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## Case Report

# Case of Cervical Carcinoma of Unknown Primary Treated Through Multidisciplinary Approach

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## Abstract

Carcinoma of unknown primary (CUP) is where the primary site remains unidentified even though metastases are present, and accounts for 3–5% of all human malignancies. Here, we report a multidisciplinary approach to the treatment of a squamous cell CUP occurring in the left cervical region. Following radical surgery for carcinoma of the colon, swelling occurred in the left cervical region in a 59-year-old man. The results of an incisional biopsy indicated a diagnosis of squamous cell carcinoma (SCC), and he was referred to our department for examination. The primary carcinoma was not identifiable despite an extensive diagnostic workup including a physical examination, fiberoptic endoscopy, computed tomography, magnetic resonance imaging, and fluorodeoxyglucose F18 positron emission tomography, resulting in a diagnosis of an SCC of unknown in the cervical region. The patient was initially treated with three cycles of docetaxel 75 mg/m<sup>2</sup>/day, cisplatin 100 mg/m<sup>2</sup>/day, and 5-fluorouracil 1,000 mg/m<sup>2</sup>/day as induction chemotherapy. This was followed by concurrent chemoradiotherapy (cisplatin 30 mg/m<sup>2</sup>/day, 70 Gy) and neck dissection. Subsequent pathological examination revealed no vestiges of the tumor. The patient has remained free from recurrence and metastasis for 6 years.

Key words: Carcinoma of unknown primary—Induction chemotherapy—  
Concurrent chemoradiotherapy—TPF—Head and neck

## Introduction

Carcinoma of unknown primary (CUP) is defined as a metastatic tumor for which no primary lesion can be detected despite clinically thorough full-body screening and follow-up observation<sup>4)</sup>. The prognosis is usually poor and it is a difficult disease to treat.

A case of squamous cell carcinoma (SCC) of unknown primary occurring in the left cervical region is reported.

## Case Report

A 59-year-old man underwent radical surgery

for carcinoma of the descending colon (adenocarcinoma, carcinoma in adenoma) at Kameda General Hospital in August 2006. Stage IIIb was diagnosed due to lymph node metastases, and six cycles of UFT/UZEL were administered over four weeks with one-week rest as supplementary chemotherapy starting November 2006. Swelling of the left cervical region was found following the end of chemotherapy, and given the possibility of metastasis, an aspiration smear was carried out under local anesthesia in June 2007. The cytodiagnosis was class V. Biopsy under general anesthesia was carried out in July 2007, and SCC was diagnosed (Fig. 1). The patient was then referred to us at the Department of Oral and Maxillofacial Surgery for treatment of cancer of the left cervical region in August 2007.

Present condition: External findings in the oral cavity revealed a sessile, tender tumor accompanied by reddening of the skin in the left cervical supraclavicular region (Figs. 2A, B). Internal findings revealed no organic changes or abnormalities. A PET-CT revealed that an abnormal accumulation in the left cervical region was a tumor 80×72 mm in size with a standardized uptake value (SUV) of 15.67 (Fig. 3). No other areas of abnormal accumulation or fine nodular opacities indicating metastases to the lung field were found. The results of MRI suggested that the tumor was necrotic internally and that it was putting pressure on the left internal jugular vein, causing constriction, and had infiltrated the internal carotid artery (Figs. 4A, B).

Clinical diagnosis: SCC of unknown primary.

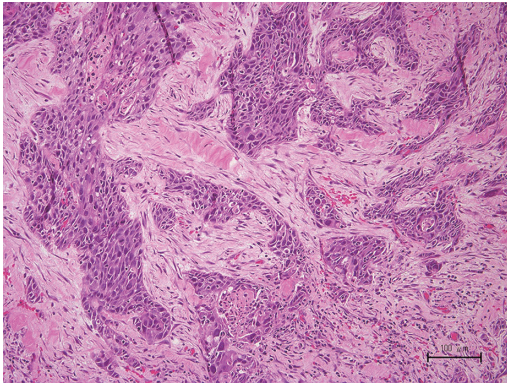
Treatment and progression: The Departments of Oncology, Gastroenterology, and Otorhinolaryngology were requested to assist in searching for the primary lesion. Despite an extensive diagnostic workup including PET-CT, thoracoabdominal CT, craniocervical CT, gastrointestinal tract endoscopy, abdominal ultrasound, nasal cavity examination, pharyngeal endoscopy, and oral cavity examination, no primary tumor was found in the craniocervical or any other region. The

cervical region tumor was therefore diagnosed as a left cervical SCC of unknown primary. Radical surgery was judged difficult because the tumor was accompanied by pressure on, and constriction of, the left internal jugular vein and infiltration of the internal carotid artery. The initial treatment plan was therefore induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT), with subsequent radical surgery if feasible following an evaluation of the results.

