

[CASE REPORT]

Signet Ring Cell Carcinoma of Unknown Primary Origin Detected Incidentally by Lymph Node Purification for Thyroid Carcinoma

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Abstract:

A 63-year-old woman underwent thyroidectomy for papillary thyroid adenocarcinoma and cervical lymph node resection. Pathological analyses revealed the presence of signet cell carcinoma in a resected lymph node, which were apparently different from the pathological findings of thyroid carcinoma. No evidence of a primary tumor could be found elsewhere despite detailed examinations, including esophagogastroduodenoscopy, colonoscopy, capsule endoscopy, CT scan, and fluorodeoxyglucose-positron emission tomography. Two and half years later, the patient developed multiple bone metastases and the pathological findings confirmed the presence of signet cell carcinoma. The primary origin remained undetermined. Metastatic signet ring cell carcinoma of unknown primary origin is extremely rare.

Key words: cisplatin, S-1, chemotherapy, unknown primary origin

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Introduction

Despite the recent development of diagnostic tools, there are still some patients with metastatic cancer in whom the site of the primary tumor cannot be determined; these patients are defined as having cancer of unknown primary origin (CUP). CUP accounts for approximately 2-5% of all cancer diagnoses (1, 2). The most commonly reported subtype of CUP is adenocarcinoma (1, 2). Although signet ring cell carcinoma (SRCC) is a poorly differentiated aggressive subtype of adenocarcinoma, SRCC of unknown primary origin has rarely been reported (3-7). We encountered an unusual case of cervical lymph node metastasis of SRCC that was found incidentally during an operation for thyroid cancer. As no evidence of a primary tumor could be found elsewhere, a diagnosis of SRCC was made. However, the patient subsequently developed multiple bone metastases without

any suggested primary lesions after careful follow-up. We herein report the clinical course and discuss metastatic SRCC of unknown primary origin.

Case Report

A 63-year-old woman presented with a thyroid mass identified on computed tomography (CT) lung cancer screening. Fine needle aspiration yielded a sample of atypical cells with papillary architecture. Subsequently, right thyroid lobectomy and regional lymphadenectomy were performed and the histology of the mass confirmed the diagnosis of thyroid papillary carcinoma (Fig. 1). However, a histological analysis of the regional lymph node revealed the presence of SRCC (Fig. 2A). An immunohistological analysis showed the specimen to be positive for periodic acid-Schiff (PAS) (Fig. 2B) and cytokeratin (CK) AE1/AE3, but negative for CK7, CK20, thyroid transcription factor-1, napsin A, thy-

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roglobulin, anaplastic lymphoma kinase, and estrogen receptors. Endoscopic examinations, including esophagogastroduodenoscopy (EGD), colonoscopy (CS), and capsule endoscopy, revealed no abnormal findings. In addition, neither systemic CT nor ^{18}F -fluorodeoxy glucose positron emission tomography (FDG-PET) revealed any abnormal findings or uptake. These examinations were repeated and a careful follow-up was continued, but the primary lesion of SRCC could not be identified. Two and half years later, she visited our department because of the relatively acute onset of lumbar pain. A review of magnetic resonance imaging (MRI) data showed multiple bone metastases, especially in the

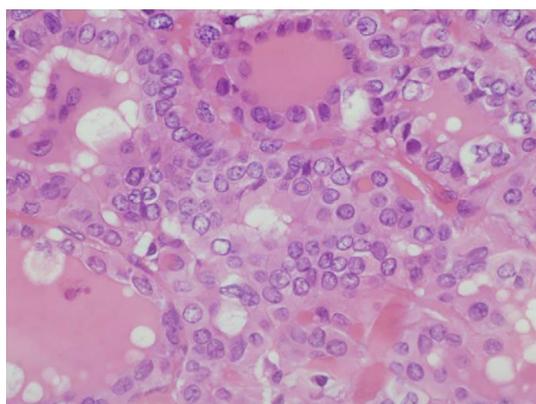


Figure 1. Histological findings of a resected thyroid tumor revealed papillary carcinoma.

lumbar vertebra (Fig. 3). Needle aspiration of the left iliac bone showed SRCC (Fig. 2C). FDG-PET scan revealed multiple bone metastases, including pubic, rib, and lumbar vertebra, but the primary site could not be identified (Fig. 4). She was treated with oxycodone at 40 mg/day and palliative radiotherapy, which allowed her to obtain some pain relief. We performed endoscopic examinations again but no primary lesion was detected. A diagnosis of metastatic SRCC of CUP was made. She received four cycles of cisplatin and S-1 combination therapy. Increased alkaline phosphatase (ALP) returned to the normal level and her pain was controlled without oxycodone (Fig. 5). The disease had been controlled with S-1 chemotherapy for over 6 months, but the patient finally developed disseminated intravascular coagulation, probably due to the bone marrow infiltration, and died 3.5 years after detection of SRCC. Autopsy was not performed.

