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Case Report

Pancreatic Body And Tail Cancer With Multiple Liver Metastases Cured By Precision Immunochemotherapy: A Case Report.

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Abstract

A 63 years-old female patient was found elevated CA19-9 levels during treatment for diabetes mellitus and further examinations led to a diagnosis of pancreatic body and tail cancer with multiple liver metastases. We performed whole-exome sequencing using a biopsy specimen and identified 70 somatic mutations, a part of which indicated generation of possible neoantigens in cancer cells. We then selected seven neoantigens that were predicted to have the high affinity to HLA molecules and administered 18 doses of neoantigen peptide-pulsed dendritic cell vaccine therapy as precision immunotherapy in addition to chemotherapies. CT images taken 3 years and 3 months later revealed the disappearance of both the primary tumor in the pancreas and all the liver metastases. Finally, we performed surgical resection of pancreatic tumor and confirmed the absence of cancer cells in the resected pancreas. Here, we report a case of advanced pancreatic cancer with multiple liver metastases where a combination therapy of precision immunochemotherapy and chemotherapy was effective, resulting in complete pathological remission confirmed in the surgically resected tissue.

Keywords : pancreatic cancer, genome analysis, precision, neoantigen, chemotherapy, multiple liver metastases, complete cure.

INTRODUCTION

In recent years, gemcitabine plus nab-paclitaxel (GEM+nab-PTX) and FOLFIRINOX have shown certain tumor suppressive effects against advanced metastatic pancreatic cancer, but it remains challenging to achieve medium- to long-term progression-free survival [1-5]. On the other hand, immunotherapy using genomic information has shown signs of improved response rates [6,7]. Immunochemotherapy is therefore expected as an important modality of a multidisciplinary treatment for refractory cancers [8-11]. Here, we report a case of pancreatic body and tail cancer with multiple liver metastases in which complete disappearance of primary and metastatic lesions was confirmed in the surgical specimen after a combination of precision immunotherapy and chemotherapy.

MATERIALS AND METHODS

Whole-exome sequencing and neoantigen prediction were performed as previously reported [12]. For the immunotherapies, PBMCs were obtained from the patient using leukapheresis, and then prepared activated T lymphocytes or neoantigen peptide-pulsed DCs were prepared following the protocols [8,9,12]. Genomic and neoantigen analyses, cell processing, and immunotherapy

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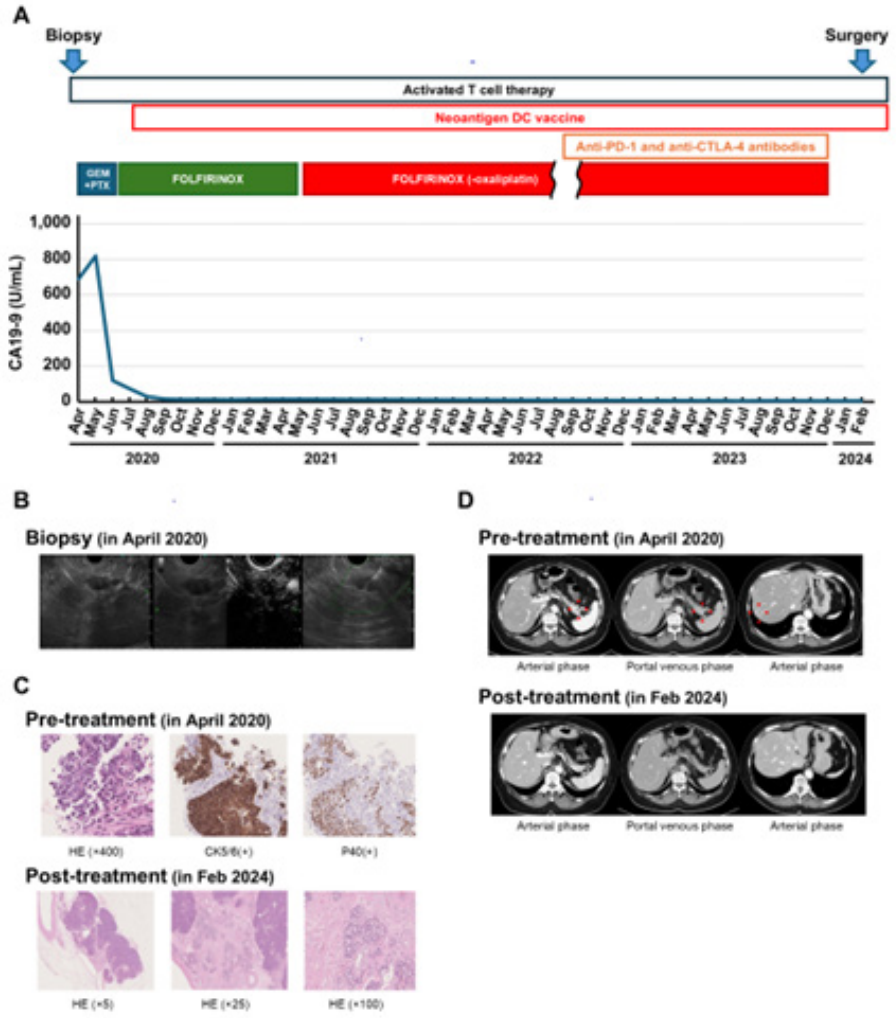
procedures were approved by the ethics committee of our institution. Written informed consent was obtained from the patient for the inclusion of their medical and treatment history as well as clinical images in this case report, in accordance with the Act on Securement of Safety of Regenerative Medicine in Japan.

