Anti-PD-1 monoclonal antibody-resistant esophageal squamous cell carcinoma showing the abscopal effect: A case report with T-cell receptor/B-cell receptor repertoire analysis

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Abstract

Background Several good results of clinical trial of nivolumab or involving nivolumab in advanced esophageal squamous cell carcinoma were reported. However, the response rate was still poor. A rare phenomenon called the "abscopal effect" refers to the regression of not only the irradiated tumor but also non-irradiated distant tumors after local radiotherapy. The mechanism is not completely clear, but it is thought that the activation of anti-tumor immunity induced by radiotherapy is the main factor. Case A 66-year-old man with recurred and nivolumab resistant esophageal squamous cell carcinoma in left-side cervical and abdominal para-aortal lymph node metastasis was treated with a total of 40 Gy (10 fractions) of radiotherapy to the left-side cervical lymph node metastasis which caused neck pain as a palliative treatment. Nivolumab was resumed the day after completion of radiotherapy. At 3 months after radiotherapy showed that the irradiated lesion in the left neck had regressed to a scar-like appearance. Notably, the abdominal para-aortal lymph nodes outside the irradiation area, which had previously tended to progress, had also shrunk (abscopal effect). The T cell receptor and B cell receptor (TCR/BCR) repertoire analysis before and after radiotherapy revealed that radiotherapy caused the changes in the TCR/BCR repertoire. Conclusion Changes in the TCR/BCR receptor repertoire repertoires were assumed to be a part of the mechanism of the abscopal effect. The findings in this patient suggest that combination of immune checkpoint inhibitors and radiotherapy can be a promising treatment approach, even for patients with immune checkpoint inhibitors resistant cancer.

Case Report

Title

Anti-PD-1 monoclonal antibody-resistant esophageal squamous cell carcinoma showing the abscopal effect: A case report with T-cell receptor/B-cell receptor repertoire analysis

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Abstract

Background

Several good results of clinical trial of nivolumab or involving nivolumab in advanced esophageal squamous cell carcinoma were reported. However, the response rate was still poor. A rare phenomenon called the "abscopal effect" refers to the regression of not only the irradiated tumor but also non-irradiated distant tumors after local radiotherapy. The mechanism is not completely clear, but it is thought that the activation of anti-tumor immunity induced by radiotherapy is the main factor.

Case

A 66-year-old man with recurred and nivolumab resistant esophageal squamous cell carcinoma in left-side cervical and abdominal para-aortal lymph node metastasis was treated with a total of 40 Gy (10 fractions) of radiotherapy to the left-side cervical lymph node metastasis which caused neck pain as a palliative treatment. Nivolumab was resumed the day after completion of radiotherapy. At 3 months after radiotherapy showed that the irradiated lesion in the left neck had regressed to a scar-like appearance. Notably, the abdominal para-aortal lymph nodes outside the irradiation area, which had previously tended to progress, had also shrunk (abscopal effect). The T cell receptor and B cell receptor (TCR/BCR) repertoire analysis before and after radiotherapy revealed that radiotherapy caused the changes in the TCR/BCR repertoire.

Conclusion

Changes in the TCR/BCR receptor repertoire repertoires were assumed to be a part of the mechanism of the abscopal effect. The findings in this patient suggest that combination of immune checkpoint inhibitors and radiotherapy can be a promising treatment approach, even for patients with immune checkpoint inhibitors resistant cancer.

Keywords

esophageal squamous cell carcinoma, abscopal effect, radiation therapy, anti-PD-1 monoclonal antibody, B-cell receptor repertoire

Main text

Introduction

Despite the fact that esophageal cancer is one of the deadliest cancers in the world, there are fewer drugs that have been proven to be effective against esophageal cancer than against cancers at other sites. In the United States and Europe, adenocarcinoma is the most common histological type, and chemotherapy regimens are often selected in a manner similar to that for gastric cancer. On the other hand, squamous cell carcinoma is the main histological type in Asia, and the combination of cisplatin and 5-fluorouracil has been used as a key approach in Japan.

With the clinical success of immune checkpoint inhibitors (ICIs), such as anti-PD-1 and anti-CTLA-4 antibodies, tumor immunity has attracted much attention in cancer treatment. In the 2000s, it became clear that immunity against tumors plays an important role in not only suppressing cancer development but also cell-killing anticancer therapies, such as radiotherapy (RT) and chemotherapy.

The ATTRACTION-3 study is a phase III clinical trial with unresectable advanced or recurrent esophageal cancer that is refractory or intolerant to combination chemotherapy (1). Nivolumab showed a significant increase in survival compared with chemotherapy (taxane), and then, nivolumab was approved as a second-line treatment for unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) by the Food and Drug Administration. and for unresectable advanced, recurrent, or metastatic esophageal cancer by the Pharmaceuticals and Medical Devices Agency, Japan, in 2020. However, the response rate was only 19%. The combination of nivolumab with other therapies to enhance its efficacy is being actively studied worldwide. Recently, the results of the CheckMate 648 Trial, a phase III clinical trial involving nivolumab combination therapy as a first-line treatment in advanced ESCC were reported (2). Nivolumab plus chemotherapy and nivolumab plus ipilimumab resulted in significantly longer overall survival than chemotherapy alone, with no new safety signals identified. However, the median overall survival period was 13.7–15.4 months, and further improvement in the treatment protocol is still needed.

