

## CASE REPORT

**DEDIFFERENTIATED ENDOMETRIAL CARCINOMA: AN ONGOING DIAGNOSTIC DILEMMA**

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Tumours of uterine corpus are the most common gynaecological malignancies. The clinicopathological features of most of these tumours are well understood; however, dedifferentiated endometrial carcinoma still requires a lot of research to establish adequate management guidelines. The entity was first described in 2006 and is an aggressive tumour with poor prognosis. We present two cases of this tumour with a literature review, emphasising morphologic and immunohistochemical features that may help in the differential diagnosis.

**Key words:** dedifferentiated endometrial carcinoma, endometrial carcinoma, endometrioid carcinoma undifferentiated carcinoma, immunohistochemistry.

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**Introduction**

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The most common gynaecological malignancy in the United States and perhaps worldwide is endometrioid adenocarcinoma [1]. Today Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynaecology and Obstetrics) (FIGO) grading is the most widely used system to grade these tumours [2]. The problem with FIGO, however, is that it only addresses the endometrioid type of endometrial carcinomas and does not account for high-grade tumours including dedifferentiated endometrial carcinoma.

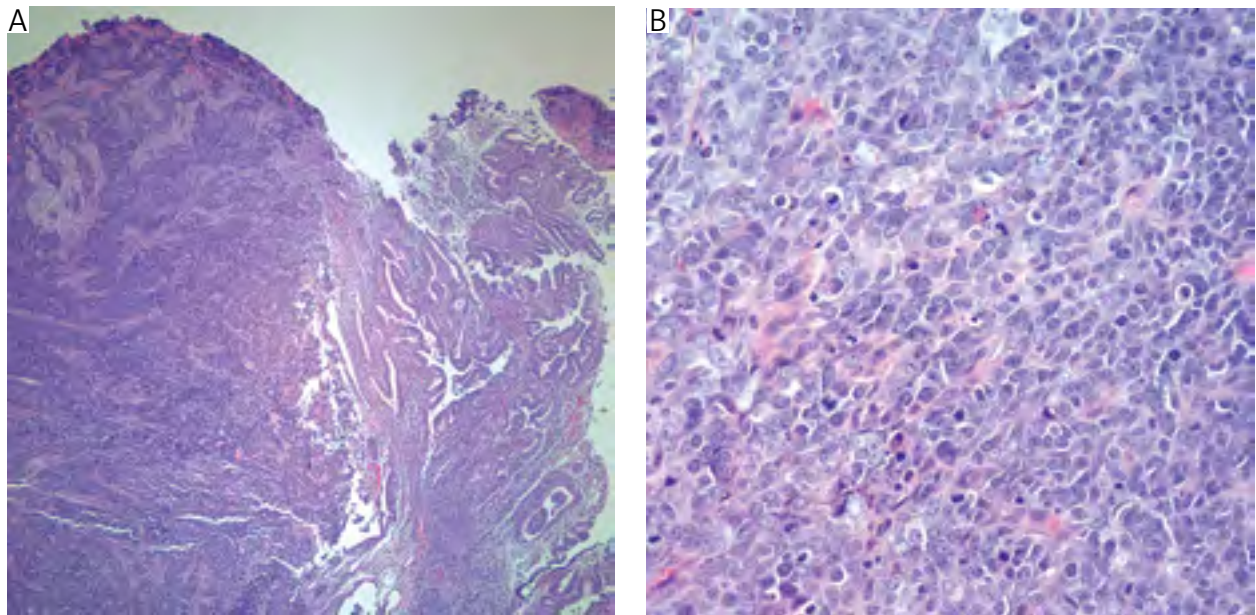
In dedifferentiated endometrial carcinoma, an undifferentiated component coexists adjacent to FIGO grade 1 or 2 tumour. Dedifferentiation has been well known in several carcinomas for a long time, but it was described in the endometrial adenocarcinoma for the first time in 2006 and was defined as “combined undifferentiated and differentiated carcinomas” [3]. Owing to the fact that the undifferentiated component of the tumour can be mistaken for a FIGO grade 3 tumour, the dedifferentiated endometrial carcinomas are still an under-recognised entity. Available data suggests that this is an aggressive tumour with poor prognosis [3, 4, 5, 6, 7, 8]. We report

two cases of dedifferentiated endometrial carcinoma. Both cases were initially diagnosed as low-grade endometrioid adenocarcinoma on the biopsy specimen. However, the hysterectomy specimen showed an undifferentiated component adjacent to the low-grade tumor.

