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【 CASE REPORT 】

Remarkable Efficacy of Capmatinib in a Patient with Cancer of Unknown Primary with *MET* Amplification

Takaaki Tanaka[1], Go Makimoto[1], Ryohei Sumii[2], Rika Omote[3], Yayoi Ando[4], Kiichiro Ninomiya[5], Eiki Ichihara[6], Kadoaki Ohashi[1], Yoshinobu Maeda[7] and Masahiro Tabata[6]

Abstract:
This case report describes a 70-year-old female with cancer of unknown primary origin (CUP) who exhibited multiple distant lymph node metastases. Despite conventional chemotherapy (carboplatin and paclitaxel) and immunotherapy (nivolumab), disease progression was noted. Genomic profiling revealed *MET* amplification, leading to the administration of capmatinib, a selective MET tyrosine kinase inhibitor. The patient experienced substantial tumor reduction with dose adjustments due to adverse effects, indicating the potential efficacy of capmatinib in treating CUP with *MET* amplification.

Key words: *MET* amplification, capmatinib, MET inhibitors, cancer of unknown primary, *MET* exon 14 skipping

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Introduction

Cancers of unknown primary origin (CUP) represent considerable diagnostic and therapeutic challenges, accounting for approximately 2% of all invasive cancers (1, 2). Despite extensive diagnostic efforts, CUPs are characterized as metastatic tumors with no identifiable primary sites. Management of CUP remains empirical and frequently involves broad-spectrum chemotherapy, including carboplatin and paclitaxel. Recent advances in genomic profiling have ushered in a new era of precision medicine, which has enabled the development of targeted therapies based on specific molecular alterations. In this report, we explored the complexity of diagnosing and treating CUP and discussed the potential of MET inhibitors, such as capmatinib, in treating such elusive cancers, especially those with significant *MET* amplification.

Case Report

In 2016, a 70-year-old female was diagnosed with HCV-associated cirrhosis. In January 2023, routine follow-up liver magnetic resonance imaging revealed enlargement of the lymph nodes around the abdominal aorta, prompting concerns regarding potential metastatic cancer. A whole-body computed tomography (CT) scan identified additional lymph node enlargement in the left axillary, supraclavicular, and neck regions (Fig. 1); although the primary organ remained elusive, the liver, despite the patient's history of hepatitis C virus-associated cirrhosis, showed no suspicious lesions, with consistently negative HCV-RNA. The possibility of hepatocellular carcinoma (HCC) was deemed to be low, so alpha-fetoprotein and protein induced by vitamin K absence or antagonist-II tests were not conducted.

A core needle biopsy of the left axillary lymph node

[1]Department of Respiratory Medicine, Okayama University Hospital, Japan, [2]Department of General Internal Medicine, NHO Fukuyama Medical Center, Japan, [3]Department of Pathology, NHO Fukuyama Medical Center, Japan, [4]Clinical Research Support Office, National Cancer Center Hospital, Japan, [5]Center for Comprehensive Genomic Medicine, Okayama University Hospital, Japan, [6]Center for Clinical Oncology, Okayama University Hospital, Japan and [7]Department of Hematology, Oncology, and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Japan
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Correspondence to Dr. Go Makimoto, gmakimoto5@okayama-u.ac.jp

