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Persistent response of an ovarian cancer patient after a short-term single-agent immunotherapy: a case report

Shaoxing Sun[a,#], Wenjie Sun[a,#], Qingming Xiang[a], Chunxu Yang[a], Min Chen[a], Zijie Mei[a], Hui Yang[a], Zihang Zeng[a], Hong Cao[b], Yueli Tian[c], Gong Zhang[a] and Hui Qiu[a]

Epithelial ovarian cancer is extremely difficult to treat due to its high recurrence rate and acquired tolerance to chemotherapy. Immune checkpoint inhibitors (ICIs) are expected to be promising solutions for treatment failure. However, the low response rate to a single ICI agent was demonstrated in approximately all published clinical trials. Surprisingly patients with complete response were also noticed as an anecdote. Proper indicators of treatment response were urgently required. Programmed death- ligand 1 expression levels in the tumor tissues provide relatively limited discrimination. Tumor mutation burden (TMB) serves as a more reliable parameter. Here we presented an ovarian cancer case with multiple gene mutations and high TMB, who benefited from a short-term treatment of pembrolizumab and experienced a long-lasting complete response of 2 years till now. The patient was irradiated in the pelvic before pembrolizumab. Our study demonstrated that ICIs might provide survival benefits for ovarian cancer with high TMB and that pelvic radiation might have synergistical effects with immunotherapy. ***Anti-Cancer Drugs*** **33: e756–e759**

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[a]Department of Radiation and Medical Oncology, [b]Department of Pathology and [c]Department of Nuclear Medicine, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China

Correspondence to Hui Qiu, PhD, Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan, Hubei 430071, China
Tel: +18986255160; e-mail: qiuhuiznyy@whu.edu.cn

#Shaoxing Sun and Wenjie Sun contributed equally to the writing of this article.

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Introduction

Ovarian cancer is the deadliest gynecological malignant cancer. Estimated 295 414 new cases and 184 799 deaths happened worldwide in 2018 [1]. Though most patients benefit from standard primary or interval debulking surgery followed by platinum-based chemotherapy, approximately 70% of cases relapse within a few years. Treatment response of the recurrent cases is poor, especially for those with a platinum-free interval of less than 6 months. It is essential to develop novel drugs or strategies to improve treatment response rate and prolong survival time.

Antiangiogenic drugs and poly ADP-ribose polymerase inhibitors (PARPi) improved progression-free survival (PFS) and overall survival (OS) in some certain circumstances [2–4]. As to immunotherapy, mainly referring to antiprogrammed death 1 (PD-1)/antiprogrammed death-ligand 1 (PD-L1) antibodies, clinical benefit in ovarian cancer was not clear as same as the results of other cancers, such as non–small cell lung cancer and melanoma. Various types of cancer, especially with high expression levels of PD-L1 or high tumor mutation burdens (TMBs), showed response to single-agent of immune checkpoint inhibitors (ICIs) or a combination treatment strategy containing ICIs [5]. However, it was disappointing that recurrent ovarian cancer responds poorly to ICIs (not exceeding 15%), and that there was no apparent response indicator. Several combination strategies were therefore being investigated including ICIs + antiangiogenic drugs, ICIs + ICIs, ICIs + PARPi and so on. Study TOPACIO displayed a relatively good response rate (23–31%) of recurrent ovarian cancer after treatment of niraparib + pembrolizumab [6].

Here we presented a rare case of ovarian cancer treated with pembrolizumab as a second-line treatment which surprisingly emerged a long-lasting tumor control. This patient harbored multiple gene mutations and was irradiated in the pelvic before pembrolizumab which might be explanation of the good response.