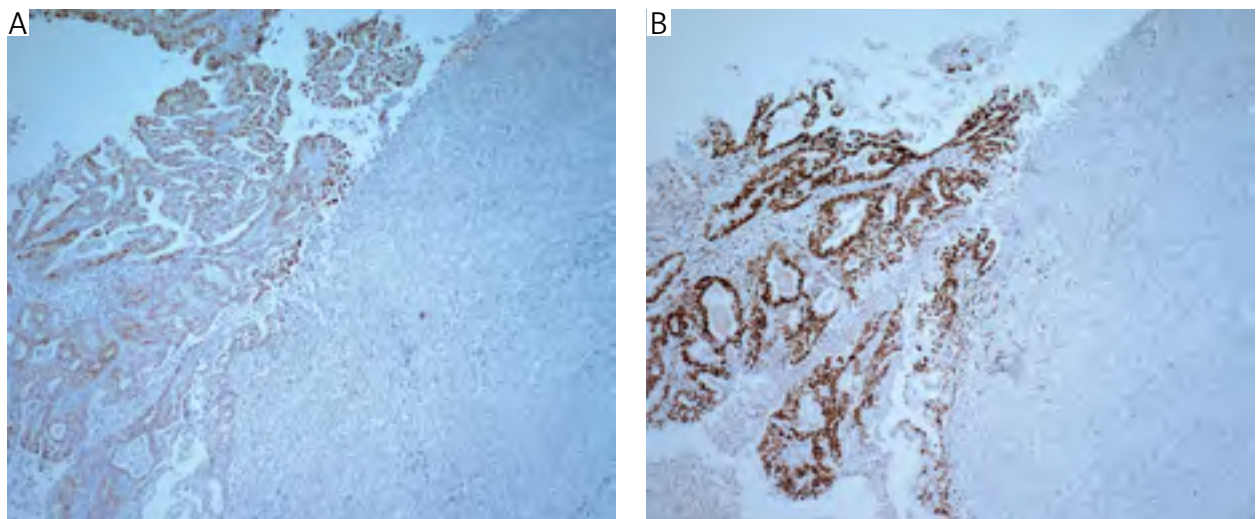
**Case 1**

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A 47-year-old woman underwent endometrial biopsy for menorrhagia that showed endometrial adenocarcinoma, FIGO grade I. The patient subsequently underwent hysterectomy. During hysterectomy, an intraoperative frozen section showed a superficially invasive endometrial adenocarcinoma, FIGO grade I. The tumour measured 5 cm in the greatest dimension. On permanent sections, the endometrial tumour from the hysterectomy specimen was composed of two adjacent patterns (Fig. 1A); the predominant component was FIGO grade 2 endometrioid carcinoma. Additionally, there were focal areas of abrupt transition to a higher-grade component that was composed of sheets and nests of slightly discohesive medium to large cells with moderately pleomorphic nuclei and some with prominent nucleoli along with brisk mitotic activity and necrosis (Fig. 1B). This



**Fig. 1.** A) Low-power (HE, 40×) photomicrograph of the endometrial tumour showing two adjacent patterns. B) Dedifferentiated component composed of sheets of pleomorphic cells with prominent nucleoli and brisk mitotic activity (HE, 400×)



**Fig. 2.** Immunohistochemical stains [A) PAX-8, 100×, and B) ER, 100×] showing non-reactive undifferentiated component adjacent to immunoreactive well-differentiated component

undifferentiated component was not immunoreactive with ER and PAX8 (Fig. 2A and B). EMA and Cam 5.2 showed a higher level of expression than expected in a typical dedifferentiated carcinoma; however, the overall morphologic and immunohistochemical profile was consistent with dedifferentiated carcinoma. The tumour showed loss of expression of MLH1 and PMS2 and was therefore positive for microsatellite instability. Postoperatively the patient received 6 cycles of systemic chemotherapy and a course of radiation therapy, given using vaginal cylinder in 5 equal fractions with a total dose of 2350 cGy. The patient was disease free 28 months post-hysterectomy.

## Case 2

A 71-year-old woman underwent endometrial biopsy for post-menopausal bleeding that showed endometrial adenocarcinoma FIGO grade 2. Intraoperative frozen section during subsequent hysterectomy showed a 4.5 cm FIGO grade 2 tumour with no definitive myometrial invasion. The permanent sections, however, showed a tumour similar in morphology to the first case. IHC stains showed the undifferentiated component to be negative for EMA, ER, and PAX 8. It was focally positive for Cam 5.2. Cytokeratin AE1/AE3 highlighted less than 25% of the undifferentiated component and synaptophysin

was negative. The tumour showed loss of expression of MSH2 and was therefore positive for microsatellite instability. The patient received 6 cycles of systemic chemotherapy and a course of pelvic brachytherapy. She was disease free 31 months post-hysterectomy.

