Carcinoma of unknown primary origin with isolated adrenal metastasis: a report of two cases

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Abstract. The adrenal glands are one of the most common sites of malignant tumor metastasis. However, metastatic adrenal carcinoma of unknown primary origin with localized adrenal gland involvement is an extremely rare condition. Herein, we reported two cases of carcinoma of unknown primary origin with isolated adrenal metastasis. In the first case, back pain was the trigger; while in the second case, the triggers were low fever and weight loss. Metabolic abnormalities such as hypertension and obesity were not detected in either case. Neither patient had relevant previous medical histories, including malignancy. However, both had a long-term history of smoking. Systemic imaging studies revealed only adrenal tumors and surrounding lesions. Primary adrenocortical carcinoma was initially suspected, and chemotherapy including mitotane was considered. However, due to difficulty in complete resection of the tumor, core needle tumor biopsies were performed. Histopathological examination of biopsy specimens led to the diagnosis of carcinoma of unknown primary origin with isolated adrenal metastasis. In both cases, additional laboratory testing showed high levels of serum squamous cell carcinoma-related antigen and serum cytokeratin fragment. Malignant lesions confined to the adrenal glands are rare. As in our cases, it could be occasionally difficult to differentiate non-functioning primary adrenocortical carcinoma from metastatic adrenal carcinoma of unknown primary origin localized to the adrenal gland. If the lesion is unresectable and there are elevated levels of several tumor markers with no apparent hormonal excess, core needle tumor biopsy should be considered to differentiate the primary tumor from the metastatic tumor.

Key words: Adrenal metastasis, Carcinoma of unknown primary origin, Tumor biopsy
carcinomas of unknown primary origin with isolated adrenal metastasis via computed tomography (CT)-guided tumor biopsy. These unilateral metastatic adrenal carcinomas of unknown primary origin were localized, which is extremely rare.

**Case Descriptions**

**Case 1**

A 57-year-old man was referred to our hospital for close examination of a right adrenal tumor. He had been experiencing right back pain for approximately 3 months. He had no relevant previous medical history, including malignancy. He had smoked 50–60 cigarettes per day for 40 years. He did not have obesity (body mass index, 22.5 kg/m²) or hypertension (blood pressure, 95/69 mmHg). CT revealed a 55-mm right-sided adrenal mass, involvement of the liver and inferior vena cava, and metastasis to the lymph nodes. The adrenal mass on unenhanced images had a density of approximately 30 Hounsfield units. His laboratory data are presented in Table 1. White blood cell counts and C-reactive protein (CRP) levels were slightly elevated. Endocrinological examination showed only a mild increase in adrenocorticotropic hormone (ACTH) levels and renin activity. Testing with a 1-mg dexamethasone suppression test decreased the serum cortisol level to 0.7 μg/dL and the ACTH level to <0.5 pg/mL. Further, 123I-metaiodobenzylguanidine (MIBG) scintigraphy revealed no accumulations. Fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT showed remarkable FDG uptake in the right adrenal tumor (maximum standardized uptake value, 14.1) but not in any other distant organ (Fig. 1). Additionally, high carcinoembryonic antigen (CEA) values were observed. Gastrointestinal endoscopy revealed a colon polyp. Initially, he was thought to have primary ACC, and surgical treatment was scheduled. However, surgical treatment was abandoned due to the fast growth rate of the tumor, extensive invasion of adjacent organs such as liver, kidney, diaphragm and inferior vena cava, and multiple lymph node metastasis. As advanced ACC was suspected, chemotherapy with mitotane was then considered. However, given the absence of endocrinological abnormalities and the presence of high CEA levels, the possibility of a metastatic tumor could not be excluded. A CT-guided core needle biopsy of the tumor was performed. Pathological examination revealed carcinoma with squamous differentiation. Immunohistochemical analysis revealed that negativity for Melan A and chromogranin and positivity for p63 and cytokeratin 5/6 (Fig. 2). In addition, immunohistochemistry showed

