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Immunophenotypic features of dedifferentiated endometrial carcinoma – Insights from BRG1/INI1-deficient tumors

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Abstract

Aims—Dedifferentiated endometrial carcinoma (DDEC) is defined by the presence of an undifferentiated carcinoma together with an endometrioid carcinoma. Inactivation of SMARCA4 (BRG1) and SMARCB1 (INI1) were recently described as potential mechanisms underlying the histologic dedifferentiation. The aim of this study is to characterize the immunophenotypic features of DDECs, particularly in cases with prototypical histologic and molecular features (BRG1/INI1-deficiency).

Methods and results—We evaluated PAX8, estrogen receptor (ER) and p53 immunostaining in the endometrioid and the undifferentiated components of 20 BRG1/INI1-deficient DDECs and 15 BRG1/INI1-intact DDECs, and compared the results to that of 23 grade 3 endometrioid carcinomas. The differentiated endometrioid component was positive for PAX8 and/or ER in 19 of 20 BRG1/INI1-deficient DDECs while the corresponding undifferentiated component of all 20 tumors showed a complete absence of PAX8 and ER staining. All except one of the BRG1/INI1-

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deficient tumors displayed a wild-type p53 staining pattern. PAX8 and ER expression in the undifferentiated component was absent in 67% and 80% of BRG1/INI1-intact DDECs respectively, while 47% of the BRG1/INI1-intact DDECs showed mutated p53 staining pattern. In comparison, absent PAX8 and ER expression were each observed in the more solid area of 48% and 48% of grade 3 endometrioid carcinomas.

Conclusions—The consistent absence of PAX8 and ER expression in molecularly defined (BRG1/INI1-deficient) DDECs suggest that the loss of PAX8 and ER expression is a fundamental feature of dedifferentiation. The frequent findings of mutated p53 staining pattern in BRG1/INI1-intact DDECs indicate that BRG1/INI1-intact DDECs may be biologically different from BRG1/INI1-deficient tumors.

Keywords

Endometrial cancer; dedifferentiated carcinoma; undifferentiated carcinoma; SMARCA4; SMARCB1; BRG1; INI1; PAX8

Introduction

Dedifferentiated endometrial carcinoma (DDEC) describes a type of clinically aggressive endometrial cancer in which an undifferentiated carcinoma occurs concurrently with an endometrioid carcinoma.[1-4] The endometrioid carcinoma component is usually low-grade and shows typical histology that is morphologically indistinguishable from other pure low-grade endometrioid carcinoma.[1, 2, 5] Therefore, the presence of the undifferentiated carcinoma component is what separates DDEC from endometrioid carcinoma. At present, undifferentiated carcinoma is defined predominantly by a combination of cytologic and architectural features as well as the exclusion of other entities in the differential diagnosis. The undifferentiated tumor is composed of monotonous medium to large round/polygonal cells growing in solid patternless sheets without evidence of glandular formation. The tumor cells usually exhibit, at least focally, cellular discohesion that imparts a lymphoid appearance; in addition, large rhabdoid cells may also be present. Immunohistochemically, DDECs show either markedly diminished to nearly completely absent expression of epithelial markers such as pankeratin, cytokeratin 7 and/or epithelial membrane antigen (EMA) in the undifferentiated component compared to the differentiated component.[1, 6-8] PAX8 and estrogen receptor (ER) expression is reported to be lost in 85-92% and in 69-85% of DDECs respectively,[7, 8] while an aberrant p53 immunostaining pattern and/or *TP53* mutations is observed in 26-33% of cases.[3, 8] There is also a tendency for DDEC to occur in a mismatch repair (MMR) protein-deficient molecular context, with 50-70% of cases exhibiting matching patterns of MMR deficiency in the differentiated and the undifferentiated tumor components.[4, 6, 8-11]