## Discussion

Dedifferentiation in uterus and ovary was proposed by Silva *et al.* [3] in 2006. The hallmark of this tumour is the presence of an undifferentiated component in a low-grade (FIGO 1 and 2) endometrioid adenocarcinoma. Inactivating mutations involving *SMARCA4* and/or *SMARCB1* genes is thought to be the underlying mechanism in a substantial number of these tumours [9, 10, 11, 12].

Dedifferentiated carcinomas account for 2-9% of endometrial adenocarcinomas [4, 13, 14]. This figure, however, may be an underestimation due to diagnostic difficulty posed by dedifferentiated tumours. The median age of patients at the time of diagnosis is 55 years however, up to 40% patients were found to be below 50 years at the time of diagnosis [6]. One of our patients was 47 years old and the other one was 71 years old, presenting with menorrhagia and post-menopausal bleeding, respectively.

For suspected endometrial carcinoma, the first diagnostic step is obtaining an endometrial biopsy by dilation and curettage. Dedifferentiated tumour is, however, likely to be missed on a biopsy as the undifferentiated component accounts only for a small proportion of the tumour and is usually present deep in the myometrium. This can pose a management problem because lymph node dissection is not performed for low-grade tumours. Intraoperative frozen section can overcome this problem and the surgeon can tailor the surgery in accordance with the frozen section diagnosis. The frozen section, however, has its limitations as well because only a representative section of the tumour is used and again undifferentiated can be focal and hence missed on a frozen section. The proportion of undifferentiated component can vary between 20% to 90% [2].

In our patients, both were diagnosed with a low-grade (FIGO 1 or 2) tumour on endometrial biopsy. On permanent sections undifferentiated tumor comprised of 20% of total volume in both cases. Limited

lymph node sampling was done and both patients had negative lymph nodes.

Morphologically dedifferentiated endometrial carcinoma can be mistaken for a FIGO grade 3 tumor, malignant mixed Mullerian tumour (MMMT) or a high-grade sarcoma. The undifferentiated component of dedifferentiated tumours is characterised by a solid growth pattern of pleomorphic epithelial cells with prominent nucleoli, brisk mitotic activity, and significant atypia. This is in contrast to the solid growth in FIGO grade 3 tumours (Table I). The cells in dedifferentiated endometrial carcinoma are epithelioid as compared to spindle cells of the sarcoma component of the MMMT. Moreover, the carcinoma component in MMMT is frequently high-grade serous carcinoma. When the undifferentiated component of a dedifferentiated tumour is extensive it can be mistaken for a high-grade sarcoma. The distinction between the two entities becomes even more difficult because the undifferentiated component of the dedifferentiated tumour can lose cytokeratin (CK) and/or epithelial membrane antigen (EMA) immunoreactivity. Most sarcomas of the uterus, however, have spindled morphology in contrast to dedifferentiated endometrial carcinoma. In both of our cases, the diagnosis was fortunately straight forward because we found areas of abrupt transition between the solid sheets of undifferentiated component and low-grade FIGO 1-2 component.

Immunohistochemically the undifferentiated component is either negative for CK and EMA or shows focal staining. This is in contrast to the solid sheets of FIGO grade 3, which shows diffuse reactivity to keratin and EMA [5, 9, 15, 16]. Tafe *et al.* [6] found CK18 to be the most commonly positive keratin stain in the undifferentiated component. Some recent studies [5, 15, 17] evaluated other immunohistochemical markers including PAX8, oestrogen receptor (OR), p16, p53, and BRG1/INI1, which can aid the diagnosis of dedifferentiated endometrial carcinoma. PAX 8 expression is lost in 85-92% of cases, while OR expression is lost in 69-85% of cases of dedifferentiated endometrial carcinomas [5, 15]. Ramalingam *et al.* [15] found that p16 was diffusely positive in 34% of cases and p53 was expressed in > 75% of the tumour cells in 31% of cases. They also found E-cadherin and CD44 to be completely lost in 50% of cases, Her-2/neu to be negative in all cases, and EGFR to

**Table I.** Morphological difference between solid component of FIGO grade 3 tumour and undifferentiated component of dedifferentiated endometrial carcinoma

SOLID AREAS IN FIGO GRADE 3	DEDIFFERENTIATED ENDOMETRIAL CARCINOMA
1. Cells similar to glandular component	1. Cells with variable histologic appearance
2. Solid areas intermixed with glandular component	2. Solid areas adjacent to glandular component
3. Cells form cords, trabeculae, or nests	3. Patternless solid growth

