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Tumor Local Microenvironment Is a Key Factor Affecting the Efficacy of PD-1 Inhibitor in Advanced Cervical Cancer: A Case Report and Literature Review

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Abstract

Introduction: Conventional radiotherapy or chemotherapy is ineffective in the treatment of recurrent and metastatic cervical cancer. In recent years, immunotherapy has shown promise in the treatment of various solid tumours, including cervical cancer. The overall response rate of the PD-1/PD-L1 inhibitor in cervical cancer is 14% - 27%, and when combined with radiotherapy or conventional chemotherapy, the overall response rate can be further improved. **Case presentation:** We report here a case of a 49-year-old female patient presenting with two metastatic lesions of cervical cancer after postoperative radiotherapy, the first was located in the para-aortic region and the second in the presacral region. The enlarged para-aortic lymph nodes had not previously received radiotherapy, while the enlarged presacral lymph nodes had previously received postoperative radiotherapy. Treatment results showed that the recurrent presacral mass did not respond to the PD-1 inhibitor (camrelizumab) alone, whereas the metastatic para-aortic lymph nodes responded favourably to camrelizumab combined with low-intensity radiotherapy. **Conclusion:** PD1/PD-L1 inhibitors combined with radiotherapy should make it possible to overcome the bottleneck of conventional radiotherapy, improve patient prognosis or achieve better local control rates with lower radiotherapy doses.

Keywords

Cervical Cancer, PD-1 Inhibitor, Recurrence and Metastasis, Radiotherapy

*Corresponding Authors: Keita Mamady, and Hong Liu contributed equally to work.

1. Introduction

Cervical cancer is a gynecological malignancy with a very high incidence. Despite advances in surgical and radiotherapy techniques and increased opportunities for early detection, the management of recurrent and metastatic cervical cancer remains a challenge for clinicians [1] [2] [3] [4] [5]. Chemoradiation combined with vascular endothelial growth factor inhibitors is a common option for patients with advanced cervical cancer. However, the efficiency is not satisfactory. With the development of immunotherapy technology, its effectiveness in the treatment of solid tumors is becoming more and more obvious. Programmed cell death receptor 1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitors are one of the most well-known immune checkpoint inhibitors and are currently widely used in clinical treatment of a variety of solid tumors [6]. However, due to the poor efficacy of immune checkpoint inhibitors alone in advanced cervical cancer, many ongoing clinical trials have refocused on evaluating PD-1/PD-L1 inhibitors in combination with chemotherapy, radiotherapy, and vascular endothelial growth factor inhibitors to improve the efficacy of immune checkpoints inhibitors [7]. Here, we report a case of a patient who developed metastases in para-aortic and presacral lymph nodes 6 months after prophylactic adjuvant pelvic radiotherapy for cervical cancer. In this patient's case, the para-aortic lymph nodes completely disappeared after receiving low-dose radiotherapy combined with immunotherapy, while the presacral and pelvic metastatic lymph nodes that did not receive a second radiotherapy showed the opposite response and progressed rapidly.

Our goal was to share the different therapeutic responses of PD-1 immunotherapy to recurrent and metastatic lymph nodes in different parts of the body of this patient and discuss the clinical considerations arising from this case.

2. Case Presentation

A 49-year-old female patient was admitted in March 2019 with a 2-month history of irregular vaginal bleeding. Her systemic examination was within normal limits. Local examination showed a <4 cm sized exophytic growth in the cervix. The fornix and the bilateral parametrium were normal. The uterus was soft. The MRI showed a cervical mass of 6.4 cm × 3.9 cm × 5.4 cm, FIGO stage IB3. Cervix uteri biopsy pathological report showed: Squamous cell carcinoma. The patient underwent laparoscopy surgery consisting of a wide hysterectomy and bilateral adnexectomy + pelvic lymph nodes and para-aortic lymph nodes dissection. Post-operative pathological report confirmed: Keratinizing squamous cell carcinoma of the cervix uteri, invading more than 2/3 of the muscle layer, with choroidal lymph vascular emboli, left pelvic lymph node 1/8N+ metastasis. Post-operative diagnosis: Keratinizing squamous cell carcinoma of the cervix, stage IIIC1p. The patient received a second chemotherapy regimen of paclitaxel + cisplatin one month after surgery, and received radiotherapy on June 17, 2019. The radiation treatment plan includes CTV and PTV. Almost, the CTV includes the upper 1/2

