Clinical Case Reports

Open Access

CASE REPORT

A transient increase and subsequent sharp decrease of chemo-refractory liver-metastasized uterine cervical small cell carcinoma to autologous formalin-fixed tumor vaccine plus anti-PD-1 antibody

Tatsu Miyoshi[1], Tatsuji Kataoka[1], Atsuko Asahi[1], Takashi Maruyama[1], Rika Okada[1], Yoji Uemae[2] & Tadao Ohno[2]

[1]Ginza-Namiki-Dori Clinic, Ginza 4-2-2 First Yayoi Bldg 7F, Chuo-ku, Tokyo 104-0061, Japan
[2]Cell-Medicine, Inc., Sengen 2-1-6, Tsukuba Science City, Ibaraki 305-0047, Japan

Correspondence
Tatsu Miyoshi, Ginza-Namiki-Dori Clinic, Ginza 4-2-2 First Yayoi Bldg 7F, Chuo-ku, Tokyo 104-0061, Japan. Tel: +81-3-3562-7773; Fax: +81-3-3562-7774;
E-mail: miyoshi@cftopia.com

Funding Information
No sources of funding were declared for this study.

Received: 11 September 2015; Revised: 14 March 2016; Accepted: 10 April 2016

Clinical Case Reports **2016; 4(7): 687–691**

doi: 10.1002/ccr3.596

Key Clinical Message

Uterine cervical small cell carcinoma is rare and aggressive with no standardized therapy. A patient bearing the advanced chemo-refractory carcinoma, treated with a tumor vaccine combined with 1 mg/kg of pembrolizumab, showed a transient increase and subsequent sharp decrease of the liver-metastasized lesion to less than half its maximum diameter.

Keywords

Anti-PD-1 antibody, cancer vaccine, radiation therapy, uterine cervical small cell carcinoma.

Introduction

Uterine cervical small cell carcinoma (UCSCC) is a rare subtype of cervical cancer, accounting for 1–6% of uterine cervical cancers, and is characterized by an aggressive behavior. No standardized therapy has been established against either early or advanced stage UCSCC owing to its rarity. Recently, Tokunaga et al. [1] tested concurrent chemoradiotherapy and a multidrug regimen in nine patients, and observed in four patients with advanced stage disease, one complete response, two partial responses, and one case of progressive disease, although all patients developed severe (grade 3–4) neutropenia.

Here, we report an advanced UCSCC case whose treatment failed after radical hysterectomy and adjuvant platinum-based chemotherapy. However, vaccination with autologous formalin-fixed tumor vaccine (AFTV) followed by treatment with 1 mg/kg of anti-PD-1 antibody (pembrolizumab), an immune checkpoint inhibitor, resulted in efficient reduction of the metastasized lesion in the liver without any severe adverse effects.

Case Report

A 54-year-old female patient was diagnosed, following bloody vaginal discharge in July 2014, with UCSCC at stage IB1 after precise pathological examination for expression of ki67, chromogranin A, and synaptophysin via a routine immunostaining system (Fig. 1A). She received surgical removal of the uterus and the ovaries and oviducts and cervix and closely related lymph nodes in September of the same year, and adjuvant chemotherapy with cisplatin (80 mg/m^2, day 1) and etoposide (100 mg/m^2, day 1–3) with the q3w regimen that is the standard first-line chemotherapy for small-cell lung carcinoma. However, metastases to two lymph nodes in the pelvis, but none to the liver, were revealed by computed tomography (CT) following six courses of chemotherapy by February 2015 (Fig. 1B).

