaginal hysterectomy, left salpingo-oophorectomy, and partial resection of ileum. Pathologically, the tumor had both well differentiated and undifferentiated carcinoma components, and it was diagnosed as DEAC. After primary surgery, the patient received four regimens of adjuvant chemotherapy, however all regimens were judged as progressive disease. Subsequently, the patient died of disease seven months after surgery. *Conclusion:* The present case of DEAC had an exceedingly poor prognosis, as was suggested in the several previous reports. The review of adjuvant therapeutic modalities revealed that there has been no effective therapy in the response-evaluable patients with DEAC. Further investigations for new strategy to treat the cases with DEAC are needed.

Key words: Uterine corpus; Endometrioid adenocarcinoma; Dedifferentiated endometrioid adenocarcinoma.

Introduction

The terminology "dedifferentiation" was first described in bone and soft tissue neoplasms [1]. Since then, the phenomenon has been reported in other epithelial tumors including renal tumor [2]. In gynecologic cancers, dedifferentiated endometrioid adenocarcinoma (DEAC) of the uterus or ovary was first described in 2006 [3]. DEAC has both low-grade and undifferentiated components which abruptly dedifferentiated from low-grade one. The prognosis of DEAC was extremely poor compared with FIGO grade 3 endometrial adenocarcinoma, suggesting that it is important to appropriately diagnose this type of tumor [3]. In 2014, DEAC was added to the World health organization (WHO) pathological classification of tumors of the uterine corpus [4]. The authors report a case of DEAC of the uterus with clinical review of literature.

Case Report

A 41-year-old woman with 0 gravida and body mass index of 32, presented with vaginal bleeding and abdominal distension. She had a surgical history of right salpingo-oophorectomy for a benign mature teratoma and had no specific family history. The patient was suspected for a uterine corpus tumor, and referred to the present hospital. On admission, she suffered from severe anemia because of continuous vaginal bleeding. Serum tumor markers were slightly elevated: CA125 46.8 U/ml and CA19-9 88.2 U/ml. Magnetic resonance imaging (MRI) showed that there was a tumor in endometrium with a size of 120 x 100mm, which had low signal area in T2-weighted MR images, and a weak Gadolinium enhancement (Figures 1A, 1B). Serum markers for thromboembolism were elevated: FDP 7 ug/ml, D-dimer 2.3 ug/ml. Thrombi were detected in splenic and portal veins by computedtomography (CT) images. In addition to the metastases of the pelvic and paraaortic lymph nodes, CT revealed several nodules in lung and liver. The pathological examination of her endometrial cytology represented suspicion of adenocarcinoma. Based on the results, the patient was diagnosed as Stage IVB malignant tumor of the uterus.

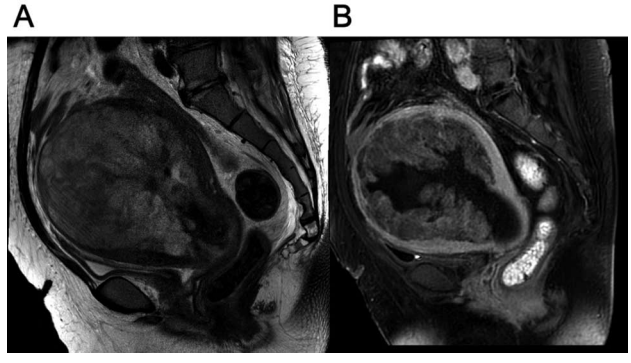

Figure 1. — MRI image of the case. A: MRI T2-weighted imaging of pelvis. B: Contrast enhanced MRI image. The tumor has grown in entire endometrial cavity with a size of 120×100 mm.

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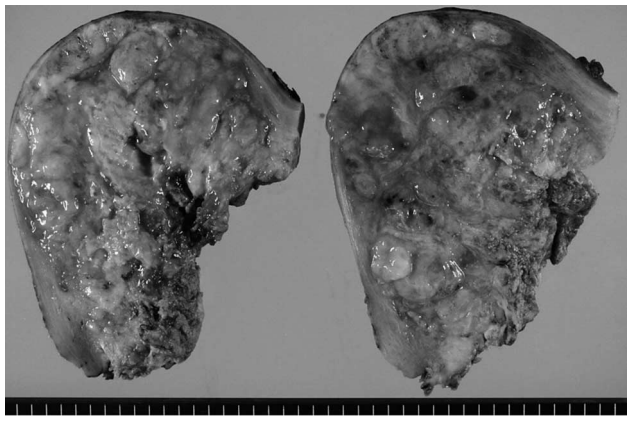

Figure 2. — Macroscopic view of the uterine tumor. The size of the uterus is 150×145×80 mm. The tumor shows necrosis and hemorrhage and the cells deeply invaded the myometrium .

