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Positive Response to Camrelizumab and Apatinib Combination Therapy in a Patient with Stage IIIC1 Cervical Cancer: A Case Report

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Abstract

Advanced cervical cancer has a poor prognosis and few effective therapy options. However, immunotherapy has been approved by the FDA and has shown promising results for patients with cervical cancer. In this report, we present the case of a patient with stage IIIC1 cervical cancer who exhibited a positive response to a combination of Camrelizumab and Apatinib after radio-chemotherapy. Our findings suggest that the combination of Camrelizumab and Apatinib may provide a valuable therapeutic option for advanced cervical cancer patients who do not respond to radio-chemotherapy alone.

Keywords: Cervical cancer • Immunotherapy • Camrelizumab • Apatinib • Radio-chemotherapy resistance

Introduction

Cervical cancer is a prevalent gynecological cancer in developing countries, with persistent human papillomavirus (HPV) infection identified as a key pathogenic factor [1]. While the incidence of cervical cancer has decreased with widespread vaccination, the number of new cases remains high due to routine screening. In 2020, it was estimated that 600,000 new cases and 340,000 deaths from cervical carcinoma occurred in 185 countries [2,3]. Advanced cervical cancer is associated with poor prognosis and limited treatment options, but promising results have been seen in recent years with the use of immune checkpoint inhibitors (ICIs) [4]. The KEYNOTE-158 study evaluated the safety and efficacy of pembrolizumab in treating advanced cervical cancer. Based on the study results, the FDA approved pembrolizumab for second-line treatment in patients with recurrent or metastatic cervical cancer who test positive for PD-L1 or have deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H). The CheckMate 358 study enrolled 19 patients with advanced cervical cancer who were treated with nivolumab, showing that the Objective Response Rate (ORR), Disease Control Rate (DCR), and Progression-Free Survival (PFS) were 26.3%, 70.8%, and 5.5 months, respectively [4-6]. However, the efficacy of ICIs as single agents is not satisfactory, with ORR ranging from 14.6% to 26.3%. Therefore, it is crucial to explore new therapeutic methods to improve the survival outcomes of patients with recurrent or metastatic cervical cancer.

The KEYNOTE-826 trial was a randomized, double-blind, multicenter Phase III study that evaluated the clinical efficacy of pembrolizumab in combination with platinum-containing chemotherapy as first-line treatment for persistent, recurrent, or metastatic advanced cervical cancer. The study found that PFS and OS were significantly longer with pembrolizumab combined with chemotherapy ± bevacizumab than with chemotherapy ± bevacizumab alone [7]. As a result, pembrolizumab + chemotherapy ± bevacizumab was approved by the FDA for the first-line treatment of recurrent or metastatic cervical cancer patients with PD-L1 positivity based on the study's results.

The CLAP study, a multicenter, single-arm, phase II trial, evaluated the efficacy and safety of the PD-1 inhibitor camrelizumab in combination with the antiangiogenic drug apatinib in the treatment of recurrent or metastatic cervical cancer. The results showed that the ORR and median PFS were 55.6% and 8.8 months, respectively, indicating that camrelizumab + apatinib had good antitumor activities and tolerable adverse events, potentially making it a new treatment option for patients with advanced cervical cancer [8].

Here, we present a case of a patient with stage IIIC1 cervical cancer who had a partial response to radio-chemotherapy and responded well to a combination of Camrelizumab + Apatinib, with a survival time of 31 months.

