**Case Report**

**Remarkable antitumor effect of nivolumab in a patient with metastatic renal cell carcinoma previously treated with a peptide-based vaccine**

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**Abbreviations & Acronyms**

- CR = complete response
- EGFR = epidermal growth factor receptor
- HLA = human leukocyte antigen
- IFNα = interferon alpha
- irAE = immune-related adverse event
- LCK = lymphocyte-specific protein tyrosine kinase
- mRCC = metastatic renal cell carcinoma
- MRP3 = multidrug resistance-associated protein 3
- PD-1 = programmed cell death-1
- PD-L1 = programmed cell death-ligand 1
- SART2 = squamous cell carcinoma antigen recognized by T cells 2
- TIL = tumor infiltrating T cell

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The safety and efficacy of combination therapy comprising immune checkpoint inhibitors and cancer-specific peptide vaccines have not yet been established. The safety and efficacy of combination therapy comprising immune checkpoint inhibitors and cancer-specific peptide vaccines have not yet been established. However, the combined therapy could have a synergistic effect of compensating for each other’s weakness and exert a remarkable antitumor effect.

**Introduction**

The treatment paradigm of mRCC has dramatically changed after the approval of anti-PD-1 monoclonal antibody nivolumab.1 However, there are some limitations, such as therapeutic effect is achieved in only 30% of mRCC patients and among 21% of patients experience grade 3–4 irAEs.2 Although peptide-based vaccines enhance immunospecificity and immunogenicity against cancer, the immunosuppressive effect can be a problem.

Here, we report a case that started nivolumab as a later-line treatment for mRCC following TKIs and peptide vaccine therapy, demonstrating remarkable tumor shrinkage that resulted in CR with a minor localized irAE.

**Case presentation**

A 71-year-old woman underwent left radical nephrectomy 4 years ago. Pathological findings showed clear cell renal cell carcinoma G2 (pT3aN0M0), but 15 months after surgery multiple lung and pleural metastases occurred. Despite sequential therapy comprising IFNα, sunitinib,
Table 1  The immunoreactivity to SART2, LCK, EGFR, and MRP3 was activated by the peptide vaccine and it was maintained after vaccination. IgG response, as defined by FIU

| HLA-A24 peptides subset | Pre vaccination | Post 1st course | Post 2nd course | After 6 months | After 12 months |
|-------------------------|----------------|----------------|----------------|---------------|---------------|
| SART2-93                | 62             | 5059           | 32 016         | 27 842        | 28 221        |
| SART3-109               | 30             | 28             | 19             | 14            | 12            |
| Lok-208                 | 56             | 60             | 171            | 168           | 342           |
| PAP-213                 | 32             | 28             | 23             | 15            | 13            |
| EGF-R-800               | 62             | 163            | 10 738         | 50 44         | 6 335         |
| MRP3-503                | 18             | 419            | 13 704         | 7 446         | 11 708        |
| MRP3-1293               | 44             | 52             | 52             | 33            | 37            |
| SART2-161               | 27             | 33             | 36             | 22            | 21            |
| Lck-486                 | 55             | 24 602         | 24 724         | 18 549        | 20 116        |
| Lck-488                 | 54             | 391            | 393            | 182           | 174           |
| EZH2-735                | 42             | 36             | 33             | 25            | 24            |
| PTHrP-102               | 40             | 80             | 38             | 25            | 21            |

(a) Schedule of peptide vaccine administration. First course (8 doses/course): 3.0 mg/1.5 ml peptide vaccine is administrated by subcutaneous injection once per week four times, and the next four administrations are at the same dose once every 2 weeks. Second course: same dose is given once per month.

(b) Fig. 1 (a) Schedule of peptide vaccine administration. First course (8 doses/course): 3.0 mg/1.5 ml peptide vaccine is administrated by subcutaneous injection once per week four times, and the next four administrations are at the same dose once every 2 weeks. Second course: same dose is given once per month. (b) Chest computed tomography shows remarkable tumor shrinkage at lung and pleural metastatic sites after induction of nivolumab.
axitinib, and pazopanib, no clinical efficacy was observed and all drugs were discontinued due to cancer progression within 6 months.

During pazopanib treatment, the patient participated in a clinical trial to receive a cancer-specific peptide vaccine at her own discretion. The patient’s HLA subtype was HLA-A24, and cancer-specific peptides such as SART2, LCK, EGFR, and MRP3 were identified in renal cell carcinoma tissue (Table 1). These cancer peptides were used to eliminate cancer cells via activation and enhancement of the exhausted immune system to improve its potential to attack cancer cells. Administration of these cancer peptides was also expected to facilitate further elimination of remaining cancer cells by the immune system, resulting in a more favorable therapeutic effect. After two courses (18 times) of vaccine therapy, no significant anti-cancer effect was detected. The patient subsequently decided to discontinue vaccine therapy, wished to receive newly approved nivolumab and was referred to our hospital.