Discussion

We herein report a case of metastatic SRCC that initially presented as a single cervical lymph node metastasis and subsequently developed multiple bone metastases. Despite a detailed diagnostic workup, the primary origin could not be identified during the total clinical course. Combined chemotherapy with cisplatin plus S-1 was effective for disease control in bone metastasis, but the patient died 3.5 years after the initial clinical manifestations and 1 year after initial che-

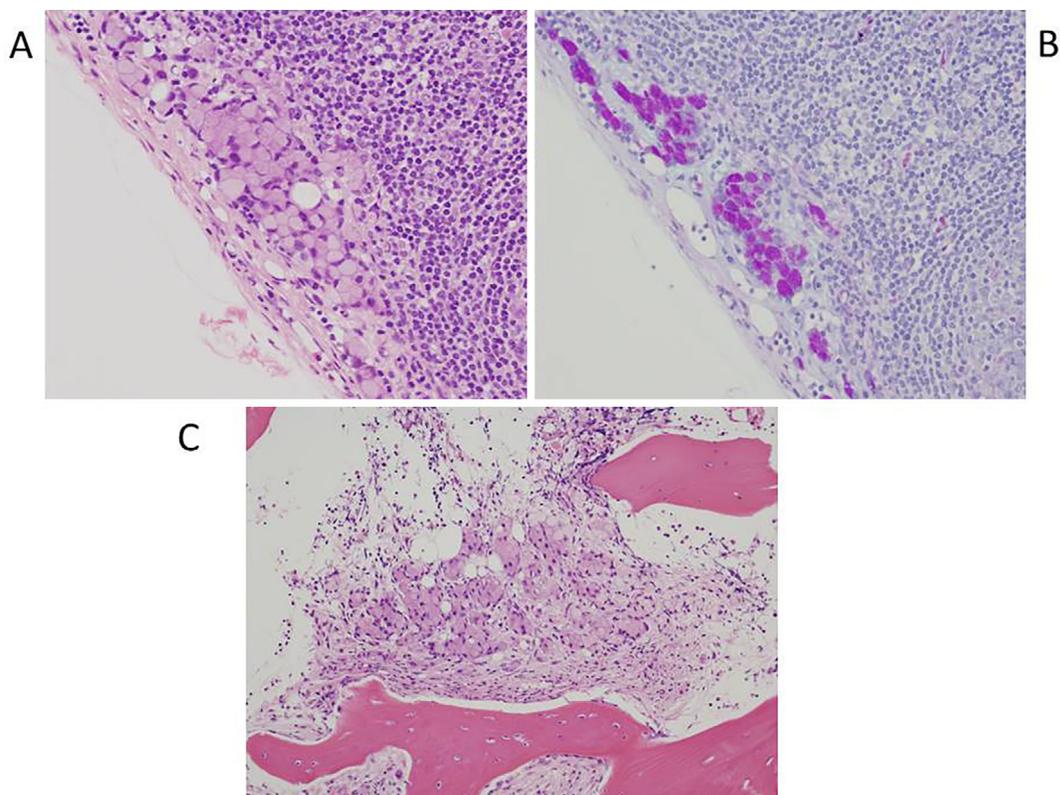


Figure 2. Histological findings of a cervical regional lymph node revealed the presence of signet ring cells (A) and the tumor cells were positive for PAS according to an immunohistological analysis (B). Histological findings by needle aspiration from the left iliac bone showed signet ring cells (C).

motherapy.