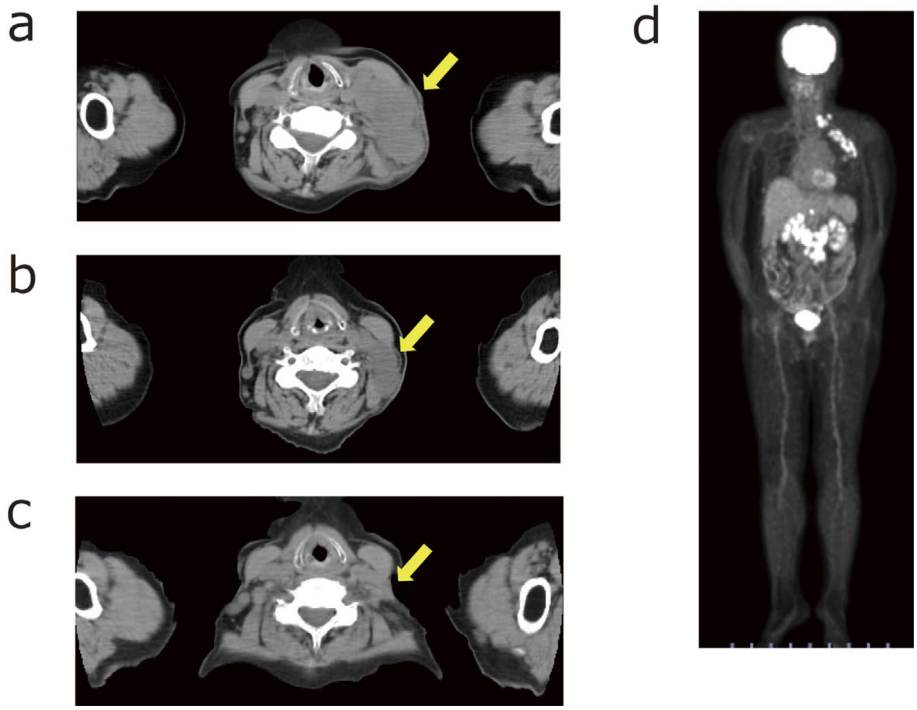

Figure 1. Comparison of computed tomography scans of the left cervical lymph nodes before and after treatment. The pretreatment lesion (a, yellow arrow) appears substantially reduced one month after commencing capmatinib therapy (b, yellow arrow). A remarkable reduction was observed in March 2024, as indicated by the yellow arrow in (c). PET-CT from January 2023 prior to treatment showed lymph node enlargement with abnormal fluorodeoxyglucose (FDG) radiotracer accumulation in the left axillary, supraclavicular, neck, and abdominal regions. No other abnormal organ-specific FDG uptake was observed (d). PET-CT: positron emission tomography-computed tomography

showed proliferation of atypical cells with prominent nucleoli, suggesting metastatic carcinoma. However, the primary focus was not determined despite morphological or immunohistochemical examinations (Fig. 2). An immunohistochemical analysis of the lymph node biopsy showed that, while typical HCC was cytokeratin7 (CK7)-negative and CK20-negative, this case exhibited CK7 positivity and partial CK 20 positivity. Based on these findings, the possibility of HCC was considered to be unlikely. Positron emission tomography-CT detected no fluorodeoxyglucose-avid lesions other than enlarged lymph nodes (Fig. 1d). Elevated carbohydrate antigen (CA) 19-9 levels (5,981 U/mL) suggested a gastrointestinal origin; however, no abnormalities were identified upon performing upper and lower gastrointestinal endoscopies or endoscopic ultrasound to screen the biliopancreatic region. The patient was diagnosed with CUP and distant lymph node metastasis.

Treatment with carboplatin and paclitaxel was initiated in February 2023. However, CT scans after the second treatment course revealed disease progression, with an increase in the size of lymph node metastases surrounding the abdominal aorta and the axillary and supraclavicular regions. Nivolumab was administered as a second-line therapy. Despite temporary shrinkage of the axillary and periaortic lymph nodes [stable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST)], subsequent CT scans showed an enlargement of these lymph nodes, thus indicating disease progression.

For cancer genomic profiling, a biopsy of the left cervical lymph node was performed in July 2023, which revealed pathological findings similar to those of the axillary lymph node. Cancer genomic profiling using a FoundationOne® assay identified *MET* amplification [60 copy number gain (CNG) and MET/centromeric portion of chromosome (CEP) 7 ratio of 5.18].

An expert panel at our hospital recommended treatment with capmatinib, a MET tyrosine kinase inhibitor. Capmatinib was chosen because the patient was enrolled in the NCCH1901 (BELIEVE) biomarker-based basket trial (3) supported by Novartis (the drug provider), which specifically assessed its efficacy in patients with *MET* amplification. The patient was enrolled in the trial and started on 800 mg/day of capmatinib in October 2023. At the time of admission, the CA 19-9 levels exceeded 30,000 U/mL, and the lymph nodes in the left anterior cervical region were further enlarged, thus indicating disease progression within a short period. Treatment initiation rapidly reduced the size of cervical lymph nodes. One week after administration, the patient experienced grade 2 nausea and anorexia (Common Terminology Criteria for Adverse Events), prompting dose

