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Case report

A patient with stage IV gastric cancer who acquired complete remission after undergoing multi-peptide dendritic cell immunotherapy in combination with standard therapies

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ABSTRACT

In this report, we describe a 62-year-old male patient with stage IV gastric cancer who was treated with chemotherapy and dendritic cell immunotherapy targeting the cancer antigens WT1, MUC1, Her-2, and survivin. He then received WT1 and MUC1 peptides in combination with adjuvants near the lymph nodes or the mucosa of the cancer lesion. Subsequently, a remarkable decrease in the size of the gastric lesion, in the swelling of metastatic lymph nodes, and the disappearance of ascites were observed. After 1 year and 2 months of the initial diagnosis, the patient underwent a robot-assisted gastrectomy and was able to return to work. In conclusion, multi-peptide dendritic cell immunotherapy in combination with conventional therapies resulted in remarkable anti-cancer effects and improved the patient's quality of life.

1. Introduction

Advanced gastric cancer is common in Japanese patients. Among the standard therapies for gastric cancer, surgical resection is a possible curative treatment; however, it is limited to the early stages of the disease. A combination of surgery and chemotherapy is typically used in patients with advanced gastric cancer. However, a favorable outcome is difficult to achieve, and the 5-year survival rate of stage IV gastric cancer patients is <10% [1].

In recent years, immunotherapies have been introduced as a new approach for cancer treatment. Dendritic cells (DC) are key regulators of both T- and B-cell immunity due to their superior ability to function as antigen-presenting cells. DC vaccine immunotherapy and antigen-specific adaptive immunotherapy aim at activating tumor-specific cytotoxic T lymphocytes (CTLs) and tumor-specific memory T-cells. CTLs recognize tumor antigens and attack tumor cells, and memory T-cells can control tumor relapse. DCs also activate natural killer (NK) cells. NK cell immunotherapy antigen non-specific innate immunotherapy have been shown to have direct cytotoxic activity against tumor cells and NK cells produce cytokines such as interleukin-1 (IL-1) and interferon-γ (IFN-γ) [2].

Tumor-associated antigens (TAAs) are key factors in the design of DC vaccine immunotherapy, and artificial tumor antigens are utilized as peptides when a patient's own cancer cells are not available. Based on the histology of the patients' primary lesions and tumor markers, Wilms tumor 1 (WT1), Mucin 1 (MUC1), carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), human epidermal growth factor receptor 2 (HER2), survivin, and telomerase have been proposed as potential gastric tumor antigens for DC vaccine immunotherapy. DC-based multi-peptide immunotherapy has been shown to be a feasible approach that generates efficient cellular antitumor responses [3].

Advanced stage malignancies often develop resistance to standard therapies. This is in part responsible for the considerable morbidity and mortality associated with advanced cancers. They have shifted the focus to more specific and targeted immunotherapy. Increasing evidence from animal studies and clinical trials has shown that DC vaccine immunotherapy may be a viable option for cancer treatment.

In this case study, multi-peptide DC vaccine and NK immunotherapy was combined with standard chemotherapy for the treatment of an inoperable advanced gastric cancer. After these therapies, the patient was able to undergo surgery and subsequently achieved complete remission.

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2. Case presentation

A 62-year-old male patient was admitted to a hospital with abdominal fluid retention and weight loss. Gastric endoscopy revealed thickening of his gastric wall with bleeding at the lesser curvature of the stomach from the body to the anterior wall. Abdominal computed tomography (CT) also showed thickening of the gastric wall as well as massive ascites and multiple nodules in the peritoneum (Fig. 1). The patient was diagnosed with inoperable stage IV HER2-positive gastric cancer with peritoneal metastasis.

After the diagnosis, he was treated with chemotherapy (cisplatin and, trastuzumab, with capecitabine or S-1) at the hospital for 10 months. During the chemotherapy, he visited our clinic to receive DC vaccine and NK cell immunotherapy every 2 weeks for a total of 9 treatments.

