Case Report

Pathologic complete response to immune checkpoint inhibitor in a stage IIIB ovarian clear cell carcinoma patient with *POLE* mutation resistant to platinum-based chemotherapy: a case report

Shuzhan Li[1,2,3], Jiali Zhang[1,2,3], Weijiao Du[1,2,3], Xiubao Ren[1,2,3], Xinwei Zhang[1,2,3]

[1]Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin, China; [2]Tianjin's Clinical Research Center for Cancer, Tianjin, China; [3]Key Laboratory of Cancer Immunology and Biotherapy, Tianjin, China

Correspondence to: Dr. Xinwei Zhang. Tianjin Medical University Cancer Institute & Hospital, Huan Hu Xi Road, Ti Yuan Bei, He Xi District, Tianjin, China. Email: zhangxinwei@tjmuch.com.

Background: Ovarian clear cell carcinoma (OCCC) is a subtype of ovarian cancer with unique features at histological and molecular levels. The prevalence of OCCC is higher in east Asia than in Western countries. As cases are usually chemo-resistant, treatment effects of platinum-based chemotherapy are not satisfactory, especially for patients with stage III or IV disease. Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of patients with advanced-stage cancers. However, whether advanced OCCC patients benefit from ICIs remains elusive.

Case Description: Herein, we report a Chinese patient with stage IIIB inoperable OCCC who was resistant to platinum-based chemotherapy and anlotinib. Next-generation sequencing (NGS) revealed a pathogenic polymerase epsilon (*POLE*) P286R mutation and a high level of tumor mutation burden (TMB) in tissue and plasma samples. The ICI sintilimab was then used with bevacizumab as third-line treatment. Tumor reduction was observed, and the patient underwent surgical resection which indicated a pathologic complete response (pCR). Maintenance therapy with sintilimab and bevacizumab was applied, and the patient has achieved overall survival (OS) of 35 months since the diagnosis. They have also achieved a progression-free survival (PFS) of 29 months since commencing ICI treatment and have been disease-free for 24 months after surgical resection.

Conclusions: The treatment effect of ICI in *POLE*-mutant OCCC patients has been rarely reported. The treatment benefits observed in the stage IIIB OCCC patient who was resistant to platinum-based chemotherapy may be associated with the presence of *POLE* mutation and a high level of TMB. Comprehensive genomic profiling could contribute to appropriate treatment decisions for OCCC.

Keywords: Ovarian cancer; PD-1 inhibition; polymerase epsilon (*POLE*); case report

Submitted Jul 13, 2022. Accepted for publication Sep 06, 2022.
doi: 10.21037/gs-22-420
View this article at: https://dx.doi.org/10.21037/gs-22-420

Introduction

Ovarian cancer is a common and life-threatening gynecological disease with different subtypes, including high-grade serous carcinoma, low-grade serous carcinoma, mucinous carcinoma, endometrioid carcinoma, and clear cell carcinoma (1). Ovarian clear cell carcinoma (OCCC) has a high prevalence in East Asia and is as high as 25% in Japan, but appears less frequently in Western populations, where the prevalence is estimated to be between 5% and 12% (2). The treatment strategies for OCCC include surgery and platinum-based chemotherapy, while the chemo-resistant nature of the disease means the effect of these therapies is unsatisfactory, especially for patients with stage III or IV disease (3). A previous study has revealed that advanced OCCC is associated with a poor prognosis that the 3-year overall survival (OS) rate is less than 45% (4).

Mutations in *ARID1A* and *PIK3CA* occur in approximately 50% of OCCC patients, while their co-occurrence occurs in up to 70% of patients (5). Numerous efforts in developing novel targeted therapies for OCCC have been made, but most studies were *in-vitro* and none of the regimens have yet been approved. To date, treatment options for inoperable OCCC patients are still limited to platinum-based chemotherapies.

