Case Report

Durable response of chemotherapy for cancer of unknown primary with unfavorable subset developed in retroperitoneal space

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Abbreviations
CT = computed tomography
CUP = carcinoma of unknown primary site
FDG-PET = Fluorodeoxyglucose-position emission tomography
GCDFP-15 = Gross Cystic Disease Fluid Protein-15
HE = Hematoxylin–eosin
MRI = magnetic resonance imaging
N/A = not available
NGS = next-generation sequencing
OS = overall survival
PCR = polymerase chain reaction
PD = progressive disease
PR = partial response
TC = paclitaxel and carboplatin

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Introduction: Carcinoma of unknown primary site is a heterogeneous group of cancer that is defined by the presence of metastatic disease with no identified primary tumor at initial presentation. Carcinoma of unknown primary site patients with unfavorable subsets particularly show poor prognosis with a median survival of 6–9 months with the treatment of empirical pactitaxel and carboplatin therapy (TC therapy). Recently, several studies have attempted to increase the response rate on the basis of prediction of the primary site by immunohistochemical tests or molecular profiling assays.

Case presentation: We report the case of a 77-year-old woman who presented with a mass on the left side of the abdominal aorta. Careful clinical and laboratory examinations could not identify the site of primary cancer. Pathologic examination of biopsied tissue revealed the tumor as undifferentiated carcinoma, which reached the diagnosis of carcinoma of unknown primary site with unfavorable subsets. She received empirical TC therapy and had prolonged survival of 26 months. After reviewing the pathological findings carefully, we noticed that Gross Cystic Disease Fluid Protein-15 showed positive in the tumor, leading to the suspicion of breast cancer as the primary site. The specific therapy for breast cancer is similar to the empirical TC therapy in carcinoma of unknown primary site, which may contribute durable response in this patient.

Conclusion: Site-specific therapy based on careful immunohistochemical tests may improve the efficacy for carcinoma of unknown primary site patients with unfavorable prognosis subset.

Key words: carboplatin, carcinoma of unknown primary site, immunohistochemical tests, paclitaxel, site-specific therapy.

Keynote message

Most patients with carcinoma of unknown primary site (CUP) have a poor prognosis despite careful clinical and laboratory examinations. We report a case in which site-specific therapy based on careful immunohistochemical tests was predicted to improve the prognosis of patients with CUP that developed in the retroperitoneal space.

Introduction

CUP is defined as histologically determined metastatic cancer for which the primary site is not identified after an appropriate diagnostic approach. CUP accounts for about 3–5% of all adult malignancies.[1] Generally, 20% of CUP patients have favorable prognostic factors and respond to specific local therapy with or without systemic therapy. However, most patients with CUP are classified as having unfavorable prognosis despite careful clinical and laboratory examinations, which force the patients to receive an empirical chemotherapy, including a platinum-taxane regimen with poor prognosis.

Recently, intensive IHC test or gene expression profiling is considered to be a promising approach to predict the origin of CUP. Several studies reported that site-specific therapy based

on predicted primary sites by these examinations could significantly improve the prognosis of CUP patients of unfavorable subset.[2–4]

Here, we report an evocative case in which the combination therapy of paclitaxel and carboplatin was significantly effective for CUP, with unfavorable prognosis, that developed in the retroperitoneal space. In this case, careful pathological diagnosis revealed the primary site of CUP might originate from breast cancer, which evokes the clinical significance of site-specific therapy based on intensive pathological diagnosis and clinical features.

Case presentation

A 77-year-old woman with no significant medical history was informed of her bilateral renal pelvis dilation by abdominal ultrasonography test. An abdominal CT examination showed a 46-mm-sized mass on the left side of the abdominal aorta (Fig. 1a,b) with right hydronephrosis due to pelvic ureteric junction stenosis. MRI examination also showed a mass on the left side of the aorta with low signal at T1-weighted image and high signal at T2-weighted image (Fig. 1c,d). Eight months later, she was referred to our hospital for the diagnosis of the growing mass of size 116 mm. FDG-PET showed strong FDG accumulation in the abdominal para-aortic region as well as the bilateral common iliac artery regions (Fig. 1e,f). We suspected malignant lymphoma from these findings and performed a laparoscopic lymph node biopsy. In the pathological examination, although there was no specific tendency for tumoral differentiation, hematoxylin and eosin staining revealed atypical cells with marked nuclear swelling and deep staining (Fig. 2a,b), leading to the diagnosis of lymph node metastasis of cancer. IHC tests revealed CK7 and CK20 were stained positive and negative, respectively, suggesting that the tumor had a potential for breast cancer, thyroid cancer, ovarian cancer, lung cancer, and endometrial cancer. We further evaluated markers for breast cancer, thyroid cancer, ovarian cancer, lung cancer, and endometrial cancer. Among them, only GCDFP-15 showed positive (Fig. 2c,d). Along with IHC tests, we also performed several examinations related with urological cancer, hematological cancer, gynecological cancer, breast cancer, and gastroenterological cancer, which did not reveal any obvious primary site of cancer. Considering these results, we diagnosed the tumor as CUP with unfavorable subsets according to the NCCN clinical practice guideline of CUP.[5]