Case presentation

A 53-year-old woman underwent a primary debulking surgery on 7 April 2015. Pathological examination revealed high-grade serous carcinoma on the left ovary (Fig. 1a). Four cycle taxel plus carboplatin chemotherapy

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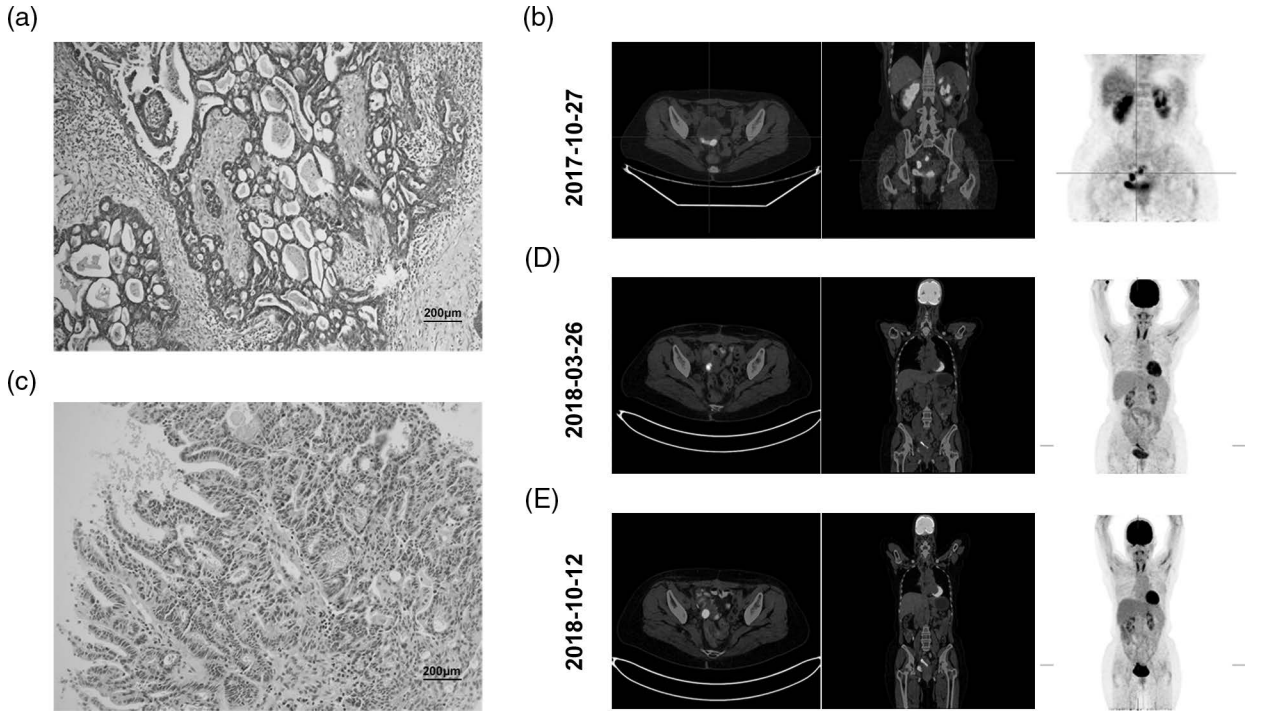
Fig. 1



Pathological examination and PET/CT scan of the patient. (a) The pathological examination revealed high-grade serous carcinoma on the left ovary in 2015 (magnification ×100); (b) PET/CT image on 27 October 2017 confirmed recurrence; (c) the pathological examination confirmed a high-grade serous carcinoma in 2017 (magnification ×100); (d) PET/CT image on 26 March 2018 revealed a local recurrence lesion in the pelvic; (e) PET/CT image on 12 October 2018 showed a solo lesion on the vaginal.

were performed. CA125 fluctuated between 36.4 and 117 in nearly one year without any further treatment.

The patient confirmed recurrence by PET/CT scan on 27 October 2017. A maximum 6 cm lesion with increased ^{18}F-FDG uptake was detected on the right pelvis (Fig. 1b). It invaded the vaginal stump and right ureter leading to dilatation and hydrop of the upper ureter. A secondary debulking surgery was performed on 10 November 2017. Tumor turned out tightly adhered to the posterior wall of the bladder, the lower right ureter and the iliac blood vessels. The pathological examination confirmed a high-grade serous carcinoma (Fig. 1c). After that, a taxel plus carboplatin chemotherapy was administrated on 18 November 2017. The patient had severe nausea, vomiting and fatigue. She refused further chemotherapy.