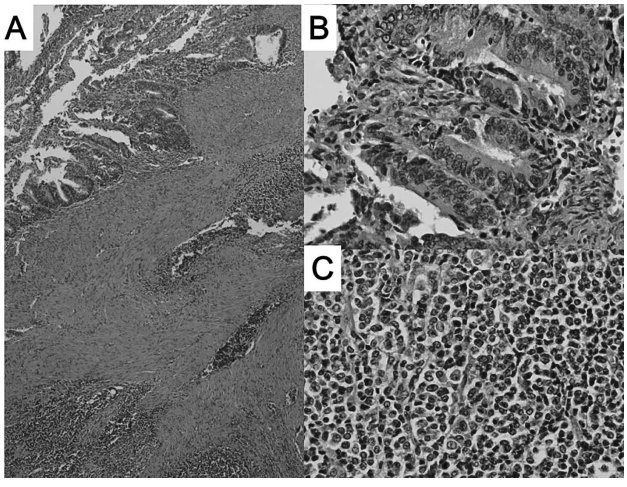

Figure 3. — Pathological findings of the tumor. A: The tumor contains both well-differentiated and dedifferentiated components. (H&E, ×4). B: Well-differentiated component shows glandular structure. (H&E, ×20). C: Dedifferentiated (undifferentiated) component shows glandular, nested, and trabecular appearance. ((H&E, ×20).

Six days after admission, the patient underwent laparotomy. The uterus and left ovary adhered to the pelvic wall and the ileum tightly and the tumor infiltrated parametrium rigidly, therefore the authors could only perform supravaginal hysterectomy, left salpingo-oophorectomy, in addition to partial resection of ileum.

Macroscopically, the size of uterine tumor was 150×145×80 mm (Figure 2). The endometrial tumor had a massive necrosis and focal hemorrhage, and deeply invaded the myometrium. Pathologically, in undifferentiated component, the tumor cells had relatively uniformed hyperchromatic nuclei and eosinophilic cytoplasm, and were organized to form non-cohesive sheets without any specific pattern. On the other hand, the tumor also had well differentiated component that could be diagnosed as FIGO grade 1 endometrioid carcinoma (Figure 3). Undifferentiated component was immunohistochemically positive for epithelial membrane antigen (EMA) and partially positive for cytokeratin (AE1/AE3). These cells were negative for h-caldesmon and desmin, although they were positive

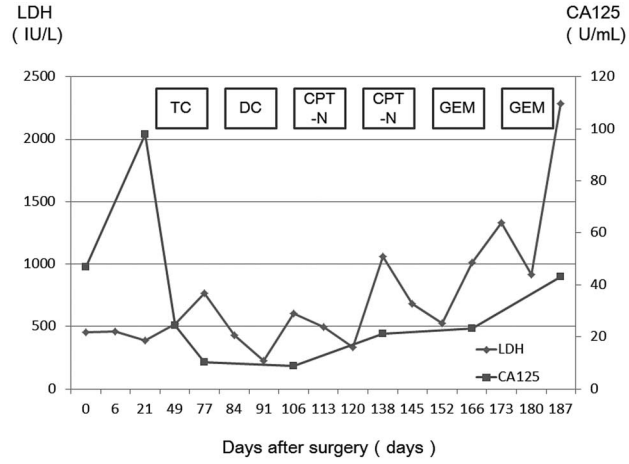

Figure 4. — Serums levels of CA125 and LD during chemotherapy. These two markers continuously increased in spite of several regimens administered. TC: paclitaxel and carboplatin; DC: docetaxel and carboplatin; CPT-N: irinotecan and nedaplatin; GEM:gemcitabine.

for α-SMA. In addition, undifferentiated areas were negative for estrogen and progesterone receptors. Based on these findings, the tumor was diagnosed as DEAC. Significant vascular and lymphatic invasion were observed and the surgical margin of uterine cervix was positive for cancer cells. Tumor dissemination was detected on the specimen of ileum.

Twenty-one days after surgery, the patient received combination chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC=5). As she developed drug-induced grade 3 hypertension according to Common Terminology Criteria for Adverse Events (CTCAE), she subsequently received combination with docetaxel (70 mg/m^2) and carboplatin (AUC=5). However, size of metastatic lymph nodes increased rapidly and she developed severe sciatic nerve pain. Therefore the patient was started on the second-line regimen of irinotecan (50 mg/m^2, days 1, 8, 15, q4 weeks) and nedaplatin (60 mg/m^2, day1, q4 weeks). After two cycles of treatment, the tumor progressed in size and her right leg had difficulty in moving because of severe edema. Next, she received two cycles of third-line regimen: gemcitabine (1,000 mg/m^2 days 1, 8, 15, q4 weeks). However the tumor size continuously increased, and the regimen was evaluated as progressive disease. Serum levels of CA125 and LD during chemotherapy are shown in Figure 4. These two markers continuously increased in spite of those regimens. Moreover, the patient developed renal failure due to right urinary obstruction, and consequently she underwent the nephrostomy, but it was not effective. The patient and her family elected best supportive care, and died of disease seven months after primary surgery.