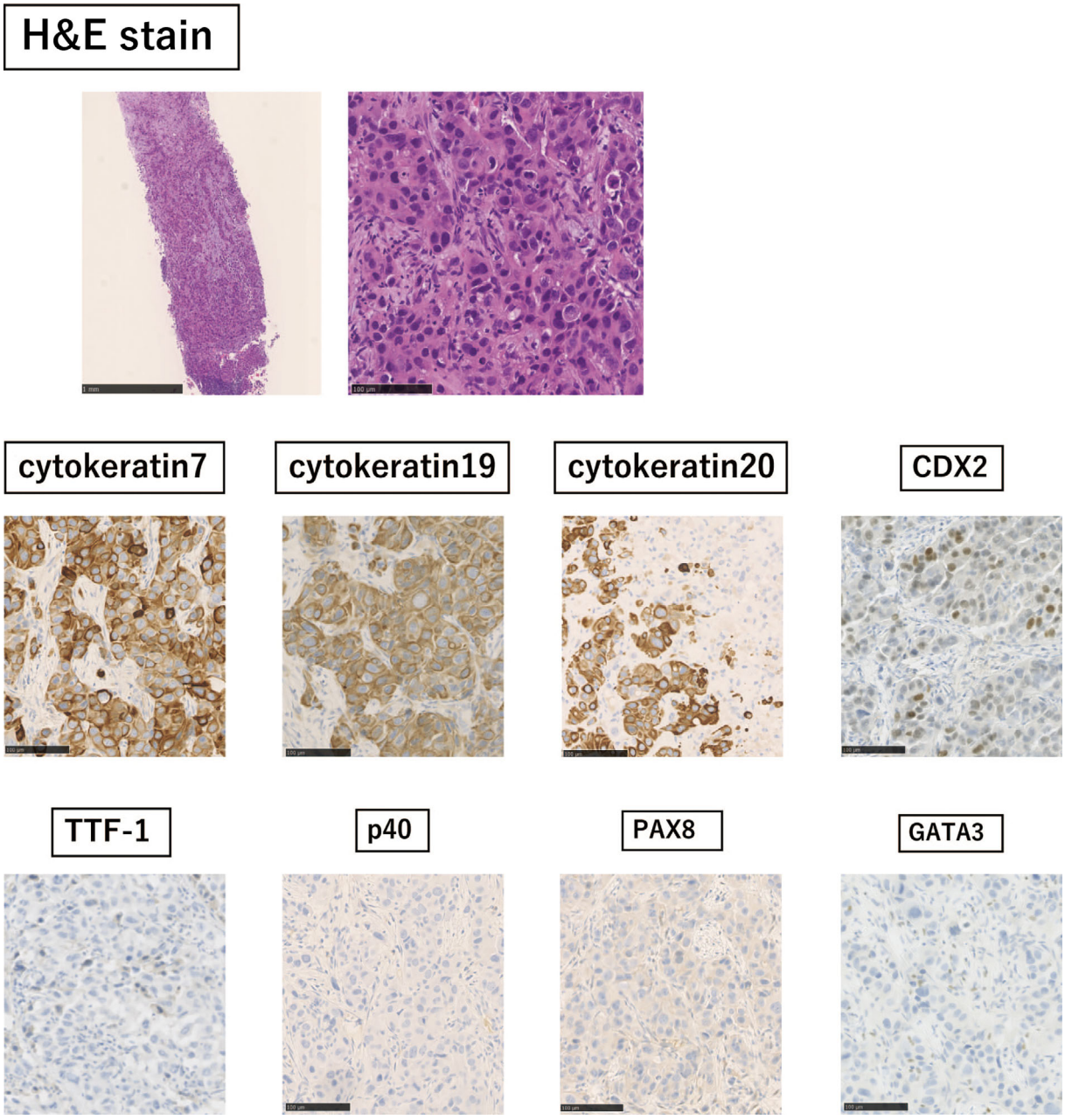

Figure 2. **Pathological findings in the axillary and cervical lymph nodes [Hematoxylin and Eosin (H&E) staining]. Representative images show the proliferation of atypical cells, which appear ovoid with prominent nucleoli forming alveolar patterns. Immunohistochemical staining showed positive markers, including CK7, CK19, CK20 (p+), CDX2 (p+), WT-1 (p+), PgR (p+), and HER2 (1-2+), along with negative markers TTF-1, GCDFP15, mammaglobin, ER, p40, PAX8, GATA3, synaptophysin, β-catenin, and D2-40 [bars; H&E staining (left): 1 mm, others: 100 μm].**

reduction to 400 mg/day on day 8. Persistent symptoms necessitated further reduction to 200 mg/day, along with the addition of antiemetic medication (metoclopramide 5 mg, 3 Tabs/day). Despite treatment breaks and dose reduction, the tumors showed substantial shrinkage. Six months after initiation of treatment, the patient continued to experience anticancer effects with minimal side effects at a dose of 200 mg/day (complete response on RECIST) (Fig. 1, 3). The serum CA 19-9 levels improved to within the normal range (23 U/mL). The patient is currently doing well and attending outpatient visits, with no signs of side effects, such as nausea or fatigue.

Discussion

CUP is recognized as a metastatic malignancy with an undetectable primary tumor site, despite comprehensive evaluation using standard diagnostic (e.g., physical examinations and histopathological analyses) and imaging methods (2).