The DC vaccine and NK cells were prepared every 2 weeks from 25 mL of the patient's peripheral blood according to the methods of Patent Number 5577472 at The Life Science Institute Co. Ltd, Tokyo, Japan. Then, the tumor antigens T1, MUC1, HER2, and survivin were selected based on the patient's HLA-A2402, histology of the patients' primary lesions and tumor markers, and were pulsed onto the monocyte-derived DCs, and incubated for 24 h. All DC vaccines and NK cells were subjected to a quality control evaluation, which involved assessing the total number of live cells, monocyte-derived DC and NK characteristics, and the percentage of viable cells.

DCs ($>10^7$ cells) were administered via intracutaneous (i.c.) injection near the bilateral inguinal lymph nodes, and NK cells ($>10^9$ cells) via intravenous drip infusion (d.i.v.) at 2-week intervals for 9 a total of times.

Four months after the DC vaccine and NK immunotherapy, gastric endoscopy and an abdominal CT showed that the gastric wall thickening, ascites, and lymph node swelling had subsided, and only a Borrmann type 2 lesion (20 mm in size) near the esophagogastric junction remained (Fig. 2). Because the size of the malignant lesions decreased dramatically by combining chemotherapy and immunotherapy, surgical therapy could then be performed. After the completion of chemotherapy and immunotherapy WT1 and MUC1 peptides with adjuvant reagents were administered every 2 weeks for 10 times total via i.c. injections near the bilateral inguinal lymph nodes or the mucosa of the cancer lesion via gastric endoscopy. During the immunotherapies, no adverse reactions were observed in the patient.

The WT1 and MUC1 peptides with adjuvant reagents were prepared at The Life Science Institute Co. Ltd, Tokyo, Japan.

Finally, a robot-assisted total gastrectomy was performed. Histology confirmed the diagnosis of a well-differentiated tubular adenocarcinoma with no lymph node metastasis. After the surgery, the patient was able to return to work.

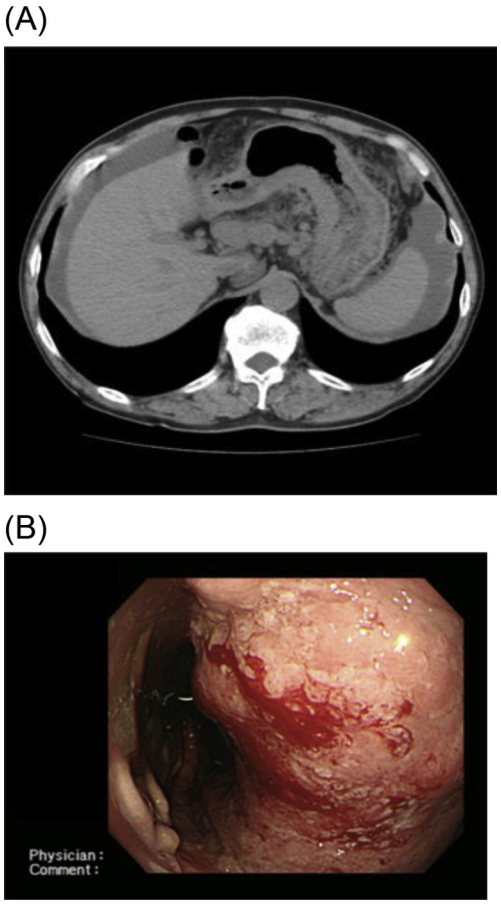

Fig. 1. Before treatment: (A) Abdominal CT: thickening of gastric wall and multiple lymph node swellings were observed. Massive ascites and multiple nodules in peritoneum were also obvious. (B) Gastric endoscope: gastric wall thickness with bleeding was observed at lesser curvature side of stomach from body to anterior wall.