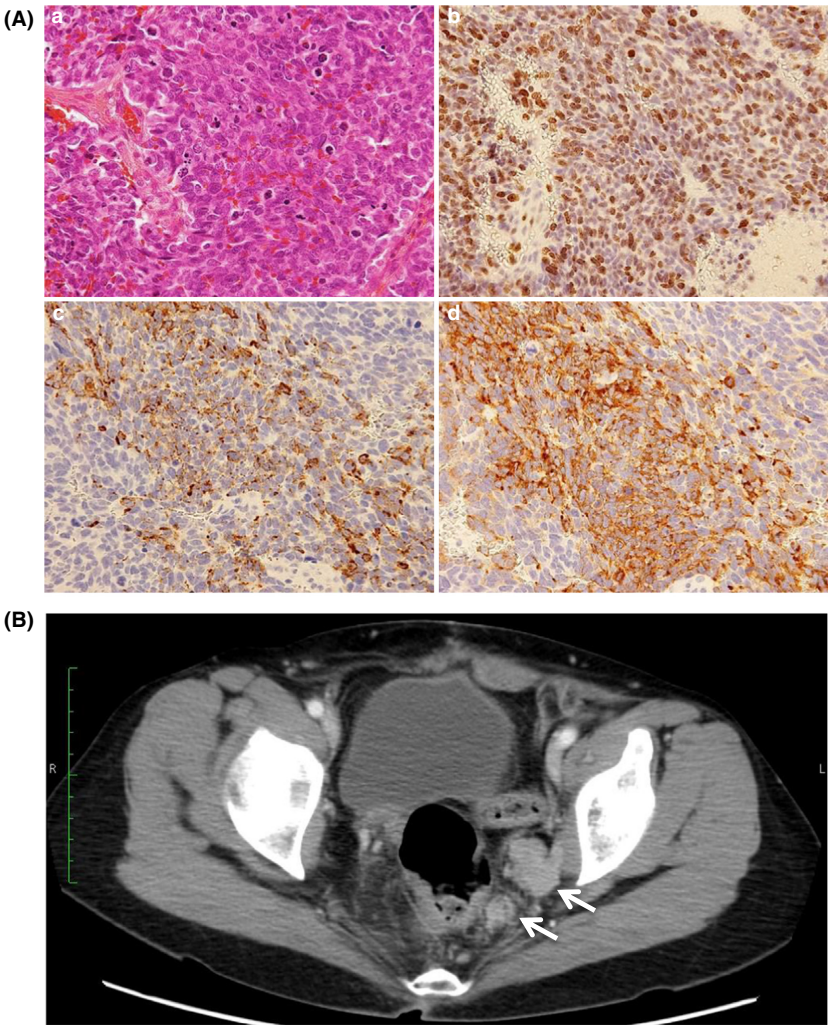

Figure 1. Pathology of the UCSCC and the pelvic metastases. (A) Pathological staining of biopsy specimen of the present case (a, H&E; b, Ki67; c, chromogranin A; d, synaptophysin) revealing a typical UCSCC with hyperchromatic nuclei and scant cytoplasm (magnification, ×400). (B) Two enlarged pelvic lymph nodes (arrows) on February 2015, after six courses of chemotherapy with cisplatin and etoposide.

With the approval from the ethical authority of Ginza-Namiki-Dori Clinic and an informed consent of the patient, we prepared AFTV as reported previously [2], using a total of 3.0 g of autologous formalin-fixed carcinoma that includes tumor-associated antigens, and injected the vaccine intradermally into her upper arms in the middle of March 2015 followed by a second injection a week later. Concurrently, we treated the pelvic lymph nodes but carefully avoided the liver with fractionated irradiation up to 60 Gy of Linac X-rays. The third vaccination with AFTV was performed 2 weeks after the initial vaccination. Although a positive response to the delayed-type hypersensitivity (DTH) test appeared when we injected her fixed carcinoma tissue fragments (without immunoadjuvant) intradermally into her forearm (Fig. 2), one new lesion in liver (Fig. 3C) together with one new and two enlarged pelvic lymph node metastases appeared in the CT image in early April.

