Clinical Case Reports

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CASE REPORT

An abscopal effect in a case of concomitant treatment of locally and peritoneally recurrent gastric cancer using adoptive T-cell immunotherapy and radiotherapy

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

Received: 24 March 2016; Revised: 8 November 2016; Accepted: 14 November 2016

Clinical Case Reports **2017; 5(4): 380–384**

doi: 10.1002/ccr3.758

Key Clinical Message

The mechanism of abscopal effect is becoming clear by the progress of cancer immunology. A 54-year-old male with recurrent gastric cancer presented an abscopal effect after radiotherapy with concurrent adoptive T-cell immunotherapy (immunoradiotherapy). Immunoradiotherapy has potential to induce abscopal effect by strengthening systemic antitumor immunity even in recurrent cancer.

Keywords

Abscopal effect, adoptive T-cell immunotherapy, gastric cancer, peritoneal dissemination, radiotherapy

Introduction

Radiotherapy is one of the treatments used for most types of cancer, regardless of the clinical stage. It is generally accepted that radiotherapy induces cancer cell death via apoptosis and/or necrosis by damaging (either directly or indirectly) the DNA. If irradiation could induce cell death just by damaging the DNA, the effect would be seen only within the irradiated field. However, the cytoreductive effects on the distant metastatic lesions outside the irradiated field, known as "abscopal effect", have been observed in patients with melanoma, lung cancer, and renal cancer, among others [1]. This phenomenon might be caused by the antitumor immunity induced by radiotherapy [2]. The emerging evidence suggests that the immunogenic cell death caused by irradiation might be another important effect of radiotherapy, in addition to the DNA damage [3]. Radiation-induced cell death elicits the damage signals, such as high-mobility group box 1 (HMGB1), which trigger the activation of antigen presentation cells (APCs). Subsequently, APCs present the tumor-derived antigens to cytotoxic T lymphocytes (CTLs), which then kill the target cells. Radiotherapy also increases the expression of HLA class I molecules, which also can activate CTLs by presenting tumor-derived antigen, on the surface of tumor cells [4]. Enhanced antigen presentation and activated CTLs have potential for an immune-mediated abscopal effect.

The abscopal effect has been reported several times over the years, reviving the interest in the progress of cancer immunology [5]. Accumulating evidence shows that the combination of radio- and immunotherapy (e.g., using immune checkpoint inhibitors) induces the abscopal effect in several types of cancers [2, 6–8]. These reports suggest that the combined radio- and immunotherapy can be an effective strategy for advanced or recurrent cancers. Here, we report a case of postoperative, locally and peritoneally disseminated, recurrent

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gastric cancer treated using a concomitant radiotherapy and adoptive T-cell immunotherapy. The treatment had an abscopal effect and achieved a complete remission of the irradiated tumor.

Case Report

A 54-year-old Japanese male was diagnosed with gastric cancer and underwent distal gastrectomy with Billroth-I. The histology and pathological stage of the tumor were poorly differentiated adenocarcinoma and pT4aN3aM0 (stage IIIC) with no residual tumor, respectively. The adjuvant chemotherapy TS-1 was prescribed. However, 10 months after the surgery, a local recurrence (invasion of the pancreas and the left kidney) and peritoneal dissemination with cancerous peritonitis were diagnosed using computed tomography (CT) and endoscopic biopsy. Then, another chemotherapy treatment (paclitaxel) was prescribed. The chemotherapy had to be stopped after two courses because of a hematological adverse effect (neutrophil count decreased to <1000/mm^3). The patient was referred to the outpatient clinic to undergo the adoptive T-cell immunotherapy and dendritic cell (DC) therapy; details of the therapies are described elsewhere [9]. Briefly, 3–10 × 10^9 adoptive T cells and 1–10 × 10^6 DCs were infused intravenously and intratumorally, respectively, at intervals of approximately 2 weeks. However, after four courses of the therapies, a progression of local recurrence and peritoneal dissemination was observed.