A rare phenomenon called the "abscopal effect" refers to the regression of not only the irradiated tumor but also non-irradiated distant tumors after local RT. The mechanism is not completely clear, but it is thought that the activation of anti-tumor immunity induced by RT is the main factor (3,4). Recently, the "abscopal effect" was reported in patients treated with a combination of ICIs and RT (ICI+RT) (5,6). Though the abscopal effect is exceedingly rare in esophageal cancer, some reports were recently published (7,8).

Here, we report a patient with anti-PD-1 monoclonal antibody (mAb)-resistant ESCC showing the abscopal effect (systemic response), and present the findings of T-cell receptor (TCR) and B-cell receptor (BCR) repertoire analysis before and after RT.

Case

A 66-year-old man was diagnosed with advanced ESCC (Mt-Lt, cT3N2M1, stage IVb). After neoadjuvant chemotherapy (1 × 5-fluorouracil+cisplatin and 1 × docetaxel+5-fluorouracil+cisplatin), he underwent esophagostomy with regional lymph node dissection. Tegafur/gimeracil/oteracil (S-1) was started as postoperative adjuvant chemotherapy from 2 months after the esophagostomy. Six months after esophagostomy, left-side cervical and abdominal para-aortal lymph node metastasis was detected on computed tomography (CT) (shown in Fig. 1A). Then, S-1 was discontinued and nivolumab 240 mg per body was administered as second-line treatment 6 times every 2 weeks. Two months later, a follow-up CT scan showed that all metastatic lymph nodes progressed, especially the left cervical lymph node (shown in Fig. 1B). In other words, these tumors were nivolumab resistant. To treat left-side neck pain caused by the progressed metastatic lymph nodes, as a palliative treatment, a total of 40 Gy (10 fractions) of RT was administered using the intensity-modulated, image-guided technique (shown in Fig. 1C).

Nivolumab was resumed the day after completion of RT. A CT scan at 3 months after RT showed that the irradiated lesion in the left neck had regressed to a scar-like appearance. Notably, the abdominal para-aortal lymph nodes outside the irradiation area, which had previously tended to progress, had also shrunk (shown in Fig. 1D). Adverse events were grade 1 oral mucositis, dry skin, pruritus, and fatigue, and no grade 2 or higher adverse events have been observed in combination with RT to date. All the adverse events were associated with nivolumab and not with RT.

The TCR and BCR repertoire analysis was outsourced to Repertoire Genesis Inc. (Tokyo, Japan). The diversity indexes of the TCR and BCR repertoire analysis before and after RT are shown in table 1 and 2. All the diversity indexes in both the TCR and BCR repertoires decreased after RT. The number of unique clones accounting for >0.01% and >0.1% of total TCRs/BCRs before and after RT are shown in Figure 2A, and the top 10 clones of TCRs/BCRs after RT compared with before RT are shown in Figure 2B. There were decreases in the number of unique clones accounting for >0.01% of total TCRs/BCRs before and after

RT (TCR: 1795–884, BCR: 1792–1212) and large increases in that of unique clones accounting for >0.1% of total TCRs/BCRs before and after RT (TCR: 60–179, BCR: 130–241). The top 10 clones were mostly similar in the TCR repertoire (8 of the top 10 clones before RT were still in the top 10 clones after RT), but there were some changes (the percentages of the 1st, 2nd, and 4th clones increased more than 0.5%). In the BCR repertoire, all the top 10 clones before RT were replaced after RT. Furthermore, 9 of the 10 clones were newly detected after RT.

Thereafter, the irradiated tumors showed complete response (for 11 months). However, re-progression of the abdominal para-aortal lymph nodes was detected at 7 months after RT, and they were irradiated. Nivolumab was stopped due to nivolumab-related skin rash (out of the irradiated area) at 10 months after the first RT (3 months after the second RT). At 11 months after the first RT, new lymph node metastases (inguinal and axillary) were detected, and the patient is living with the disease.

Discussion

Chen et al. reported that RT plays a role in antigen spread, which leads to T-cell immune activation in the cancer immunity cycle (9). Moreover, according to the review by Sharabi et al., the roles of RT in cancer immunology are as follows: 1) radiation induces changes to the tumor cell immunophenotype, 2) radiation enhances cross-presentation of tumor antigens, and 3) radiation combined with an ICI increases tumor cell susceptibility to immune-mediated cell death (2). We have reported that RT induced cancer/testis antigen-specific cytotoxic T-cell activation in ESCC patients treated with chemo-RT, and multi-antigen-specific T-cell responses were observed in some patients (4).