BRG1 (encoded by *SMARCA4*) and INI1 (encoded by *SMARCB1*) are both core component proteins of the switch/sucrose non-fermenting (SWI/SNF) chromatin remodeling complex, and inactivating mutations involving these proteins have been documented in several other types of human malignancy.[12, 13] We and others recently identified inactivating mutations involving *SMARCA4* or *SMARCB1* that result in the loss of BRG1 or INI1 expression in a significant subset of DDECs.[6, 11, 14, 15] These SWI/SNF core protein

mutations and consequent loss of expression were only found in the undifferentiated component of these tumors, whereas the differentiated component lacked these mutations and showed intact protein expression. Furthermore, loss of BRG1 or INI1 expression was not seen in the more solid areas of FIGO (The International Federation of Gynecology and Obstetrics) grade 3 endometrioid carcinomas. These findings led to the speculation that disrupted SWI/SNF complex activity due to the loss of BRG1 or INI1 is likely responsible for the apparent histologic dedifferentiation.

As most of the immunophenotypic surveys published to date predate the recent recognition of BRG1/INI1 inactivation as frequent molecular events in DDECs, currently little is known about the immunophenotypic features of BRG1/INI1-deficient tumors. The aim of this study is to evaluate the expression of PAX8, estrogen receptor (ER) and p53 in BRG1/INI1-deficient and BRG1/INI1-intact DDECs, in an attempt to gain further biologic and diagnostic insights into these tumors.

Materials and Methods

Study samples

The study included 20 DDECs that showed loss of BRG1 or INI1 expression by immunohistochemistry in the undifferentiated component of the tumor, 15 BRG1/INI1-intact DDECs and 23 grade 3 endometrioid carcinomas that were previously described.[6, 11] All of the endometrial carcinomas included in this study were from hysterectomy specimens. These cases were obtained from the pathology archives at Calgary Laboratory Services (Calgary, Canada), Royal Alexandra Hospital (Edmonton, Canada), Memorial Sloan Kettering Cancer Center (New York, United States) and King Edward Memorial Hospital (Perth, Australia). All cases were centrally reviewed (C.H.L and L.H.), fulfilling the morphologic features described by Silva *et al.*[1, 5] The study was approved by the Institutional Review Board (University of Alberta, Pro00042667).

Immunohistochemistry and interpretation

All immunohistochemistry analysis was performed on whole tissue sections (a representative section from each hysterectomy specimen). The unstained slides were processed using the Ventana Discovery XT, and the Ventana Benchmark XT automated system (Ventana Medical Systems, Tucson, Arizona, USA) as per manufacturer's protocol with proprietary reagents. Heat induced antigen retrieval method was used in Cell Conditioning solution (CC1-Tris based EDTA buffer, pH 8.0, Ventana). The mouse monoclonal PAX8, clone BC12 (catalog number: ACI 438) antibody was obtained from Biocare Medical (Concord, California, United States); the rabbit monoclonal ER, clone SP1 (catalog number: RM-9101) antibody was obtained from Thermo Fisher Scientific (Ottawa, Ontario, Canada); the mouse monoclonal p53, clone DO-7 (catalog number: M7001) antibody obtained from Dako (Burlington, Ontario, Canada). Primary incubations were performed for 60 min (37°C) at 1:100 dilution for PAX8, 60 min (37°C) at 1:25 dilution for ER and 32 min (37°C) at 1:800 dilution for p53 all using Ventana antibody diluents. The Ventana Universal Secondary Antibody was used for 32 min at 37°C. The detection system used was the Ventana DABMap kit (ER) and Ventana OptiView DAB kit (p53).

For PAX8, ER and p53, only nuclear staining was considered and evaluated; the differentiated and undifferentiated components were evaluated separately. PAX8 and ER immunostains were scored as positive if any tumor cells exhibited moderate to strong positive (definite) nuclear staining.[16, 17] Tumors were considered PAX8-negative or ER-negative only if there was adequate nuclear staining of internal positive control tissue. p53 immunostain was considered to be aberrant (mutated/inactivated) if the tumor exhibited 1) diffuse moderate to strong uniform nuclear staining in ≥ 70% of the tumor cells (diffuse), or 2) complete absence of nuclear staining in the tumor cells in the presence of focal nuclear staining of the stromal cells (complete absent). p53 immunostain was considered normal (wild type pattern) if any degree of non-diffuse nuclear staining (<70%) of the tumor cells was present.[18]

Statistical analyses

Likelihood-ratio test was performed to compare the staining patterns between the different tumor groups (JMP software; Cary, North Carolina, United States) and the raw p-values were displayed.