Subsequently, the patient received 48 Gy in 24 fractions of radiotherapy using the intensity-modulated radiotherapy (IMRT) method (Fig. 1) with concurrent adoptive T-cell immunotherapy (immunoradiotherapy). Figure 2 shows changes in local recurrence and peritoneal dissemination before, during, and after immunoradiotherapy. During immunoradiotherapy, shrinkage of the locally reoccurred tumor was observed, although the peritoneal dissemination progressed (Fig. 2A and B). Two months after the initiation of radiotherapy, the performance status was improved from 4 to 2, and CT images showed a complete remission of the locally recurrent tumor. Furthermore, the shrinkage of metastatic peritoneal tumor (i.e., the abscopal effect) was observed (Fig. 2C). However, the abscopal effect lesions could not be measured because they consisted of small (<5 mm) multiple nodular peritoneal dissemination: lesions <10 mm are categorized into "nonmeasurable" by the RECIST (version 1.1). After completion of the immunoradiotherapy, the adoptive T-cell immunotherapy was continued (11 courses). However, 5 months after the immunoradiotherapy, the patient died because of new multiple distant metastases in the peritoneum. He did not experience significant discomfort until just before his death. Figure 3 shows the clinical time course and the corresponding changes in the serum tumor marker (CEA, CA19-9) after postoperative recurrence.

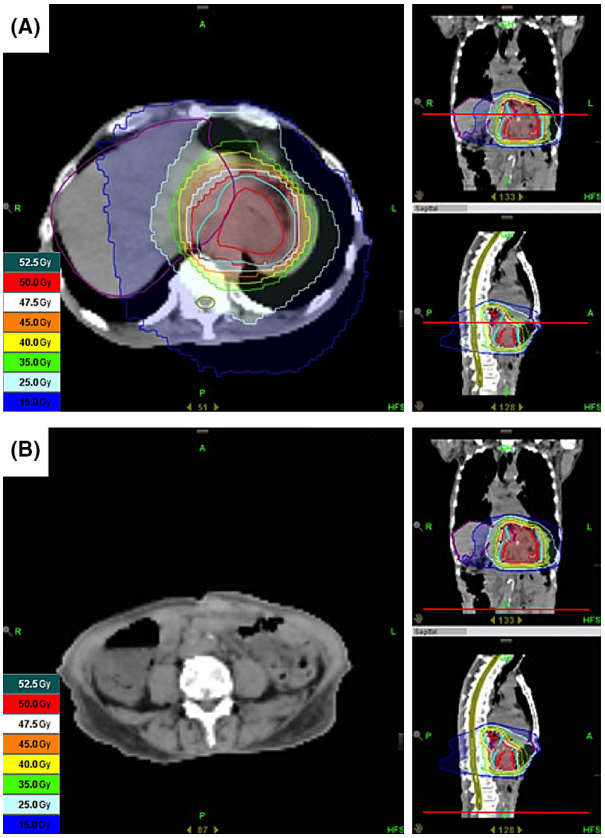

Figure 1. Dose distribution of radiotherapy. (A) Radiotherapy (48 Gy in 24 fractions) using the IMRT method was prescribed for local recurrent tumor, which includes the pancreas and the left kidney. (B) The metastatic peritoneal tumor in which the abscopal effect was observed was not included in the irradiated field.