Immune checkpoint inhibitors (ICIs) including antibodies targeting programmed cell death protein 1 (PD-1) or programmed cell death ligand-1 (PD-L1) have been approved for the treatment of various advanced cancers (6). While the efficacies of ICIs in advanced OCCC remain elusive. DNA polymerase epsilon (*POLE*) is encoded by the *POLE* gene, and *POLE*-driven tumors present increased tumor mutation burden (TMB) and the benefit of immune-combined therapy for advanced patients with solid cancers, such as non-small cell lung cancer (7). To date, the treatment effect of ICIs in *POLE*-mutant OCCC patients has been rarely documented.

Herein, we report a Chinese patient with stage IIIB *POLE*-mutant OCCC who was resistant to platinum-based chemotherapy and subsequent anlotinib. Next-generation sequencing (NGS) revealed the high levels of TMB in tissue and plasma, and in addition to frequent OCCC mutations such as *TP53*, *ARID1A*, and *PIK3CA*, the patient harbored a pathogenic mutation of *POLE* rarely reported in OCCC. A ICI sintilimab was used with bevacizumab as the third-line treatment, and tumor reduction was observed. Surgical resection indicated the patient achieved pathologic complete response (pCR). The presence of *POLE* mutation and high level of TMB might explain the remarkable treatment effect of ICI in our case. We present the following article in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-420/rc).

Case presentation

The patient was a 37-year-old Chinese woman. Before coming to our hospital, she underwent a gynecological ultrasound in September 2018 which detected the presence of ovarian masses. The patient then received positron emission tomography-computed tomography (PET-CT) in October 2018, and the results indicated bilateral ovarian masses with activated fluorodeoxyglucose (FGD) metabolism in both ovaries and the abdominal aorta. In November 2018, she attended our hospital and underwent percutaneous biopsy of the suspected tumor lesion, and the immunohistochemistry (IHC) results showed CK (+), CK7 (+), P63 (–), Ki-67 (60%), Pax-8 (+), WT-1 (–), P16 (+), NapsinA (+), ER (–), PR (–), Vim (partial+), and CA125 (partial+). Pathological evaluation of the tumor indicated a poorly differentiated adenocarcinoma, and combined with the results of imaging and IHC, the patient was diagnosed with stage IIIB (T3N1M0) bilateral ovarian cancer with multiple lymph node metastases.

Given the patient was not suitable for surgical treatment at the time of diagnosis, intrapelvic injection with cis-platinum (90 mg) and postoperative venoclysis with albumin-bound paclitaxel (nab-paclitaxel) were administered. In December 2018, she was readmitted to our hospital with low-grade fever, and a CT scan observed increased tumor lesion and the presence of pelvic effusion. The patient was then discharged after intratumoral injection with lobaplatin (40 mg). In January 2019, she experienced symptoms of neoplastic fever, and treatment was changed to gemcitabine (1,400 mg at day 1 and 8) with cis-platinum (30 mg at day 1 to 3, 25 mg at day 4). However, as the patient was intolerant due to anemia and hyponatremia, treatment was discontinued at day 8 and she was discharged. In February 2019, the tumor lesion had increased in size, and the patient received anlotinib (12 mg qd, day 1–14). However, during platinum-based chemotherapy and anlotinib treatment, the tumor continued to grow, and pelvic effusion was observed by enhanced CT scan.