We then administered an anti-PD-1 antibody (pembrolizumab) to the patient twice in April, 3 weeks apart, using a dose (1 mg/kg body weight) that was half of that recommended by the manufacturer. The dose was selected to reduce probability of possible adverse effects and based on cost considerations. Regrettably, however, the liver-metastasized UCSCC grew to a maximum diameter of 4.2 cm by the middle of May (Fig. 3D), although the irradiated pelvic lymph nodes shrank slightly and the serum tumor marker Neuron-Specific Enolase (NSE) decreased from 30.3 ng/mL to 21.5 ng/mL in 45 days.

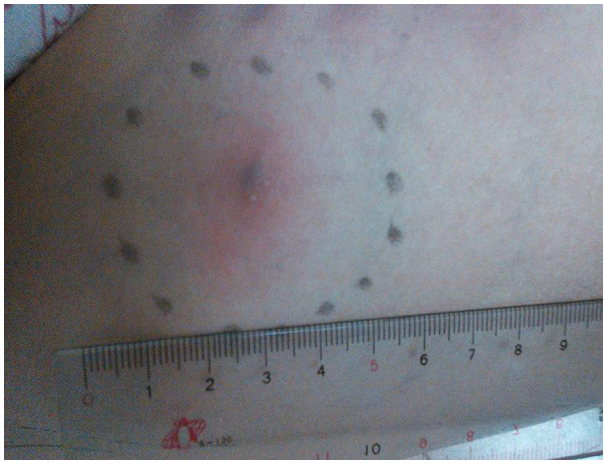

Figure 2. Delayed-type hypersensitivity response to autologous formalin-fixed UCSCC fragments (without immunoadjuvant) in the patient following vaccination with AFTV. The dotted ring is the maximum size of erythema.

The third administration of pembrolizumab was performed in the middle of May 2015, and the patient was observed 11 days later by CT. The liver-metastasized UCSCC unexpectedly showed a response and the maximum diameter was reduced to 1.9 cm (Fig. 3E). To enforce this shrinkage, we further irradiated the liver-metastasized lesion with a cyber-knife in June (7 Gy/day, a total dose of 49 Gy), which resulted in a relatively modest further reduction in tumor size (maximum diameter 1.2 cm, Fig. 3F) and a nearly linear regression of the tumor marker NSE in serum to 8.4 ng/mL by early July. These data are shown in Fig. 4, which demonstrates a rapid increase followed by a sharp decrease in the maximum diameter of the liver lesion, and a steady decrease of the level of serum NSE to within a normal range. During these treatments, no adverse effects were observed except for the appearance of a slight rash (CTCAE grade 1) following the initial pembrolizumab administration and erythema (CTCAE grade 1) at the sites of local injection of AFTV, which gradually disappeared over a few months.

Discussion

UCSCC is associated with a poor prognosis and characterized by premature distant nodal involvement. The 5-year disease-specific survival in stage I-IIA, IIB-IVA, and IVB disease was 36.8%, 9.8%, and 0%, respectively [3]. Because of its rarity, no standardized treatment has been established for this carcinoma and therefore intensive chemotherapy and/or chemoradiotherapy similar to that used for lung small cell carcinoma have been applied with only modest success [3–6]. The present case was refractory to platinum-based chemotherapy, and the patient strongly desired new treatments in addition to radiation therapy of the pelvic lymph node metastases, and we administered both AFTV and anti-PD-1 antibody, although these drugs are still unauthorized for cervical cancer in Japan.