In this case, the patient started treatment with paclitaxel and carboplatin (TC therapy), which is recommended as the first-line treatment of CUP with unfavorable subsets in line with recommendation of the guideline.[5] Four cycles of TC therapy decreased the tumor size (partial response evaluated by the Response Evaluation Criteria in Solid Tumors version 1.1) (Fig. 3). After 5 months of non-dosing period, the tumor size increased along with liver metastasis. We restarted four more cycles of TC therapy, leading to the decrease of the primary and metastatic tumors. At this stage,

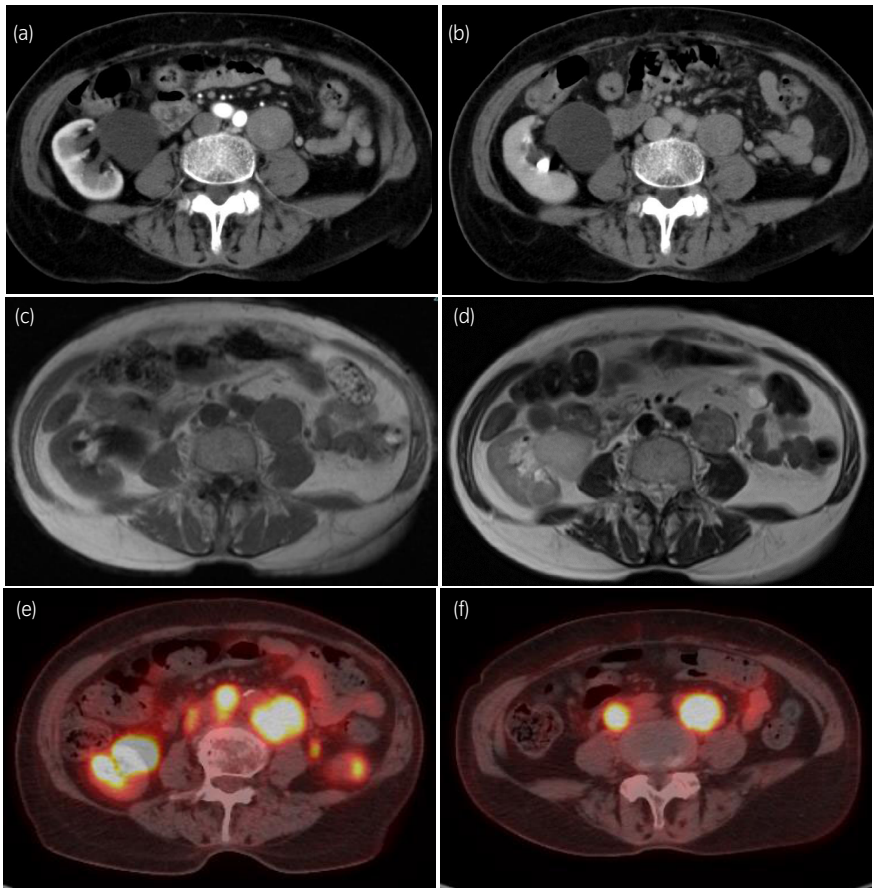

Fig. 1 Imaging tests at the first diagnosis. (a, b) Abdominal computed tomography examination shows a tumor with 46-mm diameter on the left side of the abdominal aorta and right hydronephrosis due to pelvic ureteric junction stenosis. (a) early phase, (b) late phase. (c, d) Abdominal magnetic resonance imaging shows high signal in the tumor on the left side of the aorta. (c) T1-weighted image, (d) T2-weighted image. (e, f) FDG-position emission tomography shows strong FDG accumulation for the abdominal para-aortic region (e) and the bilateral common iliac artery regions (f).

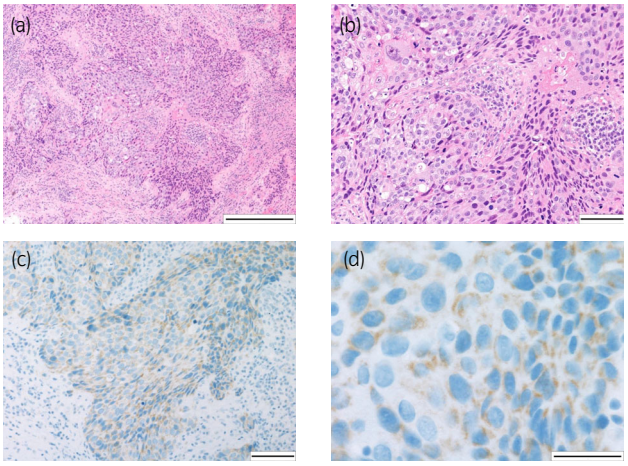

Fig. 2 Histopathological findings at the time of biopsy. (a, b) HE staining shows atypical cells with marked nuclear swelling and deep staining. Magnification: 40× for (a), 100× for (b). Scale bar: 400 μm for (a), 100 μm for (b). (c, d) GCDFP-15 staining showed positive in the tumor. Magnification: 100× for (c), 400× for (d). Scale bar: 100 μm for (c), 40 μm for (d).

we performed microsatellite instability testing and cancer genomic panel testing (FoundationOne® CDx, Cambridge, MA, USA), which revealed no specific mutation in cancer-related genes. After several terms of dosing and non-dosing periods, the patient developed liver failure due to multiple liver metastases and survived for 26 months after initiation of treatment.