Treatment commenced in late August 2007 on an inpatient basis with an IC regimen comprising docetaxel, cisplatin, and 5-fluorouracil (TPF). The doses and schedule are shown in Table 1. Three, three-week cycles were administered. In each cycle, intravenous drips in the order of docetaxel, cisplatin, and 5-fluorouracil were administered on the first day, and then 5-fluorouracil by intravenous injection until the fourth day.

Side effects attributable to the anti-cancer drugs such as nausea and other gastrointestinal symptoms and slight bone marrow suppression were found, but receded with the use of antiemetics, steroids, and granulocyte colony-stimulating factor. At the end of the three IC cycles, the swelling in the cervical region showed reduction, although redness of the skin still persisted in the left cervical region. T2-weighted MRI cross-sectional images revealed a tumor with high and low intensity signals in the dorsal area of the left sternocleidomastoid muscle, but it was clearly smaller than at pretreatment (Fig. 5).

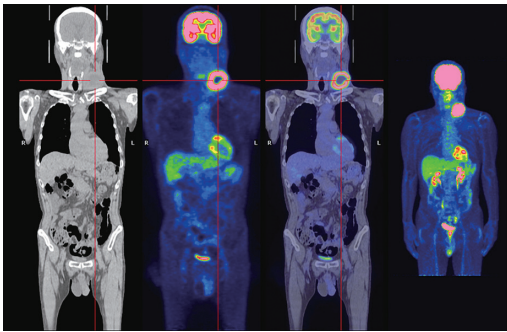
The CCRT commenced in late October 2007, roughly three weeks following the end of the three IC cycles. The doses and schedule are shown in Table 2. Radiosurgery comprised bilateral prophylactic irradiation of the cervical region and supraclavicular lymph nodes 35 times over 45 days to a total dosage of 50 Gy together with 70 Gy irradiation of the left cervical tumor mass. Initially, three, three-week cycles of cisplatin in conjunction with irradiation were scheduled. However, renal impairment was found at the end of the first cycle of cisplatin, so this was replaced from the second cycle onward with a multidrug



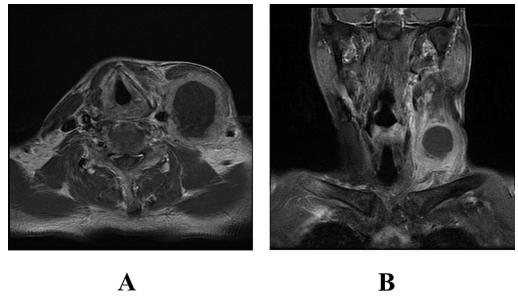
**Fig. 1** Pathological examination of biopsy  
Invasion of SCC was found in fibrous tissue. Pathological examination of resected specimen revealed no adenocarcinoma or other cancer cells.



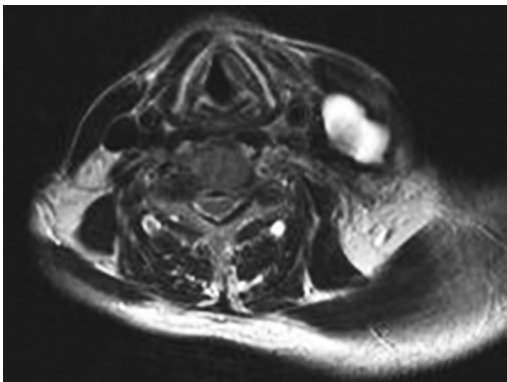
**Fig. 2** Features at first examination (A: front, B: profile)  
Clear swelling with redness observed in left cervical region.



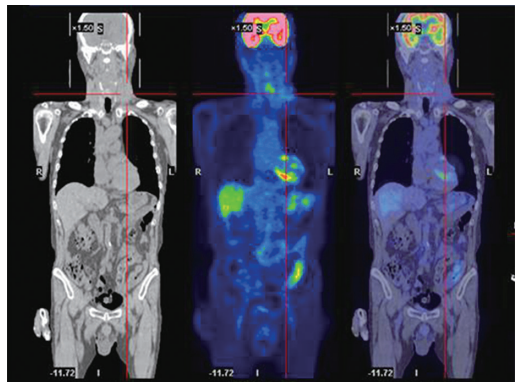
**Fig. 3** PET-CT at first examination (frontal section)  
Abnormal accumulation observed in left cervical region.



**Fig. 4** MR imaging (T1-weighted, A: transverse section, B: coronal section)  
Tumor with internal necrosis (low signal intensity at center of mass on MRI) observed in left cervical region.



