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Case report

Rapid progression of disease in two cases of undifferentiated endometrial carcinoma

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ABSTRACT

Undifferentiated endometrial carcinoma, a rare histopathologic diagnosis, has a poor prognosis with high risk of progression during or shortly after completion of adjuvant treatment. We present two cases of undifferentiated endometrial carcinoma: one in a postmenopausal female who experienced recurrent disease immediately after completion of adjuvant treatment and one in a premenopausal female who experienced disease progression while receiving adjuvant treatment. These cases exemplify the aggressive behavior of undifferentiated endometrial carcinoma and suggest the need for a more effective treatment in the upfront setting than the current standard of care for endometrioid endometrial adenocarcinoma.

1. Introduction

The American Cancer Society estimates 63,230 new cases of uterine cancer and 11,350 uterine cancer-related deaths in 2018 (Siegel et al., 2018). The World Health Organization defines undifferentiated endometrial carcinoma as “those lacking any evidence of differentiation” (Silverberg et al., 2003). A historically underrecognized and underreported subtype, undifferentiated carcinoma is present in approximately 9% of endometrial carcinomas, with only 29% purely undifferentiated endometrial carcinoma and the remaining 71% admixed with differentiated carcinoma (Altrabulsi et al., 2005; Silva et al., 2007). Undifferentiated endometrial cancers have been gaining attention in the pathology literature, with reports of hypermutated (mismatch repair deficiency), ultramutated (*POLE* mutated), copy number low (*PTEN* mutated) or copy number high (*TP53* mutated) molecular pathways (Rosa-Rosa et al., 2016), but literature regarding early clinical management is limited.

Undifferentiated histology has not been observed in hereditary nonpolyposis colorectal cancer (HNPCC) patients, but a subset of sporadic, *MLH1*-methylated tumors demonstrate undifferentiated histology (Broaddus et al., 2006; Garg et al., 2009). The undifferentiated tumors were weakly/patchy positive for pancytokeratin but negative for estrogen and progesterone receptor (Broaddus et al., 2006). In comparison to high grade endometrioid endometrial adenocarcinoma, which has 1–49% of glandular differentiation, patients with undifferentiated endometrial carcinoma also present with vaginal bleeding and/or pelvic pain but more often (54%–58%) present with advanced stage disease and more frequently (75%) die within 5 years of diagnosis (Altrabulsi et al., 2005; Tafe et al., 2010). Pelvic and para-aortic lymph nodes are the common sites of metastasis (Tafe et al., 2010; Al-Loh and Al-Hussaini, 2013), and advanced stage disease cases do not generally respond to conventional chemotherapy for endometrial adenocarcinoma.

2. Case reports (Table 1)

2.1. Case 1

A 69-year-old female (BMI 22.9 kg/m^2) with postmenopausal bleeding was referred for undifferentiated endometrial carcinoma diagnosed on endometrial biopsy. She underwent an uncomplicated robotic assisted total laparoscopic hysterectomy with bilateral pelvic and para-aortic lymphadenectomy. Her pathology demonstrated International Federation of Gynecology and Obstetrics (FIGO) stage IA undifferentiated endometrial adenocarcinoma with intact expression of mismatch repair proteins. She completed 6 cycles of adjuvant carboplatin and paclitaxel. One month after completion of adjuvant chemotherapy, she reported clear fluid per vagina but had a normal pelvic examination. Computed tomography (CT) urogram showed no evidence of urinary tract fistula but demonstrated a soft tissue density above the

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Table 1
Clinical and pathologic features of 2 patients with undifferentiated endometrial carcinoma.