of the vagina, the vaginal vault, the pelvic cavity, and the internal iliac, external iliac, presacral, common iliac, and para-abdominal aorta lymph nodes. The upper limit is the middle of the 4th lumbar vertebra, and the lower limit: the lower edge of the obturator foramen. The prescribed dose to the PTV was 45 Gy/25 fractions, and post-loading brachytherapy was delivered at 11 Gy/2 fractions under 0.5 cm vaginal vault submucosal. Six months after radiotherapy, the haematological tumors markers SCC and CEA increased up to 35.78 ng/mL and 12.64 ng/mL, respectively. The PET/CT showed metastases in the para-aortic and presacral lymph nodes (Figure 1). The patient voluntarily decided to drop chemotherapy treatment. Therefore, to avoid interference from chemotherapeutic factors, we opted for a strategy combining radiotherapy and immunotherapy. For the target volume delineation, the presacral lymph node metastases did not receive secondary radiotherapy because of their location (within the radiotherapy field) and their very small size (less than 1.0 cm). Unlike the presacral lymph node, the para-aortic lymph node metastasis had not previously received radiotherapy. The CTVn, includes para-aortic metastatic lymph nodes and para-aortic lymph node drainage area, upper limit: upper edge of the 1st lumbar vertebra, lower limit: mid-section of the 4th lumbar vertebra. The prescribe dose to 100% GTVn was 60 Gy/25 fractions. However, after 19.2 Gy/8 fractions of external beam radiation therapy and 3 cycles of Camrelizumab the patient voluntarily requested to be withdrawn from treatment. Three months later she was seen in outpatient room for presacral discomfort. The CT re-evaluation revealed that the enlarged lymph node in the para-aortic region had completely disappeared, while the very small presacral lymph nodes, anterior presacral soft tissue shadow and rectal wall had rapidly increased in size. This new change in the presacral region was considered to be a progressive disease according to the RECIST criteria. The presacral tumor received brachytherapy, 24 Gy/4 fractions. One month later,

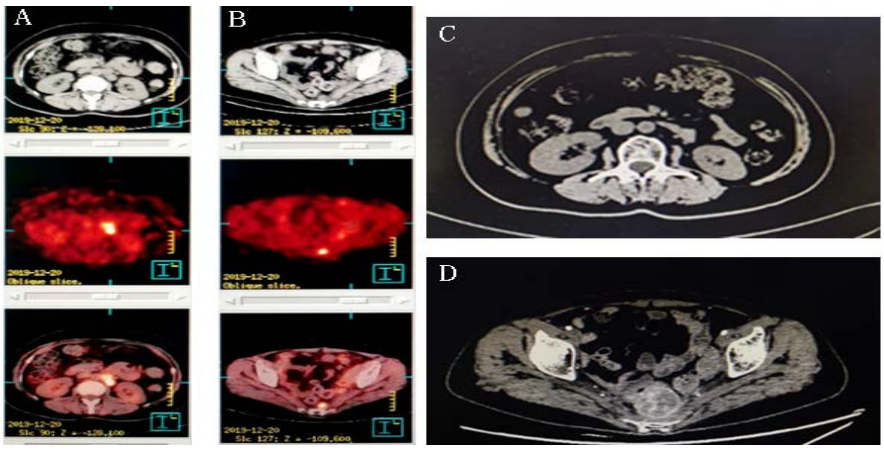

Figure 1. (A) PET/CT showed metastatic lymph nodes adjacent to the abdominal aorta; (B) PET/CT showed pre-sacral metastatic lymph nodes; (C) The metastatic lymph nodes adjacent to the abdominal aorta regressed after 19.2 Gy/8 fractions and 3 courses of kareolizumab outside radiotherapy; (D) The small pre-sacral lymph nodes that did not receive radiotherapy were significantly enlarged.

