Gynecologic Oncology Reports 53 (2024) 101380

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Long-term disease-free survival with chemotherapy and pembrolizumab in a patient with unmeasurable, advanced stage dedifferentiated endometrial carcinoma

Joy M. Davis *, Tullia Rushton, Felicity Nsiah, Rebecca L. Stone, Anna L. Beavis, Stéphanie L. Gaillard, Alice Dobi, Amanda N. Fader

Kelly Gynecologic Oncology Service, Department of Gynecology and Obstetrics, Johns Hopkins School of Medicine, Baltimore, MD, USA

ARTICLE INFO

Keywords:
Dedifferentiated endometrial carcinoma
Pembrolizumab
Mismatch repair deficient

ABSTRACT

Dedifferentiated endometrial carcinoma is a rare, highly aggressive subtype of endometrial cancer associated with poor survival outcomes. Current guidelines recommend treatment of advanced-stage disease with surgical staging or cytoreduction and platinum/taxane-based chemotherapy. Despite these approaches, the achievement of long-term remission or prolonged survival is challenging. Recent Phase III studies demonstrate that the addition of PD-1 inhibitors to standard chemotherapy significantly improves progression-free survival in patients with measurable, mismatch repair deficient (dMMR) and proficient (pMMR) advanced-stage or recurrent endometrial carcinoma. However, the role of PD-1 blockade in the treatment of undifferentiated and dedifferentiated endometrial carcinoma remains unclear, as very few patients with these cancer subtypes were included in the trials. In this case report, we present a patient with dMMR dedifferentiated endometrial carcinoma, treated with primary surgery to no gross residual disease, followed by carboplatin/paclitaxel chemotherapy and a short course of maintenance pembrolizumab. To date, the patient remains with a prolonged disease-free survival of 61 months, supporting the potential use of PD-1 inhibitors in the upfront treatment of unmeasurable, advanced-stage, dMMR dedifferentiated endometrial carcinoma.

1. Introduction

Undifferentiated endometrial carcinoma (UDC) and dedifferentiated endometrial carcinoma (DDC) are rare, biologically aggressive subtypes of endometrial cancer associated with poor prognoses (Tafe et al., 2010; Altrabulsi et al., 2005). UDC is characterized by cells without overt cell lineage differentiation, complete absence of glandular differentiation, and absent or minimal neuroendocrine differentiation (Altrabulsi et al., 2005; Silva et al., 2006). DDC shares a similar histologic appearance, however additionally contains regions of well-differentiated low-grade endometrioid adenocarcinoma (Tafe et al., 2010; Silva et al., 2006). It is estimated that UDC makes up approximately 9 % of all endometrial cancer cases, of which 40 % meet the criteria for DDC (Silva et al., 2006). Although representing only a fraction of endometrial cancer cases, UDC and DDC are associated with disproportionately higher rates of recurrence and significantly poorer survival outcomes when compared to endometrioid carcinoma (Tafe et al., 2010; Altrabulsi et al., 2005). While the overall prognosis of endometrial cancer is favorable, UDC has a reported median survival rate of 6 months (Tafe et al., 2010). Over half of UDC cases present with advanced-stage disease, with extremely high recurrence and mortality rates of 75 % (Altrabulsi et al., 2005). Current treatment guidelines for UDC and DDC recommend primary surgical resection (in those who are surgical candidates) and adjuvant treatment (systemic platinum/taxane-based chemotherapy and possible radiation) irrespective of stage due to their aggressive nature and poor prognoses (NCCN, 2023). Thus, there is a critical unmet need to identify optimal treatment strategies for patients with undifferentiated/dedifferentiated disease.