Case Presentation

In December 2019, a 53-year-old Chinese woman presented with abnormal heavy vaginal bleeding and was treated for hemostasis and received a contraceptive device in the outpatient clinic. However, the patient refused further examination and abandoned treatment. Due to the COVID-19 pandemic, she continued to suffer from sporadic vaginal bleeding without consulting a doctor. On August 29, 2020, the patient again experienced extremely heavy vaginal bleeding. A color Doppler ultrasonography examination showed a borderless and uneven hypoechoic mass in the cervix, measuring approximately 7.9 cm × 8.1 cm × 8.7 cm. A cervical biopsy revealed squamous cell carcinoma (Figure 1). A systemic PET-CT (Positron Emission Tomography-Computed Tomography) examination was performed on September 24, 2020, which showed a cervical mass measuring 8.9 cm × 9.7 cm × 6.5 cm, with observed bilateral extrailiac para-vascular lymph node metastasis (Figure 2A). Based on the 2019 FiGO staging system, the patient was diagnosed with stage IIIC1 uterine cervical cancer.

On September 25, 2020, the patient was treated with albumin paclitaxel (260

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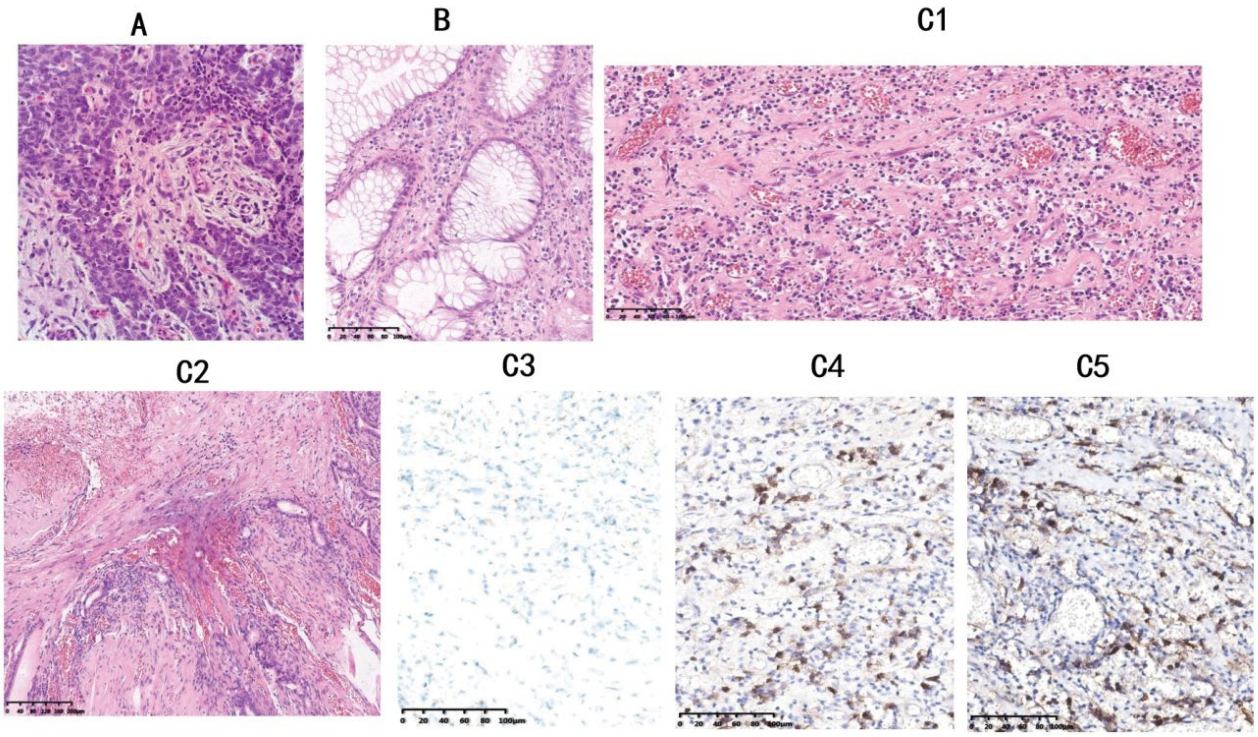

