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Case Report

Dedifferentiated endometrial carcinoma – unveiling the complexities of an aggressive tumour

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Abstract

Uterine corpus tumours represent the most common gynaecological malignancies, with their pathological characteristics largely well-documented. However, dedifferentiated endometrial carcinoma (DEC) remains a subject requiring extensive research to establish appropriate management guidelines. Here, we present two cases of DEC, highlighting its morphological and immunohistochemical features that may aid in differential diagnosis. Recognizing this subtype is crucial, as it is associated with worse clinical outcomes and a poorer prognosis compared to high-grade endometrioid carcinoma.

Keywords: Endometrial carcinoma, Endometrioid carcinoma, Dedifferentiated, Undifferentiated, Immunohistochemical.

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1. Introduction

Dedifferentiated Endometrial Carcinoma (DEC) is a uterine corpus neoplasm characterized by the presence of both a low-grade endometrioid carcinoma (LGEC) component and a high-grade solid undifferentiated carcinoma component.[1] This distinct form of dedifferentiation in the uterus and ovary was first described by Silva et al. in 2006 and is recognized as an aggressive tumour with a poor prognosis.[2] Undifferentiated endometrial carcinomas (UEC) are characterized by patternless, sheet-like growth of discohesive cells with an aggressive clinical course. Notably, Silva et al.'s studies highlight that DEC remains a fulminant malignancy, even when the undifferentiated carcinomatous component constitutes only 20% of the total tumour volume.[3]

2. Case Presentation

1.1. Case 1

A 61-year-old postmenopausal woman with no significant medical history presented with two months history of postmenopausal bleeding. She underwent dilatation and curettage (D&C) at an outside facility, and the biopsy revealed a poorly differentiated neoplasm. A computed tomography (CT) scan identified a hypoechoic lesion measuring 4.3 × 4.2 × 3 cm within the endometrial cavity, without evidence of parametrial invasion or distant metastasis (**Figure 1**). A PET-CT scan further confirmed a metabolically active hypodense lesion within the endometrial cavity, with no signs of metastatic spread.

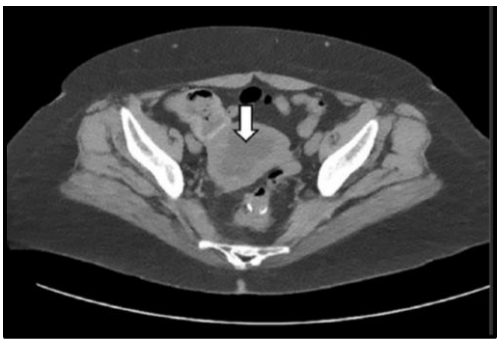

Figure 1: CT PELVIS showing a hypoechoeic lesion (white down arrow) within the endometrial cavity

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The patient underwent a radical hysterectomy. Gross examination revealed that the endometrial cavity was occupied by an ulceroproliferative, gray-white, fleshy lesion measuring 4.7 × 4.1 × 2.3 cm. The lesion infiltrated more than half of the myometrium and extended to the lower uterine segment. The ovaries, fallopian tubes, and omentum appeared unremarkable (**Figure 2**).

Figure 2: Panhysterectomy specimen showing an ulceroproliferative growth (blue arrow) within the endometrial cavity

Histology of the resected specimen showed a tumour with a well differentiated component- Figo Grade 1 (**Figure 3**) and an undifferentiated component (**Figure 4**) with abrupt transition between the two (**Figure 5**). The well-differentiated component consisted of low-grade tumour cells arranged in papillary and glandular structures. In contrast, the undifferentiated component was characterized by solid sheets of discohesive, monomorphic cells, lacking any glandular differentiation. Focal area showed squamous metaplasia with abrupt keratinisation in the poorly differentiated areas (**Figure 6**). The neoplasm infiltrated into more than half of the myometrium, and was seen extending inferiorly into the isthmus. Brisk mitotic activity (6-8/hpf) was noted along with extensive areas of necrosis and lymphovascular emboli. Both parametrium, cervix and adnexa were free of neoplasm. Pelvic lymph node sampling showed no evidence of metastasis. Overall, a diagnosis of DEC was established. The patient was refused to take adjuvant chemotherapy, and is now on regular follow up.