Results

Clinicopathologic features of BRG1/I NI1-deficient and BRG1/INI1-intact dedifferentiated endometrial carcinomas

This study included 20 BRG1 or INI1-deficient DDECs, 19 of which were previously described.[6, 11] Among these 20 tumors (Table 1), 15 showed absent BRG1 nuclear expression in the undifferentiated component in contrast to intact expression in the corresponding endometrioid component. This included a case of MMR protein-intact, *SMARCA4*-mutated and BRG-deficient DDEC that was not previously reported (case 16). The 5 remaining tumors showed absent INI1 nuclear expression in the undifferentiated component in contrast to intact expression in the corresponding endometrioid component. The observed BRG1 or INI1 deficiency was mutually exclusive.[6, 11]

The patients with BRG1/INI1-deficient DDEC ranged from 46 to 82 years in age at the time of initial diagnosis (average age of 62.6 years). The differentiated endometrioid component was histologically low-grade (FIGO grade 1 or 2) in all except 1 case in which the differentiated component was a FIGO grade 3 endometrioid carcinoma. Six patients (30%) presented with extrauterine disease spread. MMR protein deficiency was found in 65% of the cases by immunohistochemistry (9 with concurrent MLH1 and PMS2 deficiencies, 3 with isolated PMS2 deficiency and 1 with concurrent MSH2 and MSH6 deficiencies) (Table 1).[6, 11] The patients with BRG1/INI1-intact DDEC ranged from 43 to 93 years in age (average age of 62.5 years) (Table 1). There were no appreciable differences in terms of histologic features between BRG1/INI1-deficient and BRG1/INI1-intact DDECs as noted previously.[11]

Immunophenotype of BRG1/INI1-deficient dedifferentiated endometrial carcinomas

PAX8, ER and p53 immunostaining was performed in all 20 cases (Table 2). PAX8 was expressed in the differentiated/endometrioid component in 19 of 20 cases (95%) while ER

was expressed in the differentiated/endometrioid component in 16 of 18 cases (89%) with interpretable findings (Figure 1). PAX8 expression was typically diffuse and strong when present, while ER expression was more variable in intensity. In comparison, the undifferentiated components of all 20 BRG1/INI1-deficient tumors showed a complete absence of nuclear staining for both PAX8 and ER in the tumor cells (Figure 1). The lack of nuclear staining was not due to suboptimal specimen fixation as there was a satisfactory internal positive control present (i.e. benign endometrial glands or corresponding differentiated component of the tumor).

All 20 tumors except one showed wild-type nuclear p53 staining in both the differentiated and the undifferentiated components, though there was typically greater p53 nuclear staining present (albeit still with a wild-type staining pattern) in the latter (Figure 1). One tumor, the only case that contained a grade 3 endometrioid carcinoma in the differentiated component, showed a complete absence of nuclear p53 staining in both the grade 3 endometrioid and the undifferentiated carcinomas, suggesting the presence of inactivating *TP53* mutations in both histologic components. This was a BRG1-deficient tumor with intact MMR protein expression which lacked PAX8 and ER expression in both the differentiated and the undifferentiated components.

Comparison to BRG1/INI1-intact dedifferentiated carcinomas and FIGO grade 3 endometrioid carcinomas

We included a series of BRG1/INI1-intact DDECs and grade 3 endometrioid carcinomas that were previously described for comparison. The results are summarized in Table 2. For BRG1/INI1-intact DDECs, PAX8 and ER expression was observed in the undifferentiated component in 33% and 20% of the cases respectively. It is worth noting that none of the five patients with a PAX8 and/or ER-positive undifferentiated component died of their disease (cases 21-25) while five of the ten patients with a PAX8 and ER-negative undifferentiated component died of their disease (cases 26-35) (with four patients succumbing within one year of diagnosis). Seven of 15 BRG1/INI1-intact DDECs showed a mutated p53 staining pattern in the undifferentiated component (Figure 2) ($p = 0.0053$ compared to BRG1/INI1-deficient DDECs). Four of these tumors showed wild-type p53 staining in the corresponding differentiated component (Figure 2) and 6 were deficient for MMR protein(s). Two of these 7 tumors showed PAX8 and ER expression in both the endometrioid and the undifferentiated components. For grade 3 endometrioid carcinomas, the solid area lacked PAX8 and ER expression in 48% of the cases and there was concurrent absence of PAX8 and ER expression in 39% of the cases (9/23).