	Case 1	Case 2
Clinical features		
Age at diagnosis, years	69	43
Age at menopause, years	52 (surgical, BSO)	Not applicable
Body mass index (kg/m^2)	22.9	23.2
Presentation	Postmenopausal bleeding	Abnormal uterine bleeding
Initial diagnosis	High grade carcinoma, favor undifferentiated carcinoma	Poorly differentiated carcinoma, unclear breast versus uterine origin
Imaging findings	TVUS: Uterus normal size and shape, anteverted. Endometrium 0.8 mm anteriorly, 0.9 mm posteriorly with fluid in cavity. Total endometrial thickness 17 mm. Polyp on stalk with proximal attachment versus intracavitary fibroid measuring 2.3 × 1.6 × 2.0 cm. Ovaries not visualized. No free fluid.	TVUS: 5.9 cm intrauterine mass, 3.3 cm complex right ovarian mass, no free fluid. CT CAP: Uterus markedly enlarged with suggestion of multiple fibroids. Uterine cavity filled with fluid. No lymphadenopathy. Small 2 mm focus of pleural thickening in left chest.
Surgical management	RATLH BPPALND	RAH BSO BPPALND omental biopsies
Operative findings	Superficial myometrial invasion. Large amount of necrotic tumor in lower uterine segment.	Uterus bulbous and irregular with distended lower uterine segment. Parametria free. 200 mL bloody ascites upon abdominal entry. Enlarged, firm bilateral pelvic and right para-aortic lymph nodes.
FIGO surgical stage	IA	IIIB
Postoperative management	Chemotherapy (6 cycles carboplatin + paclitaxel)	Chemotherapy (3 cycles of carboplatin + paclitaxel)
First postoperative recurrence or progression	6 months	4 months
Imaging findings at recurrence	PET: 5.1 × 3.5 cm midline pelvic mass with SUV 39.4, 3.7 × 3.0 cm left pelvic mass with SUV 33.8, ill-defined hypermetabolic soft tissue along right pelvic sidewall with SUV 20.5	CT CAP: 13 × 15 × 9 cm pelvic mass occupying the pelvis, displacing the urinary bladder and encasing vasculature including the iliac vessels
Recurrence or progression management	Chemotherapy (1 cycle pegylated liposomal doxorubicin) followed by inpatient hospice	Left percutaneous nephrostomy tube placement, Immunotherapy (1 cycle of pembrolizumab), followed by transfer to other care provider
Clinical history	GERD	Breast cancer at age 30
Family history	Breast cancer (sister at 47, mother at 42), Appendiceal cancer (mother at 78), Ovarian cancer (maternal aunt at 54), Colon cancer (paternal grandfather at 80)	No family history of cancer
Genetic testing	BRCA 1/2 wildtype	ATM VUS c.22117C > T, BRIP1 VUS c.1442G > A, CHEK2 VUS c.1111C > T
Status at last follow-up	Deceased (7 months after initial diagnosis)	Unknown (moved out of country)
Pathologic features		
Tumor location	Right uterine cornu	Endometrial cavity
Tumor size	1.7 × 1.5 × 1.0 cm	6.7 × 3.5 × 3.0 cm
Myometrial invasion	20% of myometrium (2/10 mm)	50% myometrium (8/16 mm)
Lymphovascular space invasion	Absent	Present in parametrium
Cervical stromal invasion	Absent	Absent
Ovaries and fallopian tubes	Absent	Present in ligamentous soft tissues adjacent to left ovary
Pelvic lymph nodes	Absent	Absent
Para-aortic lymph nodes	Absent	Absent
Mismatch repair protein expression	Present	MLH-1, PMS-2 absent; MLH1 promoter methylation detected
Estrogen and progesterone receptor expression	Absent	Not done

BSO bilateral salpingo-oophorectomy, *TVUS* transvaginal ultrasound, *CT CAP* computed tomography of the chest, abdomen and pelvis, *RATLH* robotic assisted total laparoscopic hysterectomy, *BPPALND* bilateral pelvic and para-aortic lymph node dissection, *RAH* radical abdominal hysterectomy, *PET* positron emission tomography, *GERD* gastroesophageal reflux disease, *BRCA 1/2* breast cancer genes 1 and 2, *ATM* ataxia telangectasia mutated, *VUS* variant of unknown significance, *BRIP1* BRCA1 interacting protein C-terminal helicase 1, *CHEK2* checkpoint kinase 2.

