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Case series

Dedifferentiated endometrioid adenocarcinoma of the uterus: A case series and review of literature

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ABSTRACT

Introduction Dedifferentiated endometrioid adenocarcinoma (DEAC) was first described in 2007. However, it has only been recognised as a distinct subtype of endometrioid adenocarcinoma in the last 1–2 years. DEAC is a more aggressive histological subtype and carries a poorer prognosis. Patients with DEAC tend to present with advanced disease compared the other endometrioid adenocarcinomas. Methodology The study is a retrospective review of patients with DEAC diagnosed in two institutions in Singapore between January 2012 and October 2017. Results 7 patients were diagnosed with DEAC. The mean age was 56.4 years. All patients presented with either abnormal uterine bleeding or post menopausal bleeding. Out of the 7 patients, one was diagnosed with Stage 2 disease, 5 were diagnosed with Stage 3 disease and 1 was diagnosed with Stage 4 disease. One patient had neoadjuvant chemotherapy, followed by surgery, and completion chemotherapy post surgery. The other 6 patients (87.5%) underwent primary debulking surgery. Out of these 6 patients, 5 patients had adjuvant chemotherapy post surgery and one patient had both adjuvant chemotherapy and radiotherapy. Lymphovascular invasion was found in 71.4% of the cases. Conclusion DEAC is a more aggressive histological subtype of endometrioid adenocarcinomas. Better awareness of this condition can lead to proper diagnosis and treatment.

1. Introduction

Dedifferentiated adenocarcinoma (DEAC) of the uterus was first described by Silva et al. in 2006 (Silva et al., 2006). It is a rare subtype of endometrial cancer with less than 50 cases reported thus far. In the current International Federation of Obstetrics and Gynecology (FIGO) grading system, the diagnosis of DEAC is made based on the presence of any proportion of undifferentiated carcinoma component in coexistence with an endometrioid carcinoma component (usually low grade; i.e. grade 1 or 2). DEAC can sometimes be misdiagnosed as FIGO grade 2 or 3 endometrioid carcinoma (Murali et al., 2019). Distinguishing DEAC from poorly differentiated endometrioid adenocarcinoma is important as the former carries a poorer prognosis.

2. Materials and methods

This study is a retrospective review of all cases of dedifferentiated endometrial cancer diagnosed in two institutions in Singapore between January 2013 and October 2017. Prospectively maintained gynaecologic oncology tumour databases were used to identify all patients diagnosed with DEAC. These cases underwent multidisciplinary tumour board discussion with histopathological review and recommended treatment. Disease was staged according to the FIGO classifications. Ethics approval was obtained from the SingHealth Centralised Institutional Review Board, Singapore. Data analysis was performed using SPSS software version 19.

3. Results

Seven patients were diagnosed with DEAC. The median age was 55 years (range: 44–67 years). All patients presented with either abnormal uterine bleeding or post-menopausal bleeding. The clinical features, investigations and treatments of these patients are summarised in Table 1. Table 2 is a summary of the surgical staging, pathological features and outcomes of the patients with DEAC. One patient had Stage 2 disease, 5 had Stage 3 disease and one had Stage 4

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Table 1
Summary of clinical features, investigations and treatments DEAC patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Clinical features							
Age at diagnosis (years)	55	65	67	52	44	57	55
Parity	3	3	3	1	1	3	1
BMI	21.6	19.5	27.2	25.4	21.2	28	19.7
History of other cancers	–	–	–	–	Synchronous left breast IDC	–	–
Presentation	PMB	PMB LOA/LOW	PMB	PMB	AUB	PMB	AUB
Duration of symptoms	2 months	2 months	1 week	2 weeks	5 years	1 year	1 year
Investigations							
Preoperative Hb (g/dL)	13	7.5	12.7	11	4.5	15.5	11.7
CA 125	–	77.3	–	–	41.9	14.9	–
Endometrial biopsy	Complex atypical hyperplasia with suggestion of endometrioid adenocarcinoma	*Cervical tumour biopsy: endometrioid adenocarcinoma, favouring endometrial origin	Grade 1 endometrioid adenocarcinoma	High grade malignant tumour	Endometrioid adenocarcinoma with undifferentiated areas	Grade 3 endometrioid adenocarcinoma	Grade 2 endometrioid adenocarcinoma with focal solid areas
Initial Management							
Surgery	THBSO/PLND	Modified radical hysterectomy BSO/PLND/PAND	THBSO/PLND	LAVHBSO/PLND/ omentectomy	THBSO/PLND	THBSO/PLND/ PAND/ omentectomy/ bladder mass resection	THBSO/PLND/ PAND/ omentectomy
Debulking	Optimal	Optimal	Optimal	Optimal	Optimal	Optimal	Optimal
Chemotherapy	6 cycles PTX + CBDCA	6 cycles PTX + CBDCA	5 cycles CDDP + PTX	5 cycles PTX + CBDCA	2 cycles PTX + CBDCA (neoadjuvant) then 1 cycles PTX + CBDCA	6 cycles PTX + CBDCA	1 cycle CDDP + PTX then 2 cycles CBDCA + PTX
Radiotherapy	–	EBRT 45/25# + 3BT	–	–	–	–	–