Discussion

We examined by immunohistochemistry the expression of PAX8, ER and p53 in a series of BRG1/INI1-deficient DDECs, and compared the staining patterns to that of a series of BRG1/INI1-intact DDECs and FIGO grade 3 endometrioid carcinomas. We observed consistent absence of PAX8 and ER expression in the undifferentiated components of all BRG1/INI1-deficient DDECs, while the corresponding differentiated endometrioid component displayed PAX8 and/or ER expression in the great majority of the cases.

PAX8 is a nuclear transcription factor that is important in the development of the Müllerian system and it is frequently expressed by endometrial carcinomas (including endometrioid-type) with a reported frequency of about 95%.[17, 19] ER is a hormone-activated nuclear transcription factor that is important in endometrial function. While the reported frequency of ER positivity varies between different tumor subtypes, endometrioid carcinomas show ER expression in the great majority of cases.[20, 21] The current observation of frequent PAX8 and ER expression in the differentiated endometrioid component of DDECs are therefore in keeping with these prior findings. In contrast, the corresponding undifferentiated component in BRG1/INI1-deficient tumors consistently lacked PAX8 and/or ER expression. Spatially, the loss of PAX8 and ER expression coincide with the loss of BRG1 or INI1 expression in these tumors. Given that BRG1 and INI1 are both core members of the SWI/SNF chromatin remodeling complex, the inactivation of BRG1/INI1 is expected to cause significant disruption in the transcriptional regulation mediated by this complex.[13] Such transcriptional dysregulation may contribute to the loss of PAX8 and ER expression seen in the undifferentiated component of the tumor. The loss of PAX8 and ER expression also provides further immunohistochemical support for cellular dedifferentiation as the typically low-grade PAX8 and ER-positive endometrioid tumor (in the differentiated component) progresses to become a histologically and immunophenotypically undifferentiated tumor. However, it is important to point out that PAX8 and ER expression can be influenced by other factors beyond BRG1 and INI1, as the majority of BRG1/INI1-intact DDECs and about half of FIGO grade 3 endometrioid carcinomas also lacked PAX8 and/or ER expression in the undifferentiated component and the more solid tumors area, respectively.

Two earlier published studies have examined the expression of PAX8 and ER in DDECs.[7, 8] Ramalingam *et al.* examined 20 cases and found that PAX8 and ER expression were each absent in the undifferentiated component in 85% of the tumors.[8] Interestingly, they also studied 15 cases of undifferentiated endometrial carcinomas which are believed to be closely related to DDEC; PAX8 and ER expression was absent in 80% and 87% of the cases respectively. In another study by Li and Zhao including 13 DDECs, PAX8 and ER expression in the undifferentiated component was absent in 92% and 69% of the cases respectively, while the differentiated/endometrioid component was consistently positive for both proteins.[7] In the present series, the undifferentiated component of BRG1/INI1-deficient DDECs consistently lacked PAX8 and ER expression, while the undifferentiated component of BRG1/INI1-intact tumors showed PAX8 and/or ER expression in a subset of the cases. It is worth noting that the mutation and the expression status of BRG1 and INI1 were not defined in these two previous studies and as such, the diagnosis of DDEC was defined based on histology and conventional immunohistochemical markers (utilized mainly to exclude histologic mimics including neuroendocrine carcinoma, carcinosarcoma/sarcoma and lymphoma).[7, 8] In comparison, our series incorporated an additional defining molecular feature, namely BRG1/INI1 inactivation (loss of protein expression). As we have previously shown, BRG1/INI1 loss is present in about half of morphologically classic DDECs and is not found in grade 3 endometrioid carcinomas that mimic DDECs.[11] The use of BRG1/INI1 loss in our study as an objective molecular reference ensured that the immunophenotypic features that we describe here represent that of a biologically definitive group of cases. This is an important consideration as the histologic diagnosis of DDEC can sometimes be