Figure 1. **(A)** Pathology results of cervical biopsy and colonoscopy biopsy obtained during the treatment course. The pathology of the cervical biopsy before treatment revealed squamous cell carcinoma (H&E stain, 20X). **(B)** The pathology of the preoperative colonoscopy biopsy after immunotherapy showed infiltration of mucosal inflammatory cells, primarily lymphocytes and plasma cells, with a few neutrophils (H&E stain, 20X). **(C)** Postoperative pathology findings of cervical cancer: **(C1)** presence of cervical hemorrhage, necrosis, inflammatory cell infiltration, fibroblastic proliferation, focal hemosiderin deposition, granulation tissue formation, and no tumor cells observed, (H&E stain, 20X); **(C2)** chronic inflammation of the rectal mucosa, interstitial hemorrhage, hyperplasia of fibrous tissue, and focal serous suppurative inflammation, (H&E stain, 10X); **(C3)** Immunohistochemistry results: CK (-); **(C4)** immunohistochemistry results: scattered CD38 positive; **(C5)** immunohistochemistry results: scattered CD138 positive.

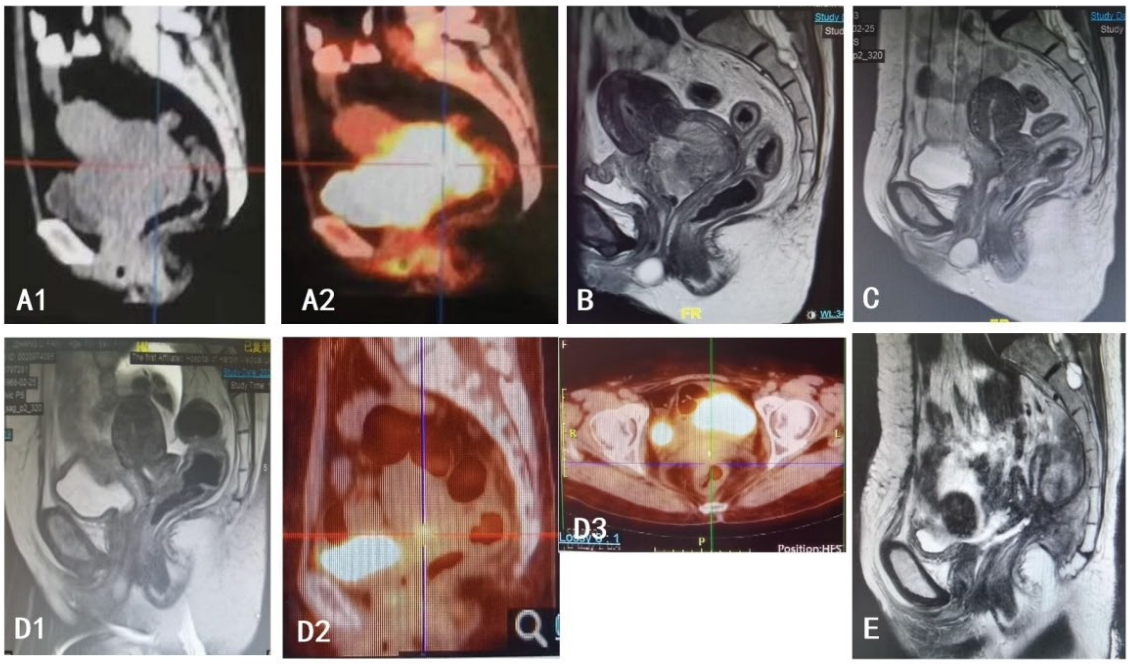

Figure 2. Pelvic PET-CT and MRI images obtained during the treatment course. The whole body PET-CT examination at the initial diagnosis showed a mass in the cervix measuring 8.9 × 9.7 × 6.5cm. **(A1)** The corresponding CT image is shown, while **(A2)** shows the PET-CT image, which indicated an abnormally high uptake of 18F-FDG with a maximum standard uptake value (SUV) of 14.5. Following radical radiotherapy and chemotherapy, a pelvic Magnetic Resonance Imaging (MRI) displayed a high signal mass located at the cervix of the T2-weighted MRI image. The signal was not homogeneous, with a size of approximately 6.6 × 5.7 × 4.2cm, and the border of the uterine body was indistinct. After Camrelizumab + apatinib treatment, patient reached complete response which indicated in Pelvic MRI. Pelvic MRI: T2-weighted MRI showed irregular uterine cervical morphology, the solid mass was not found, but there were patchy slightly high T2 signal shadows, and the cervical matrix was poorly displayed. **(D)** Preoperative pelvic MRI, **(D1)** T2-weighted MRI showed irregular uterine cervical morphology, with patchy slightly elongated T2 signal shadows in the posterior lip of the cervical canal. The T2 signal band in the posterior lip of the cervical canal matrix was poorly displayed. The boundary between the upper posterior wall of the cervix-vagina and the anterior wall of the rectum was unclear, with a loss of fat space in between, and the local signal of the rectal mucosa was uneven, suggestive of possible rectal invasion or adhesion. **(D2)** PET-CT showed focal increased 18F-FDG uptake in the cervical area, with SUVmax of 4.9, and the lesion size was approximately 1.4cm × 1.2cm. **(D3)** PET-CT showed adhesion between the cervix and rectum, with unclear demarcation, without accompanying increased 18F-FDG uptake. **(E)** Postoperative pelvic MRI: T2-weighted images showed absence of uterine adnexa, residual lower rectum was observed, and no sigmoid colon structure was seen.