vagina that was concerning for recurrent disease. A positron emission tomography (PET) demonstrated 3 distinct masses in the pelvis, ranging from 3.7–5.1 cm in single longest diameter and from 20.5 to 39.4 in SUV. Since her initial tumor was microsatellite stable, she was not a candidate for off-protocol pembrolizumab. A new biopsy was sent for molecular testing and estrogen and progesterone receptor status. The estrogen and progesterone receptors were not expressed. While awaiting those results, she elected to start cytotoxic chemotherapy. Several weeks after receiving her first cycle of single agent pegylated liposomal doxorubicin, she experienced rapid peritoneal disease progression, cachexia, and functional status decline. She transitioned to inpatient hospice and died within 3 weeks of initiating chemotherapy and < 6 weeks from the time her recurrence was diagnosed.

2.2. Case 2

A 43-year-old female (BMI 23.2 kg/m^2) with a personal history of breast cancer 12 years prior presented with several weeks of abnormal uterine bleeding. Endometrial biopsy demonstrated a poorly differentiated carcinoma of breast versus endometrial origin. She underwent radical abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, right para-aortic lymphadenectomy and omental biopsies. Her surgical pathology was initially reported as FIGO stage IB poorly differentiated endometrial adenocarcinoma. Outside pathology review reported a FIGO stage IIIB dedifferentiated carcinoma (predominantly undifferentiated with focal adenocarcinoma with mixed endometrioid and mucinous features), with lymphovascular invasion present in the parametrium and metastatic adenocarcinoma involving the ligamentous soft tissues adjacent to the left ovary, though there was no metastatic carcinoma involving the ovaries proper or fallopian tubes. She started adjuvant carboplatin and paclitaxel six weeks after surgery. During her office follow up after her third cycle of chemotherapy, she complained of sciatic nerve pain that had been worsening over several weeks. A CT was ordered for further evaluation and demonstrated a 13 × 15 × 9 cm pelvic mass displacing the urinary bladder, encasing vasculature (including iliac vessels), tracking beneath the psoas muscle and causing moderate left hydronephrosis. Given progression of disease while on active treatment,

her fourth cycle of carboplatin and paclitaxel was held. A left percutaneous nephrostomy tube was placed for management of her hydronephrosis. Her immunohistochemistry demonstrated loss of expression of MLH1 and PMS2, so she was started on pembrolizumab. Shortly after her first treatment, she and her family felt that continued declined was inevitable and elected to return to her country of origin to seek medical care with more family and social support.