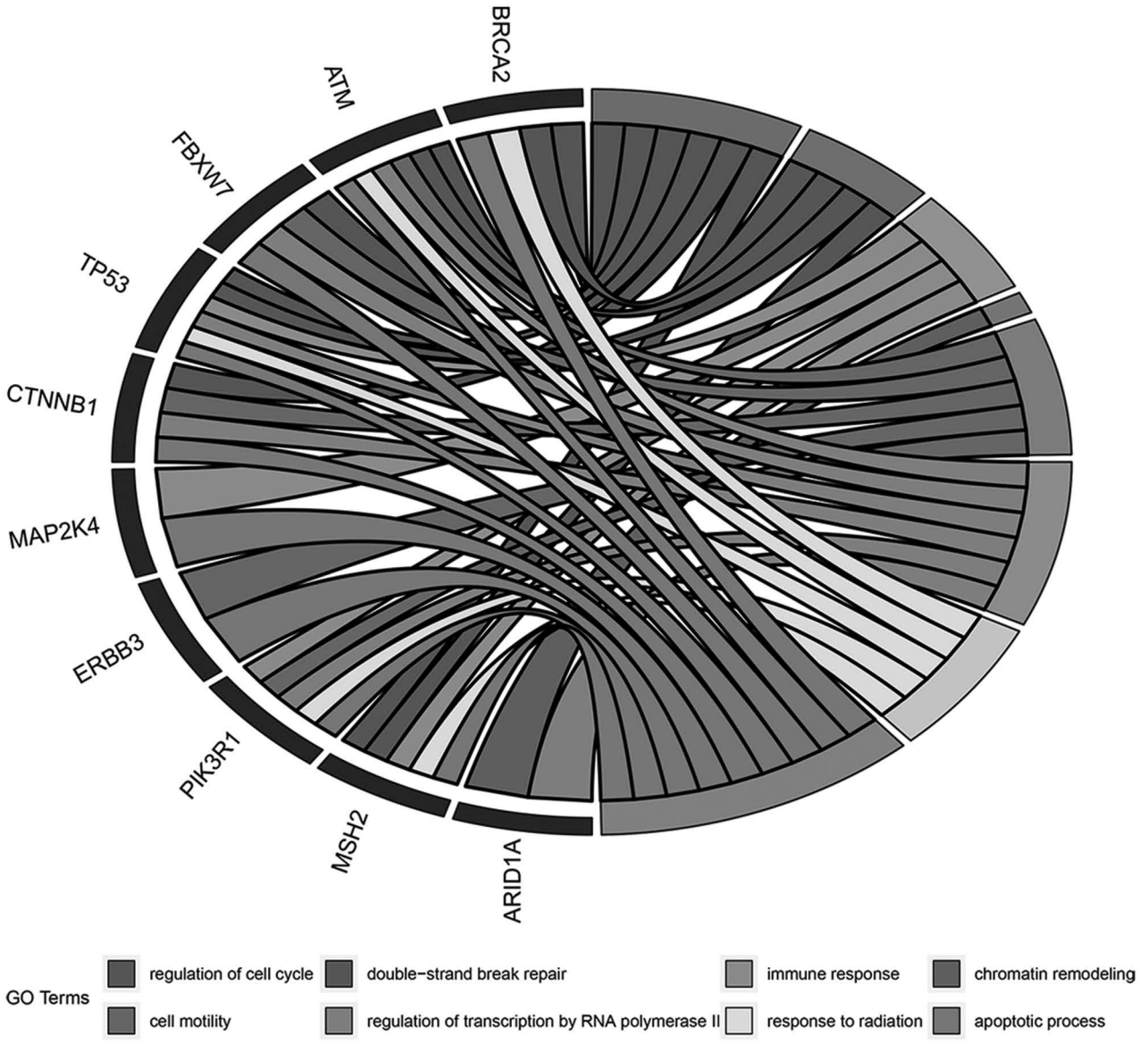
After a short period of break, she started to receive whole pelvic radiation (45 Gy/25 fractions) and a simultaneous boost (60 Gy/25 fractions) on the residual lesion on 18 December 2017. The MRI scan showed shrinkage of the residual lesion on 28 February 2018. She received no other treatments after that. The residual lesion was found with increased ^{18}F-FDG uptake on 26 March 2018 (Fig. 1d), indicating a slow progression. In July, she experienced vaginal bleeding. Gynecological examination found a larger lesion on the anterior vaginal wall fuse with the vaginal residual. A short-term brachytherapy of 30 Gy/5 fractions was performed with vaginal tube during July. Vaginal bleeding disappeared shortly after the treatment, but the new lesion persistently existed. PET/CT scan showed a clear lesion on the same location on 12 October 2018 (Fig. 1e).