Progressive disease (PD) was evident in April 2019 (*Figure 1A*) and the patient underwent a second biopsy of the tumor lesion. The IHC results were: Pax-8 (+), P53 (40%+), WT-1 (–), ER (–), PR (–), CK (+), and Ki-67 (70%+), and pathological evaluation of the tumor indicated a poorly differentiated adenocarcinoma. Given positive PAX-8 in the IHC and the presence of transparent cytoplasm, the tumor was diagnosed as OCCC. Tissue and plasma samples of the patient were also analyzed by NGS with the former showing mutations with potential clinical significance in several genes related to ovarian cancer such as *TP53*, *PIK3CA*, *ARID1A*, and *POLE* (*Table 1*). In the plasma sample, *PIK3CA* p.E81K, and *POLE* p.P286R mutations were also identified (*Table 1*). Notably, high levels of TMB were observed in tissue (188.9 mutations/Mb) and plasma samples (65.9 mutations/Mb), while the microsatellite stability (MSS) was present in tissue. The patient then received bevacizumab (300 mg) and sintilimab (100 mg) for four treatment cycles from May to August 2019. At the end of August 2019, adverse events were observed,

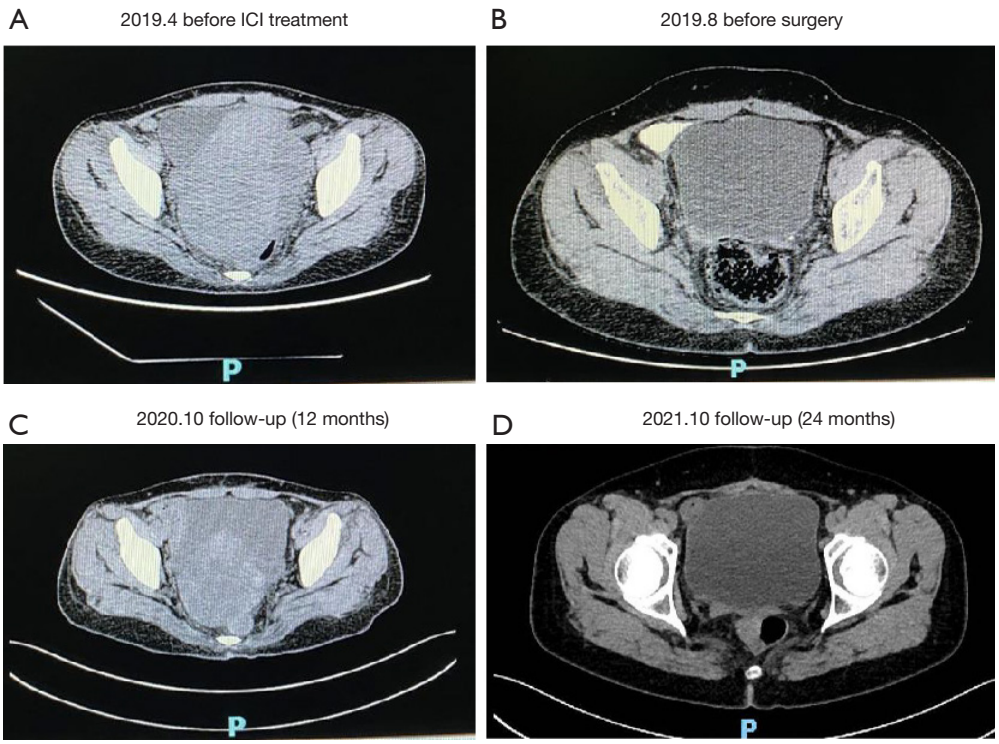

Figure 1 Treatment evaluation by CT scans. (A) Before ICI treatment; (B) before surgical resection; (C) 12 months after surgery; (D) 24 months after surgery. ICI, immune checkpoint inhibitor; CT, computed tomography.