3. Discussion

Although the pathology literature addressing undifferentiated and dedifferentiated endometrial carcinoma has increased over the past few years, PubMed search results using terms undifferentiated endometrial carcinoma and dedifferentiated endometrial carcinoma demonstrate scant medical or surgical oncology literature regarding management of these patients. Undifferentiated carcinomas represent a rare but extraordinarily aggressive subset of endometrial cancers. Multiple reports characterize the immunohistochemical profile and molecular pathways (Rosa-Rosa et al., 2016; Broaddus et al., 2006; Garg et al., 2009; Tafe et al., 2010; Al-Loh and Al-Hussaini, 2013; Espinosa et al., 2017; Kobel et al., 2018; Ramalingam et al., 2016; Romero-Perez et al., 2015; Tessier-Cloutier et al., 2018; Yokomizo et al., 2017), including rates of loss of expression of mismatch repair proteins as high as 58% (n = 7) in undifferentiated endometrial carcinoma (Tafe et al., 2010). Also referenced as “grade 4” tumors, undifferentiated carcinomas have higher likelihood of advanced stage at diagnosis and higher 5-year mortality as compared to high grade endometrioid endometrial adenocarcinomas (Altrabulsi et al., 2005; Tafe et al., 2010). Undifferentiated carcinomas of the endometrium can be associated with a differentiated component, most often FIGO grade 1–2 endometrioid adenocarcinoma (Silva et al., 2006). The University of Texas MD Anderson Cancer Center describes these as “dedifferentiated” (Altrabulsi et al., 2005; Silva et al., 2007; Silva et al., 2006) while the Memorial Sloan Kettering Cancer Center describes them as “combined undifferentiated and differentiated carcinomas” (Tafe et al., 2010). The Department of Pathology at the MD Anderson Cancer Center put forth a refined definition of undifferentiated carcinoma as being characterized by proliferation of medium- or large-sized, monotonous epithelial cells growing in solid sheets without a pattern, with a complete absence of glandular differentiation and with absent or minimal (< 10%) neuroendocrine differentiation (Altrabulsi et al., 2005; Silva et al., 2007). Some of the earlier literature on undifferentiated carcinoma of the endometrium included cases of large and small cell carcinomas with neuroendocrine differentiation; however, more recently these have been classified as neuroendocrine carcinomas rather than included among undifferentiated carcinomas since they do display a form of differentiation (Al-Loh and Al-Hussaini, 2013). Undifferentiated carcinomas of the endometrium demonstrate heterogeneous expression of epithelial markers, with only 5–10% of cells positive for keratin in approximately 80–90% of cases (Silva et al., 2007). Regardless of the nomenclature, anywhere from 37 to 87% of undifferentiated carcinomas have been reported to be admixed with endometrioid adenocarcinoma (Altrabulsi et al., 2005; Tafe et al., 2010; Silva et al., 2006) and carcinomas with an undifferentiated component are consistently reported to be more aggressive than high grade endometrioid adenocarcinomas (Yokomizo et al., 2017; Han et al., 2017). Perinuclear staining of cytokeratin and EMA, loss of expression of PAX-8, ER, PR and E-cadherin have been shown to be helpful in distinguishing undifferentiated carcinoma from endometrioid adenocarcinoma (Han et al., 2017).

Undifferentiated carcinoma may develop from any of the four molecular pathways described by The Cancer Genome Atlas for endometrial carcinoma: hypermutated (mismatch repair deficiency), ultramutated (*POLE* mutated), copy number low (*PTEN* mutated) or copy number high (*TP53* mutated) (Rosa-Rosa et al., 2016). Among undifferentiated carcinomas, *POLE*-mutated tumors have been shown to have favorable prognosis, with diagnosis at earlier stages (8 of 9 patients stage I or II) and no deaths from disease after 4 years in one retrospective study of 21 patients (Espinosa et al., 2017).

The only case series identified in Obstetrics and Gynecology literature is a 20-year retrospective cohort in Turkey with 1690 cases of endometrial cancer identified, 18 (1.1%) of which were reported to be undifferentiated carcinomas (Ureyen et al., 2015). Four (22.2%) of those patients had early (stage I or II) disease, while fourteen (77.8%) had advanced (stage III or IV) disease. Six (33.3%) of the eighteen patients were lost to follow up after surgery. Among the remaining twelve patients, two (16.6%) experienced disease progression while on active treatment and died of the disease 6–7 months after initial surgery. Another two (16.6%) experienced disease recurrence 12 and 14 months after initial surgery: one had a distal vaginal recurrence treated with surgery and chemotherapy and had no evidence of disease six years later and one had a vaginal cuff and lung recurrence and was subsequently lost to follow up. While this study is one of the larger case reports available and the only one with a clinical rather than pathologic focus, it is limited by the large number of patients lost to follow up, lack of rigorous pathologic review and immunohistochemistry and diversity of adjuvant treatment.

In conclusion, reliable classification of undifferentiated carcinoma represents the first step in learning more about this clinical entity and which subset of patients may have a more favorable course; however, data remain scarce regarding approach to adjuvant treatment in this population. We have reported two patients who failed to achieve disease control after surgery with no evidence of residual disease followed by adjuvant carboplatin and paclitaxel; both rapidly declined in functional status shortly after institution of second line therapy. Given the poor response to standard therapy and the high portion of undifferentiated carcinomas of the endometrium with mismatch repair deficiency, it raises the question of whether early molecular testing and non-standard chemotherapy including immunotherapy should be considered as frontline therapy for this subset of patients.

Conflicts of interest and disclosures

The authors have no conflicts of interest to declare.

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