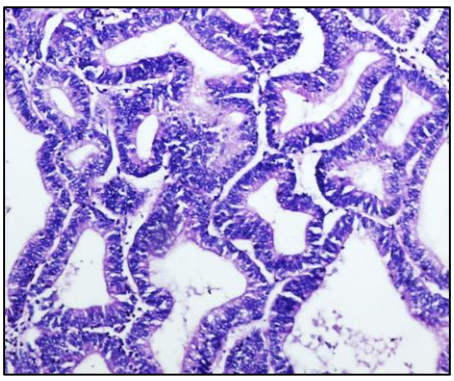

Figure 3: Differentiated component composed of low grade tumour cells arranged in glandular pattern (H&E, 40X)

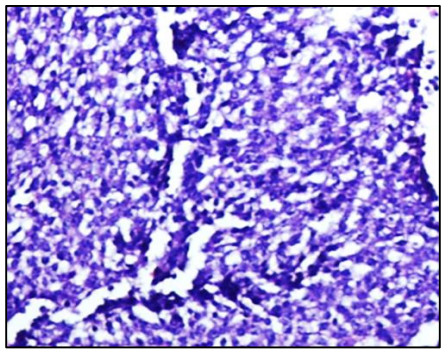

Figure 4: Undifferentiated component composed of solid sheets of poorly cohesive and monomorphic neoplastic cells (H&E, 40X)

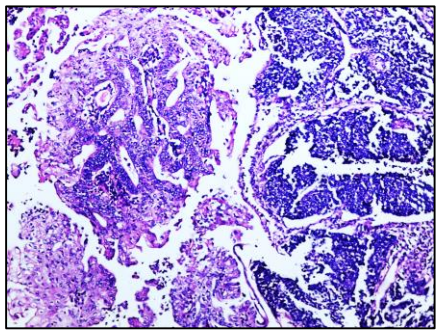

Figure 5: Abrupt transition from villoglandular well differentiated pattern to poorly differentiated component composed of cells arranged in solid sheets (H&E, `10X)

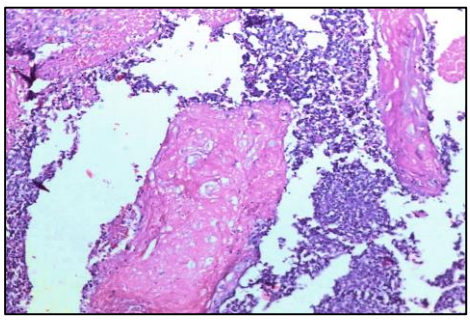

Figure 6: Squamous metaplasia with abrupt keratinisation in the poorly differentiated areas (H&E, 10X)

2.2. Case 2

A 65 year old female presented with complaints of postmenopausal bleeding along with pain over left buttocks, which is radiating to posterior thigh since 2 months. Pipelle biopsy was done, which showed atypical endometrial hyperplasia with foci of in-situ carcinomatous change. A subsequent CECT abdomen and chest showed thickened uterine endometrium (2.3cm) and a subcentemetric pulmonary nodule of size 0.4cm in the right upper lobe, with no evidence of intra-abdominal metastasis.

The patient underwent a radical hysterectomy. Gross examination revealed that the endometrial cavity was dilated and occupied by an ulcer proliferative growth measuring 3 × 2.8 × 1.5 cm. The tumour infiltrated less than 50% of the

myometrium and extended to the lower uterine segment. The ovaries, fallopian tubes, and omentum appeared unremarkable (**Figure 7**).

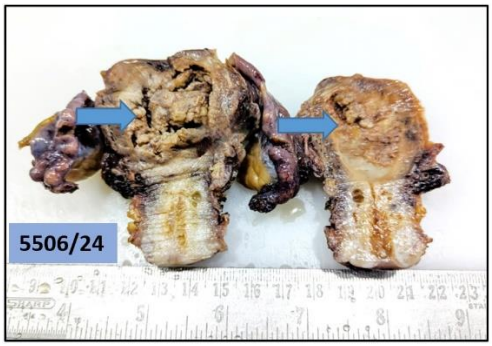

Figure 7: Panhysterectomy specimen showing an ulcer proliferative growth (blue arrow) within the endometrial cavity

Histopathological examination of the endometrial tumour revealed two distinct patterns. The predominant component was FIGO grade 2 endometrioid carcinoma, with focal areas showing an abrupt transition to an undifferentiated component (**Figure 8**). The undifferentiated component was composed of sheets and nests of slightly discohesive monomorphic cells lacking glandular structures, exhibiting brisk mitotic activity and necrosis (**Figure 9**). The tumour infiltrated less than half of the myometrium and extended inferiorly into the isthmus. Both parametrium, cervix, and adnexa were free of neoplasm, and pelvic lymph node sampling showed no evidence of metastasis.

