Endometrial dedifferentiated carcinoma: a case report. 
Pathological review at a single institution and systematic review of published literature

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Summary

Background: Endometrial dedifferentiated carcinoma (DC) is a rare histological subtype with an unclear clinical outcome. Materials and Methods: The authors conducted a pathological review of patients with endometrial endometrioid carcinoma treated in this hospital between 1990 and 2013 according to 2014 World Health Organization criteria. They systematically reviewed PubMed literature and the present case concerning the clinical features of DC. Results: One (0.25%) of 375 DC patients was identified. A PubMed search detected 46 patients in 13 studies. Stage information was detailed in 45 patients, as follows: 9 (20%) Stage I, 5 (11%) Stage II, 10 (22%) Stage III, and 21 (47%) Stage IV. Surgical details were reported for 12 patients; 7 (58%) with complete resection, and 5 (42%) with incomplete resection. Early stage and complete resection improved overall survival (p < 0.01, p = 0.02, respectively). Conclusion: DC is a rare and aggressive histological subtype. Further research is needed to investigate new treatment strategies for DC.

Key words: dedifferentiated carcinoma, dedifferentiated endometrioid adenocarcinoma, endometrioid adenocarcinoma, endometrial cancer, endometrial dedifferentiated carcinoma

Introduction

Endometrial carcinoma is the most common gynecologic malignancy. Determining the histological subtype has been an important factor in predicting the prognosis, along with using the International Federation of Gynecology and Obstetrics (FIGO) staging system. Of these subtypes, dedifferentiated carcinoma (DC) was first added to the World Health Organization (WHO) criteria in 2014. The 2014 WHO criteria defined DC as undifferentiated carcinoma complicated with Grade 1 or 2 endometrioid carcinoma as a secondary component. Moreover, the differentiated endometrioid component lines the endometrial cavity, while the undifferentiated component grows beneath it.

Several reports have demonstrated the clinical outcome regarding DC. DC has been assumed to be an aggressive tumor that induces a poor clinical outcome regardless of aggressive treatment that includes surgery and chemotherapy. However, there have been fewer reports clearly detailing the clinical behavior of DC.

Our study aimed to identify DC through a central pathological review of all grades of endometrioid carcinoma at our institution, through a systematic review of the current literature, and a review of our 1 DC patient identified at our institution.

Materials and Methods

The authors identified patients with all grades of endometrioid carcinoma treated with primary surgery, including hysterectomy and bilateral salpingo-oophorectomy, at this hospital between 1990 and 2013. The stages were defined according to the 2008 FIGO staging system. For all patients, central pathological reviews and re-diagnosis were conducted according to 2014 WHO criteria. Briefly, DC is composed of undifferentiated carcinoma and is defined as a malignant epithelial neoplasm with no differentiation and a second component of either FIGO grade 1 or 2 endometrioid carcinoma. The research project was approved by the Institutional Ethical Review Board Committee of the National Defense Medical College Hospital, Tokorozawa, Japan.

A PubMed search was undertaken using the following keywords: dedifferentiated carcinoma, dedifferentiated endometrioid adenocarcinoma, differentiated endometrial cancer, endometrial dedifferentiated, and endometrioid adenocarcinoma. These keywords were combined using the word OR. The authors included literature written in English and published between February 1950 and November 2017 that reported clinical outcomes and clinicopathological features. Case reports complicated with other cancers, such as ovarian cancers, were excluded. The literature was selected based on the titles. Furthermore, relevant references cited within the reviewed literature were added to this review. Cases with several key factors missing from the reports were defined as unknown. Percentages were calculated using the case details provided in the reports.

Data analyses were undertaken using STAT View software ver. 5.0. The χ²-test, Fisher’s exact test, and Mann-Whitney U test were used to evaluate the clinical significance of clinicopathological factors. Overall survival (OS) was defined as the interval from primary surgery to death, and OS curves were generated using the Kaplan-Meier method. Comparisons of the survival distribution were made using a log-rank test. A statistically significant difference was defined as p < 0.05.