RESULTS AND DISCUSSION

A 63-year-old woman presented to our hospital with a chief complaint of elevated CA19-9 levels that were detected during treatment for diabetes mellitus. She had a history of uterine corpus cancer (hysterectomy) at age 53, but with no recurrence. Nothing particular in her social history and family history. She was diagnosed with pancreatic body and tail cancer with multiple liver metastases (histological type is adenocarcinoma with squamous differentiation) based on computed tomography (CT) scans and histological examination of the biopsy sample (**Figure 1A-1D**). Blood test results at the time of visit to our clinic were as follows: total bilirubin (T-Bil) 0.4 mg/dL, aspartate transaminase (AST) 17 IU/L, alanine aminotransferase (ALT) 18 IU/L, gamma-glutamyl transpeptidase (γ-GTP) 25 IU/L, alkaline phosphatase (ALP) 361 IU/L, lactate dehydrogenase (LDH) 166 IU/L, creatinine (Cr) 0.49 mg/dL, white blood cells (WBC) 6100/μL, red blood cells (RBC) 430×104/μL, and CA19-9 820 U/mL. On pre-treatment CT, a 4×5-cm mass was found in the pancreatic body and tail as a primary tumor, and 1- to 2-cm metastatic masses were found in segments 4, 5, and 6 of the liver (Figure 1D upper). Since the long-term progression-free survival was generally not expected for stage IV pancreatic cancer (the 5-year survival rate of 1-2 percent) under chemotherapy [1-5], considering that patient's performance status (PS) was 0, we provided immunotherapy combined with chemotherapy as a multidisciplinary approach for the purpose of improving treatment outcome.

Figure 1. Tumor regression mediated by immunotherapies combined with chemotherapy. (A) Treatment schema, with changes in CA19-9 levels during the treatment. (B) Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) biopsy performed in April 2020. (C) Histopathological images of the EUS-FNA biopsy specimen (upper) and the surgically resected tumor (lower). (D) Dynamic computed tomography (CT) images before (upper) and after (lower) treatment.



From April 2020, 2 cycles of GEM+nab-PTX were provided, but since tumors showed the progression, we switched to FOLFIRINOX. We removed oxaliplatin from the FOLFIRINOX regimen due to severe bone marrow suppression and peripheral neuritis after 13 cycles. We provided FOLFIRINOX (-oxaliplatin) in the two-week interval at the beginning but sometimes extended to up to the six-week interval when the adverse events became severe. As of the end of December 2023, a total of 37 cycles of chemotherapy were administered.

For personalized neoantigen peptide-pulsed dendritic cell (DC) vaccine, we extracted genomic DNAs from the tumor biopsy and normal control samples, and applied for whole-exome sequencing [12]. We identified 70 somatic mutations including 43 missense/indel mutations that substituted amino acids (**Table 1**). We also defined her HLA class I genotypes to be A2401/A3101, B3901/B5502, and C0102/C0702, and used for prediction of possible neoantigens that are likely to bind to each of 6 HLA class I types with the affinity of <500 nM. Among 115 neoantigen peptides predicted, we selected 7 candidate peptides in LTBP2, PLEKHH2, SLC22A15, NISCH, ZNRF3, COL18A1, and FAAH2, which showed the HLA binding affinity of <50 nM (**Table 2**).

Table 1. Summary of whole-exome sequencing and neoantigen prediction.

Mutations/neoantigens	N
Somatic mutations[a]	70
Somatic mutations with amino acid changes	43
Predicted neoantigen peptides[b]	115

[a]Number of somatic mutations including insertions, deletions, and nonsense/missense mutations.

[b]Number of neoantigen peptides predicted to bind to HLA class I (HLA-A, -B and -C) with the affinity of <500 nM (including different lengths of peptide sequences derived from the same mutation).