Immunohistochemical analysis demonstrated that the differentiated areas were positive for estrogen receptor (ER) and progesterone receptor (PR), while these markers were negative in the undifferentiated carcinomatous areas (**Figure 10**, **Figure 11**). Aberrant p53 expression was observed in the undifferentiated areas (**Figure 12**). The overall histopathological and immunohistochemical findings were consistent with a diagnosis of dedifferentiated endometrial carcinoma (DEC). The patient was started on adjuvant chemotherapy and is now on regular follow up.

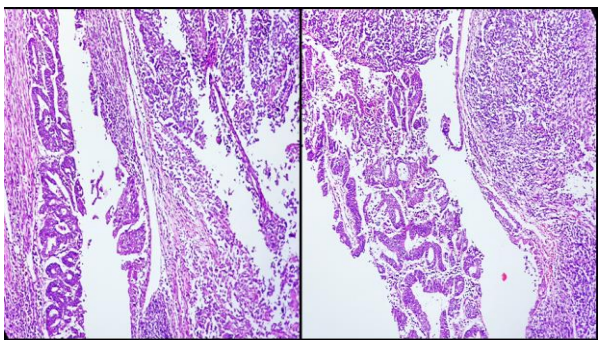

Figure 8: Abrupt transition from WD to UD component in two different areas (H&E, 10X) (WD: well differentiated UC: undifferentiated)

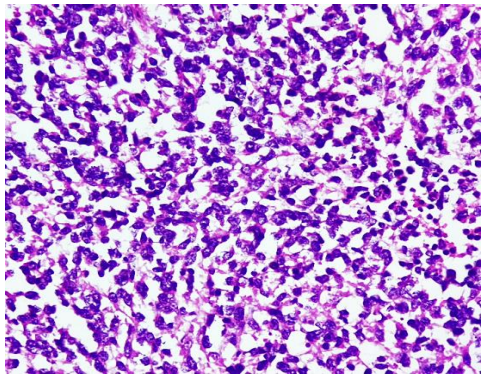

Figure 9: The undifferentiated component showing sheets of pleomorphic cells with prominent nucleoli and brisk mitotic activity (40X, H&E)

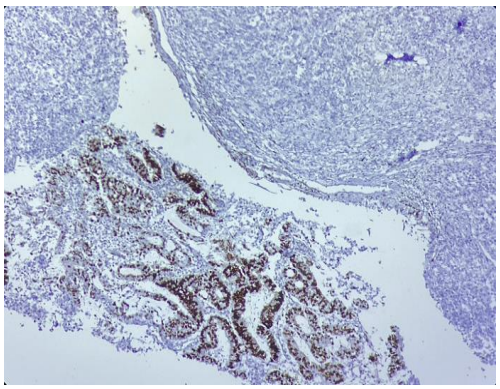

Figure 10: Immunohistochemical staining for estrogen receptor (ER) at 10X magnification showing a non-reactive undifferentiated carcinomatous component adjacent to an immunoreactive well-differentiated carcinomatous component.

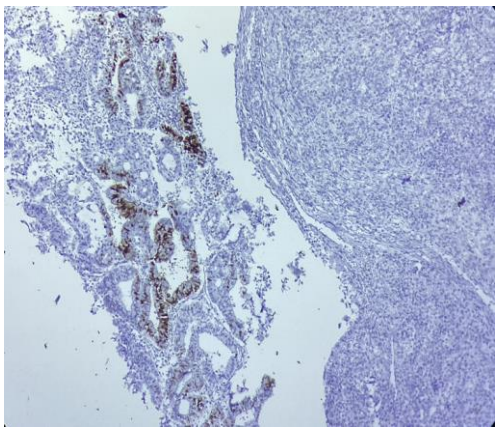

Figure 11: Immunohistochemical staining for progesterone receptor (PR) at 10X magnification demonstrating a non-reactive undifferentiated carcinomatous component adjacent to an immunoreactive well-differentiated carcinomatous component.