IDC: intraductal carcinoma; PMB postmenopausal bleeding; AUB abnormal uterine bleeding; LOA: loss of appetite; LOW: loss of weight; Hb: haemoglobin; THBSO: total hysterectomy and bilateral salphingoopherectomy; LAVHBSO: laparoscopic assisted vaginal hysterectomy and bilateral salphingoopherectomy; PLND: pelvic lymphadenectomy; PAND: para-aortic lymphadenectomy; CDDP: cisplastin; PTX: paclitaxel; CBDCA: carboplatin.

Table 2
Surgical staging, pathological features and outcomes of the patients with DEAC.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Pathological features							
Size of tumour (cm)	1.8 × 1.2 × 0.8	8.1 × 6.7x 4	5.0 × 2.8	5.1 × 2.8 × 2.0	13 × 3.5 × 3.5	10 × 9.5 × 10	10.5 × 5.5
FIGO Grade of differentiated component	Grade 1	Grade 2	Grade 1–2	Grade 1	Grade 2	Grade 2	Grade 2
Percentage of undifferentiated component	25%	20%	Unknown	95%	50%	95%	Unknown
Myometrial invasion (mm)	3	25	20	4	19	40	37
Lymphovascular involvement (LVSI)	+	–	+	–	+	+	+
Peritoneal washings	–	–	–	+	–	–	–
Margins	Not involved	Involved (cervical margins)	Not involved	Not involved	Involved (bilateral parametrial margins)	Involved (connective tissue of LNs)	Not involved
Lymph node metastasis	Endometrioid	Nil	Undifferentiated	Nil	Undifferentiated	Undifferentiated	Nil
Stage	3C1	2	3C1	3A	3C1	4	3A
Outcome	On follow-up	On follow-up	Death	On follow-up	Death	Death	Lost to follow-up (follow-up with private oncologist)
DFI (months)	58	15	9	5	1	0	2
OS (months)	58	15	25	21	6	9	2

DFI: disease-free interval; OS: overall survival.

Table 3
Expression of antigens known to be related to dedifferentiated endometrioid adenocarcinoma, as well as microsatellite instability related genes by immunohistochemistry in the undifferentiated component of the tumours.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Pax8	N/A	Neg	Neg	Neg	N/A	N/A	N/A
ER	Neg	Pos	Neg	Neg	Neg	Neg	N/A
PR	Neg	N/A	N/A	Neg	N/A	N/A	N/A
Vimentin	Pos	Pos	Focal	Pos	Pos	Pos	N/A
TP53	N/A	N/A	WT	N/A	N/A	WT	N/A
EMA	N/A	Focal	Pos	N/A	Focal	N/A	N/A
CK	Focal	Focal	Pos	Focal	Focal	N/A	Focal
MLH1	N/A	Loss	N/A	Intact	Loss	Loss	N/A
MSH2	N/A	Intact	N/A	Loss	Intact	Intact	N/A
MSH6	N/A	Intact	N/A	Loss	Intact	Intact	N/A
PMS2	N/A	Loss	N/A	Intact	Loss	Loss	N/A

Pos: ≥50% staining; Focal: less than50% staining; Neg: No staining; N/A: Not performed; Pax8: Paired Box 8; ER: Estrogen Receptor; PR: Progesterone Receptor; MUTP53: Mutant p53; WTP53: Wild-type p53; EMA: Epithelial membrane antigen; CK: Cytokeratins; MLH1: MutL homolog 1 colon cancer nonpolyposis type 2; MSH2: MutS Homologue 2; MSH6: Muts Homologue 6; PMS2: PostMeiotic Segregation increased 2.

disease. Lymphovascular invasion was found in 71.4% of the cases. Table 3 is a summary of immunohistochemistry stains of the tumours. Fig. 1 shows the histological findings from selected cases. The overall survival (OS) ranged from 2 months to 58 months, and the 2-year OS was 31.3%.