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Case Report

A 74-year-old gravida 4, para 4 postmenopausal woman visited a local gynecology clinic, complaining primarily of continuous vaginal bleeding over a one-year period. She experienced menopause at an age of 50 years. The pathological examination of her endometrial cytology indicated a suspected adenocarcinoma and she was referred to this hospital. Her medical history included cancer of the rectum. Her serum tumor marker level was not elevated: CA 125; 8.0 U/ml and CA 19-9; 12.0 U/ml. MRI showed a polypoid mass in the endometrial cavity with a low signal intensity on T2-weighted imaging. CT did not reveal distant metastasis. The posterior wall of the uterus adhered tightly to the inferior part of the sacrum; therefore, a supra-vaginal hysterectomy and a bilateral salpingo-oophorectomy had been performed. The polypoid mass had filled the entire endometrial cavity and the depth of invasion was slight on gross examination. Her disease had been diagnosed as a Grade 3 endometrioid carcinoma at FIGO Stage IA. Adjuvant treatment was not performed as patient consent was not obtained. The patient has been disease-free for 67 months after surgery.

During the study period, 375 patients were identified and, through a central pathological review, 1 (0.25%) patient was diagnosed with DC. Histopathological findings showed an abrupt transition at the border between the well-differentiated endometrioid carcinoma and the undifferentiated carcinoma component. In the undifferentiated carcinoma component, the tumor cells had relatively monotonous hyperchromatic nuclei and scant eosinophilic cytoplasm and formed a discohesive sheet structure without any glandular formation. On the other hand, the Grade 1 endometrioid carcinoma formed a well-differentiated tubular structure (Figures 1 a-c).

A PubMed search identified 474 articles, of which 465 were excluded and eight were added from cited references. Finally, 13 articles were reviewed (Figure 2). The authors reviewed the reported DC patients in these 13 studies, and the pathology report of the present patient, and 46 patients were included. The overall patient characteristics are summarized in Table 1. Data regarding age were obtained for all patients. The median age was 58 (range, 41-79 years). The FIGO stage data were determined in 45 patients, as follows: 9 (20%) patients at Stage I, 5 (11%) at Stage II, 10 (22%) at Stage III, and 21 (47%) at Stage IV. Surgical treatment details had been provided for 12 patients. Seven (58%) of 12 patients achieved complete resection. Information regarding lymphovascular invasion was reported for 13 patients, with 12 (92%) of 13 patients having had positive lymphovascular invasion. Data regarding lymphovascular invasion was reported for 13 patients, with 12 (92%) of 13 patients having had positive lymphovascular invasion.
Figure 3.—Overall survival curves were generated using the Kaplan–Meier method according to several factors. (A) The overall survival (OS) for Stage I and II patients is better than for Stages III and IV ($p < 0.01$). (B) OS for patients with complete resection is better than for those with incomplete resection ($p = 0.02$). (C) OS differences are not evaluated in patients with or without lymphovascular invasion. (D) There are no differences of OS in patients with or without adjuvant therapy ($p = 0.19$).

concerning adjuvant therapy were reported for 19 patients, with 15 (79%) of 19 patients having received adjuvant therapy. The adjuvant treatment strategies for the DC patients were chemotherapy and/or radiotherapy. Five (38%) of 13 patients had been treated with chemotherapy and four (31%) had been treated with radiotherapy. Six (41%) patients had been treated with both chemotherapy and radiotherapy. Four of five patients (80%) received taxane and platinum combination chemotherapy. They recurred within 12 months and died of diseases. One patient received the combination with adriamycin and cisplatin and was alive for 24 months. Three of four (75%) patients received pelvic radiotherapy or brachytherapy. They recurred within four, five, and 14 months from adjuvant therapy and died of diseases. One patient underwent external beam radiotherapy and intracavitary radiotherapy and lived for 39 months. Five of six (83%) patients underwent the combination with cisplatin-based chemotherapy and radiotherapy and died of diseases. One patient received taxane and platinum chemotherapy and radiotherapy and was alive for 78 months. According to several factors, the OS is shown in Figure 3. The OS of patients at Stage III and IV was poorer than for those at Stage I and II ($p < 0.01$). Additionally, the OS of patients with incomplete resection was poorer than for those with complete surgery ($p = 0.02$). Other factors did not statistically influence OS.