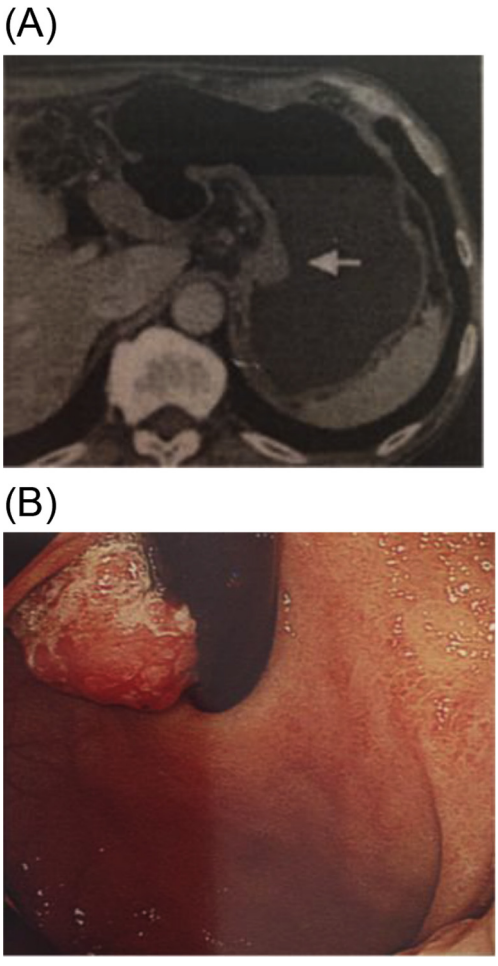

Fig. 2. Six months after completion of DC immunotherapy: (A) Abdominal CT: disappearance of gastric wall thickening, ascites, and LN swellings were observed. (B) Gastric endoscope: only a Borrmann type 2, 20 mm lesion near EG junction was observed, which was finally surgically treated.

3. Discussion

DC vaccine immunotherapy has been a focus of promising strategies for cancer treatment. A central aim of DC-based immunotherapy is the generation of an antigen-specific CTL response. TAAs and DCs play essential roles in activating CTL. DCs are well known to have the most powerful antigen-presenting capacity among immune cells. DCs pulsed with various TAAs have been shown to be effective in producing specific antitumor effects.

In this study, we selected 4 promising peptides, WT1, MUC1, HER2, and survivin, as TAAs for the treatment of advanced gastric cancer. WT1 is a transcription factor that negatively affects cell differentiation, promotes the proliferation of progenitor cells, and plays an important role in angiogenesis. The oncogenic properties of WT1 have been demonstrated in various hematological malignancies and solid tumors, including gastric cancers. WT1 is highly immunogenic and has been identified as a molecular target for cancer immunotherapy [4]. MUC1 is a membrane glycoprotein expressed by many types of epithelial cells, including those of the gastrointestinal tract. In cancer cells, it is overexpressed and aberrantly glycosylated, and is involved in cell-to-cell adhesion, signal transduction, and modulation of the immune system. Nearly 70% of cancers overexpress MUC1. As it is immunogenic, MUC1 is suitable as a target for cancer immunotherapy [5]. HER2 is a protein receptor with tyrosine kinase activity belonging to the human epidermal growth factor receptor family and is overexpressed in breast and gastric cancer [6]. Histological studies showed HER2-positive staining in the patient described in this case report. Survivin negatively regulates apoptosis by inhibiting caspase activity. It is highly expressed in most human tumors [7,8].

After completion of DC vaccine immunotherapy, WT1 and MUC1 peptides with adjuvant reagents were administered via i.c. injection near lymph nodes or the mucosa of the cancer lesion to boost the patient's antitumor immune response. It has been shown that intratumoral immune stimulation allows a higher concentration of the immunostimulatory products in the tumor microenvironment [9].

A multicenter clinical study of 60 advanced cancer patients who were previously treated with conventional therapy followed by multi-peptide immunotherapy or no therapy showed that patients undergoing immunotherapy had significantly higher progression-free survival rates. Furthermore, patients with peptide-specific CTL responses confirmed by the Enzyme-Linked ImmunoSpot (ELISpot) assay had better overall survival rates [10].

This case report indicates that therapeutic mutle-peptide DC immunotherapy in combination with standard therapy might improve the prognosis of advanced stage cancer patients. The therapeutic approach described herein is likely as effective as preoperative immunotherapy. Moreover, no severe adverse effects were noted in this patient.

Conflicts of interest

The authors declare no conflicts of interest.

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