Table II. Immunohistochemical profile of our cases

IHC STAIN	CK CAM 5.2	CK AE1/AE3	CK 5/6	EMA	PAX 8	ER	E-CADHERIN	p53	p16	SYNAPTO-PHYSIN
Case 1	> 50%	Focal	Focal	> 50%	Negative	Negative	Positive	Wild type	Negative	< 10%
	Undifferentiated Component									
	Positive	Focal	Focal	Positive	Positive	Positive	Positive	Negative	Positive	< 10%
Case 2	Focal	< 25%	Negative	Negative	Negative	Negative	50%	Wild type	Positive	Negative
	Undifferentiated Component									
	Positive	Positive	Focal	Positive	Positive	Positive	Positive	Wild type	< 25%	Negative
	Differentiated Component									

be negative in 67% of cases. Li *et al.* [5] compared the immunohistochemical profile of the undifferentiated component of the dedifferentiated tumours to the solid form of FIGO grade 3 endometrioid adenocarcinoma and concluded that the undifferentiated component of the dedifferentiated tumours is variably positive for cytokeratin, EMA, and ER and negative for PAX 8, whereas solid FIGO grade 3 endometrioid carcinomas stain positive for all these markers. Hoang *et al.* [17] divided the dedifferentiated endometrial carcinomas into BRG1/INI1-deficient and BRG1/INI1-intact. They found complete loss of PAX 8 and ER staining in the undifferentiated components of all the cases of BRG1/INI1-deficient tumours. Wild-type nuclear p53 staining was observed in 95% of BRG1/INI1-deficient cases. Results were slightly different in BRG1/INI1-intact cases, where PAX 8 expression was observed in 33% of cases, ER was expressed in 20% of cases, and 47% cases showed mutated p53 staining pattern. Sakuragi *et al.* [18] found that decreased E-cadherin expression in endometrial carcinoma is associated with tumour dedifferentiation. They found this well before dedifferentiated endometrial carcinoma was identified as a separate entity. Stewart *et al.* [19] found diffuse fascin expression in the undifferentiated component of 94% of cases of dedifferentiated endometrial carcinomas. Onder *et al.* [20] found diffuse expression of fascin in 82% of cases and loss of E-cadherin expression in 55% of cases.

To summarise, it appears that the undifferentiated component of dedifferentiated endometrial carcinomas tends to lose cytokeratin, PAX 8, and ER expression, which can be helpful in the differential diagnosis. Also, most cases express fascin. On the other hand, p53 does not seem to be of much help in this regard, but this may very well be due to the subjectivity associated with interpretation of different staining patterns of p53. Loss of E-cadherin is found in about 50% of cases. The immunohistochemical profile of our cases are summarised in Table II. We found PAX 8 and ER to be the most useful markers in differential diagnosis.

Genetic association of dedifferentiated endometrial adenocarcinomas is not clear; however, rare cases have been identified in patients with Lynch syndrome [6, 21]. About half of the dedifferentiated tumours show microsatellite instability with MLH1 promoter methylation and loss of expression of MLH1 and PMS2 [21]. Ramalingam *et al.* [15] found that MLH1 and PMS2 were concurrently lost in 50% of cases, whereas MSH2 and MSH6 were lost in 3% of cases. We found loss of MLH1 and PMS2 in the first case and loss of MSH2 in the second case.

Hysterectomy with bilateral salpingo-oophorectomy followed by systemic chemotherapy and pelvic radiotherapy is the mainstay of the treatment. Both

of our patients received systemic chemotherapy and radiotherapy post-surgery.

The prognosis for dedifferentiated carcinomas is extremely poor, with recurrence or death in 55-95% of cases [3, 4, 5, 6, 7, 8]. Undifferentiated component, as little as 20% confers these tumours poor prognosis [3]. Li *et al.* [5] found that most cases presented at advanced stage. They found lymph-vascular invasions in 73%, lymph node metastases in 46%, and distant metastasis in 38% of cases. Except one, all patients in their study either had metastatic or recurrent diseases within three years of diagnosis. Mouka *et al.* [7] found adrenal metastasis even in an otherwise early-stage dedifferentiated endometrial carcinoma. Berretta *et al.* [8] described a case of dedifferentiated endometrial carcinoma that was first diagnosed from cerebellar and adrenal metastases. Han *et al.* [4] reported survival as low as 7 weeks in one of the 4 cases they reported. No evidence of recurrent or metastatic disease was found in our patients 28 and 31 months post hysterectomy.

*The authors declare no conflict of interest.*

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