3.1. Disease free (Case 1 and Case 2)

3.1.1. Case 1

A 55-year-old woman presented with post-menopausal bleeding. She underwent a hysteroscopy that was complicated by uterine and small bowel perforation requiring laparotomy and small bowel resection. Histology for endometrial curettage showed complex atypical hyperplasia with suggestions of endometrioid adenocarcinoma. Her pre-operative CA125 level was elevated at 38.9 U/mL. She underwent a laparoscopic assisted vaginal hysterectomy with bilateral salphingoopherectomy and pelvic lymph node dissection. 1 out of 8 lymph nodes was positive for cancer. She was diagnosed with FIGO Stage 3C1 DEAC, with only a small undifferentiated component present – interestingly, the invasive component, as well as the tumour deposit in the lymph node was endometrioid. She remained asymptomatic and disease free at 58 months post-surgery.

3.1.2. Case 2

A 65-year-old woman presented with post-menopausal bleeding and loss of weight. Pelvic examination revealed a uterine tumour involving the cervix and posterior fornix of the vagina. Biopsy of the tumour showed endometrioid adenocarcinoma favouring endometrial origin. The pre-operative MRI pelvis showed an endometrial mass with more than 50% myometrial invasion extending to the posterior vaginal fornix. Her pre-operative CA125 level was 77.3 U/mL. She underwent a modified abdominal radical hysterectomy bilateral salphingoopherectomy, pelvic and para-aortic lymphadenectomy. The cervical resection margin was involved by tumour. She was diagnosed with FIGO Stage 2 DEAC, again with a relatively small undifferentiated component, which retained ER expression. Postoperatively, she completed 6 cycles of adjuvant carboplatin and paclitaxel and a combination of extended beam radiotherapy and brachytherapy. She was asymptomatic and disease-free at 15 months.