challenging and it may be difficult to discern from some of its histologic mimics. As such, our findings in the undifferentiated component of histologically typical and molecularly defined DDECs suggest that the loss of PAX8 and ER expression is a fundamental phenomenon associated with dedifferentiation. Even though a subset of BRG1/INI1-intact DDECs in our series showed PAX8 and/or ER expression in the undifferentiated component, we know that they do not harbor BRG1/INI1 inactivating mutations and interestingly none of these patients died of their disease. It is reasonable to speculate that these may represent biologic outliers in our series, despite our best screening effort in the centralized histologic review as well as the lack of appreciable histologic differences between BRG1/INI1-deficient and BRG1/INI1-intact tumors. More studies however are needed to determine whether immunophenotypically atypical tumors (showing PAX8 and/or ER expression in the undifferentiated component) are indeed clinically and/or biologically different from histologically and immunophenotypically typical DDECs. In the meantime, our findings and those previously reported suggest that retained PAX8 and ER expression in the undifferentiated component of DDEC is uncommon and it may have diagnostic utility in morphologically equivocal cases.

All except one of the BRG1/INI1-deficient DDECs showed wild-type p53 staining pattern in both tumor components, indicating *TP53* mutation is probably not involved in the development or progression (dedifferentiation) of these tumors. The case with aberrant p53 staining was the only tumor that had a grade 3 endometrioid carcinoma as the differentiated component, where both the differentiated and undifferentiated component showed complete loss of p53 staining. In this particular case, the high-grade endometrioid component appeared to have already acquired a *TP53* mutation before a further mutation involving *SMARCA4* resulted in tumor dedifferentiation. Only two published studies have systemically evaluated *TP53* mutation status in DDECs.[8] Kuhn *et al.* identified *TP53* mutations by Sanger sequencing in 33% of DDECs.[3] Ramalingam *et al.* observed aberrant p53 expression (diffuse) in 26% of DDECs and 38% of undifferentiated endometrial carcinomas.[8] These frequencies are considerably greater than the rate of mutation pattern p53 staining seen in BRG1/INI1-deficient DDECs in our present series, but comparable to the frequency of aberrant p53 expression seen when BRG1/IN1-deficient and intact groups were combined. This observation suggests that there may be significant biologic differences between BRG1/INI1-deficient tumors (5% with mutation pattern p53 staining) and BRG1/INI1-intact tumors (47% with mutation pattern p53 staining). Moreover, about half of the BRG1/INI1-intact DDECs with mutated p53 staining in the undifferentiated component showed wild-type p53 staining pattern in the differentiated endometrioid component. Therefore, it is possible that *TP53* mutation may either contribute in part to dedifferentiation or facilitate the growth of the undifferentiated component in these cases. Additional molecular insights are however needed to gain a better understanding of the biology of BRG1/INI1-intact DDECs, particularly in terms of its relationship to BRG1/INI1-deficient tumors. This may become increasingly relevant with therapeutic advances in targeting chromatin-remodeling proteins.[22]

In summary, we identified a typical immunoprofile of BRG1/INI1-deficient DDECs, characterized by loss of PAX8 and ER, and wild-type p53 staining pattern in the undifferentiated tumor component. The loss of PAX8 and ER expression further supports the

dedifferentiated nature of these tumors. More studies are needed to better define the molecular basis of BRG1/INI1-intact DDECs and their relationship to BRG1/INI1-deficient tumors.