Discussion

In this case, we observed an abscopal effect and a complete local response of the recurrent gastric cancer to a multimodal therapy. The treatment consisted of 48 Gy in 24 fractions of radiotherapy and concurrent T-cell immunotherapy. To date, the optimal irradiation dose for recurrent gastric cancer is unknown. Previous studies have demonstrated that neoadjuvant chemoradiotherapy (using 45 Gy in 25 fractions) showed a pathological complete response rate of 16–30% [10]. From these data, 48 Gy in 24 fractions seemed to be an insufficient dose to achieve a complete response on its own. It suggested that the combination therapy not only caused the abscopal

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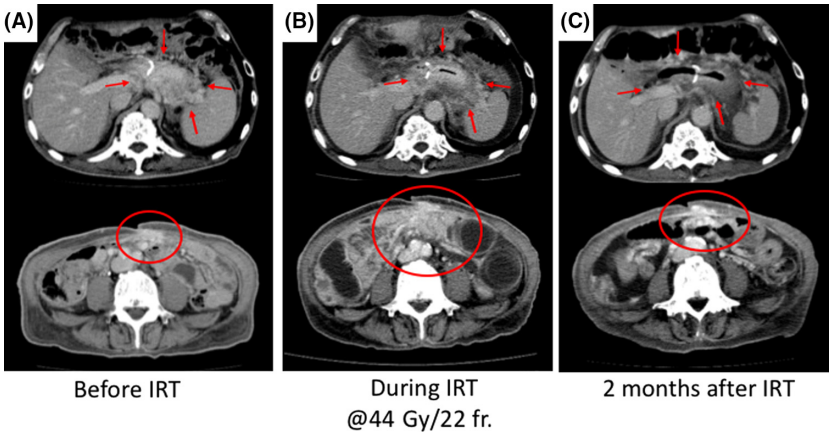

Figure 2. CT images of local recurrence and peritoneal dissemination before, during, and after immunoradiotherapy. (A) CT images before immunoradiotherapy: 2 months after the first paclitaxel treatment followed by immunotherapy. Progression of the local recurrence lesion and peritoneal dissemination was confirmed. (B) CT image was acquired during immunoradiotherapy at 44 Gy in 22 fractions point. Shrinkage of the locally reoccurred tumor (red arrow) and progression in peritoneal dissemination (red circle) were observed. (C) CT image was taken 2 months after the start of the therapy. A complete remission of the locally recurrent tumor and an abscopal effect were observed. IRT, immunoradiotherapy.

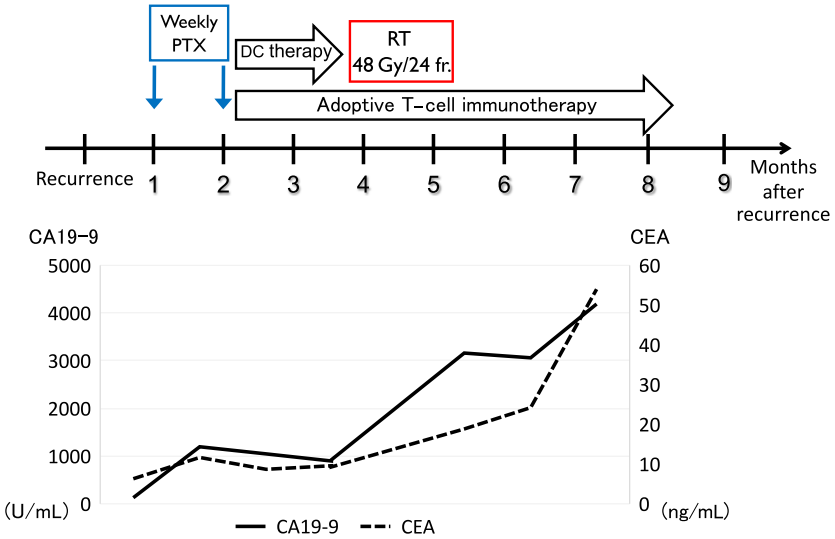

Figure 3. The clinical time course and corresponding changes in the serum tumor marker after postoperative recurrence. CA19-9 temporally decreased in response to complete remission of the locally recurrent tumor and abscopal effect after immunoradiotherapy, whereas CEA steadily increased. However, both of tumor markers were eventually uncontrolled. PTX, paclitaxel; DC, dendritic cell; RT, radiotherapy; IRT, immunoradiotherapy.

effect but also affected the locally irradiated tumor. To confirm the mechanism and obtain a detailed validation of the immune response, the immune status and tumor environment should be examined by analyzing the tumor-infiltrating T lymphocytes and the expression of HLA class I molecules. However, this was ethically unfeasible because of the worsening general health of the patient.