mg/m^2) plus carboplatin (AUC=5 mg/mL•min), which successfully controlled vaginal bleeding after one cycle of chemotherapy. Physical examination revealed the presence of a cauliflower-like mass occupying the cervix, with no visible normal cervix and fornix. The surface of the mass displayed dark red rotten tissue, with the mass growing into the vagina and occupying the upper half. Additionally, a firm swelling was found bilaterally and was immobilized to the pelvic wall. The patient then received pelvic radiotherapy, concurrent chemotherapy with cisplatin (30 mg/m^2/week) for 4 cycles, and brachytherapy (HR-CTV D90 7Gy) with intrauterine tube and needle insertion for 3 cycles. However, the brachytherapy was discontinued due to grade IV neutropenia. The patient resumed treatment on January 11, 2021, after neutrophil counts returned to normal, and received the fourth brachytherapy with a prescription dose of HR-CTV D90 7Gy and one cycle of chemotherapy with albumin paclitaxel (260 mg/m^2) combined with carboplatin (AUC=5 mg/mL•min). Pelvic magnetic resonance imaging (MRI) conducted on February 21, 2021, after radical chemoradiotherapy showed that the size of the mass had shrunk to 6.6 cm × 5.7 cm × 4.2 cm (Figure 2B), with partial response being evaluated as the effective treatment outcome.

In September 2020, the paraffin-embedded tissue of cervical biopsies was subjected to Next-Generation Sequencing (NGS) and Immunohistochemistry (IHC). The results, as shown in table 1, indicated that the expression of PD-L1 was positive, and the tumor genetic mutations comprised PTEN exon8 T319X, MTOR exon47 S2215F, ARID1A exon15 R1276X, PTEN exon2 P30Qfs*24, PIK3CA exon3 G118D, FGFR2 exon13 E565A mutations. On February 22, 2021, the patient underwent treatment with camrelizumab (200 mg/) + apatinib mesylate (250mg/qd.po) every 3 weeks/ cycle for six cycles. Following the six cycles of treatment, pelvic MRI showed that the cervical mass had disappeared (Figure 3C), and the treatment effect was evaluated as complete response. Gynecological examination indicated that the vaginal atrophy was narrow, no tumor was detected in the cervix, with normal morphology and rough surface mucosa. The cervix was slightly tough, and the cervical mass was not palpated during bimanual pelvic examination. The patient continued the combined therapy for two cycles. In August 2021, the oral administration of apatinib was stopped due to hemorrhoids and hematochezia, while camrelizumab was continued for three cycles (Table 1).