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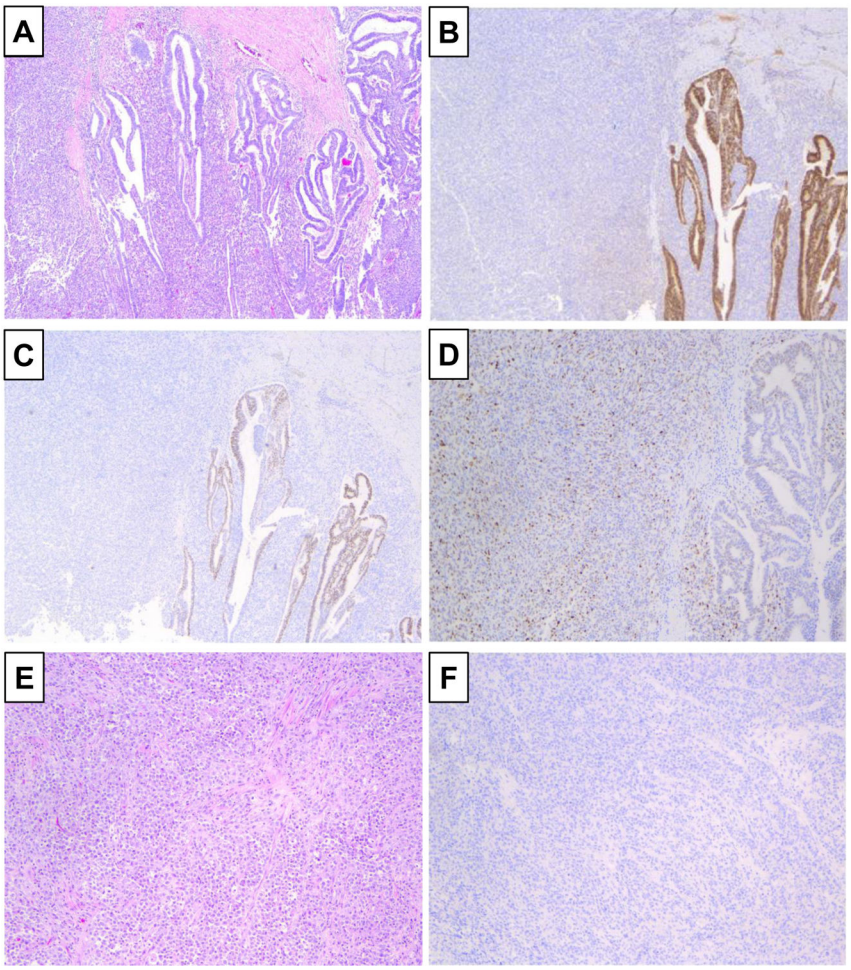

Figure 1. PAX8, ER and p53 immunostaining in BRG1-deficient or INI1-deficient dedifferentiated endometrial carcinomas

A). A BRG1-deficient dedifferentiated carcinoma showing a FIGO grade 1 endometrioid carcinoma with associated undifferentiated carcinoma. B). This BRG1-deficient tumor showed PAX8 expression in the endometrioid component but absent PAX8 expression in the undifferentiated component. C). This BRG1-deficient tumor showed ER expression in the endometrioid component but absent ER expression in the undifferentiated component. D). Both the endometrioid and the undifferentiated components of this BRG1-deficient dedifferentiated carcinoma showed wild-type p53 staining pattern. E-F). The undifferentiated component of a INI1-deficient dedifferentiated carcinoma showing a complete absence of PAX8 staining.