Approximately half of UDC and DDC tumors demonstrate mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H), suggesting a treatment role for immunotherapeutic agents (Travaglino et al., 2020). Immune checkpoint inhibitors (ICIs), specifically those that target programmed death ligand 1 (PD-1), have emerged as a new promising adjuvant treatment in primary advanced or recurrent endometrial cancer, particularly in those with dMMR-MSI-H tumors (Eskander et al., 2023; Mirza et al., 2023). Two recent Phase III trials

* Corresponding author at: 600 N. Wolfe St, Phipps 21, Baltimore, MD 21287.
E-mail address: jdavi251@jh.edu (J.M. Davis).

https://doi.org/10.1016/j.gore.2024.101380
Received 7 February 2024; Received in revised form 23 March 2024; Accepted 26 March 2024
Available online 27 March 2024

demonstrated impressive improved progression-free survival when PD-1 inhibition was added to carboplatin/paclitaxel chemotherapy in patients with measurable advanced-stage or recurrent endometrial cancer, irrespective of MMR status (Table 1) (Eskander et al., 2023; Mirza et al., 2023). In the NRG-GY018 clinical trial of patients with advanced-stage or recurrent, largely measurable, endometrial carcinoma treated in the first-line setting with carboplatin/paclitaxel with or without 14 cycles of pembrolizumab, only eight of the 816 patients enrolled had DDC (Eskander et al., 2023). Further, the efficacy of PD-1 blockade as maintenance therapy in patients with unmeasurable disease who are treated in the upfront setting remains unclear. Here we present a patient with advanced stage, dMMR DDC, treated with primary cytoreductive surgery and adjuvant platinum/taxane chemotherapy to no measurable disease, followed by a short course of pembrolizumab, who remains without evidence of disease for more than five years.

2. Case description

A 58-year-old female, with a BMI of 34.6 kg/m^2 and no significant past medical history, presented to an outside institution with postmenopausal bleeding. Pelvic examination demonstrated a prolapsing, friable mass through the cervical canal, which was biopsied. This biopsy showed a FIGO grade 3 endometrial adenocarcinoma, endometrioid type (architectural grade 3, nuclear grade 2, p53 normal/wild-type on immunohistochemistry staining). The patient was referred to our institution to discuss her diagnosis and treatment options. Computed tomography (CT) imaging of the chest, abdomen, and pelvis demonstrated lobulated soft tissue within the endometrial cavity (4.7 x 6.7 cm) and prominent left paraaortic lymph nodes (up to 6 mm). Shortly after, she underwent an exploratory laparotomy, radical abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and paraaortic lymphadenectomy, with no gross residual disease noted after surgery. Her surgical pathology demonstrated a FIGO stage IIIC1 high-grade, dedifferentiated endometrioid adenocarcinoma with loss of MLH1 and PMS2 (intact MSH2 and MSH6) (Fig. 1). Four weeks following surgery, she was started on adjuvant carboplatin and paclitaxel. She completed six cycles, which she tolerated well. On repeat CT imaging of the chest, abdomen, and pelvis, she had no evidence of metastatic disease. Due to her known mismatch repair deficient tumoral status, she was subsequently started on intravenous pembrolizumab off clinical trial. She received three cycles of pembrolizumab before discontinuation due to the development of presumed immune-mediated thyroiditis and spongiotic dermatitis. Her symptoms were successfully treated and resolved; she remains on thyroid replacement therapy. The patient has subsequently undergone cancer surveillance per National Comprehensive Cancer Network guidelines (NCCN, 2023). She remains disease-free and without treatment toxicities for 61 months.

3. Discussion

In this case report, we present a patient with unmeasurable, advanced-stage dMMR DDC, treated with only three cycles of maintenance pembrolizumab after endometrial cancer staging surgery and platinum/taxane-based chemotherapy, who has experienced long-term disease-free and overall survival. In the Phase III NRG-GY018 clinical trial of patients with advanced-stage or recurrent endometrial carcinoma treated with carboplatin and paclitaxel with or without 14 cycles of pembrolizumab, fewer than 1 % of patients enrolled had DDC (Eskander et al., 2023). Additionally, histology-based response rates in the trial have not yet been reported, the vast majority of patients enrolled on the NRG-GY018 trial had measurable disease, and FDA approval for this new upfront combinatorial strategy is pending. Acknowledging our reported results are in a singular patient, our case suggests there may be a potential benefit of a short course of PD-1 blockade following adjvuvant chemotherapy in patients with dMMR, advanced-stage, unmeasurable dedifferentiated endometrial carcinoma.