Discussion

Type II endometrial cancers including grade 3 endometrioid adenocarcinoma, comprising approximately 30% of all uterine malignancies, but the prognosis is poorer compared with Type I tumors [5, 6]. In addition to this subtype of tumors, Silva *et al.* reported that a part of grade 3 endometrioid adenocarcinomas had both low-grade endometrioid adenocarcinoma and undifferentiated carci-

Table 1. — *Review of effectiveness of adjuvant therapy for DEAC.*

Author	Age	Surgery	Stage	Residual tumor	Adjuvant therapy	Response	Outcome
Vita *et al.* [7]	45	TAH+BSO	IIIA (ovary)	No	Cisplatinum+anthracycline+ taxane	NE	AWD
Wu *et al.*[9]	62	None (only biopsy)	IV (bone, lung, adrenals)	Yes	Radiation (60 Gy) Tamoxifen	PD PD	OS 3 months
Shen *et al.* [10]	51	TAH+BSO+PN	II	No	Radiation Cisplatinum+ docetaxel Taxanes	 NE	NED 11 months
Berretta *et al.* [11]	67	TAH+BSO+ right adrenalectomy	IV (adrenals)	No	Carboplatin+paclitaxel	NE	AWD
Chen *et al.* [12]	63	TAH+BSO+PN+Omx +appendectomy	IV (lung, liver)	Yes	Paclitaxel+carboplatin/ paraplatin	PD	OS 7 months
The present case	41	SVH+LSO+ ileal resection	IV (lung, liver)	No	Carboplatin+paclitaxel/docetaxel, CPT-11+nedaplatin Gemcitabine	PD PD PD	OS 7 months

TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; PN: pelvic lymphadenectomy; PAN: para-aortic lymphadenectomy; Omx: omentectomy; SVH: supravaginal hysterectomy; LSO: left salpingo-oophorectomy; NE: not evaluable; PD: progressive disease; OS: overall survival; EFS: event free survival; AWD: arrive with disease.

noma and that this type of tumor was described as DEAC in 2006 [3]. The pathological features of DEAC are that FIGO grade 1 or 2 endometrioid component often lines the endometrial cavity and undifferentiated component grows beneath it [7]. DEAC might be misdiagnosed as carcinosarcoma for its resemblance. In contrast to DEAC, carcinosarcoma contains high-grade endometrioid component or most frequently serous adenocarcinoma [8]. Meanwhile, the undifferentiated component of DEAC consists of non-cohesive, small, and rounded cells without spindle and pleomorphic cells which are usually seen in the sarcomatous component of carcinosarcoma [8].

Immunohistochemically in the undifferentiated component, the cells are negative for muscle-specific and neuroendocrine markers. However, the cells are usually positive for epithelial membrane antigen (EMA) and cytokeratin [8]. The present case was successfully diagnosed as DEAC using immunohistochemical analyses.

The number of reports concerning treatment of DEAC is quite limited. A review of English literature was conducted via PubMed, from 1970 until now. Including the present case, all cases that had clinical information regarding effectiveness of adjuvant therapy for DEAC are listed in Table 1 [7, 9-12]. The present case included metastases at diagnosis, and the authors could not accomplish complete debulking surgery. After surgery, the patient received four regimens of chemotherapy; however, all the regimens were not effective against the tumor. The review suggested that there seems to be no effective treatment so far for the cases with DEAC that have residual tumors.

Currently, endometrioid adenocarcinoma are commonly classified into three groups by FIGO grading system based on architectural features, especially in the amount of non-glandular solid endometrioid component in neoplasm. However some DEACs may have been misdiagnosed as grade 3 endometioid adenocarcinomas because the histological definition of solid component is not determined [7]. The prognosis of the patients with DEAC is extremely poor and the present authors could not find any effective regimens for patients with DEAC. Hence making correct diagnosis is very important. Further investigations for treatment against DEAC including chemotherapy using molecular target therapy are needed to establish a new treatment strategy.

Conclusion

The authors report a case with DEAC with review of the literature. The tumor seems to be extremely aggressive, showing chemo-resistant phenotype. An extremely rare case report described here would be helpful for decision-making, when a case with DEAC is presented.

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