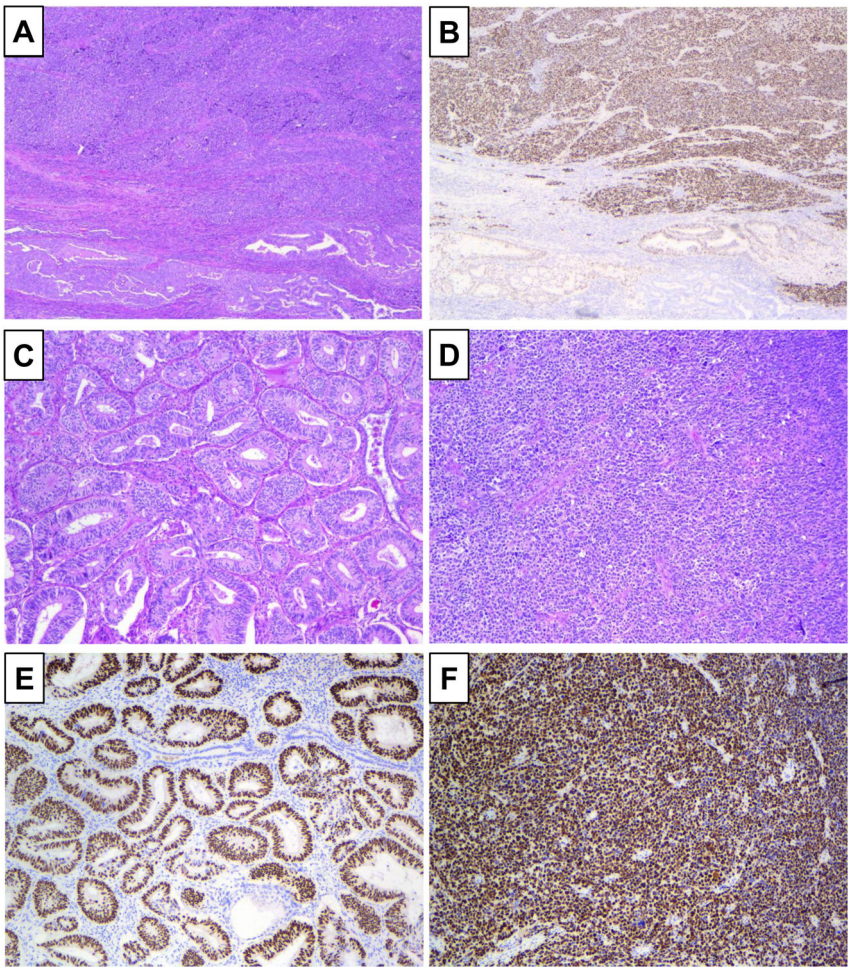

Figure 2. p53 immunostaining in BRG1/INI1-intact dedifferentiated endometrial carcinomas

A-B). A BRG1/INI1-intact dedifferentiated carcinoma showing wild-type p53 staining pattern in the low-grade endometrioid component but mutated (diffuse and strong nuclear) staining pattern in the undifferentiated component. C-F). A BRG1/INI1-intact dedifferentiated carcinoma showing mutated (diffuse and strong nuclear) p53 staining pattern in both the low-grade endometrioid and the undifferentiated components.

Table 1

Clinicopathologic features of dedifferentiated endometrial carcinomas

The study included 20 BRG1 or INI1-deficient dedifferentiated endometrial carcinomas (DDEC) (cases 1-20) and 15 BRG1 and INI1-intact dedifferentiated endometrial carcinomas (cases 21-35). MMR: mismatch repair protein; NED: no evidence of disease; DOD: died of disease.

Case	Age	Diagnosis	BRG1	INI1	MMR	Status at last follow-up	Follow-up duration (year)
1	54	DDEC	Loss	Intact	PMS2 loss	NED	0.75
2	75	DDEC	Loss	Intact	MLH1/PMS2 loss	NED	2.75
3	54	DDEC	Loss	Intact	MLH1/PMS2 loss	NED	2.62
4	51	DDEC	Loss	Intact	MLH1/PMS2 loss	DOD	1.51
5	66	DDEC	Loss	Intact	MLH1/PMS2 loss	NED	2.50
6	69	DDEC	Loss	Intact	Intact	DOD	0.61
7	70	DDEC	Loss	Intact	PMS2 loss	DOD	1.17
8	73	DDEC	Loss	Intact	MLH1/PMS2 loss	DOD	1.17
9	66	DDEC	Loss	Intact	PMS2 loss	NED	4.00
10	54	DDEC	Loss	Intact	Intact	DOD	1.12
11	65	DDEC	Loss	Intact	Intact	DOD	0.13
12	55	DDEC	Loss	Intact	Intact	DOD	0.17
13	82	DDEC	Loss	Intact	MLH1/PMS2 loss	DOD	0.83
14	65	DDEC	Loss	Intact	MLH1/PMS2 loss	NED	3.92
15	59	DDEC	Loss	Intact	Intact	DOD	0.50
16	56	DDEC	Intact	Loss	MLH1/PMS2 loss	DOD	0.25
17	54	DDEC	Intact	Loss	Intact	NED	1.25
18	57	DDEC	Intact	Loss	MLH1/PMS2 loss	NED	0.33
19	46	DDEC	Intact	Loss	Intact	NED	4.13
20	81	DDEC	Intact	Loss	MSH2/MSH6 loss	NED	3.67
21	57	DDEC	Intact	Intact	MLH1/PMS2 loss	NED	1.34
22	60	DDEC	Intact	Intact	MLH1/PMS2 loss	NED	6.37
23	68	DDEC	Intact	Intact	PMS2 loss	NED	0.50
24	69	DDEC	Intact	Intact	MSH2/MSH6 loss	NED	2.20
25	39	DDEC	Intact	Intact	Intact	NED	2.00
26	56	DDEC	Intact	Intact	Intact	NED	0.42