Historically in endometrial cancer, PD-1 inhibitor use has been reserved as second-line therapy. A landmark Phase II trial demonstrated that in previously treated advanced-stage or recurrent endometrial cancer, pembrolizumab monotherapy led to impressive response and progression-free survival rates for patients with dMMR or MSI-H tumoral status (O'Malley et al., 2022). These results and others led to the FDA approval of pembrolizumab to treat dMMR or MSI-H agnostic of tumor type (FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. U.S. Food Drug Administartion. Published May 30, 2017). Although particularly effective in the dMMR-MSI-H population, treatment with pembrolizumab in combination with lenvatinib, a tyrosine kinase inhibitor, demonstrated clinical benefit regardless of MMR status (Makker et al., 2022). More recently, two Phase III trials have examined PD-1 blockade in patients with primary advanced-stage or recurrent endometrial cancer (Eskander et al., 2023; Mirza et al., 2023). The RUBY/GOG-3031 trial investigated the addition of the PD-1 inhibitor, dostarlimab, to standard platinum-based therapy. The study results demonstrated an increased progression-free survival with the addition of dostarlimab, especially in the dMMR–MSI-H population (Mirza et al., 2023). Additionally, the NRG-GY018 trial examined the addition of pembrolizumab to standard platinum-based therapy. Similarly, a 70 % lower risk of disease progression or death in patients with dMMR advanced or recurrent endometrial cancer was observed with the addition of pembrolizumab (Eskander et al., 2023). While these studies support the use of adjuvant PD-1 blockade in advanced-stage or recurrent disease, there were no patients with dMMR DDC included in the GOG-3031 trial and fewer than 1 % of enrolled patients in NRG-GY018 (Table 1) (Eskander et al., 2023; Mirza et al., 2023). While the histology-based treatment outcomes and potential FDA

Table 1
Trials Investigating PD-1 Inhibitor Plus Platinum-based Chemotherapy in Primary Advanced or First Recurrent Endometrial Cancer.

Trial	PD-1 inhibitor	Disease status at treatment initiation	No. of cycles received (max allowed per protocol)	Progression free survival (PFS)*	Serious adverse events*	No. of dMMR MSI-H cases	No. of UDC or DDC cases
GOG-3031	Dostarlimab	Measurable	6 (32)	24-month PFS	Grade 3 or higher	0	3
				Treatment arm: 36.1 %	Treatment arm: 70.5 %		Treatment arm: 1
				Placebo arm: 18.1 %	Placebo arm: 59.8 %		Placebo arm: 2
NRG-GY018	Pembrolizumab	Measurable	6 (20)	12-month PFS	Grade 3 or higher	8	8
				Treatment arm: 74 %	Treatment arm: 28.8 %		Treatment arm: 4
				Placebo arm: 38 %	Placebo arm: 22.7 %		Placebo arm: 4