Table 1 Mutations with potential clinical significance identified by sequencing

Gene	Mutation description			Allelic frequency	
	The change at the DNA level	The change at the protein level	Mutation type	Tissue	Plasma
TP53	c.637C>T	p.Arg213*	Nonsense	13.69%	N/A
ARID1A	c.5965C>T	p.Arg1989*	Nonsense	11.96%	N/A
ARID1A	c.4381C>T	p.Arg1461*	Nonsense	10.63%	N/A
ATM	c.46G>T	p.Glu16*	Nonsense	18.51%	N/A
ATRX	c.988A>T	p.Lys330*	Nonsense	14.77%	N/A
FGFR2	c.1646A>C	p.Asn549Thr	Missense	14,72%	N/A
IDH1	c.394C>T	p.Arg132Cys	Missense	16.96%	N/A
PIK3CA	c.241G>A	p.Glu81Lys*	Missense	14.61%	0.51%
POLE	c.857C>G	p.Pro286Arg	Missense	14.41%	0.46%
PTEN	c.1021T>G	p.Phe341Val	Missense	21.07%	N/A
RB1	c.967G>T	p.Glu323*	Nonsense	14.47%	N/A
RB1	c.2501C>A	p.Ser834*	Nonsense	12.40%	N/A
SETD2	c.871G>T	p.Glu291*	Nonsense	16.81%	N/A

*, indicates a stop codon. N/A, not available.

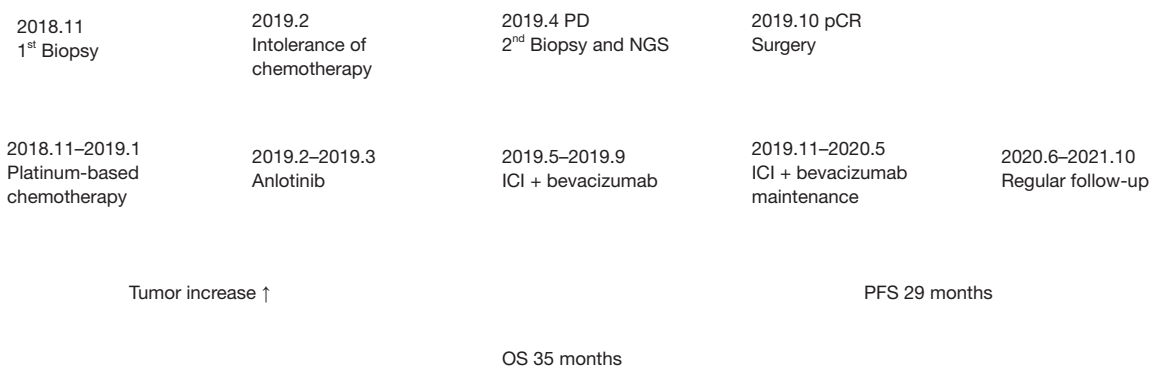

Figure 2 Summary of treatment timeline. PD, progressive disease; NGS, next-generation sequencing; ICI, immune checkpoint inhibitor; pCR, pathologic complete response; PFS, progression-free survival; OS, overall survival.

including infection (grade 3), and thrombocytopenia (grade 3) which were controlled by administration of meropenem, prednisone, and levothyroxine. In September 2019, the patient continued with the fifth treatment cycle of bevacizumab and sintilimab, during which a decrease in tumor lesion size was seen along with absorption of pelvic effusion (*Figure 1B*).

In October 2019, the patient underwent surgical resection of the uterus, bilateral adnexa, omentum majus, and pelvic lesions, and postoperative evaluation indicated pCR without residual cancerous tissue. Bevacizumab and sintilimab were used as maintenance therapy from November 2019 to May 2020, and no recurrence was observed. CT scans also revealed no recurrence in October 2020 (*Figure 1C*). Until the most recent follow-up in October 2021 (*Figure 1D*), the patient had a disease-free survival of 24 months after surgical resection, a progression-free survival (PFS) of 29 months since ICI treatment, and an OS of 35 months since diagnosis. The treatment timeline of the patient is summarized in *Figure 2*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). 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 editorial office of this journal.