On October 12, 2021, there was an increase in glutamate aminotransferase to 170.70 U/L (normal range 5-35 U/L) and aspartate aminotransferase to 71.10 U/L (normal range 8-40 U/L), which was determined to be drug-induced liver hepatic insufficiency, leading to the suspension of camrelizumab. To manage this, the patient took Bicyclol tablets (50mg once, three times a day) and Glutathione tablets (400 mg once, three times a day) for three weeks, without glucocorticoid treatment, until the two transaminases returned to normal. On November 8, 2021, the patient resumed camrelizumab treatment.

On November 16, 2021, the physical examination showed vaginal adhesion and poor cervical inspection. The results of the color doppler ultrasonography of the rectum and crissum on November 07, 2021, revealed that the local intestinal wall's echo about 4 cm away from the anal margin was not uniform, with an irregular outline and unclear boundaries, suspected rectal invasion or adhesion with the cervix and vagina. The strong echo line in the soft tissue between the cervix and rectum's continuity was also interrupted. The pelvic MRI on November 08, 2021, showed an unclear posterior wall of the superior segment of the vagina from the anterior wall of the rectum, with a disappearance of the fat space, which raised suspicion of rectal invasion or adhesion. The colonoscopy and cystoscopy on November 23, 2021, indicated moderate chronic inflammation of the mucosa, with ruptured hyperemia in the posterior wall of the bladder near the triangle caused by radiotherapy. The patient then underwent PET-CT on November 25, 2021, which revealed elevated standard uptake value (SUV) of the cervical focal mass, and the cervical area was adhered to the rectum, resulting in unclear demarcation (Figure 3D2 and Figure 3D3).

The gynecologic-oncology Multiple Disciplinary Team (MDT) discussed the patient's case, and most doctors believed that the invading rectum backward was likely caused by cervical tumor recurrence, recommending radical surgery.

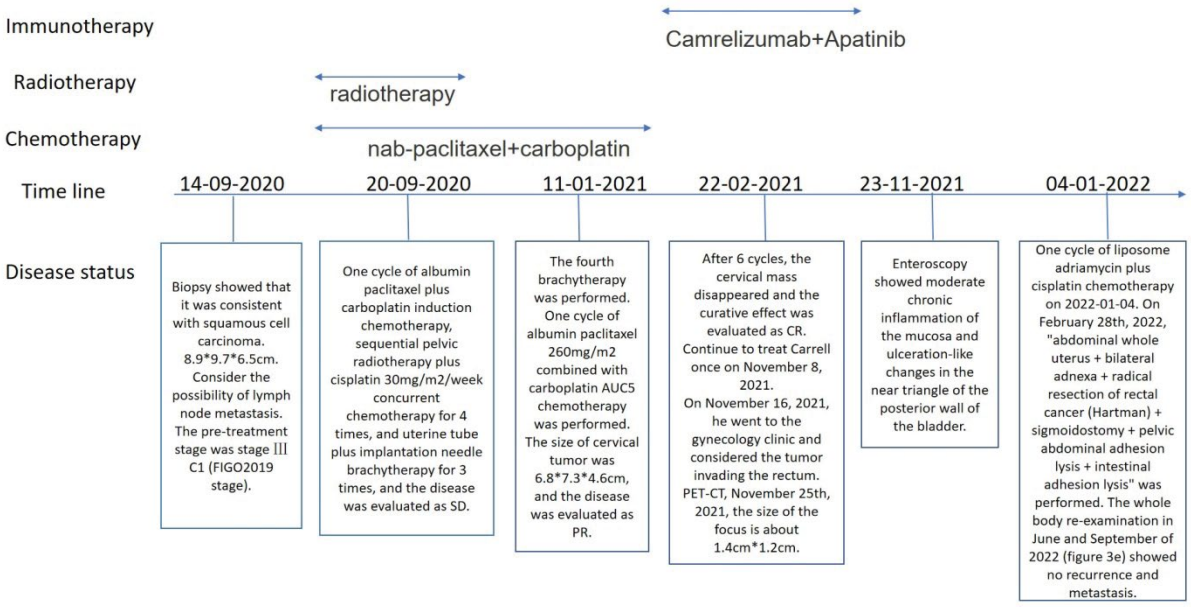

Figure 3. Timeline of the clinical course.