In non-small cell lung cancer (NSCLC), *MET* exon 14 (*MET*ex14) skipping mutations have been detected in 3-4%

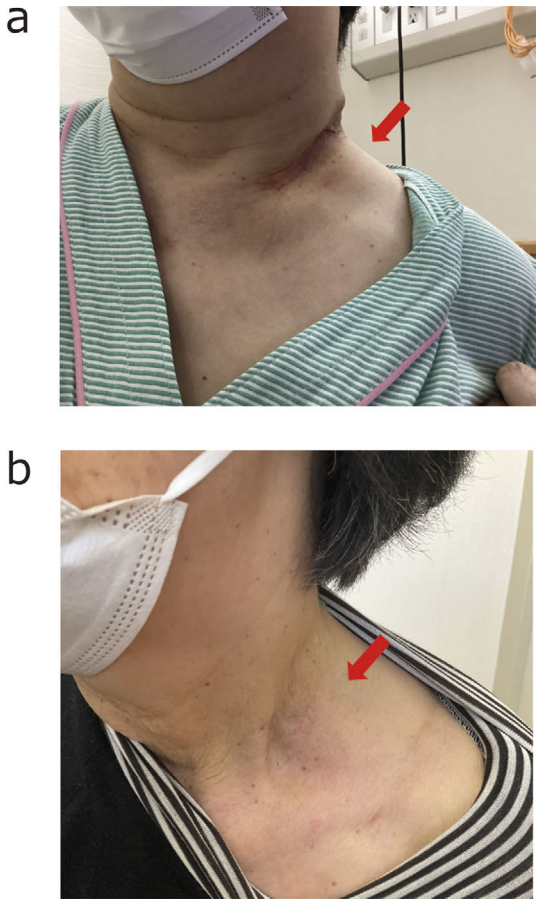

Figure 3. Gross comparison of lesions before and after treatment. Enlargement of the lymph nodes on the left side of the neck is visibly reduced when observed externally (red arrow) (a: before treatment, b: 5 months after initiating capmatinib treatment).

of cases, with *MET* amplifications identified in 1-6% of cases (4). *MET* amplification serves as a potent oncogenic driver and valid therapeutic target. Before the availability of *MET* inhibitors, high-level *MET* amplification correlated with poorer survival outcomes, underscoring its role as a driver alteration in NSCLC (5). High-level stable chromosomal *MET* amplification confers sensitivity to MET inhibitors in patients with NSCLC and gastric cancer (6). The threshold at which *MET* amplification functions as a cancer driver gene is not universally defined and depends on the specific tumor type. In NSCLC, "MET-high" has been defined as *MET* CNG ≥5, with a *MET*/CEP 7 ratio ≥2 for amplification (7). Reportedly, high-level *MET* amplification (e.g., *MET*/*CEP7* ratio ≥5) tends to occur exclusively with *MET*ex 14 skipping mutations, which can be mutually exclusive of major driver genes (5). Ou patient exhibited significant *MET* amplification, with a CNG of 60 and *MET*/*CEP* 7 ratio of 5.18, thus indicating a marked overexpression.

Capmatinib, a selective MET tyrosine kinase inhibitor, was approved by the U.S. Food and Drug Administration in 2020 specifically for metastatic NSCLC with *MET*ex14 skipping mutations. Capmatinib inhibits the *MET* signaling pathway, which is crucial for tumor growth and metastasis. Reportedly, capmatinib may be ineffective in *MET*-amplified NSCLC with gene copy numbers <10. For patients with a gene copy number ≥10, untreated patients exhibited an overall response rate of 40%, which did not meet the significance threshold (8). As of 2024, capmatinib is yet to be approved for the treatment of *MET*-amplified NSCLC. We posit that the significant *MET* overexpression detected in this patient contributes to the therapeutic efficacy of capmatinib.

Evidence from one study indicates a notably higher prevalence of *MET* mutations in CUP, although *MET* amplification has not been addressed (9). In Japan, under the Patient-Proposed Healthcare Service, which allows patients to use unapproved drugs and therapies in combination with standard treatments, capmatinib was initiated for patients with cancers exhibiting *MET* amplification. This system responds to the needs of patients with serious illnesses, enabling them to receive innovative therapies from familiar medical institutions, while ensuring treatment safety and efficacy.

During capmatinib administration, adverse reactions led to permanent discontinuation/dose interruption in 17% and 57% of the participants in a Phase II trial. The most frequent adverse reactions (≥20%) included edema, nausea, musculoskeletal pain, fatigue, vomiting, dyspnea, cough, and a reduced appetite (8). Patients who have received prior treatments, including immune checkpoint inhibitors, may experience severe adverse events with capmatinib therapy (8). Our patient experienced recurrent vomiting and anorexia, potentially related to prior nivolumab therapy, prompting dose adjustments in consultation with the patient. Dose reduction without enforcing strict continuation can therefore lead to favorable outcomes.

Conclusion

We encountered a case of CUP with *MET* amplification, which showed the remarkable efficacy of capmatinib. Thus, capmatinib may be effective in treating *MET*-amplified CUP. To the best of our knowledge, no report has specifically demonstrated the efficacy of capmatinib in CUP, thus warranting the accumulation of direct evidence supporting its use in this context.

The authors declare that informed consent to publish the information and images was obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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