**Fig. 5** MR imaging after IC (coronal section T2-weighted)  
Tumor showed reduction in size after IC.



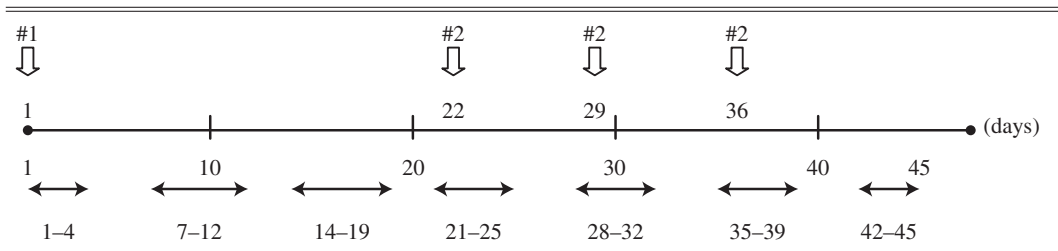
**Fig. 6** PET-CT following CCRT (frontal section)  
Clear improvement, with almost complete disappearance of abnormal accumulation in left cervical region.

Table 1 Summary of induction chemotherapy

regimen	1	2	3	4	5	6	7 (day)
DTX 130 mg/body (75 mg/m <sup>2</sup> /day)	○						
CDDP 180 mg/body (100 mg/m <sup>2</sup> /day)	○						
5-FU 1,750 mg/body (1,000 mg/m <sup>2</sup> /day)	○	○	○	○			

DTX: Docetaxel, CDDP: Cisplatin, 5-FU: 5-fluorouracil

Table 2 Course of concurrent chemoradiotherapy



Day 1: CDDP 170 mg/body (100 mg/m<sup>2</sup>/day)

Day 22: CBDCA 180 mg/body (Auc2) + PTX 50 mg/body (30 mg/m<sup>2</sup>/day)

Day 29: CBDCA 180 mg/body + PTX 50 mg/body

Day 36: CBDCA 180 mg/body + PTX 50 mg/body

#1: CDDP, #2: CBDCA + PTX,  $\longleftrightarrow$ : external irradiation

CBDCA: Carboplatin, PTX: Paclitaxel

regimen comprising carboplatin and paclitaxel to be administered every week. No severe renal impairment was found following the change. Side effects such as bone marrow suppression were slight, and the symptoms improved.

At the end of CCRT, the swelling and redness in the left cervical region had disappeared, with only scabs due to the effects of radiation dermatitis remaining. PET-CT showed a post-chemoradiotherapy decline in the SUV value compared with at pretreatment to 2.24, indicating an improvement (Fig. 6). MRI showed only a round tumor mass with high signal intensity of less than 10 mm in the left cervical region, and while it was somewhat biased toward the common carotid artery, tumor infiltration of the blood vessels had disappeared (Fig. 7). At this point, the tumor was in a state of almost complete remission, but radical surgery was scheduled as there was residual tumor mass. In late January 2008, tracheotomy was carried out followed by

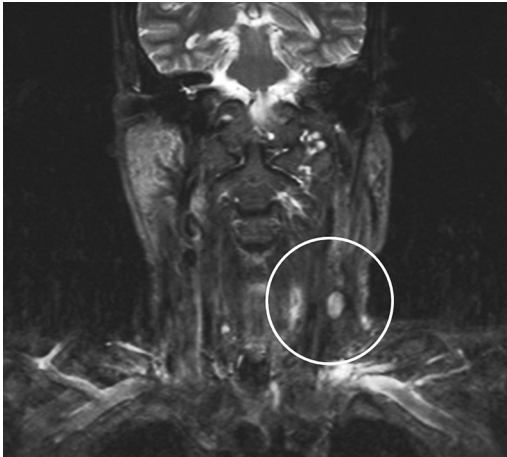
radical left neck dissection and reconstruction using a D-P flap under general anesthetic. Reconstruction using a D-P flap was necessary because the cervical skin directly above the tumor was resected. The common carotid artery and the tumor mass, which had become scarred as a result of the treatment, had coalesced, and this was resected, with the vascular wall of the common carotid artery being conserved (Figs. 8A–D). Pathological examination of the resected specimen showed no vestigial tumor tissue or lymph node metastasis (Fig. 9).

Postoperative healing was favorable, and at six years postoperatively, no reoccurrence of the tumor has been found.

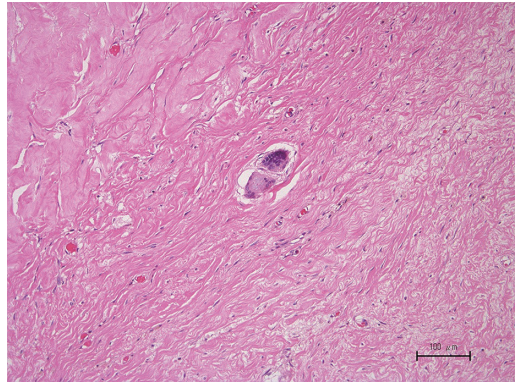
## Discussion

Some 3–5% of all malignant solid tumors are diagnosed as CUPs, and 5% of these are SCCs<sup>4)</sup>. The diagnosis in CUP is often poor.