Discussion

Many aspects of the systematic review were unclear because DC, defined as a combination of an undifferentiated carcinoma component with a Grade 1 or 2 endometrioid carcinoma component, was first recognized in 2014 as a rare histological subtype [20]. Therefore, the present study focused on the endometrioid carcinoma component and the authors conducted a central pathological review of all grades of endometrioid carcinoma. As a result, one (0.25%) patient with DC (of 375 patients) was identified. In a previous report that reviewed all the pathological histology, the frequency of undifferentiated carcinoma was 2.9% [9], which was higher than the results of the present study. Furthermore, that report identified four patients with DC and demonstrated that two (50%) of four patients had been initially diagnosed with poorly-differentiated carcinoma. If the present authors had added all the patients initially diagnosed with pathological histology, including poorly-differentiated carcinoma or undifferentiated carcinoma to the pathological review, the frequency of DC in this study would likely have increased.

In this study, the initial diagnosis for the patient re-diagnosed with DC was a Grade 3 endometrioid carcinoma. According to the WHO grading system criteria, endometrioid carcinoma has been primarily graded through calculating the percentage of solid parts. Moreover, the presence of Grade 3 nuclei involving < 50% of the tumor is associated with aggressive behavior and, therefore, justifies upgrading the tumor by one grade [20]. In the present study, the one patient initially diagnosed with Grade 3 endometrioid comprising < 50% solid parts but not with nuclei atypia, was later diagnosed as DC. Therefore, the present authors recommend that careful attention be paid to a diagnosis of Grade 3 endometrioid carcinoma with more than 50% of solid parts in future. Some reports have indicated that no clear definition of solid parts may result in misdiagnosis [6-9, 12, 15]. To achieve a more precise diagnosis of DC, a clear definition of solid parts is needed. The present authors consider this to be an important issue because the biological behavior and prognosis of Grade 3 endometrioid carcinoma is clearly different from DC [7]. Therefore, to improve the treatment strategy, a more exact diagnosis is required.

No reports systematically explored the efficacy of treatment such as surgery and adjuvant therapy [8, 13, 19]. Therefore, the present authors aimed to systematically review and investigate appropriate treatments, using current available information. According to the review in this study, more patients with DC had been diagnosed with advanced-staged diseases and positive lymphovascular invasion. These results imply that DC might be an aggressive histological subtype. Furthermore, as a better prognostic factor, Stages I and II and complete resection have been identified, and the most important treatment strategy was early diagnosis and complete surgical resection. This study did not seek to determine the usefulness of adjuvant therapy. More DC patients were identified at an advanced stage, and the authors assumed that those patients had not received complete resection. Further studies are required to investigate those patients with incomplete resection to develop new treatment strategies. On the other hand, loss of mismatch repair protein and switch/sucrose non-fermenting complex protein were frequently observed in DC [21, 22] and these biological characteristics might provide useful information.
in developing new therapies.

The present study was limited in that this was a limited case review of a small number of available reports concerning DC. However, this study identified that the disease stage and the surgical treatment were important prognostic factors, and that improvements in new adjuvant therapy are required. Furthermore, because DC has been assumed to be an aggressive tumor, and considering the results of the present study, future studies are needed to evaluate more patients with DC.

In conclusion, DC is a rare and aggressive histological subtype of endometrial carcinoma. More exact diagnosis would likely clarify the biological features of DC, which may then help to determine new treatment strategies to combat this disease.

References


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