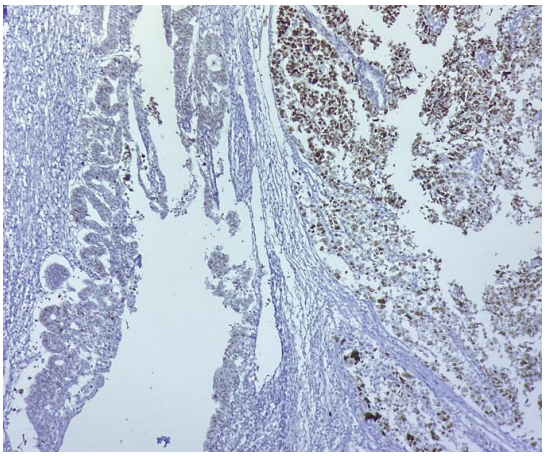

Figure 12: Immunohistochemical stains, P53, 10X shows an aberrant expression in the undifferentiated carcinomatous area

3. Discussion

Undifferentiated endometrial carcinoma (UEC) is an aggressive subtype of endometrial carcinoma, characterized by a total lack of glandular differentiation and a patternless solid growth of tumour cells.[4] Dedifferentiated endometrial carcinoma (DEC) is a rare variant, accounting for approximately 2-9% of endometrial adenocarcinomas. This incidence rate may be an underestimation due to the diagnostic challenges posed by dedifferentiated tumors.[4] In 2014, the WHO classification of tumours of the female reproductive organs (4th edition) recognized DEC as a distinct pathological subtype of endometrial carcinoma. DEC is defined as a tumour that contains both well-differentiated (FIGO grade 1 or 2) and undifferentiated components, with a sharp, abrupt transition between the two tumour components. Silva et al. first identified this entity in 2006, describing 25 cases of DEC and concluding that the undifferentiated component represents a progression from preexisting low-grade endometrioid adenocarcinoma.[5]

The median age at diagnosis for dedifferentiated endometrial carcinoma (DEC) is typically around 55 years, although up to 40% of patients are diagnosed before the age of 50. The first step in diagnosing suspected endometrial carcinoma is obtaining an endometrial biopsy through dilation and curettage. However, DEC is often missed on biopsy since the undifferentiated carcinomatous component typically makes up a small portion of the tumour and is often located deeper within the myometrium. This presents a challenge in management, as low-grade endometrial tumours are usually treated with total hysterectomy alone. Intraoperative frozen section can sometimes help identify DEC, but it has its limitations. Since only a small portion of the tumour is examined, and undifferentiated areas are usually focal, these areas are often missed. The proportion of the undifferentiated carcinomatous component can vary significantly, ranging from 20% to 90%.[6] In our patient, the permanent sections revealed that the undifferentiated component accounted for only 20% of the total tumour volume.

In both our cases, DEC could not be accurately diagnosed through biopsy, curettage, or imaging studies. The correct diagnosis was only established after a pathological examination of the surgical specimen. Initially, both cases were diagnosed as poorly differentiated carcinoma. Recent research indicates that while endometrial biopsy or curettage is generally effective in detecting endometrial cancer, its sensitivity diminishes for high-risk histological subtypes.[7] Furthermore, diagnosing high-grade endometrial carcinomas has shown lower interobserver reproducibility compared to low-grade tumours. Consequently, when preoperative findings suggest high-grade endometrial carcinomas, it is crucial for the surgeon to consider comprehensive surgical staging.

To accurately diagnose DEC, it is essential to identify the undifferentiated carcinomatous (UC) component. While the histological features of UC may overlap with those of high-grade endometrioid adenocarcinoma, key distinctions exist. UC is characterized by tumour cells that lack intercellular cohesion, forming pattern less solid sheets without gland formation. In contrast, high-grade endometrioid adenocarcinoma exhibits at least focal areas of gland formation with cohesive cells.

In our cases, UC tumour cells also demonstrated larger nuclei with more prominent nucleoli compared to conventional endometrioid adenocarcinoma. Additionally, these cells displayed areas of brisk mitotic activity and focal regions of abrupt keratinization, further distinguishing UC from other histological subtypes.