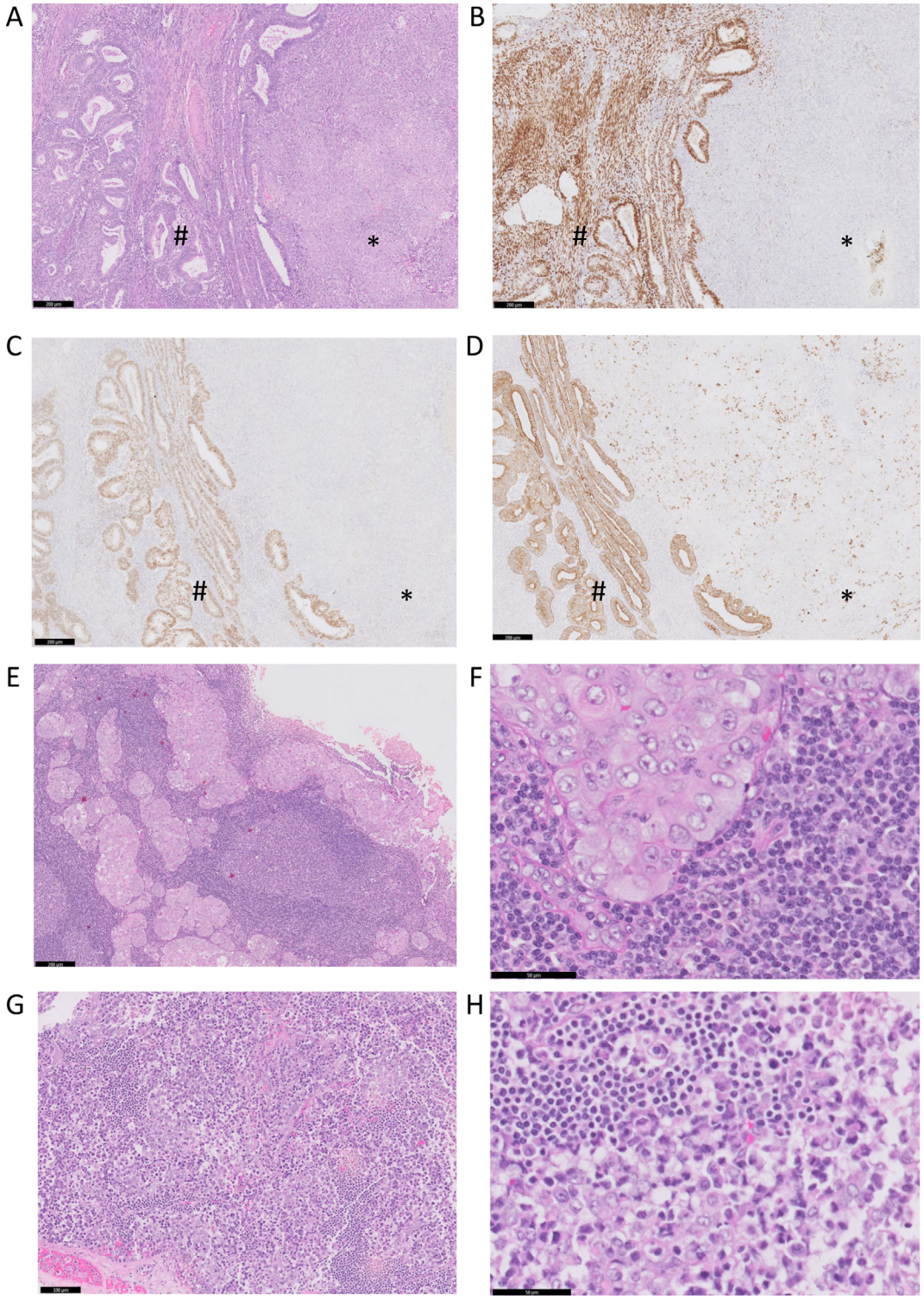

Fig. 1. Representative photomicrographs of uterine tumours and lymph node metastases from selected cases. A–D) Haematoxylin and eosin stained section of the primary uterine mass from Case 4, highlighting FIGO G1 endometrioid carcinoma on the left (#), and undifferentiated carcinoma component on the right (*), along with Estrogen receptor (B), PAX8 (C), and MNF116 (pancytokeratin) (D) immunoperoxidase stained sections of the same mass (50× magnification, 5× objective). E–F) Haematoxylin and eosin stained sections of a lymph node from Case 1 showing metastatic FIGO G3 endometrioid carcinoma in the node (E – 50× magnification, 5× objective; F – 400× magnification, 40× objective). G–H) Haematoxylin and eosin stained sections of a lymph node from Case 6 showing metastatic undifferentiated carcinoma in the node, featuring diffuse, poorly cohesive tumour cells. (G – 100× magnification, 10× objective; H – 400× magnification, 40× objective).

3.2. Early recurrence (Case 3 to 5)

3.2.1. Case 3

A 62-year-old patient presented with one-week of post-menopausal bleeding. An endometrial sampling showed Grade 1 endometrioid adenocarcinoma. Pre-operative imaging showed no distant metastasis or enlarged pelvic lymph nodes. She underwent a laparoscopic converted to laparotomy total hysterectomy and bilateral

salphingoopherectomy and pelvic lymph node dissection. Intraoperatively, there were grossly enlarged obturator and common iliac lymph nodes. Histology revealed DEAC on the background of grade 1–2 endometrioid adenocarcinoma. 10 out of 26 pelvic lymph nodes were positive for malignancy. She underwent 5 cycles of adjuvant paclitaxel and carboplatin. Disease recurrence occurred 9 months post surgery. The patient presented with abdominal pain and constipation. A CT thorax, abdomen and pelvis performed showed left supraclavicular and left axillary lymphadenopathy. Histology from the left supraclavicular node and left axillary mass biopsies confirmed invasive carcinoma resembling the dedifferentiated component of the previous endometrial tumour. The tumour was also negative for TTF1, GATA3 and mammaglobin, suggesting likely metastasis from the endometrial tumour. She underwent palliative radiotherapy to the left chest mass but eventually succumbed to progressive disease. Her OS was 23 months.