Table 2. List of neoantigen peptides used for the treatment

No.	Gene	Amino acid change	Neoantigen peptide			Wild-type peptide			HLA allele[b]
			Peptide length	Position of amino acid change[a]	Amino acid sequence	Predicted binding affinity to HLA [nM]	Amino acid sequence	Predicted binding affinity to HLA [nM]	
1	LTBP2	G1673W	9	6	IYGPDWAPF	13	IYGPDGAPF	61	A24:02
2	PLEKHH2	S549Y	11	3	FPYWESRIYAV	13	FPSWESRIYAV	36	B55:02
3	SLC22A15	L281Q	11	5	CTFSQTHPANR	16	CTFSLTHPANR	13	A31:01
4	NISCH	I1483L	8	3	KLLSLLAR	25	KLISLLAR	26	A31:01
5	ZNRF3	H331Y	9	2	AYRCGLEHR	29	AHRCGLEHR	1,360	A31:01
6	COL18A1	H1275Y	11	4	VQLYDSNPYPR	42	VQLHDSNPYPR	56	A31:01
7	FAAH2	P234R	11	1	RAFFNGIFGHK	46	PAFFNGIFGHK	4,155	A31:01

[a]Position of a mutated amino acid in each neoantigen peptide (N-terminus is 1).

[b]Predicted affinity of neoantigen peptide to each HLA molecule.

While conducting genomic analysis and neoantigen peptide synthesis from early April to the end of June 2020, activated autologous T lymphocytes were infused biweekly (a total of 4 times) as an adjunct to chemotherapy during the chemotherapy intervals (Figure 1A). From early July 2020, neoantigen peptide-pulsed DC vaccine (a total of 12 doses of about 2 months-interval) was administered via subcutaneous and axillary lymph node injections. Additionally, activated autologous T lymphocyte therapy was continued in combination with chemotherapy and neoantigen peptide-pulsed DC vaccine. As an adjuvant [8,9], low-dose anti-PD-1 antibody (12.5 mg) and extremely low-dose anti-CTLA-4 antibody (1 mg) begun to be administered by intravenous infusion in mid-August 2022. Because of the normalization of CA19-9 levels and the imaging results, a combination of anti-PD-1 antibody and anti-CTLA-4 antibody was suspended at early December 2023. After the surgical resection, neoantigen peptide-pulsed DC vaccines was further administered along with activated autologous T lymphocyte therapy (6 times in total).

CA19-9 levels were initially 800 U/mL and rapidly decreased after starting immunochemotherapy, reducing to normal levels within 5 months (Figure 1A). For the past 3 years and 7 months, we have not observed the elevation of CA19-9. CT images in February 2024 also showed the disappearance of the primary tumor as well as the liver metastatic masses (Figure 1D lower). Blood test results at that time were as follows: T-Bil 0.3 mg/dL, aspartate aminotransferase 14 IU/L, alanine transaminase 16 IU/L, γ-glutamyltransferase 35 IU/L, alkaline phosphatase 153 IU/L, acetate dehydrogenase 168 IU/L, creatinine 0.47 mg/dL, white blood cell count 4500/μL, red blood cell count 418×104/μL, and we then performed partial resection of the pancreas

and liver, and confirmed complete pathological remission of her tumors (Figure 1C lower). Currently, the patient has been engaging in social activities with good quality of life, and there have been no signs of recurrence.

Although pancreatic cancer has a very poor prognosis, our case of pancreatic cancer with multiple liver metastases remaining disease-free at 3 years and 7 months after the beginning of chemotherapy is extremely rare compared with reported median overall survivals of 6.7-11.1 months under chemotherapy [4,5]. In this case, we provided multidisciplinary immunotherapies, including neoantigen peptide-pulsed DC vaccination, low-dose immune checkpoint inhibitors, and activated autologous T lymphocyte therapy in combination with chemotherapy. Considering the immune cascade following neoantigen administration [6-9], the use of anti-PD-1 and anti-CTLA-4 antibodies was deemed necessary. The decision on how long to continue chemotherapy after tumor disappearance was left to pathological examination through surgery, given that cases of long-term survival and complete cure of pancreatic cancer with multiple liver metastases are rare. Further studies will be needed to determine the duration of neoantigen peptide-pulsed DC vaccine therapy by evaluating the persistence of the efficacy through the immunological peptide activity in peripheral blood.

CONCLUSION

We found a case of advanced pancreatic cancer who showed the sensitivity to precision immunotherapy combined with chemotherapy resulted in remarkable effectiveness contributing to long-term disease-free survival. In the future, personalized neoantigen vaccines are considered to be promising from the perspective of immunological anti-tumor effects.

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Disclosure statement

The authors report that there are no competing interests to declare.

Author contributions

Taizo Hoshino was responsible for the conception, design, and implementation of the study, acquisition of data, and drafting of the manuscript. Kazutoshi Kaketani was responsible for the conception and design of the study. Takao Itoi was responsible for the conception, design, and implementation of the study, acquisition and analysis of data, and revision of the manuscript. Yuichi Nagakawa was responsible for the conception and implementation of the study and acquisition of data. Tetsu Fukunaga was responsible for the conception, design, and implementation of the study and acquisition of data. Hajime Orita was responsible for the conception, design, and implementation of the study, acquisition and analysis of data, and revision of the manuscript. Tadashi Okabe was responsible for the conception and design of the study.

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