Histopathologically, dedifferentiated endometrial carcinoma (DEC) is often misdiagnosed as endometrial serous carcinoma - solid variant, high grade endometrial endometrioid adenocarcinoma, SMARCA4 deficient uterine sarcoma and endometrial or ovarian carcinosarcoma (malignant mixed Müllerian tumour (MMMT).[9] In DEC, the undifferentiated carcinomatous component is characterized by a solid growth pattern of pleomorphic epithelial cells with prominent nucleoli, brisk mitotic activity, and significant atypia. This can be mistaken for the solid growth pattern seen in FIGO grade 3 tumours (**Table 1**).

Unlike the spindle cells seen in sarcomas, the cells in DEC are epithelioid. In MMMT, the carcinomatous component typically consists of high-grade serous carcinoma. When the undifferentiated component of DEC is extensive, it can even be mistaken for a high-grade sarcoma. Differentiating between the two entities can be challenging, as the undifferentiated component of DEC may lose cytokeratin (CK) and/or epithelial membrane antigen (EMA) immunoreactivity.[4]

Table 1: Comparison between solid areas in FIGO grade 3 endometrioid carcinoma and dedifferentiated endometrial carcinoma (DEC)

Features	FIGO Grade 3 Endometrioid Carcinoma	Dedifferentiated Endometrial Carcinoma (DEC)
Cell Appearance	Cells resemble the glandular component	Cells show variable histological patterns
Tumour Architecture	Solid areas are intermixed with glandular components	Solid areas adjacent to glandular components with an abrupt transition
Growth Pattern	Cells form cords, trabeculae, or nests	Pattern less solid growth is predominant

While most uterine sarcomas exhibit a spindled cell morphology, which differs from the epithelioid pattern of DEC, the overlapping features can make diagnosis difficult. In our cases, we needed to sample extensively to identify the undifferentiated carcinomatous areas, as these were only a minor component of the tumour.

Table 1 highlights the differences between the solid areas in FIGO grade 3 endometrioid carcinoma and DEC, helping to differentiate the two entities in histopathological evaluation.

Differentiating the undifferentiated component of dedifferentiated endometrial carcinoma (DEC) from high-grade endometrial cancer is crucial for accurate diagnosis. Immunohistochemical studies play a key role in this differential diagnosis. The differentiated components of DEC typically show strong immunoreactivity for keratins, epithelial membrane antigen (EMA), estrogen receptor (ER), and progesterone receptor (PR). In contrast, the undifferentiated components exhibit almost complete loss of expression of these markers or only focal staining for keratins and EMA.[9]

Pure undifferentiated endometrial carcinoma (UEC) is a high-grade tumour with a poor prognosis, with the overall 5-year survival rate reported to range from 5% to 25%.[5] It is important to note that DEC and UEC are distinct entities. Although the high-grade components of both tumours may appear similar—consisting of monotonous medium- to large-sized discohesive cells arranged in solid sheets with no characteristic morphological pattern—DEC also includes a low-grade endometrioid carcinoma component.

Furthermore, the immunohistochemical profile of UEC may show focal staining for cytokeratin (AE1/AE3), while DEC must show clear evidence of epithelial origin in its immunohistochemical markers.[10] This distinction is essential for accurate diagnosis and prognosis.

4. Conclusion

Dedifferentiated endometrial carcinoma (DEC) is an extremely aggressive neoplasm with a very poor prognosis. The likelihood of recurrence or death is high, affecting 55-95% of cases.[8] Even when the undifferentiated component comprises as little as 20% of the tumour, it significantly worsens the prognosis.[11] The coexistence of low-grade endometrioid carcinoma (LGEC) and solid undifferentiated carcinoma often leads to diagnostic challenges, and DEC can be mistakenly identified as Grade 2 or Grade 3 endometrial carcinoma, which may result in under-recognition.[2]

It is crucial to distinguish Grade 3 endometrioid carcinoma from DEC due to the latter's aggressive behavior and poorer prognosis. DEC should not be misdiagnosed or overlooked as conventional endometrioid adenocarcinoma, as it follows a fulminant clinical course. Therefore, it is essential to accurately recognize and diagnose undifferentiated carcinoma, including DEC, using appropriate diagnostic methods. Early and correct identification allows for more intensive treatment, which can potentially improve patient survival.

5. Source of Funding

None.

6. Conflict of Interest

None.

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