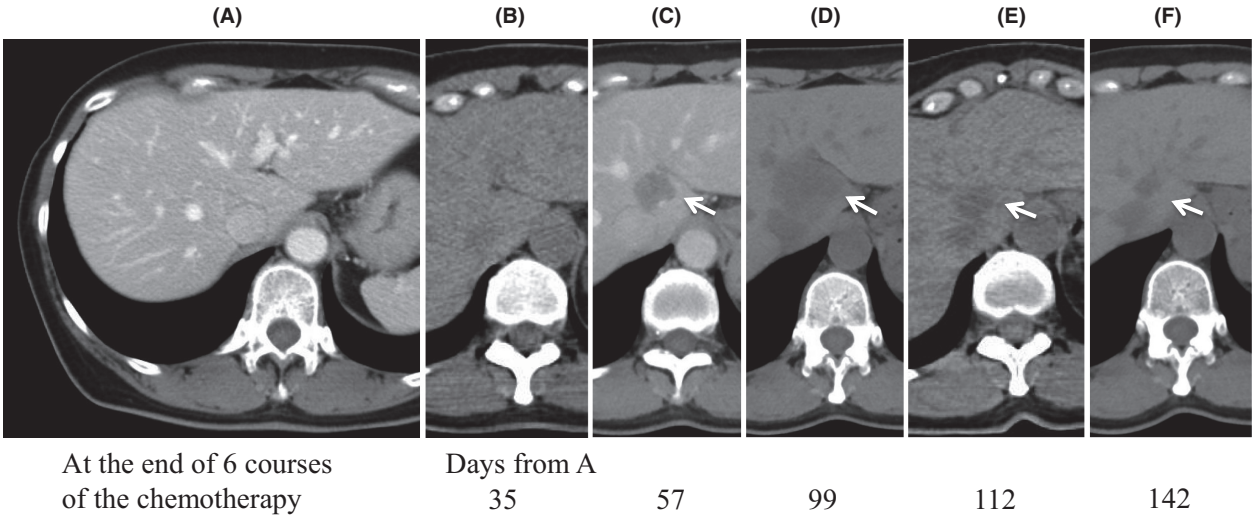

Figure 3. CT images in the metastasized liver lesion. (A) After three courses of chemotherapy. (B) Just before the first vaccination with AFTV. (C) After the third vaccination with AFTV. Arrow indicates the metastasized lesion. (D) Two days before the third treatment with 1 mg/kg pembrolizumab. The liver lesion reached a maximum diameter of 4.2 cm. (E) Eleven days after the third treatment with pembrolizumab. (F) After additional irradiation of the liver-metastasized lesion with a cyber-knife (49 Gy) and the fourth treatment with pembrolizumab. Below the arrow, inferior vena cava is seen. (A, C) Contrast-enhanced images. (B, D–F) Non contrast-enhanced images.

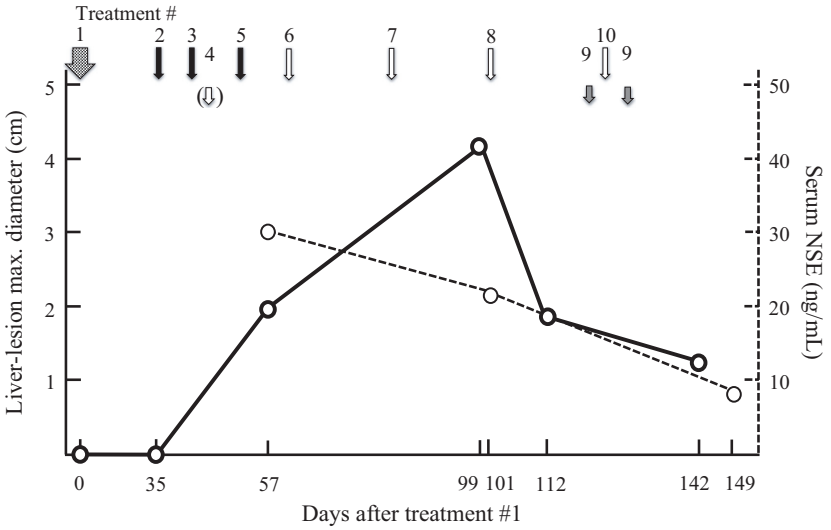

Figure 4. Time course of liver-metastasized lesion and serum NSE. Treatment #1, six courses of the chemotherapy; Treatment #2, 3, and 5, AFTV vaccination; Treatment #4, X-ray irradiation of the pelvic lymph nodes (60 Gy, but carefully avoiding the liver); Treatment #6–10, administration of 1 mg/kg pembrolizumab; Treatment #9, additional radiation therapy with a cyber-knife (49 Gy).