After obtaining informed consent about the possibility of severe irAEs, we started nivolumab at a dose of 3 mg/kg. Soon after the start of nivolumab, the multiple lung and pleural metastatic lesions began to shrink markedly and we finally achieved almost CR without any specific serious adverse events (Fig. 1).

Ten months after the start of nivolumab administration, fever and erythema with induration over a 10-cm area of bilateral thigh developed. Skin biopsy of the lesion was performed and pathological findings showed infiltration of a number of inflammatory cells, such as lymphocytes, plasma cells, foam cells, and epithelioid cells, resulting in a diagnosis of immune-related cellulitis (Fig. 2). Interestingly, these skin reaction areas corresponded to peptide vaccine inoculation sites.

Because this irAE occurred, we ceased nivolumab treatment and continued close follow-up without any anti-cancer treatment. The patient has maintained CR without any clinical symptoms for more than a year since discontinuation of nivolumab.

**Discussion**

Cancer vaccine therapy is one of the major immunotherapies, which induces specific anti-cancer activity of lymphocytes through administration of specific cancer antigens. There are several methodologies, one of which is administering the identified cancer antigen peptide or protein with an adjuvant, and the other is transferring autologous lymphocytes that acquire tumor specificity by antigen stimulation. In addition, another strategy is the use of an autologous cancer vaccine cell, which has been made more immunogenic by transferring a cytokine or chemokine gene. This treatment has had an excellent therapeutic effect for urological cancers, especially prostate cancer.

Immune checkpoint inhibitors targeting molecules expressed in tumor cells and immune cells have strong modification effects. PD-1 is expressed on activated T lymphocytes and functions through a checkpoint mechanism for T lymphocyte activation. Immune checkpoint inhibitors, including nivolumab, release immune tolerance by acting directly on these target molecules, and introduce cytotoxicity to tumor cells.

In this case, there is a possibility that cancer-specific T lymphocytes induced by cancer peptide vaccines were exhausted due to the expression of PD-1. Such memory T-cell exhaustion induced by the PD-1 pathway was reactivated by nivolumab, resulting in strong and specific cytotoxicity with high-affinity recognition of multiple cancer antigens.

![Fig. 2](image-url)
induced by the peptide vaccine. This possibility is also supported by the skin reaction that occurred as an irAE was seen at vaccine inoculation sites. We confirmed that the infiltrating T lymphocytes are CD8-dominant and PD-L1- and PD-L2-positive cells in infiltrating around the lymphocytes. It is highly likely that the remainder of the inoculated vaccine was later activated by nivolumab (Fig. 2). We also performed immunohistochemistry in the primary tissues. Cancer cells are all strongly positive for HLA-class I (A/B/C), and focally positive for HLA-DR. The density of CD8-positive TIL was 3–10 cells/HPF in 90% area (low TIL area); however, high infiltration (more than 100 cells/HPF) of CD8-positive TIL was seen in the HLA-DR-positive area. Increased numbers of PD-1- and FOXP3-positive cells were also detected in high TIL areas. PD-L1-positive cells and CD163-positive M2-like macrophages were also increased in high TIL areas (Fig. 3). Taken together, these results suggest that the induced CD8 lymphocytes may have been immunosuppressed by M2-like macrophages such as TAM. Therefore, there were no tumor suppressive effects with peptide vaccine alone, and it seems that the antitumor effects were induced by administration of nivolumab.

Therefore, cancer vaccine therapy and immune checkpoint inhibitors can be expected to have a synergistic therapeutic effect compensating for each other’s weakness with completely different mechanisms, exerting an antitumor effect. In fact, Ali et al.11 reported that combination therapy comprising an immune checkpoint inhibitor and cancer-specific vaccine showed a remarkable tumor reduction effect in a melanoma xenograft murine model. In addition, randomized clinical trials are currently underway to examine the efficacy of this combination therapy in patients with melanoma and lung cancer (Clinical Trials.gov identifiers: NCT03047928 and NCT03406715).

When considering combination immunotherapy with immune checkpoint inhibitors and cancer-specific vaccines, we have to pay attention to the possibility of severe irAE due to unexpected immune reactions such as excessive cytokine release leading to general inflammation.12 In this case, we started nivolumab after providing adequate information about such risks, and fortunately, there were no severe irAEs. Further study about the safety and efficacy of combined treatment comprising a peptide vaccine and immune checkpoint inhibitor is warranted.

**Conclusion**

This is a unique clinical case that demonstrated a remarkable antitumor effect of nivolumab following previous treatment with a cancer-specific peptide vaccine. Combination therapy comprising an immune checkpoint inhibitor with a cancer-specific peptide vaccine could be a promising treatment option for patients with mRCC.

**Conflict of interest**

The authors declare no conflict of interest.

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