Already, the concept of ICI+RT (so-called immunoradiotherapy) has been clinically proven in non-small-cell lung cancer (NSCLC) (10,11). The anti-PD-L1 antibody durvalumab administered every 2 weeks for 12 months after radical chemo-RT for stage 3 NSCLC (PACIFIC trial) improved the progression-free survival rate by about 20% at 1 year (10) and the overall survival rate by about 15% at 4 years (11). This ICI+RT regimen has already become the standard therapy for stage 3 NSCLC. At present, many clinical trials of ICI+RT are underway for cancers at other sites, including esophageal cancer (12).

Regarding the adverse effects of ICI+RT, severe (grade 3 or higher) adverse effects were not increased in the PACIFIC trial. Furthermore, Sha et al. performed a systemic review and meta-analysis, and reported comparable grade 3–4 toxicity using ICI+RT compared with ICI alone in CNS melanoma, NSCLC, and prostate cancer, and they concluded that ICI+RT was safe (13).

A change in the TCR/BCR repertoire after treatment is proof of a treatment-induced immunoresponse. Changes in the TCR and BCR repertoires by treatment have already been reported (14,15). Moreover, changes in the TCR repertoire by RT and chemo-RT have been reported in myeloma (14), and head and neck cancer (15). The usefulness of analyzing the TCR repertoire to detect the efficacy of anti-PD-1 antibody (clonality [1 – Pielou's evenness] (16) and frequency of the top 30 most frequent clonotypes: 17)) and the BCR repertoire to detect the efficacy of autologous cellular immunotherapy (clonality (18)) has been reported. Analysis of the TCR and BCR repertoires may facilitate the dissection and understanding of the immune response in human cancer patients and may be useful as a biomarker of RT or ICI+RT. In our patient, the BCR repertoire ranking greatly changed with RT and the TCR repertoire also changed. All diversity indexes for both the TCR and BCR repertoires decreased after RT. These changes in the TCR and BCR repertoires may be associated with RT-induced tumor-specific anti-tumor immunity, resulting in the abscopal effect in the patient with nivolumab-resistance. In other words, it is possible that further antigen spread by RT may retrieve the effect of nivolumab in patients with nivolumab-resistance. Since each metastatic tumor is not the same (homogenous), RT to another metastatic tumor may induce new or more immune responses (19).

In our patient, RT was performed as a palliative local treatment after disease progression during nivolumab treatment, and the abscopal effect was observed. Changes in the TCR and BCR repertoires were observed after RT, and these were assumed to be a part of the mechanism of the abscopal effect. The findings in this patient suggest that ICI+RT can be a promising treatment approach, even for patients with ICI-resistant cancer.

Ethical Statement

Patient consent The authors declare that they have obtained written informed consent from the patient.

Data Availability Statement

Data available on request due to privacy/ethical restrictions.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Author's Contributions

Yuka Takehara: resources(equal), data curation(equal), visualization(equal), writing-original draft(lead), writing-review and editing(equal)

Kosaku Mimura: conceptualization(equal), resources(equal), data curation(equal), writing-review and editing(equal)

Yoshiyuki Suzuki: conceptualization(equal), data curation(equal), visualization(equal), supervision(equal), writing-review and editing(equal), Funding Acquisition(lead)

Yohei Watanabe: resources(equal), writing-review and editing(equal)

Yuya Yoshimoto: resources(equal), writing-review and editing(equal)

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Tomoaki Tamaki: resources(equal), writing-review and editing(equal)

Koji Kono: supervision(equal), writing-review and editing(equal)

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Figure Legends

Figure 1.

Results of diagnostic and radiotherapy simulation imaging throughout the disease course. Axial computed tomography (CT) images are shown, corresponding to the timeline showing therapy. White arrows indicate left-neck lymph node metastasis, and red circles indicate abdominal para-aortal lymph node metastasis. (A) Representative figures before treatment with nivolumab. (B) Figures showing enlargement of the left-neck lymph node and abdominal para-aortal lymph node metastases. (C) Figure showing the CT simulation image for radiotherapy planning. The isodose paint represents total doses of >40 Gy (red), 20–36 Gy (green), and 12–20 Gy (blue). (D) Figures showing findings 3 months after radiotherapy. The irradiated left-neck lymph node metastasis regressed to a scar-like appearance. Furthermore, disease response outside of the radiation field was seen.

Figure 2.

(A) Enrichment of the T-cell receptor (TCR)/B-cell receptor (BCR) pool in clones. There are slight increases in the percentage of unique clones accounting for >0.01% of total TCRs/BCRs before and after radiotherapy, and large increases in that of unique clones accounting for >0.1% of total TCRs/BCRs. (B) Top 10 TCR/BCR clones after radiotherapy. In the TCR repertoire, the top 10 clones are mostly similar to that before radiotherapy, but there are some changes (the percentages of the 1st, 2nd, and 4th clones

increased more than 0.5%). In the BCR repertoire, all the top 10 clones before radiotherapy are replaced after radiotherapy. Furthermore, 9 of the 10 clones are newly detected after radiotherapy.

: before radiotherapy; : after radiotherapy; *: not detected

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