3.2.2. Case 4

A 52-year-old woman presented with a post-menopausal bleeding. Endometrial curettage showed a dedifferentiated carcinoma. Preoperative imaging showed no evidence of distant metastasis or lymphadenopathy. She underwent a total abdominal hysterectomy bilateral salphingoopherectomy, pelvic lymphadenectomy and infracolic omentectomy. The left fallopian tube and cervix were involved by tumour. She was diagnosed with FIGO Stage 3A DEAC. She underwent 5 cycles of paclitaxel and carboplatin. Prior to her 6th cycle of chemotherapy, she was found to be anaemic with a haemoglobin level of 5.9 g/dL. A CT of the thorax, abdomen and pelvis performed showed ascites with extensive nodular peritoneal thickening in the pelvis suspicious for peritoneal tumour recurrence. There was a dominant mixed solid-cystic 5.6 cm deposit in the left pelvis, anterior to the left common iliac artery. Her DFI was 5 months. The patient was started on second line treatment with pembrolizumab and gemcitabine. Her last positron emission tomography-computed tomography (PET-CT) done 15 months post-operatively showed stable disease and resolution of ascites.

3.2.3. Case 5

A 44-year-old woman presented with a 5-year history of abnormal uterine bleeding. Pelvic examination revealed a fleshy cervical tumour. Biopsy of the cervical tumour showed areas of an undifferentiated carcinoma consistent with that from an endometrioid carcinoma. Histology from an endometrial biopsy showed endometrioid adenocarcinoma with undifferentiated areas. The pre-operative MRI pelvis showed a mass within the endometrial cavity extending to the lower two-third of the vaginal vault. At the same time, the patient was diagnosed with concomitant left breast intraductal carcinoma. The PET-CT performed showed hypermetabolic bilateral obturator adenopathy. There was no distant metastasis seen. The patient was initially planned for 6 cycles of neoadjuvant carboplatin and paclitaxel followed by surgery (combined breast and gynaecology), and completion adjuvant radiotherapy. However, her treatment was complicated by non-neutropenic sepsis secondary to pyometra after her 2nd cycle of chemotherapy. A restaging CT thorax and abdomen and MRI pelvis showed progressive disease. She underwent total abdominal hysterectomy and bilateral salphingoopherectomy with pelvic lymph node dissection. Histology showed involvement of bilateral parametrial margins by tumour. 3 out of 9 pelvic lymph nodes were positive for malignancy. She was diagnosed with Stage 3C1 DEAC. Post-operatively, patient completed the 3rd cycle of carboplatin and paclitaxel. However, local vaginal recurrence occurred one month post-surgery. The patient declined palliative radiotherapy and sought alternative therapy. Her diseased progressed with spread to the vagina vault, liver, supraclavicular lymph nodes, para-aortic lymph nodes, pelvic lymph nodes, omentum and peritoneum. She passed away 3 months post-surgery with an OS of 6 months.

3.3. Progression of disease despite neoadjuvant chemotherapy, surgery and post-operative chemotherapy and radiotherapy (Case 6)

3.3.1. Case 6

A 57-year-old woman presented with a one-year history of post-menopausal bleeding. Endometrial curettage showed poorly differentiated endometrioid adenocarcinoma. A CT scan of the thorax, abdomen and pelvis showed a 4.7 cm uterine mass with invasion into the bladder and rectus abdominis. There were multiple enlarged pelvic lymph nodes along the ovarian veins, up to the level of the left renal vein. The patient underwent a total abdominal hysterectomy, bilateral salphingoopherectomy, bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy, infragastric omentectomy and bladder mass resection. Optimal debulking was achieved. She was diagnosed with stage 4 DEAC. She underwent 5 cycles of neoadjuvant carboplatin and paclitaxel. Post-operatively, the patient continued to have persistent gross haematuria. A CT neck, thorax, abdomen and pelvis done 3 months post-operatively showed progressive disease with new left level IV adenopathy, left common iliac, bilateral surgical obturator and left external iliac adenopathy. There was also a bony lesion at the left pubic ramus suggestive of metastasis. She declined second line palliative chemotherapy. Eight months post-surgery, the patient developed bilateral lower limb weakness. A MRI thoracolumbar spine showed a T2 vertebral body metastasis causing severe spinal canal stenosis and cord compression. She underwent 5 cycles of palliative radiotherapy to C6 to T3 spine. The patient eventually succumbed to her progressive disease with an OS of 9 months.