a follow-up CT scan showed that the presacral tumor was smaller than before, and the rectal wall was thickened and swollen (Figure 2). Because of the presacral mass close to the small bowel, the pelvic cavity received prophylactic radiation at 45 Gy before September. The patient developed a sigmoid fistula after radiotherapy and underwent a colostomy in our digestive surgery department. Five months later, she again presented in outpatient clinic room for a clinical follow-up. On investigation, the patient observed significant relief from pain and there was partial regression of swellings, while retaining the colostomy. The presacral tumor was found to be stable when comparing with last follow-up CT scan. She once declined an offer of chemotherapy. Finally, she did not attend for further follow-up.

3. Discussion

Lymph node metastasis is the most common phenomenon in carcinoma of the uterine cervix. Kim HS *et al.* reviewed 2303 patients treated for carcinoma of the cervix and found that the frequency of lymph node metastasis was low for early cervical cancers, but increased significantly as the clinical stage of the disease became more advanced. They found that pelvic cavity and para-aortic lymph node are common sites of metastasis [8]. In this sitting, the traditional treatment is concomitant chemoradiotherapy combined with targeted vascular therapy. For metastatic lymph nodes in areas that have not received radiotherapy, the radiotherapy dose should usually be at least 60 Gy, and the maximum dose should generally not exceed 68 - 70 Gy. One of the limitations of radiotherapy is that some large metastatic lymph nodes do not completely regress after receiving up

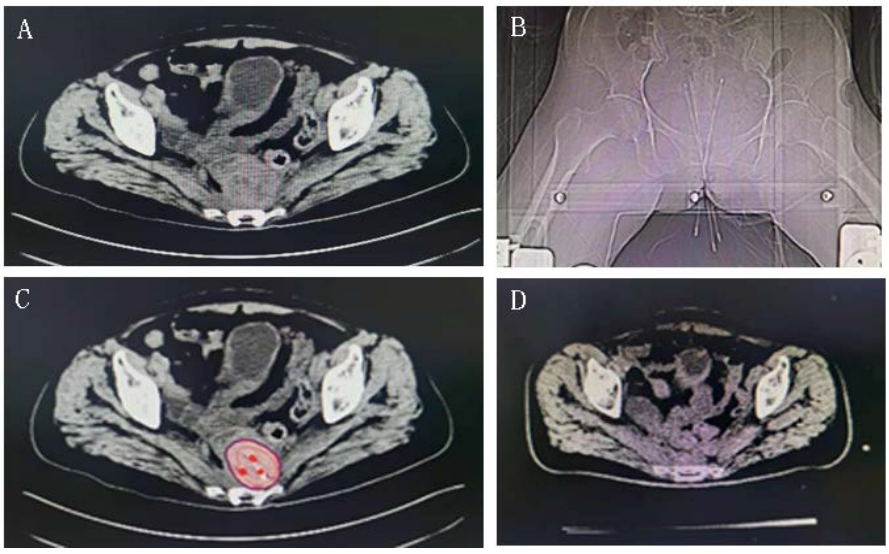

Figure 2. (A) CT showed a small pre-sacral recurrent mass that had increased signify-cantly in size over 3 months; (B) Radiation therapy with brachytherapy interposition was given; (C) HRCTV with brachytherapy was highly conformal to the pre-sacral recurrent mass; (D) CT showed a significant reduction of the mass after 24Gy/4 fractions of brachytherapy.