* Reported results are based on entire study population

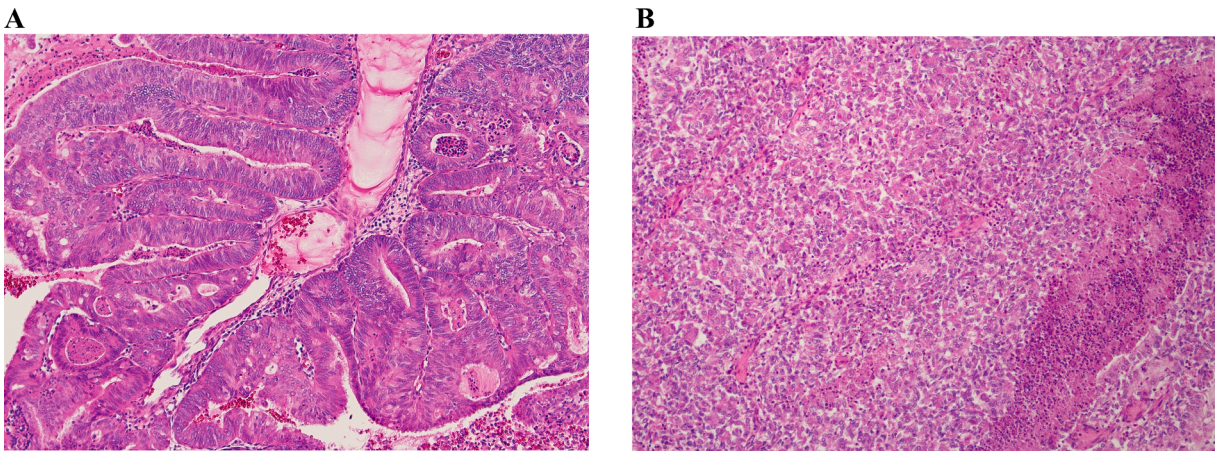

Fig. 1. Dedifferentiated endometrial carcinoma. (A) Well-differentiated endometrioid carcinoma component. (B) The undifferentiated carcinoma component shows a diffuse growth of non-cohesive tumor cells with necrosis in the right of the image.

approval from the NRG-GY018 trial are awaited, this case report provides evidence that the addition of anti-PD1 therapy to adjuvant treatment may be beneficial in dMMR DDC.

Additionally, the optimal duration of maintenance anti-PD1 therapy in advanced-stage endometrial cancer is unknown. Most trials continue patients on maintenance immunotherapy for at least two years. Recent evidence suggests that immune system reprogramming may occur even after one dose of immune checkpoint inhibitor treatment (Valpione et al., 2020). Furthermore, anti-PD1 therapy may be associated with considerable immune-related toxicities and cost. A recent Phase II trial examined the addition of pembrolizumab to standard carboplatin/paclitaxel chemotherapy in patients with advanced endometrial cancer (Barber et al., 2022). Although limited by a small cohort of 9 patients, the study investigators found that only six cycles of pembrolizumab during platinum-based therapy treatment, as opposed to the increased number of cycles utilized in NRG-GY018 and GOG-3031, respectively, led to an objective response rate of 88.9 % in patients with dMMR and/or MSI-H status (Barber et al., 2022). Our patient received significantly fewer cycles than other studies, yet continues to demonstrate long-term progression-free and overall survival with resolution of associated side effects on thyroid replacement therapy. Although notably limited by exhibition in one patient, our case report demonstrates that even three doses of anti-PD1 therapy following platinum/taxane-based chemotherapy may contribute to long-term disease-free survival in advanced-stage dMMR DDC. Conversely, it also illustrates that it can take exposure to few cycles of anti-PD1 therapy to incur major toxicity. Further investigation into the optimal duration of maintenance immunotherapy is necessary to determine a balance between maximal survival benefit and limited potential toxicity and cost.

4. Conclusion

Dedifferentiated endometrial carcinoma is a biologically aggressive subtype of endometrial cancer, often diagnosed at later stages and associated with poorer survival outcomes. Thus, there remains a pressing need to identify optimal adjuvant therapy in this setting. We present a patient with advanced-stage, unmeasurable, dMMR dedifferentiated carcinoma, treated with primary cytoreductive surgery and platinum/taxane-based chemotherapy, followed by a short course of pembrolizumab, with more than five years of progression-free and overall survival. Further studies are needed to determine if fewer maintenance cycles of pembrolizumab than studied in recent randomized controlled trials may be adequate to treat the disease. We eagerly await the histology-specific results of NRG-GY018 and the potential FDA approval for pembrolizumab treatment in the upfront setting for patients with advanced-stage and recurrent endometrial cancer. Further investigation of anti-PD1 therapy in patients with poor-prognostic endometrial histologic subtypes and in all comers to determine the optimal number of treatments is warranted.