SRCC is a rare poorly differentiated aggressive subtype of adenocarcinoma that most commonly arises from the gastrointestinal tract, in particular the stomach and colon (8, 9). The breast and lung have been reported as other potential primary organs in SRCC (8, 10, 11). In the present case, careful examinations, including serial EGD, CS, capsule endoscopy, CT scan, and FDG-PET, failed to detect the primary site until death. Al-Tae et al. (3) described a case of

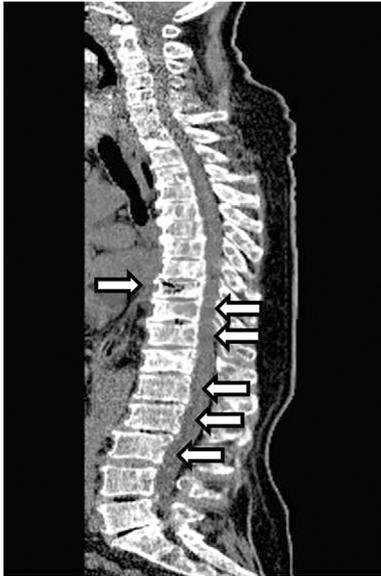


Figure 3. A review of magnetic resonance imaging (MRI) showed multiple bone metastases in the lumbar bones, especially the lumbar vertebra.

SRCC presenting peritoneal carcinoma and reviewed five cases of SRCCs of unknown primary origin. We also searched for similar case reports and found two more cases of SRCC of unknown primary origin published after the review of Al-Tae et al. (3, 12). SRCC of unknown origin is thus considered to be an extremely rare clinical manifestation.

Immunohistochemical studies can be useful in suggesting the primary origin and treatment options for CUP (8, 9, 13-16). In particular, the patterns of results of CK7 and CK20 immunohistochemical staining are relatively specific in adenocarcinoma and important for cancers of the gastrointestinal tract (13, 14). In the present case, both CK7 and CK20 were negative, and this pattern has been not observed in previously reported SRCC of unknown primary origin. In general, CK7(+)/CK20(-) in gastric cancer and CK7(-)/CK20(+) in colorectal cancer are the most typical staining patterns (8, 9, 13, 14). The CK7 (-)/CK20 (-) phenotype suggested metastatic adenocarcinoma, most often of the prostate, and urothelial carcinoma in previous studies (8, 9, 13, 14). However, among the phenotypes in CK7/CK20 positive or negative distribution, the rates of the CK7 (-)/CK20(-) phenotype in gastric and colon carcinoma were reported to be 10% and 9%, respectively (13). In addition, Terada performed an immunohistochemical analysis of 42 SRCCs in gastric and colorectal cancer and described a similar distribution pattern of CK7 and CK20 with gastric and colorectal cancer without SRCC components (9). Thus, immunohistological staining for other biological markers was performed, but there were no specific findings in the search for a primary site in the present case. The present