Discussion

The primary treatment strategy for OCCC includes standard staging surgery and optimal cytoreduction combined with post-operative chemotherapy. Some patients with stage III or IV disease may not be eligible for surgical treatment, and platinum-based chemotherapy is usually used to reduce tumor burden. However, OCCC seems to be less sensitive to conventional platinum-based chemotherapy, with the response rate of paclitaxel plus carboplatin in OCCC ranging from 22% to 56% (8). In one study more than 50% of patients with stage III or IV OCCC had chemotherapy refractory or resistant disease (9). In our case, the patient with stage IIIB OCCC commenced with platinum-based chemotherapy, while adverse effects and tumor increase were observed until PD. Very low response rates (<10%) of chemotherapy were reported in patients with recurrent OCCC and development of novel therapeutic strategies has been an unmet clinical need.

Previous molecular profiling revealed unique features of OCCC compared with other subtypes of ovarian cancer. In OCCC, *ARID1A* and *PIK3CA* mutations occur frequently and usually coexist, while *BRCA*1/2 mutations are less common (2). In our study, 171 mutations were identified in tissue sample including 13 with potential clinical significance. Consistent with previous studies, mutations in our case involved the PI3K/AKT/mTOR pathway (*PIK3CA* and *PTEN*) and the SWI/SNF chromatin remodeling complex (*ARID1A* and *ATRX*). In addition, we identified *POLE* p.Pro286Arg mutation in tissue and plasma samples of the patient. The *POLE* gene encodes the catalytic subunit of DNA polymerase ε. The exonuclease domain mutations (EDMs) of POLE such as p.P268R, p.S297F,p.V411L, and p.S459F have been reported in endometrioid and serous carcinomas of ovarian cancer and colorectal

cancer (10,11). The presence of POLE EDMs in cancer patients is usually concurrent with an extremely high TMB level, which has been recognized as a positive predictor of cancer immunotherapy. In OCCC, no pathogenic *POLE* mutations were identified as previously reported. Our study first reported an OCCC patient harboring POLE EDM p.P286R and showed high levels of TMB in tissue and plasma. The use of ICIs in OCCC is limited due to the rarity of the disease. A phase II trial evaluated the use of nivolumab in patients with platinum-resistant ovarian cancer, and complete response was observed in one of two OCCC patients. In our case, the patient achieved pCR after ICI treatment. The treatment effect of ICI might be explained by the presence of *POLE* mutation and high level of TMB.

In addition to ICI, other potential therapeutic targets for OCCC such as PIK3CA and ARID1A have been investigated. The PI3K/AKT/mTOR pathway is involved in various cellular functions, and several inhibitors targeting it showed antitumor activity *in-vitro* and have been evaluated in ongoing clinical studies (12,13). The mTOR inhibitor everolimus showed treatment benefits in a 36-year-old relapsed OCCC patient harboring mutations in *PTEN* and *PIK3CA* (14). In a phase II trial, another mTOR inhibitor, temsirolimus, was used in combination with carboplatin and paclitaxel as first-line treatment for stage III-IV OCCC but failed to show treatment benefit compared with controls (15). The ARID1A encoding a key component of the SWI/SNF chromatin remodeling complex is another candidate target for OCCC, and the rationale of this target is based on synthetic-lethal approaches which have been validated *in-vitro* (12).

There are some limitations associated with our study. Only 1 patient was included in this work. Large cohorts or clinical trials are needed to explore the treatment effects of ICIs as late-line treatment of OCCC patients who carry *POLE* mutations.

In conclusion, our study reported that a patient with stage IIIB OCCC who was resistant to platinum-based chemotherapy benefited from ICI, and the treatment effects may be associated with the presence of pathogenic *POLE* mutation and high TMB level. As a distinct subtype of ovarian cancer, OCCC has unique molecular features which may act as actionable therapeutic targets. Comprehensive genomic profiling could contribute to identifying and understanding these emerging targets of OCCC.

Acknowledgments

The authors thank the patient, her family, and medical and research staff who participated in this study.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-420/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-420/coif). All authors report that genomic profiling of the patient was performed at Burning Rock Biotech, Guangzhou, China. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). 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 editorial office of this journal.