| Table 1 | Laboratory test data |
|---------|----------------------|
| **Test** | **Case 1** | **Case 2** | **Reference interval** |
| WBC (×10³/μL) | 10.5 | 7.3 | 3.3–8.8 |
| RBC (×10⁶/μL) | 4.3 | 2.7 | 4.5–5.5 |
| Hb (g/dL) | 12.8 | 7.6 | 13.5–17.0 |
| Ht (%) | 39.3 | 24.0 | 39.7–51.0 |
| Plt (×10³/μL) | 263 | 294 | 130–350 |
| CRP (mg/dL) | 6.6 | 5.8 | <0.3 |
| T-Bil (mg/dL) | 0.5 | 0.4 | 0.3–1.2 |
| AST (U/L) | 14 | 14 | 13–33 |
| ALT (U/L) | 16 | 10 | 8–42 |
| LDH (U/L) | 164 | 212 | 119–229 |
| ALP (U/L) | 388 | 251 | 115–359 |
| Na (mEq/L) | 140 | 139 | 135–149 |
| K (mEq/L) | 4.3 | 4.3 | 3.5–4.9 |
| Cl (mEq/L) | 104 | 104 | 96–108 |
| Ca (mg/dL) | 9.3 | 8.2 | 8.0–10.5 |
| P (mg/dL) | 3.5 | 3.5 | 2.5–4.5 |
| BUN (mg/dL) | 14 | 5 | 8–22 |
| Cr (mg/dL) | 0.6 | 0.6 | 0.6–1.0 |
| CEA (ng/mL) | 11.5 | 4.1 | <5 |
| CA19-9 (U/mL) | 10.0 | 3.0 | <37 |
| ProGRP (pg/mL) | 29.5 | 31.7 | <80 |
| CYFRA (ng/mL) | 89.1 | 4.9 | <3.5 |
| SCC (ng/mL) | 7.1 | 2.8 | <1.5 |
| AFP (ng/mL) | 5 | 3 | <10 |
| ACTH (pg/mL) | 96.3 | 17.1 | ≤40 |
| Serum cortisol (μg/dL) | 7.8 | 13.1 | 6.2–19.4 |
| PAC (pg/mL) | 61 | 102 | 20–130 |
| PRA (ng/mL/h) | 3.7 | 3.3 | 0.2–2.7 |
| Plasma adrenaline (ng/mL) | <0.01 | <0.01 | <0.17 |
| Plasma noradrenaline (ng/mL) | 0.43 | 0.43 | 0.15–0.57 |
| DHEA-S (μg/dL) | 147 | — | 38–313 |

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Plt, platelet; CRP, C-reactive protein; T-Bil, total bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ProGRP, pro gastrin releasing peptide; CYFRA, cytokeratin 19 fragment; SCC, squamous cell carcinoma antigen; AFP, α-fetoprotein; ACTH, adrenocorticotropic hormone; PAC, plasma aldosterone concentration; PRA, plasma renin activity; DHEA-S, dehydroepiandrosterone-sulfate. Abnormal values are marked in bold.
Fig. 1 Imaging findings in Case 1
(A) shows the computed tomography (CT) finding, while (B) and (C) show the PET-CT findings. No significant accumulation other than in the adrenal mass.

Fig. 2 Pathological findings in Case 1
A, Hematoxylin-eosin staining. B, Immunostaining for SF-1. C, Immunostaining for p63. D, Immunostaining for TTF-1. The tumor cells were immunohistochemically positive for p63 but negative for SF-1 and TTF-1.
negativity for steroidogenic factor (SF)-1, suggesting that the tumor was by no means of adrenal origin. Additional laboratory testing showed high levels of serum squamous cell carcinoma-related antigen (SCC-Ag) and serum cytokeratin fragment (CYFRA). Based on these results, the patient was diagnosed with adrenal metastasis from squamous cell carcinoma of unknown primary origin. He refused aggressive chemotherapy and opted for palliative therapy at another hospital.