We have reported the prophylactic effect of AFTV (one course, i.e., three vaccinations as mentioned for the present case, which is sufficient to induce a DTH response) on suppression of recurrence in hepatocellular carcinoma (HCC) in a randomized study [7], in a re-recurrent case of HCC which led to the development of glypican-3-specific cytotoxic T lymphocytes following vaccination [8], and in a multiple-recurrent HCC case who had previously been treated 29 times with various modalities, including three laparotomies [9]. A typical therapeutic effect of AFTV was also observed, that is, eradication of bone-metastasized triple-negative mammary carcinoma [10]. More importantly, we are studying the clinical effect of AFTV mainly in newly diagnosed glioblastoma multiforme (GBM) where complete resection is not possible. While the present standard therapy for newly diagnosed GBM provides a median over-all survival (mOS) of 14.6 months [11], the mOS reached 22.2 months in our clinical trial [12]. Patients who showed a positive DTH response to autologous formalin-fixed GBM fragments (without immunoadjuvant) following vaccination with AFTV survived longer than those showing a negative DTH response ($P = 0.0071$, log-rank test) [12]. We consider that AFTV is able to provide the patient- and tumor-specific antigens irrespective of previous oncogenic virus infection.

As shown in Fig. 2, the positive DTH response of the present case suggests that cytotoxic T lymphocytes (CTL) were induced in vivo following vaccination, while the metastasized lesion grew rapidly in the liver (Fig. 3). We assume that a course of AFTV therapy acted sufficiently as an accelerator for induction of CTL, but the resulting CTL could not kill the UCSCC cells in the liver, probably because of an immune checkpoint, that is, PD-1 ~ PD-L1 ligation between the CTL and the carcinoma cells. The ligation acts as a strong brake on the local site immune response [13, 14], and therefore, the anti-PD-1 antibody worked efficiently to release this brake. We assume this "accelerator-on, brake-off" strategy has probably driven the cancer-immunity cycle [15], although more than 2 months were required after the first vaccination to obtain efficient shrinkage of the metastasized UCSCC in the liver (Fig. 4).

There is much debate over the efficacy of cancer therapies, the incidence of adverse events, and the cost of immune checkpoint inhibitory antibodies. We chose a dose of pembrolizumab, 1 mg/kg, that was half that recommended by the manufacturer mainly owing to cost considerations. Fortunately, however, this dose was sufficient to cause a response in the liver lesion without any severe adverse effects when it was preceded by three vaccinations (one course) with AFTV, suggesting that it may be possible to reduce both the cost of treatment with the highly expensive pembrolizumab as well as the incidence of severe adverse events. In addition, after observing a modest effect of the prior treatment with X-ray irradiation to the pelvic lymph nodes (Fig. 4, treatment #4), the patient received additional irradiation to the liver lesion as a precautionary treatment routine (treatment #9). These radiation treatments might have contributed to the suppression of serum NSE via a nonredundant immune mechanism, as discussed by Victor et al. [16]. We

therefore recommend combined therapy with a tumor vaccine, immune checkpoint blockade, and additional cycles of radiation for the treatment of rare and aggressive solid cancers.

Conclusion

The present case is the first one to show an effect of a tumor vaccine and an immune checkpoint inhibitor on a rare, chemo-refractory, and therefore uncontrollable metastatic cancer. The results suggest that AFTV, including ultimately personal tumor-antigen, plus specific immune checkpoint inhibitors (plus radiation, if possible) should be taken into consideration to test in a larger scale clinical trial.

Conflict of Interest

None declared.