to 60 Gy of radiation. The current radiotherapy techniques make it difficult to achieve higher doses of local integrated boost due to the dose limitation to nearby organs at risk (OAR). For the lymph nodes in the area that received the second course of radiotherapy, the effect of radiation therapy does not seem obvious, and the side-effects of second radiation therapy are also significant. Recently, the advent of immune checkpoint inhibitors has changed the treatment paradigm and is expected to break the bottleneck of traditional treatment [9]. Several studies have shown a synergistic relationship between radiotherapy and immunotherapy [10]. The use of Durvalumab, a PD-L1 inhibitor, after radiotherapy for stage III NSCLC was found to improve overall survival [11]. The combination of radiotherapy and PD-1/PD-L1 inhibitors in cervical cancer has not been reported before, except for some ongoing clinical trials. Here we share a case worthy of review and discussion by clinicians. The patient was clinically diagnosed with stage IIIC1p cervical squamous cell carcinoma based on postoperative histopathology report. She received prophylactic pelvic external beam radiotherapy 45 Gy/25 fractions using IMRT one month after surgery. The upper edge of the radiation field was located in the middle of the 4th lumbar vertebra and the lower edge at the lower edge of the obturator foramen. Brachytherapy was performed at 11 Gy/2 fractions, 0.5 cm vaginal vault under submucosa. Six months after radiotherapy, the patient's tumor marker CEA and SCC abnormally increased. PET/CT showed para-aortic and presacral lymph node metastasis. The patient himself voluntarily decided to stop chemotherapy, not because he was resistant to chemotherapy. As the presacral lymph node metastases were located in the pelvic region that had already received radiotherapy, they did not receive a second radiotherapy because of the potential side-effects induce by second radiotherapy, poor expected radiotherapy effect, and very small size of the lymph nodes (less 1.0 cm). The metastatic para-aortic lymph nodes had not previously been irradiated, and we had therefore planned to administer 60 Gy to the GTVn. However, the patient voluntarily requested to stop treatment after receiving 19.2 Gy/8 fractions of external beam radiotherapy and three cycles of PD-1. Three months after discontinuation of treatment for pain and presacral discomfort. CT re-evaluation revealed that the enlarged para-aortic lymph nodes had completely disappeared, while the very small presacral lymph nodes had rapidly increased in size during this period. It is believed that this patient exhibited a very positive anti-tumor effect of PD-1 monoclonal antibody combined with low-dose radiation therapy. However, single PD-1 inhibitors have no therapeutic effect on tumors located within previously irradiated fields. This is because immunotherapy alone is not effective as immunotherapy and low-dose radiation therapy combined. The interesting feature in our case was that the patient had previously received pelvic radiotherapy, and the pelvic microcirculation was damaged after radiotherapy, resulting in an insufficient number of immune cells in the microenvironment of the tumor. Therefore, immunotherapy alone was unable to stimulate local immunogenic cell death in cancer, so it

could not stimulate a local immune response. The differential response to treatment in this patient with recurrence and metastasis at different sites suggests that the local tumor microenvironment may be the root cause of the efficacy of immunotherapy. In tumors with good local microcirculation, the curative effect of low-dose radiotherapy combined with PD-1 monoclonal antibody is significantly different from that of traditional treatment. However, in patients with local tumor microcirculation disorders, immunotherapy is ineffective due to the inability to recruit sufficient immune cells in the local microenvironment where the tumor is located, resulting in a lack of immune cells. For smaller presacral masses that recur in previous radiation fields, early radiation therapy, including possibly external or brachytherapy may provide better outcomes and reduce the incidence of severe radiation therapy toxicity (eg, enteritis or fistula). This patient gave us a clear indication for immunotherapy. For recurrent tumors with good local microcirculation, immunotherapy combined with low-dose radiotherapy is an effective measure to improve the efficacy of immunotherapy. Most of the current research on radiotherapy and immunotherapy is mostly at a preclinical stage, and the optimal timing of combining radiotherapy and immune checkpoint inhibitor therapy, as well as the optimal radiotherapy dose is still unclear. However, given the regression of recurrent tumors at various sites after treatment, the use of immunotherapy combined with low-dose radiotherapy for recurrent tumors, where possible, is a promising and useful measure to improve the efficacy and outcome of immunotherapy.