**Fig. 7** MR imaging following CCRT  
Round tumor with high signal intensity observed in left cervical region, but clear improvement evident.



**Fig. 9** Histopathological findings  
A 1-cm necrotic focus was found where tumor was believed to have been; infiltration of multinucleated giant cells was found around this site, but no vestigial tumor cells.



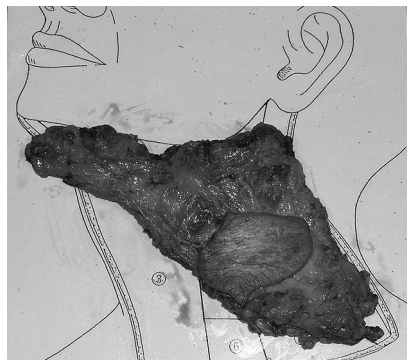
A



B



C



D

**Fig. 8** Intraoperative findings

- A: Submaxillary transverse incision and wave-like vertical incision made directly above tumor, avoiding anteroposterior approach.
- B: Resection, including skin directly above tumor, carried out in accordance with classical neck dissection.
- C: Following neck dissection, with residual tumor resected.
- D: Excised tissue.

However, Yoshii *et al.* reported that they were able to carry out neck dissection in 13 out of 15 (86.7%) cases of metastatic carcinoma of the cervical region of unknown primary; and it was also noted that two of four unresectable cases treated with CCRT became resectable, leading to an improvement in prognosis after subsequent neck dissection<sup>9</sup>. The same course was observed in the present study: radical surgery was initially judged impossible, but the tumor showed a clear reduction in size following IC and CCRT, allowing neck dissection to be performed, which appears to have contributed to an improvement in the prognosis. The histopathological appearance of SCC with upper and middle cervical lymph node metastases only suggests head and neck carcinoma; metastasis to the lower cervical or supraclavicular lymph nodes suggests lung cancer, esophageal cancer, breast cancer, or stomach cancer, and careful examination of the gastrointestinal tract is considered necessary<sup>1</sup>.

In head and neck cancer, local treatment such as surgical resection, radiotherapy, or chemotherapy is the preferred option once a primary lesion of the alimentary system has been ruled out<sup>1</sup>. In the present case, there was a large lymph node metastatic tumor in the left cervical region. Full-body screening, including endoscopy was performed, but no primary lesion was identified, so treatment was carried out for head and neck cancer. CCRT is considered the standard treatment in such cases, where radical surgery is impossible because the tumor is accompanied by constriction of the left internal jugular vein and infiltration of the internal carotid artery.

Induction chemotherapy is not considered a standard treatment. At this department, however, it is our policy to select IC followed by radical surgery and CCRT in unresectable cases or cases of advanced localized stage III/IV cancer in which there would be a notable functional disorder as a result of resection. Radical surgery may also sometimes be carried out after CCRT.

A number of reports have suggested that TPF is superior to PF (cisplatin, 5-fluorouracil)

as IC before CCRT<sup>5,7,8</sup>. Few reports, however, have directly compared IC followed by either radiotherapy or CCRT with standard CCRT alone<sup>3</sup>, and while at the present time TPF is preferred to PF as the IC regimen, the efficacy of IC itself remains uncertain. Moreover, the optimum TPF regimen for IC remains to be established in terms of dose and number of administrations. At this department, TPF is administered at 75 mg/m<sup>2</sup> docetaxel, 100 mg/m<sup>2</sup> cisplatin, and 1,000 mg/m<sup>2</sup> 5-fluorouracil on the basis of the schedule used in Western countries<sup>6</sup>.

Katori *et al.* recommend 60 mg/m<sup>2</sup> docetaxel, 70 mg/m<sup>2</sup> cisplatin, and 750 mg/m<sup>2</sup> 5-fluorouracil for TPF as a schedule that will allow dose-limiting toxicities to be avoided and a good response rate<sup>2</sup>. Furthermore, in Western countries, TPF comprises 60–95 mg/m<sup>2</sup> docetaxel, 75–100 mg/m<sup>2</sup> cisplatin, and 700–1,000 mg/m<sup>2</sup> 5-fluorouracil, with the dose of each drug, the number of administrations, and the route of administration varying among different facilities. Further investigation is needed, therefore, to establish the optimum schedule.

Although six years have passed since surgery, the site of the primary lesion in the present patient remains to be identified. Swift treatment is essential in the event of its detection. Therefore, the patient is still undergoing multilateral follow-up including PET-CT and MRI at this department and the Departments of Oncology and Otorhinolaryngology to ensure a timely response should it eventually be detected.

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