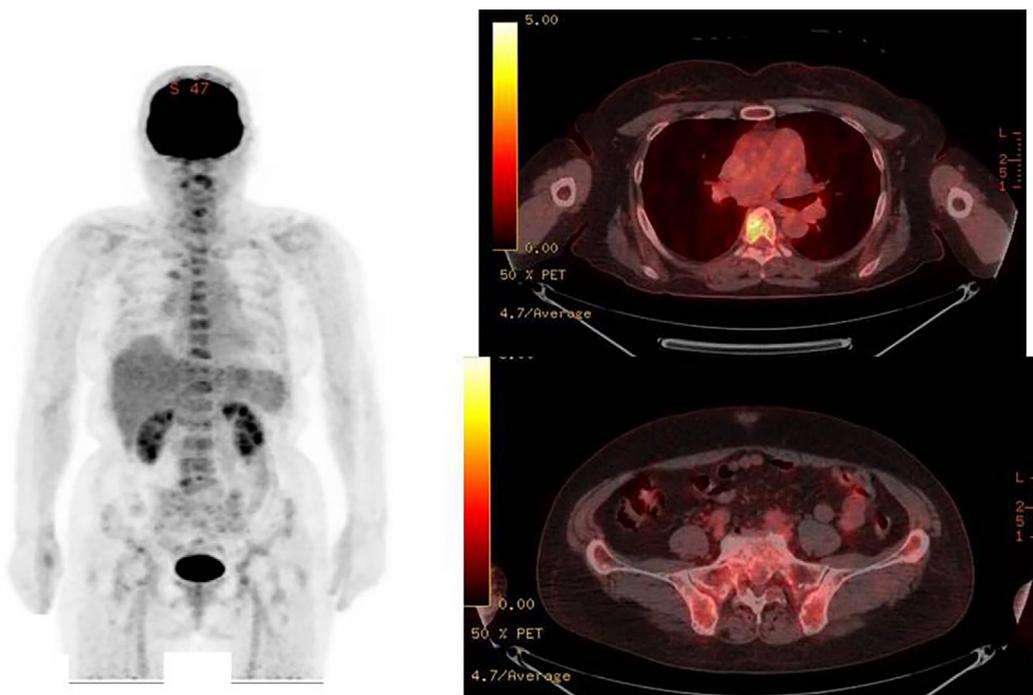


Figure 4. ^{18}F -fluorodeoxy glucose positron emission tomography revealed multiple bone metastases, including pubic, rib, and lumbar bones, but the primary site could not be identified.

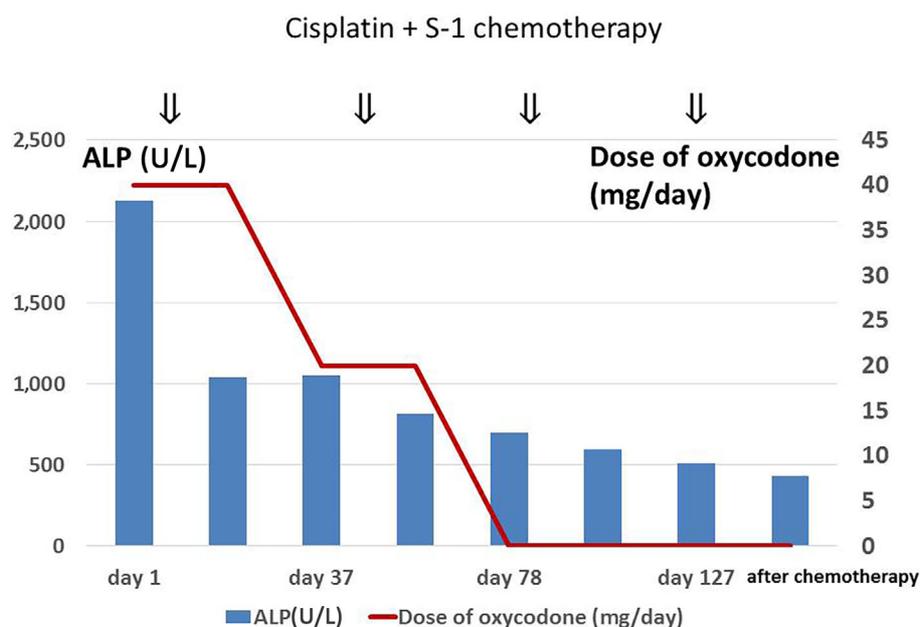


Figure 5. Clinical course in the present case after cisplatin plus S-1 chemotherapy.

case suggested intratumoral heterogeneity of SRCC of unknown primary origin.

As SRCC progresses rapidly, its prognosis seems to be worse than that for tumors without an SRCC component, or for tumors with a known primary origin (1). In addition, because of the rarity of SRCC of unknown primary origin, data regarding the efficacy of cytotoxic chemotherapeutic agents are limited (3-7). Cytotoxic agents or regimens including cisplatin/irinotecan, 5-fluorouracil, cisplatin/S-1, etc., have been tried, and survival periods of 24-37 months have been reported (3-7, 13). In the present case, cisplatin plus S-1, a standard chemotherapy regimen for advanced gastric cancer (16), was useful for disease control of the bone lesions and for pain relief. Thus, cisplatin plus S-1 chemotherapy was effective and a progression-free survival over one year was obtained with S-1 maintenance therapy in our case. Although there was no evidence that the primary site was the stomach in the present case, our experience suggests that cisplatin plus S-1 therapy is useful for SRCC of unknown primary origin.

In summary, although SRCC of unknown primary origin is extremely rare, the disease could exhibit a variety of clinical and pathological features. Our experience demonstrates the importance of detailed clinical observation, immunohistochemical analyses, and treatment options in patients with SRCC of unknown primary origin. Further clinical experience and studies are therefore required to determine the clinical and pathological characteristics in signet-ring cell carcinoma of unknown primary origin.

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

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