3.4. Lost to follow-up

3.4.1. Case 7

A 55-year-old patient underwent staging surgery for DEAC at our centre. She was diagnosed with Stage 3A DEAC with involvement of the left ovary. She underwent three cycles of adjuvant chemotherapy. She subsequently decided to pursue treatment with a private oncologist and was lost to follow-up.

4. Discussion

There is limited literature consisting of case reports and small case series on DEAC. Prior reports (Pfaendler and Randall, 2019; Morioka et al., 2018; Han et al., 2017; Wu et al., 2013; Shen et al., 2012) have shown poor outcomes with early recurrences, rapid progression of disease, local invasion into bladder and rectum and decreased survival. In our centre, the 2-year OS was 31.3%, compared to 82.8% in patients with Grade 3 endometrioid adenocarcinoma treated in the same centre.

Nonetheless, in our case series, one of the patients had a favourable outcome of a DFI and OS of 56 months. This was despite having a Stage 3C1 disease and experiencing an inadvertent uterine and bowel perforation during diagnostic hysteroscopy requiring bowel resection. A review of histology showed that the DEAC component was a small focus and that the primary tumour was also small (1.8 cm). Moreover, the invasive component, as well as the tumour deposit in the lymph node was endometrioid, not undifferentiated. Interestingly, the other patient who achieved long term disease free survival also had a relatively small proportion of undifferentiated carcinoma. This may suggest that the percentage of DEAC in the primary tumour can affect prognosis. However, there is limited literature where the proportion of undifferentiated carcinoma in the primary tumour is reported. Prospective data on percentage involvement of DEAC may be useful to aid in prognostication.

Previous studies have shown that the undifferentiated component of DEAC tends to lose the expression of markers associated with endometrioid adenocarcinoma, with some markers being focally retained. The undifferentiated portion, despite losing expression of Pax8/ER/PR, usually retains some focal positivity for epithelial markers such as EMA

and CK (Murali et al., 2019). Our series saw a similar pattern of expression to previous studies, with all but one of the cases losing expression of ER, all of the cases positive for vimentin, and the majority of the cases at least focally positive for EMA/CK (Ramalingam et al., 2016).

Recent work has linked loss of MMR enzymes in the dedifferentiated component to expression of PD-L1 (Ono et al., 2019), implying that these tumours may respond to immunotherapy. Interestingly, there was loss of expression of at least one mismatch repair gene in all cases where MMR protein IHC was performed (4 cases) in this series, compared to about 50% in two previously published series on undifferentiated endometrioid adenocarcinoma (Ramalingam et al., 2016; Soyama et al., 2016), though we are unable to tell from our data if any of the cases were due to germline mutations. A review of adjuvant therapeutic modalities revealed that there has been no effective therapy in the response-evaluable patients with DEAC (Soyama et al., 2016). Nonetheless, in our series, a patient (Case 4) with early disease recurrence managed to achieve disease control with the use of prembrolizumab, an anti-PD-1 immunotherapy, which is an approved treatment for solid tumours which are deficient in DNA mismatch repair enzymes. There was successful control of her disease for a following 16 months from start of the immunotherapy.

5. Conclusion

DEAC is a more aggressive histological subtype and present with more advanced disease compared the other endometrioid adenocarcinomas. Better awareness of this condition can lead to proper diagnosis and treatment. As many of these tumours are deficient in DNA mismatch repair enzymes, they may be eligible for further treatment with anti-PD-1 immunotherapy.

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Author contribution

C Goh: methodology, formal analysis, investigation, data curation, writing – original draft. **Farah BL**: formal analysis, data curation, writing – original draft **Ho WY**: supervision, writing – review & editing, **Wong SL**: supervision, resources. **Goh CHR**: supervision, resources. **Chew SH:** supervision, resources. **Nadarajah R:** supervision, resources. **YK Lim**: supervision, resources. **TH Ho**: conceptualisation, supervision, project administration

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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