References

1. Tamura R, Yoshihara K, Enomoto T. Therapeutic Strategies Focused on Cancer-Associated Hypercoagulation for Ovarian Clear Cell Carcinoma. Cancers (Basel) 2022;14:2125.

2. Iida Y, Okamoto A, Hollis RL, et al. Clear cell carcinoma of the ovary: a clinical and molecular perspective. Int J Gynecol Cancer 2021;31:605-16.
3. Zhu C, Xu Z, Zhang T, et al. Updates of Pathogenesis, Diagnostic and Therapeutic Perspectives for Ovarian Clear Cell Carcinoma. J Cancer 2021;12:2295-316.
4. Zhu C, Zhu J, Qian L, et al. Clinical characteristics and prognosis of ovarian clear cell carcinoma: a 10-year retrospective study. BMC Cancer 2021;21:322.
5. Oliveira DVNP, Schnack TH, Poulsen TS, et al. Genomic Sub-Classification of Ovarian Clear Cell Carcinoma Revealed by Distinct Mutational Signatures. Cancers (Basel) 2021;13:5242.
6. Xia L, Liu Y, Wang Y. PD-1/PD-L1 Blockade Therapy in Advanced Non-Small-Cell Lung Cancer: Current Status and Future Directions. Oncologist 2019;24:S31-41.
7. Fu Y, Zheng Y, Wang PP, et al. Immunotherapy for a POLE Mutation Advanced Non-Small-Cell Lung Cancer Patient. Front Pharmacol 2022;13:817265.
8. Sugiyama T, Okamoto A, Enomoto T, et al. Randomized Phase III Trial of Irinotecan Plus Cisplatin Compared With Paclitaxel Plus Carboplatin As First-Line Chemotherapy for Ovarian Clear Cell Carcinoma: JGOG3017/GCIG Trial. J Clin Oncol 2016;34:2881-7.
9. Christie EL, Bowtell DDL. Acquired chemotherapy resistance in ovarian cancer. Ann Oncol 2017;28:viii13-5.
10. Davila JI, Chanana P, Sarangi V, et al. Frequent POLE-driven hypermutation in ovarian endometrioid cancer revealed by mutational signatures in RNA sequencing. BMC Med Genomics 2021;14:165.
11. Oh CR, Kim JE, Hong YS, et al. Phase II study of durvalumab monotherapy in patients with previously treated microsatellite instability-high/mismatch repair-deficient or POLE-mutated metastatic or unresectable colorectal cancer. Int J Cancer 2022;150:2038-45.
12. Khalique S, Lord CJ, Banerjee S, et al. Translational genomics of ovarian clear cell carcinoma. Semin Cancer Biol 2020;61:121-31.
13. Tewari D, Patni P, Bishayee A, et al. Natural products targeting the PI3K-Akt-mTOR signaling pathway in cancer: A novel therapeutic strategy. Semin Cancer Biol 2022;80:1-17.
14. Elvin JA, Chura J, Gay LM, et al. Comprehensive genomic profiling (CGP) of ovarian clear cell carcinomas (OCCC) identifies clinically relevant genomic alterations (CRGA) and targeted therapy options. Gynecol Oncol Rep 2017;20:62-6.
15. Farley JH, Brady WE, Fujiwara K, et al. A phase II evaluation of temsirolimus in combination with carboplatin and paclitaxel followed by temsirolimus consolidation as first-line therapy in the treatment of stage III-IV clear cell carcinoma of the ovary. American Society of Clinical Oncology 2016. Available online: https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.5531

Cite this article as: Li S, Zhang J, Du W, Ren X, Zhang X. Pathologic complete response to immune checkpoint inhibitor in a stage IIIB ovarian clear cell carcinoma patient with *POLE* mutation resistant to platinum-based chemotherapy: a case report. Gland Surg 2022;11(9):1562-1567. doi: 10.21037/gs-22-420