Discussion

CUP is a heterogeneous group of cancers defined by the presence of metastatic disease without an identified primary tumor despite histopathological and radiological laboratory investigations. Generally, 80% of CUP patients are classified as unfavorable group[6] that has poor prognosis with a median survival of 6–9 months[7] through treatment with empirical platinum-taxane chemotherapy. So far, several studies have attempted to improve the prognosis of CUP patients with site-specific treatment on the basis of intensive IHC tests or molecular profiling.[8,9]

In this study, we report a patient who experienced durable response of more than 2 years with paclitaxel and carboplatin treatment. At initial diagnosis, we were not able to identify the primary site by IHC tests, various cancer-screening tests, and imaging findings, which led to the diagnosis of CUP with unfavorable subset. Interestingly, the patient achieved long survival with chemotherapy, which reminded us to review the result of IHC tests attentively. Among various IHC tests, we confirmed that GCDFP-15 was stained positive, which was highly specific for breast cancer,[10] for which specific therapy is either identical or similar to the empirical TC therapy. Hasegawa et al. reported that site-specific therapy based on predicted primary sites by pathological examination and clinical features significantly improved the prognosis of CUP patients with unfavorable subset with median survival of 20.3 months, whereas those treated with empirical therapy without consideration of pathological examination showed median survival 10.8 months.[2] With respect to molecular tumor profiling, Hainworth et al. reported that using a 92-gene reverse transcriptase polymerase chain reaction assay could help identify clinically responsive and resistant tumors (median survival: 13.4 months vs. 7.6 months, $P = 0.04$).[3] More recently, Hayashi et al. evaluated site-specific treatment including molecular targeted therapy based on profiling gene expression and gene alterations by next-generation sequencing, contributing to the increase of OS in patients with unfavorable subset of CUP.[4] These findings suggest that prediction of original tumor for CUP patients with IHC tests and/or gene expression profiling improves the prognosis of certain population with specific types of primary tumor (Table 1). If intensive IHC is insufficient to predict the primary site of CUP at the initiation of therapy, reimbursed cancer genomic panel testing should be considered to detect possible specific gene alterations of amplification in clinical settings based on the results of clinical trials.[3,4]

In conclusion, site-specific therapy based on careful IHC tests or gene expression profiling may improve the efficacy for CUP patients with unfavorable prognosis subset. Further study is necessary to determine the type of cancer which benefits from predicting the primary site with algorithms on the basis of these testings.

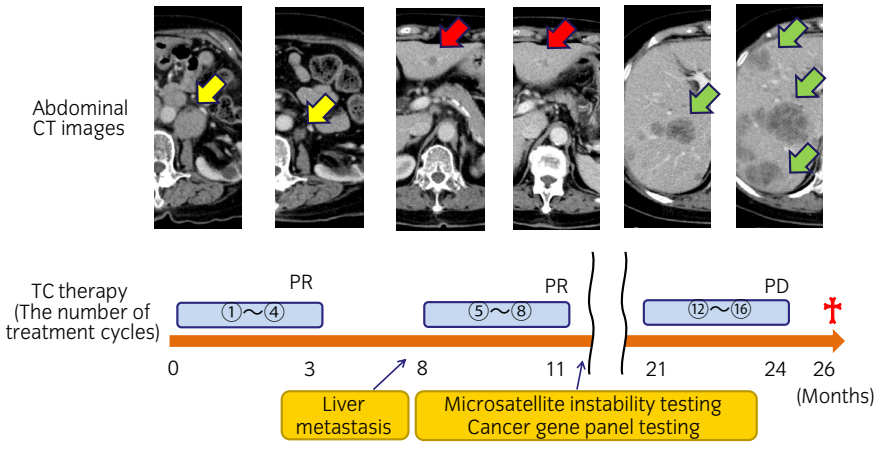

Fig. 3 Clinical course of the case in the present study. After several terms of dosing and non-dosing period with paclitaxel and carboplatin therapy, the patient showed durable response of 26 months after initiation of treatment.

Table 1 Summary of the previous reports on the effectiveness of the site-specific therapy for unfavorable CUP

Authors	Number of patients	Prediction of primary site	Site-specific therapy OS (month)	Empirical therapy OS (month)	Hazard ratio (HR)
Hainsworth et al.[3]	194	Genes expression profiling by PCR	12.5 (95% CI, 9.1–15.4)	N/A	N/A
Hasegawa et al.[2]	56	Immunohistochemical analysis	20.3	10.7	0.57 (95% CI 0.34–0.94, $P = 0.03$)
Hayashi et al.[4]	97	Combined gene expression profiling and the detection of gene alterations by NGS	13.7 (95% CI, 9.3–19.7)	N/A	N/A

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Conflict of interest

The authors declare no conflict of interest.

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