**Case 2**
A 64-year-old man was referred to our hospital for close examination of a 60-mm right-sided adrenal tumor. He presented with slight fever and loss of appetite and had experienced weight loss amounting to 10 kg in the past 4 months. He had no relevant previous medical history, including malignancy. He had smoked 20 cigarettes a day for 40 years. He did not have obesity (body mass index, 20.2 kg/m²) or hypertension (blood pressure, 105/66 mmHg). CT showed a tumor in the right adrenal gland, as well as the formation of tumor emboli in the inferior vena cava and right pulmonary artery due to tumor invasion, extensive tumor invasion of the liver and lymph node metastasis. His laboratory data are provided in Table 1. His red blood cell count and hemoglobin level were reduced, and his CRP level was elevated. Endocrinological examination revealed only a mild increase in renin activity. FDG-PET/CT showed remarkable FDG uptake in the right adrenal tumor (maximum standardized uptake value, 30.1) but not in any other distant organ (Fig. 3). In addition, ¹²³I-MIBG scintigraphy showed no accumulations. Gastrointestinal endoscopy revealed a colon polyp. In this case, based on the experience with case 1, tumor marker levels were evaluated, and a mildly elevated level of SCC was found. A CT-guided core needle biopsy of the tumor was performed to differentiate ACC from adrenal metastasis. Poorly differentiated carcinoma suggestive of metastatic cancer was considered based on the examination of hematoxylin and eosin-stained tissue sections. Immunohistochemical analysis revealed that the tumor cells were positive for p63, cytokeratin 7, and cytokeratin 5/6; partially weakly positive for thyroid transcription factor-1 (TTF-1); and negative for SF-1 (Fig. 4), S100 and SOX10. These findings were consistent with squamous cell carcinoma suspected of having a focal adenocarcinoma component. Additional laboratory testing revealed high levels of CYFRA. However, bronchoscopy did not reveal any abnormal findings. Based on these results, a diagnosis of carcinoma of unknown primary tumor with isolated adrenal metastases was made; however, lung cancer was deemed the most probable. The patient subsequently...
started chemotherapy with carboplatin plus paclitaxel. He died approximately 2 years after the diagnosis.

**Discussion**

We reported two cases of carcinoma of unknown primary origin with isolated adrenal metastasis diagnosed via tumor biopsy in which the lesions were initially discovered as localized adrenal tumors. First, one of the common features in our two cases was that the patients had a long history of smoking. However, they had no history of malignancy, and systemic imaging, including FDG-PET, revealed no findings suggestive of a primary tumor. Second, the tumors were found to be solitary unilateral adrenal tumors in the absence of adrenocortical hormone and catecholamine excess. Finally, the tumors were deemed difficult to resect. Tumor biopsy led to the diagnoses of carcinoma of unknown primary origin with isolated adrenal metastasis.

A carcinoma of unknown primary origin is defined as a malignancy in which the primary tumor is unknown and the lesion is found to be histologically metastatic, regardless of adequate searching. PET-CT has been reported to be useful in cases of unknown primary cancer, particularly in cases involving solitary metastases, as in our cases [13]. However, in our cases, various imaging studies, including PET-CT, failed to identify the primary tumor. The adrenal glands are the most prone to metastasis from lung cancer, followed by gastric cancer [14]. Therefore, both patients underwent repeated contrast-enhanced CT and upper and lower gastrointestinal endoscopy, which did not lead to identification of the primary cancer. In the second case, additional bronchoscopy was performed, which also failed to identify the primary cancer.

Localized metastasis to the adrenal glands from carcinomas of unknown primary origin is extremely rare. A previous study reported that 4 (0.2%) of 1,639 patients with unknown primary cancer showed involvement limited to the adrenal glands [15]. Furthermore, in only one of the four cases, the disease was confined to the unilateral adrenal gland, as in our cases; adrenal metastases tend to present as bilateral lesions. Another study indicated that 0 of 30 biopsies performed for incidentaloma of the adrenal gland indicated metastatic adrenal carcinoma [16]. Carcinoma of unknown primary origin with isolated adrenal metastasis is considered an exceedingly rare condition. Therefore, differentiating non-functioning ACCs from unilateral metastatic adrenal carcinomas may be extremely difficult.

Patients with functioning ACC often have high levels of adrenocortical hormones and exhibit signs of Cushing’s syndrome, such as hypertension, obesity, hyperglycemia, and moon face; these are important distinctions from the manifestations of patients with adrenal metastasis. Patients should be carefully evaluated for such clinical signs. Blood and urine tests should also be performed to evaluate excess hormone levels. The ACC...
working group of the European Network for the Study of Adrenal Tumours has proposed standards for diagnostic procedures in patients with suspected ACC [17]. Although the evaluation of hormonal excess is time-consuming, it should be performed along with careful assessment of the clinical stage and possibility of adrenal metastasis.