Informed consent and patient details

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Joy M. Davis: Writing – review & editing, Writing – original draft, Conceptualization. **Tullia Rushton:** Writing – review & editing, Conceptualization. **Felicity Nsiah:** Writing – review & editing. **Rebecca L. Stone:** Writing – review & editing. **Anna L. Beavis:** Writing – review & editing. **Stéphanie L. Gaillard:** Writing – review & editing. **Alice Dobi:** Data curation. **Amanda N. Fader:** Writing – review & editing, Supervision, Conceptualization.

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.

References

Altrabulsi, B., Malpica, A., Deavers, M.T., Bodurka, D.C., Broaddus, R., Silva, E.G., 2005. Undifferentiated carcinoma of the endometrium. Am J Surg Pathol. 29 (10), 1316–1321. https://doi.org/10.1097/01.pas.0000171003.72352.9a.

Barber, E.L., Chen, S., Pineda, M.J., et al., 2022. Clinical and biological activity of chemoimmunotherapy in advanced endometrial Adenocarcinoma: a phase II trial of the big ten cancer Research consortium. Cancer Res Commun. 2 (10), 1293–1303. https://doi.org/10.1158/2767-9764.crc-22-0147.

Eskander, R.N., Sill, M.W., Beffa, L., et al., 2023. Pembrolizumab plus chemotherapy in advanced endometrial cancer. N Engl J Med. 388 (23), 2159–2170. https://doi.org/10.1056/NEJMoa2302312.

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. U.S. Food & Drug Administartion. Published May 30, 2017. Accessed January 28, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication.

Makker, V., Colombo, N., Casado Herráez, A., et al., 2022. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med. 386 (5), 437–448. https://doi.org/10.1056/NEJMoa2108330.

Mirza, M.R., Chase, D.M., Slomovitz, B.M., et al., 2023. Dostarlimab for Primary advanced or recurrent endometrial cancer. N Engl J Med. 388 (23), 2145–2158. https://doi.org/10.1056/NEJMoa2216334.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Endometrial Cancer V.1.2023.

O'Malley, D.M., Bariani, G.M., Cassier, P.A., et al., 2022. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. J Clin Oncol off J Am Soc Clin Oncol. 40 (7), 752–761. https://doi.org/10.1200/JCO.21.01874.

Silva, E.G., Deavers, M.T., Bodurka, D.C., Malpica, A., 2006. Association of low-grade endometrioid carcinoma of the uterus and ovary with undifferentiated carcinoma: a new type of dedifferentiated carcinoma? Int J Gynecol Pathol off J Int Soc Gynecol Pathol. 25 (1), 52–58. https://doi.org/10.1097/01.pgp.0000183048.22588.18.

Tafe, L.J., Garg, K., Chew, I., Tornos, C., Soslow, R.A., 2010. Endometrial and ovarian carcinomas with undifferentiated components: clinically aggressive and frequently underrecognized neoplasms. *Mod Pathol Off J U S Can Acad Pathol Inc*. 23 (6), 781–789. https://doi.org/10.1038/modpathol.2010.41.

Travaglino, A., Raffone, A., Mascolo, M., et al., 2020. TCGA Molecular subgroups in endometrial undifferentiated/dedifferentiated Carcinoma. Pathol Oncol Res POR. 26 (3), 1411–1416. https://doi.org/10.1007/s12253-019-00784-0.

Valpione, S., Galvani, E., Tweedy, J., et al., 2020. Immune-awakening revealed by peripheral T cell dynamics after one cycle of immunotherapy. Nat Cancer. 1 (2), 210–221. https://doi.org/10.1038/s43018-019-0022-x.