4. Conclusion

From this case, we can see that low-dose radiotherapy combined with PD-1 monoclonal antibody immunotherapy can achieve good local tumor control effect. However, how to adjust the dose of radiotherapy combined with immunotherapy and how to determine the activation of immune cells by changing the local microenvironment of the tumor needs further research with large sample size.

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Compliance with Ethical Standards

The research involved human participants only and institutional ethical clearance was obtained. Informed consent was obtained from every participant of the study in the presence of neutral witnesses.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Puspitasari, I.M., Legianawati, D., Sinuraya, R.K., *et al.* (2021) Cost-Effectiveness Analysis of Chemoradiation and Radiotherapy Treatment for Stage IIB and IIIB Cervical Cancer Patients. *International Journal of Women's Health*, **13**, 221-229. https://doi.org/10.2147/IJWH.S289781

[2] Chung, H.C., Ros, W., Delord, J.P., *et al.* (2019) Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results from the Phase II KEYNOTE-158 Study. *Journal of Clinical Oncology*, **37**, 1470-1478. https://doi.org/10.1200/JCO.18.01265

[3] Wang, Y.M. and Li, G.L. (2019) PD-1/PD-L1 Blockade in Cervical Cancer: Current Studies and Perspectives. *Frontiers of Medicine*, **13**, 438-450. https://doi.org/10.1007/s11684-018-0674-4

[4] Keita, M., Xi, C., Bah, M., Diallo, F.B., Fang, Z., *et al.* (2022) The Impact of Prophylactic Para-aortic Lymph Nodes Radiotherapy in Small Cell Carcinoma of the Cervix: A Case Report and Literature Review. *Journal of Oncology Research and Treatment*, **7**, Article No. 4.

[5] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. and Jemal, A. (2018) Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **68**, 394-424. https://doi.org/10.3322/caac.21492

[6] Dong, H.D., Strome, S.E., Salomao, D.R., *et al.* (2002) Tumor-Associated B7-H1 Promotes T-Cell Apoptosis: A Potential Mechanism of Immune Evasion. *Nature Medicine*, **8**, 793-800. https://doi.org/10.1038/nm730

[7] Zheng, S., Lu, J.J., Liu, Y.H., *et al.* (2020) Synergistic Antitumor Effect on Cervical Cancer by Rational Combination of PD1 Blockade and CRISPR-Cas9-Mediated HPV Knockout. *Cancer Gene Therapy*, **27**, 168-178. https://doi.org/10.1038/s41417-019-0131-9

[8] Kim, H.S., Kim, T., Lee, E.S., *et al.* (2013) Impact of Chemoradiation on Prognosis in Stage IVB Cervical Cancer with Distant Lymphatic Metastasis. *Cancer Research and Treatment*, **45**, 193-201. https://doi.org/10.4143/crt.2013.45.3.193

[9] Liu, Y., Wu, L., Tong, R., *et al.* (2019) PD-1/PD-L1 Inhibitors in Cervical Cancer. *Frontiers in Pharmacology*, **10**, Article No. 65. https://doi.org/10.3389/fphar.2019.00065

[10] Antonia, S.J., Villegas, A., Daniel, D., *et al.* (2018) Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *The New England Journal of Medicine*, **379**, 2342-2350. https://doi.org/10.1056/NEJMoa1809697

[11] Kasmann, L., Taugner, J. and Manapov, F. (2019) Chemo-/Immuno-/Radiotherapy Combination in Treatment of Solid Cancer. *Oncotarget*, **10**, 5387-5388. https://doi.org/10.18632/oncotarget.27141