Clinical reports of abscopal effect are scarce. Reynders et al. have reviewed five recent clinical case reports showing an abscopal effect after radiotherapy combined with immunotherapy [11]. The studies have used various radiation doses (24 Gy in 3 fractions, 28.5 Gy in 3 fractions, 30 Gy in 5 fractions, 54 Gy in 3 fractions, and 58 Gy in 29 fractions), examined varied histology (melanoma and lung adenocarcinoma), and employed different types of immunotherapy (ipilimumab and BCG vaccine). Hence, the optimal dose and number of fractions to achieve the abscopal effect has remained unclear. Interestingly, the abscopal effect was observed after the

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shrinkage of the locally reoccurred tumor suggesting that the activation of systemic immune-stimulation through elicited damage signals followed by radiation-induced cell death plays a critical role in the abscopal effect.

Accumulating evidence suggests that a dysfunction in the host systemic immunity and/or low immunogenic characteristics of the tumor may favor the progression of cancer [12]. Therefore, the therapies restoring or strengthening the immune functions might constitute an effective treatment. Kim et al. have reported that T-cell-based immunotherapy destroys the human gastric cancer cells (MKN74) in vitro and inhibits the growth of these cells in the nude mouse [13]. Recent studies have shown that radiotherapy can act as an immunostimulant, causing the immunogenic cell death and releasing the danger signals such as HMGB1 [14, 15]. We have also shown that chemoradiotherapy releases HMGB1 and induces tumor antigen-specific T-cell response in esophageal cancer patients [16], and that hyperthermo-chemoradiotherapy enhances the HLA class I expression in rectal cancer patients [16, 17]. These results suggest that radiotherapy could be profitably combined with immunotherapy.

With the recent advances in diagnostic and treatment modalities, the prognosis of gastric cancer has become more favorable, particularly in the early stages. However, the postoperative recurrence is one of the most crucial factors associated with the cancer-related deaths of gastric cancer patients [18]. Spolverato et al. have reported such recurrence (local, peritoneal, and hematogenous) in 29.9% of patients, including those who had undergone radiotherapy and/or chemotherapy as adjuvant treatment [19]. They observed a rate of 24.2% and 19.3% for local and peritoneal recurrence, respectively, with the median survival period of only 9.1 and 2.7 months after local and peritoneal recurrence, respectively. Recently, Yang et al. have reported that the combined intravenous and intraperitoneal chemotherapy effectively prevents peritoneal recurrence. A meta-analysis has shown that this therapy prolongs the survival period in comparison with intravenous chemotherapy alone [20]. However, there is still no standard treatment for postoperative recurrence.

Recently, immunotherapy has been attracting increasing attention. Nivolumab, a PD-1 immune checkpoint inhibitor antibody, has shown a significant superiority over chemotherapy in phase III trials for melanoma and squamous cell carcinoma of the lung [21, 22]. However, despite prolonged survival, the disease progression rate has remained around 30%. These results suggest that immunotherapy should be combined with an effective local treatment, such as radiotherapy. Hence, immunoradiotherapy is a promising treatment for postoperative recurrent gastric cancer, although further investigation is warranted.

Informed Consent

Written informed consent was obtained from the patient, agreeing to the publication of this case report and any accompanying images.

Conflict of Interest

The authors declare that they have no competing interests.

Authorship

HS, YS, and YT: summarized case information and drafted the manuscript. YS, YY, SN, TS, and TN: coordinated the clinics, prescribed and carried out the immunotherapy, and participated in the follow-up of the patient. KM: carried out the contouring of the patient and simulated the radiotherapy dose. KM, AO, and TS: participated in patient care in the hospital. All authors read and approved the final manuscript.

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