



## Dedifferentiated Endometrioid Adenocarcinoma of the Uterus: Highly Aggressive and Poor Prognostic Tumor

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Dedifferentiated endometrioid adenocarcinoma (DEAC) is a recently described, rare uterine neoplasm containing both low-grade endometrioid adenocarcinoma and undifferentiated carcinoma.<sup>1</sup> Undifferentiated carcinoma in DEAC may originate secondary to transformation or dedifferentiation of low-grade endometrioid adenocarcinoma and appears to be more aggressive than endometrial endometrioid adenocarcinoma.<sup>2</sup> The undifferentiated component in DEAC can be misdiagnosed as the solid component of grade 3 endometrioid adenocarcinoma.<sup>3</sup> Therefore, accurate diagnosis of this neoplasm is important in treatment and prognosis. Here we report a case of DEAC of the uterus.

### CASE REPORT

A 55-year-old Korean woman was admitted to our hospital because of vaginal bleeding that had lasted eight months. She was well except for a history of left salpingo-oophorectomy for benign ovarian cyst seven years ago. Ultrasonography revealed a thickened endometrium. An endometrial biopsy revealed well-differentiated endometrioid adenocarcinoma. She underwent total hysterectomy with right salpingo-oophorectomy and pelvic lymphadenectomy.

The uterus measured 8×6×4 cm. Right adnexa was grossly unremarkable. A 7×7×1-cm-sized protruding mass was found in the endometrial cavity. The mass was infiltrating into the

myometrium and there were leiomyomas beneath the tumor mass (Fig. 1A, B).

Microscopically, the tumor consisted of a low-grade endometrioid adenocarcinoma (40% of the tumor volume) on the surface and underlying undifferentiated carcinoma (60%) with a sharp border between the two components (Fig. 2A, B). The undifferentiated component exhibited a solid growth of monomorphic discohesive cells, lacking any differentiating features (Fig. 2C). The tumor cells were round with prominent nucleoli and frequent mitosis, and rhabdoid cells with eosinophilic cytoplasm and eccentric nuclei were noted in myxoid background (Fig. 2D). Numerous vascular and endolymphatic tumor emboli were present. Immunohistochemically, cytokeratin (CK), epithelial membrane antigen (EMA), estrogen receptor (ER), and progesterone receptor (PR) were diffusely expressed in the well-differentiated component. The undifferentiated cells were diffusely positive for vimentin and focally positive for CK and EMA (Fig. 2E, F). ER, PR, smooth muscle actin and neuroendocrine markers including chromogranin, synaptophysin, and CD56 were all negative. No metastasis was present in 24 pelvic lymph nodes. According to the International Federation of Gynecology and Obstetrics (FIGO) system, this case was FIGO stage IB.

After surgery, the patient received vaginal radiation. Two months later, she complained of hip pain. A follow-up positron emission tomography-computed tomography revealed multiple pulmonary, peritoneal, pelvic bone, and mediastinal lymph node metastases (Fig. 3). A brain computed tomography revealed multiple metastatic nodules. Although the patient underwent three cycles of chemotherapy, including paclitaxel, cisplatin, and doxorubicin, she died seven months after the diag-