Table 1.The Next Generation sequencing genetic testing results.

Gene Name	Mutation Status	Mutation Frequency (%)
PTEN	Exon 8 T319X	15.60
MTOR	Exon 47 S2215F	16.90
ARID1A	Exon 15 R1276X	20.80
PTEN	Exon 2 P30Qfs*24	24.10
PIK3CA	Exon 3 G118D	13.90
FGFR2	Exon 13 E565A	35.70

Table 2.The lymphocyte subsets alteration during treatment course.

Abbreviation	Entry Name	Reference Range	Date(before Camrelizumab)		Date (Camrelizumab in use)						
			2020 11-18	2021 02-22	2021 04-07	2021 05-24	2021 07-09	2021 08-91	2021 09-30	2022 01-11	
CD3	Total T lymphocytes	723-2737Cell/ul	345.07	172.77	492.63	434.09	722.51	647.35	658.85	654.76	↑
CD8+/CD3+	T8 lymphocyte count	220-1129 Cell/ul	166.11	77.67	332.26	186.49	360.53	340.62	335.58	347.59	↑
CD4+/CD3+	T4 lymphocyte count	404-1612 Cell/ul	166.77	91.31	125.53	226.09	299.79	245.3	287.21	264.75	↑
CD3+/CD4+/CD8+	Double-positive T lymphocyte count	6-56 Cell/ul	1.81	3.08	0.68	0.64	2.92	1.81	0.85	1.66	↓
CD16+/CD56+	NK lymphocyte number	150-1100 Cell/ul	47.74	40.36	289.62	56.2	446.53	348.75	291.45	303.19	↑
CD19+	B lymphocyte count	90-560 Cell/ul	8.23	7.99	37.56	34.28	53.45	87.64	97.58	147.45	↑
CD45+	Total lymphocyte count (CD45+)		409.61	229.1	830.3	535	1248.7	1091.8	1061	1110.7	↑
H/S	H/S	0.68-2.47	1	1.8	0.38	1.12	0.83	0.72	0.86	0.76	↓

However, surgery was not performed due to the patient's inability to tolerate colostomy. On January 4, 2022, the patient received one cycle of liposomal doxorubicin + cisplatin, achieving stable disease status after chemotherapy based on pelvic MRI and rectal and perianal color doppler ultrasonography. Therefore, abdominal total hysterectomy + bilateral adnexectomy + radical resection of rectal cancer (Hartman) + sigmoidostomy were performed on February 28, 2022. The postoperative pathological findings revealed inflammation and necrosis (Figure 2C), with no tumor cells found in the whole uterus, double appendages, part of the vagina, rectum, and part of the colon.

The timeline of the clinical course is shown in Figure 3. During this process, the main adverse event was grade 2 Reactive Cutaneous Capillary Endothelial Proliferation (RCCEP). Despite receiving no postoperative antitumor therapy, there was no observed tumor recurrence or metastasis during the systemic review in June, September, and December 2022 (Figure 2E).