Case	Age	Diagnosis	BRG1	INI1	MMR	Status at last follow-up	Follow-up duration (year)
27	72	DDEC	Intact	Intact	MLH1/PMS2 loss	NED	1.42
28	63	DDEC	Intact	Intact	Intact	DOD	0.45
29	93	DDEC	Intact	Intact	MLH1/PMS2 loss	DOD	0.40
30	73	DDEC	Intact	Intact	PMS2 loss	DOD	0.86
31	55	DDEC	Intact	Intact	MLH1/PMS2 loss	DOD	0.17
32	60	DDEC	Intact	Intact	MSH6 loss	NED	1.83
33	56	DDEC	Intact	Intact	Intact	DOD	3.41
34	73	DDEC	Intact	Intact	MLH1/PMS2 loss	NED	3.75
35	43	DDEC	Intact	Intact	MSH2/MSH6 loss	NED	2.40

Table 2

Summary of PAX8, ER and p53 immunostaining results.

	BRG1/INI1-deficient DDECs (n=20)	BRG1/INI1-intact DDECs (n=15)	FIGO Grade 3 ECs (n=23)
PAX8			
Positive in both D and UD/PD	0/20 (0%)	5/15 (33%)	12/23 (52%)
Positive in D and negative in UD/PD	19/20 (95%)	10/15 (67%)	11/23 (48%)
Negative in both D and UD/PD	1/20 (5%)	0/15 (0%)	0/23 (0%)
		$p = 0.0056^{\dagger}$	$p < 0.0001^{\ddagger}$
ER			
Positive in bothD and UD/PD	0/18 (0%)*	3/15 (20%)	12/23 (52%)
Positive in D andnegative in UD/PD	16/18 (89%)*	10/15 (67%)	9/23 (39%)
Negative in bothD and UD/PD	2/18 (11%)*	2/15 (13%)	2/23 (9%)
		$p = 0.056^{\dagger}$	$p < 0.0001^{\ddagger}$
p53			
Wild-type pattern in bothD and UD/PD	19/20 (95%)	8/15 (53%)	18/23 (78%)
Wild-type pattern in D andmutated pattern in UD/PD	0/20 (0%)	4/15 (27%)	3/23 (13%)
Mutated pattern in bothD and UD/PD	1/20 (5)%	3/15 (20%)	2/23 (9%)
		$p = 0.0053^{\dagger}$	$p = 0.115^{\ddagger}$

DDECs: dedifferentiated endometrial carcinomas; ECs: endometrioid carcinomas; D: differentiated/endometrioid component of dedifferentiated carcinoma or better differentiated area of grade 3 endometrioid carcinoma; UD/PD: undifferentiated component of dedifferentiated carcinoma or poorly differentiated/solid area of grade 3 endometrioid carcinoma;

*For BRG1/INI1-deficient dedifferentiated carcinomas, 2 of the 20 tumors showed negative ER staining of the undifferentiated component but the well-differentiated component was not available for evaluation in the section tested;

†The p-values displayed were derived from likelihood-ratio test comparing BRG1/INI1-intact DDECs to BRG1/INI1-deficient DDECs;

‡The p-values displayed were derived from likelihood-ratio test comparing FIGO grade 3 ECs to BRG1/INI1-deficient DDECs