References

1. Tokunaga, H. S., K. Nagase, S. Yoshinaga, S. Tanaka, T. Nagai, H. Kurosawa, et al. 2013. Small cell carcinoma of the uterine cervix: clinical outcome of concurrent chemoradiotherapy with a multidrug regimen. Tohoku J. Exp. Med. 229:75–81.
2. Ishikawa, E., K. Tsuboi, T. Yamamoto, A. Muroi, T. Enomoto, S. Takano, et al. 2007. A clinical trial of autologous formalin-fixed tumor vaccine for glioblastoma multiforme patients. Cancer Sci. 98:1226–1233.
3. Cohen, J. G., D. S. Kapp, J. Y. Shin, R. Urban, A. E. Sherman, L. M. Chen, et al. 2010. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. Am. J. Obstet. Gynecol. 203(347):e1–e6.
4. Silva-Meléndez, P.E., P. F. Escobar, S. Héctor, S. Gutiérrez, and M. Rodríguez. 2015. Small cell carcinoma of the uterine cervix: a case report and literature review. Bol. Asoc. Med. P. R. 107:55–57.
5. Chen, T. C., H. J. Huang, T. Y. Wang, L. Y. Yang, C. H. Chen, Y. M. Cheng, et al. 2015. Primary surgery versus primary radiation therapy for FIGO stages I-II small cell carcinoma of the uterine cervix: a retrospective Taiwanese Gynecologic Oncology Group study. Gynecol. Oncol. 137:468–473.
6. Wang, Q., Y. H. Liu, L. Xie, W. J. Hu, and B. R. Liu. 2015. Small cell carcinoma of the uterine cervix in pregnancy: a case report and review of the literature. Oncol. Lett. 9:91–95.
7. Kuang, M., B. G. Peng, M. D. Lu, L. J. Liang, J. F. Huang, Q. He, et al. 2004. Phase II randomized trial of autologous formalin-fixed tumor vaccine for postsurgical recurrence of hepatocellular carcinoma. Clin. Cancer Res. 10:1574–1579.
8. Kawashima, I., Y. Kawashima, Y. Matsuoka, K. Fujise, H. Sakai, M. Takahashi, et al. 2015. Suppression of postsurgical recurrence of hepatocellular carcinoma treated with autologous formalin-fixed tumor vaccine, with special reference to glypican-3. Clin. Case Rep. 3:444–447.
9. Inui, T., and T. Ohno. 2012. Autologous formalin-fixed tumor vaccine suppressed re-recurrence of HCV-related hepatocellular carcinoma following 29 unsuccessful treatments with extensive conventional therapy: a case report. World J. Surg. Oncol. 10:144.
10. Kuranishi, F., and T. Ohno. 2013. Eradication of breast cancer with bone metastasis by autologous formalin-fixed tumor vaccine (AFTV) combined with palliative radiation therapy and adjuvant chemotherapy: a case report. World J. Surg. Oncol. 11:127.
11. Stupp, R., W. P. Mason, M. J. van den Bent, M. Weller, B. Fisher, M. J. Taphoorn, et al. 2015. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N. Engl. J. Med. 352:987–996.
12. Ishikawa, E., Y. Muragaki, T. Yamamoto, T. Maruyama, K. Tsuboi, S. Ikuta, et al. 2014. Phase I/IIa trial of fractionated radiotherapy, temozolomide, and autologous formalin-fixed tumor vaccine for newly diagnosed glioblastoma. J. Neurosurg. 121:543–553.
13. Ott, P. A., F. S. Hodi, and C. Robert. 2013. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. Clin. Cancer Res. 19:5300–5309.
14. Homet Moreno, B., and A. Ribas. 2015. Anti-programmed cell death protein-1/ligand-1 therapy in different cancers. Br. J. Cancer 112:1421–1427.
15. Chen, D. S., and I. Mellman. 2013. Oncology meets immunology: the cancer-immunity cycle. Immunity 39:1–10.
16. Twyman-Saint Victor, C., A. J. Rech, A. Maity, R. Rengan, K. E. Pauken, E. Stelekati, et al. 2015. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 520:373–377.