Discussion

We present a case study of a patient diagnosed with stage IIIC1 cervical cancer who displayed positive response to treatment with the PD-1 inhibitor, camrelizumab, in conjunction with the antiangiogenic agent, apatinib, after experiencing resistance to radio-chemotherapy. Six cycles of this treatment led to a complete disappearance of the tumor as indicated by a pelvic MRI. However, a pathology examination performed nine months later revealed pseudoprogression. Immunotherapy presents a significant challenge to clinical work as traditional criteria for evaluating tumor therapy are often inadequate. In a secondary analysis of the CLAP trial, it was discovered that PIK3CA, STK11, FBXW7, and PTEN were the most common genetic mutations and that the PI3K/AKT pathway was the most frequently dysregulated pathway in advanced cervical cancer. This analysis also revealed that genetic alterations in PIK3CA, PTEN, ERBB3, and the PI3K/AKT pathway could serve as novel predictive biomarkers for PD-1 inhibitor combination therapy in cervical cancer patients [9]. In a prospective phase II trial involving 42 efficacy-evaluable patients with recurrent or metastatic cervical cancer, sintilimab combined with anlotinib showed an ORR and median PFS of 54.8% and 9.4 months, respectively. An exploratory analysis revealed that patients with higher PD-L1 CPS scores and those with PIK3CA mutations had a higher ORR [10]. Our patient was found to have positive PD-L1 expression and PTEN, MTOR, ARID1A, PIK3CA, and FGFR2 mutations based on an immunohistochemical test and next-generation sequencing. We treated the patient with a combination of PD-1 inhibitor and antiangiogenic agents, which showed significant efficacy and good tolerance based on the results of these studies and examinations.

Peripheral Blood Lymphocytes (PBLs) have emerged as biomarkers that can predict the clinical prognosis of various malignant tumors [11-14]. Depending on their biological functions and the expression of cell surface antigens, lymphocyte subsets can be classified into T cells, B cells, and Natural Killer (NK) cells. T lymphocytes reflect the state of human cellular immune function, while B lymphocytes can present antigens to T cell immune responses and activate with macrophages to kill tumor cells [15-17]. Natural killer (NK) cells, on the other hand, play a key role in tumor immune surveillance [18]. In our case, the total number of T lymphocytes, B lymphocytes, and NK cells showed a significant increase after treatment with camrelizumab plus apatinib (Table 2), indicating the efficacy of this treatment for advanced cervical cancer patients (Table 2).

Clinicians must remain vigilant for the occurrence of pseudoprogression when administering immunotherapy. Updating the immunotherapy-related clinical efficacy evaluation system and relevant biomarkers could assist clinicians in accurately identifying pseudoprogression and other unconventional immunotherapy-related reactions, leading to better patient outcomes. Overall, our case demonstrates that PD-L1–positive cervical cancer patients who cannot tolerate chemotherapy and radiotherapy may benefit from the combination of camrelizumab and apatinib. The positive response observed in our patient warrants further investigation of Immune Checkpoint Inhibitors (ICIs) in combination with antiangiogenic agents in advanced cervical cancer patients. Moreover, genetic alterations detected by NGS could potentially serve as predictive biomarkers for PD-1 inhibitor combination therapy in cervical cancer patients

Conclusion

Our case demonstrates that PD-L1–positive cervical cancer patients who cannot tolerate chemotherapy and radiotherapy may benefit from camrelizumab combined with apatinib. Our patient's positive outcome supports further investigation of immune checkpoint inhibitors (ICIs) in combination with antiangiogenic agents for advanced cervical cancer patients. Furthermore, NGS-detected genetic alterations could potentially serve as predictive biomarkers in cervical cancer patients undergoing PD-1 inhibitor combination therapy.

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Authors' Contributions

ZPL and SHL were responsible for the conceptualization of the present study and writing the manuscript. HZ, FYR, BX and DX acquired the majority of the data, analyzed the data and prepared the original draft. BX and DX was responsible for editing and performing critical review of the manuscript. All authors read and approved the final manuscript for publication.

Ethics Approval and Consent to Participate

The study involving a human participant was reviewed and approved by The First Affiliated Hospital of Harbin Medical University, Harbin city,

Heilongjiang Province, China. Written informed consent was obtained from the patient and all procedures were conducted in accordance with the Declaration of Helsinki.

Patient Consent for Publication

The patient provided consent for publication.

Competing Interests

The authors declare that they have no competing interests.

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