Gene analysis was performed and a variety of mutations were found (Fig. 2). The TMB was 47.18 muts/Mb, which was classified as high TMBs. On the basis of this result, pembrolizumab (100 mg) were given for five cycles between 24 October 2018 and 14 January 2019. MRI examinations during treatment showed that the original residual lesion disappeared and no new lesion occurred. Treatment was discontinued because the patient developed symptoms of systemic edema, which was believed to result from hypothyroidism. Thyroid function indexes returned to normal and edema disappeared after hormone replacement therapy for about 2 months. Since then, the patient has not received any clearly effective antitumor treatment. Repeated tests of CA125 and pelvic magnetic resonance multiple times found no sign of recurrence until December 2020.

Discussion

The use of single-agent ICI drugs showed relatively low response rates around 10–15% [7]. Somehow there was a complete response case in nearly all trials [8,9].

Fig. 2



Gene analysis of the patient.

This phenomenon indicated a potential cohort of ovarian cancer patients who markedly benefited from ICIs, though we have not identified the key characteristics of those patients. Combined positive score (CPS) served as a promising parameter to predict treatment response. Patients with CPS >10 had a better overall responsive rate (ORR) (17.1%) than those with CPS <1 [10]. However, this is obviously not good enough to distinguish a profitable group.

A large pooled analysis [11] including 103 078 cancer patients showed that TMB was associated with better OS (hazard ratio [HR] = 0.4, 95% confidence interval [CI], 0.30-0.53), PFS (HR = 0.37, 95% CI, 0.26–0.53) and ORR (OR = 4.62, 95% CI, 2.90–7.34) when treated with immunotherapy. This study fully demonstrated that TMB was a good indicator for predicting the efficacy of ICI treatment. This reported patient had a TMB of 47.18 muts/Mb, which may be the major reason for well-response. Except for that, this patient also harbored mutations of BRCA2, ATM, FBXW7, TP53, CTNNB1, MAP2K4, ARID1A, ERBB3, PIK3R1 and MSH2 (Fig. 2). Those mutations participate in several biological processes including double-strand break repair, cell motility, cell cycle and immune response. This might be a major reason for tumorigenesis and long-lasting treatment response in this patient.

Radiotherapy is not a proper treatment of ovarian cancer after secondary debulking surgery and can be carefully used for oligo-metastasis recurrence lesions in certain circumstances [12]. In this case, whole pelvic radiation provided a local control for 7 months. After vagina recurrence, brachytherapy was conducted as palliative care and turned out to be a failure. However, we believed that previous radiation might promote tumor antigen release and stimulate immune system like a vaccine. This might be the second reason for durable response. It was well recognized that radiation played synergistic effects with immunotherapy through complex immune processes [13]. Some clinical studies revealed beneficial preference in patients with previous radiation. Subgroup analysis of PACIFIC study showed that non–small cell lung cancer patients receiving immunotherapy within 14 days after radiotherapy had better outcomes [14]. In this case, the patient started immunotherapy in less than 3 months. Treatment lasted for five cycles and was discontinued due to hypothyroidism. Some preclinical studies found that hyperfractional radiation was more conducive to the release of tumor antigens and the activation of the immune system. Brachytherapy with a dose of 30 Gy/5 fractions was typically high-dose fraction radiation. Moreover, the physical advantage of brachytherapy makes itself a potentially more effective immune booster. Until now there is a rare study on this topic.

Conclusion

In a conclusion, we presented a patient who benefited from a single ICI agent with a long-lasting PFS period. Multiple gene mutations and radiotherapy before pembrolizumab were thought to be the reasons.

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Conflicts of interest

All authors have completed the ICMJE uniform disclosure form. There are no conflicts of interest.

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