In our present cases, it was noteworthy that the serum levels of some tumor-associated biomarkers were elevated, although endocrinological tests did not show any abnormalities. The first patient exhibited a mild increase in serum CEA levels. Elevated CEA levels are mainly used as an indicator of adenocarcinomas, such as colorectal, stomach, lung, ovarian, and uterine adenocarcinomas. However, CEA values could also increase due to smoking. In addition, both patients had high levels of SCC and CYFRA. The levels of both these markers are increased in patients with squamous cell carcinoma. Particularly, CYFRA has been found to be elevated in a variety of tumors [18], but it has established its position especially in non-small cell lung cancer [19]. CYFRA evaluation may be useful in the diagnosis of non-small cell lung cancer. Non-small cell lung cancer has been reported to be closely associated with smoking. An exhaustive analysis of tumor markers does not seem to be a viable option. However, for adrenal tumors in patients without endocrine abnormalities, an evaluation of tumor markers specific to the malignancy inferred from the patient’s medical history may be useful in determining the optimal treatment plan.

Our patients were diagnosed with malignancy via tumor biopsy. However, if ACC is suspected, a tumor biopsy constitutes a risk of seeding. Therefore, the efficacy of tumor biopsy for the diagnosis of adrenal tumors has not been established. A previous retrospective review revealed that biopsies were not useful in patients with localized adrenal incidentalomas because of the inability to differentiate between benign and malignant primary adrenal tumors. However, the authors stated that biopsy can be used to differentiate primary adrenal tumors from metastatic tumors [16]. In particular, SF-1 has been demonstrated to be useful for distinguishing tumors of adrenocortical and non-adrenocortical origins [20]. The value of this marker has also been confirmed in a large cohort study [21]. Both our cases were considered malignant, given the invasion of surrounding organs. Even if it is not clear whether the tumor is primary or metastatic, adrenalectomy should be the treatment of choice if it is feasible. A previous study revealed that adrenalectomy improved the overall survival of patients with metastatic disease arising from the soft tissues, kidney, lung, and pancreas [22]. Several other studies have recommended aggressive resection, especially in cases of solitary metastases to the adrenal glands [23, 24]. Therefore, a biopsy may be an option for diagnosis when the tumor cannot be resected. In such cases, a biopsy should be considered to confirm the presence of ACC before administering mitotane. It may also be useful to measure the levels of tumor markers, particularly those related to lung cancer, based on the history and frequency of ACC.

Although adrenal carcinoma is considered to have a poor prognosis, carcinoma of unknown primary origin with isolated adrenal metastasis may remain latent in some cases, particularly in those diagnosed with non-functioning ACC. The treatment strategy for adrenal tumors needs to be determined by establishing a histological diagnosis. Although tumor biopsy may not be consistently effective for establishing a histological diagnosis, it should be actively considered in cases of suspected non-functioning ACC or possible carcinoma of unknown primary origin with isolated adrenal metastasis, based on the medical history and high levels of certain tumor markers, when surgical resection is difficult.

This report, particularly the first case, described a patient with squamous cell carcinoma without an estimation of the primary tumor. Although high CYFRA levels were found, recent years, certain genetic tests have been used to estimate the primary site of unknown primary cancers; and treatment according to the estimated primary site may now be considered. In SCC, the relationship between various genetic mutations and the primary tumor site has been clarified, and the development of next-generation sequencers has further accelerated this process [25].

In summary, we report two cases of carcinoma of unknown primary origin with isolated adrenal metastasis. Tumor biopsy was effective for establishing the diagnosis, and in one case, multidisciplinary treatment was able to prolong survival, compared to that reported previously. In cases of localized adrenal tumors that are unresectable, tumor biopsy may be actively considered to determine the optimal course of treatment. In addition, the evaluation of tumor markers, particularly those specific to lung cancer, might be useful in cases involving a history of smoking.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.
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