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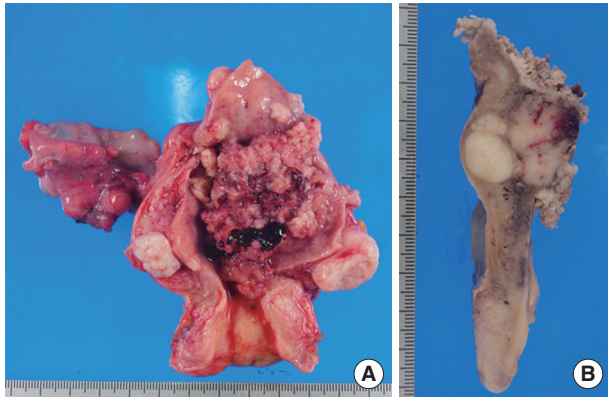
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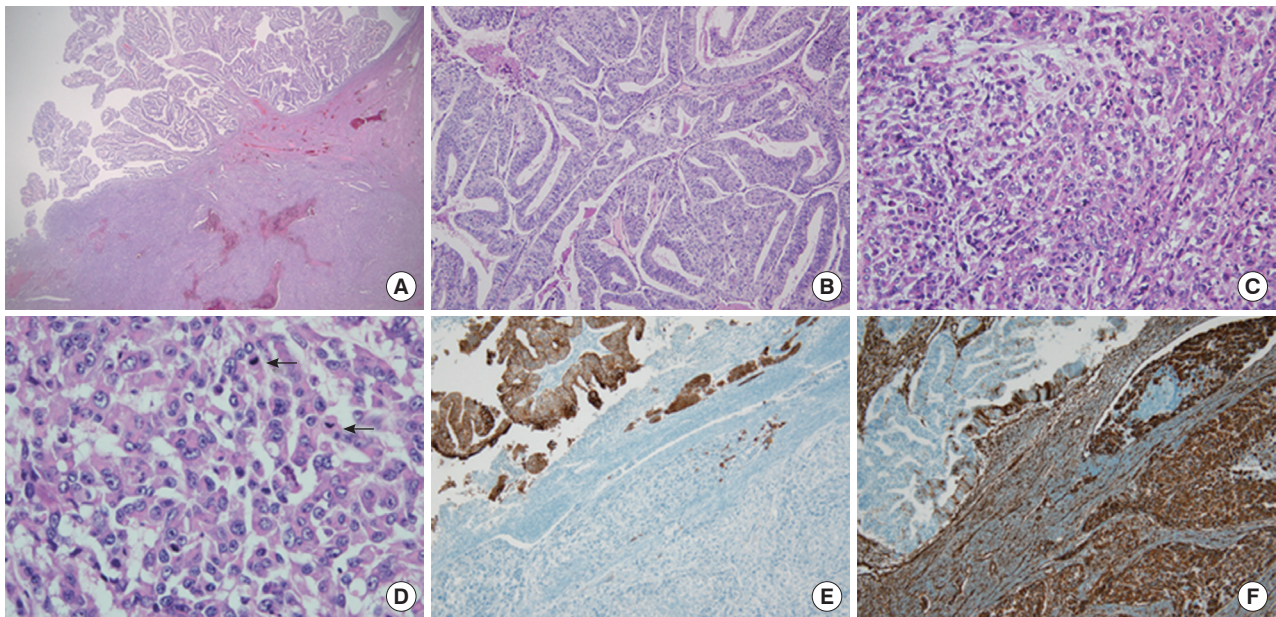
nosis of DEAC.

## DISCUSSION

Undifferentiated carcinoma of the endometrium is a poorly defined neoplasm. The World Health Organization (WHO) classification defines endometrial undifferentiated carcinoma as a

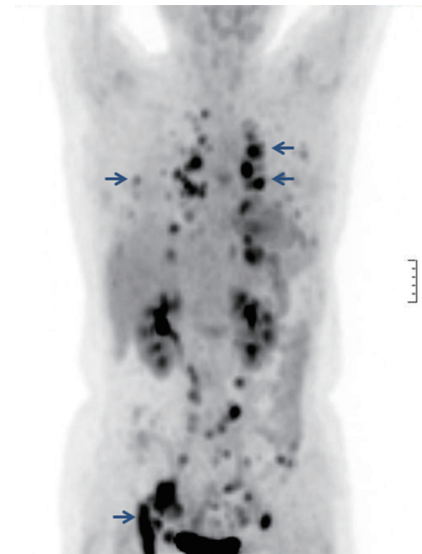


**Fig. 1.** Gross photographs of dedifferentiated endometrioid adenocarcinoma. The uterine corpus is occupied by a huge polypoid mass that fills the endometrial cavity (A), and an underlying solid mass infiltrates less than one half of the myometrium with two underlying leiomyomas (B).



**Fig. 2.** Dedifferentiated endometrial adenocarcinoma (A–D). (A) The transition between low grade endometrioid adenocarcinoma and undifferentiated carcinoma is abrupt with a sharp border. Superficial area is composed of low-grade endometrioid adenocarcinoma (B), and deep undifferentiated area consists of monotonous undifferentiated cells, forming a solid sheet without a specific pattern (C). (D) The undifferentiated carcinoma shows dyshesive round cells with rhabdoid features, prominent nucleoli, and numerous mitotic figures (arrows). The differentiated component is diffusely positive for cytokeratin (E) and focally positive for vimentin (F). On the contrary, tumor cells in the undifferentiated area are focally positive for cytokeratin and diffusely positive for vimentin.

malignant tumor with an epithelial structure that is too poorly differentiated to be placed in any other category of carcinomas.<sup>4</sup> The MD Anderson group reviewed 633 cases of endometrial adenocarcinomas and found that cases of undifferentiated carcino-



**Fig. 3.** Follow-up positron emission tomography-computed tomography. Multiple pulmonary and pelvic bone metastases, peritoneal seeding, and mediastinal lymph node metastases are shown (arrows).

ma of the endometrium represent 9% of endometrial carcinomas.<sup>2,3</sup> In their series, 71% of cases of undifferentiated carcinoma were admixed with low-grade endometrioid adenocarcinoma referred to as DEAC.<sup>2,3</sup> They suggested that the undifferentiated carcinoma originated secondary to the transformation or the dedifferentiation of the low-grade endometrioid adenocarcinoma.<sup>2</sup> A recent study suggests that undifferentiated carcinoma is associated with a defect in the DNA mismatch repair pathway, as in Lynch syndrome.<sup>5</sup>

Dedifferentiation refers to the progression of cells toward a less differentiated state in which the original line of differentiation is no longer evident.<sup>5</sup> Dedifferentiation was first proposed by Dahlin and Beabout in 1971<sup>6</sup> when they described dedifferentiated chondrosarcoma as a distinct clinicopathological entity characterized by a low-grade chondrosarcoma juxtaposed to a histologically different high-grade sarcoma.<sup>6</sup> Lately, dedifferentiation has been recognized in a variety of epithelial malignancies, including those affecting salivary gland, kidneys, and thyroid.<sup>7</sup>

DEAC is part of the spectrum of undifferentiated carcinomas of the endometrium. The biological behavior of DEAC is determined by the undifferentiated component. The presence of even a small undifferentiated component appears to be associated with poor clinical outcomes.<sup>2</sup>

Patients with undifferentiated carcinoma often present with advanced stage disease, and more than 60% of these patients die from the disease within five years of being diagnosed.<sup>8</sup>

Taraif *et al.*<sup>9</sup> reported that 80% of patients died within 12 months of diagnosis. In our case, the pathological stage was low at the time of the surgery. However, despite postoperative chemoradiation therapy, the patient died seven months after the diagnosis due to extensive tumor metastasis.

The undifferentiated component of DEAC can be misdiagnosed as the solid component of a FIGO grade 3 endometrioid adenocarcinoma. FIGO grade 3 endometrioid adenocarcinoma always exhibits a solid growth pattern, with focal glandular differentiation.<sup>3</sup> The nuclear features of tumor cells in both the glandular and the solid areas tend to be cytologically similar.<sup>1</sup> In contrast, the solid areas in DEAC are characterized by dysplastic cells which grow in a sheet-like sarcomatoid pattern. The cytological features of the undifferentiated and differentiated components are distinct. Usually, the differentiated components tend to be superficial, whereas the undifferentiated components are deep and invade the myometrium.<sup>10</sup> These two components often display an abrupt transition which resembles a collision tumor. As in this case, the immunohistochemical expression of CK and EMA are diffusely positive in FIGO grade 3 endome-

trioid adenocarcinoma, whereas the expression of CK and EMA is focal (<10%) in the solid area of DEAC.

The undifferentiated component of DEAC can be confused with other tumors, including carcinosarcoma, undifferentiated endometrial sarcoma, poorly differentiated neuroendocrine carcinoma, and lymphoma. DEAC can be misdiagnosed as carcinosarcoma due to its biphasic appearance. The sarcomatous component of a carcinosarcoma is usually composed of spindle cells, and the epithelial component usually consists of high grade tumor cells.<sup>10</sup> Undifferentiated endometrial sarcomas are frequently much more pleomorphic and at least focally spindled.<sup>10</sup> Neuroendocrine carcinomas and lymphomas can be differentiated on the basis of their immunohistochemistry.

In summary, DEAC is an uncommon, highly aggressive, and frequently misdiagnosed tumor. The recognition of the undifferentiated component associated with low-grade endometrioid adenocarcinoma is very important. A range of differentials needs to be considered and ruled out on the basis of the clinical profile, morphology, and immunohistochemical features of this tumor.

### Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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