

## Squamous Cell Carcinoma of Unknown Primary that Metastasized to an Inguinal Lymph Node: A Case Report

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Carcinoma of unknown primary (CUP) is a malignant tumor with histological characteristics indicating metastasis in a patient with an unidentified primary lesion after whole-body evaluation at the time of examination. CUP incidence is similar in men and women, and average age at diagnosis is 60 years. Reports of overall incidence vary but CUP is believed to account for 1-5% of all cancers. We encountered a case of apparently metastatic squamous cell carcinoma of the inguinal region in a patient without a detectable primary lesion. We report this case and review the literature on CUP, to increase awareness of this rare lesion. (*J Nippon Med Sch* 2022; 89: 454-459)

**Key words:** carcinoma of unknown primary, squamous cell carcinoma, lymph node metastasis

### Introduction

Carcinoma of unknown primary (CUP) is a malignant tumor with histological characteristics suggesting metastasis in a patient with no evidence of a primary lesion after whole-body evaluation. Reports of overall incidence vary but CUP is believed to account for 1-5% of all cancers<sup>1-6</sup>. We encountered a case of squamous cell carcinoma in the lymph node area of the inguinal region that appeared metastatic in a patient without a detectable primary lesion. Here, we report the characteristics of this case, describe how it was diagnosed and treated, and review the relevant literature.

### Case Report

Patient: A woman in her seventh decade of life

Height: 151 cm; Weight: 38 kg

Chief complaint: Induration of the skin of the left inguinal region, which was revealed to be a subcutaneous nodule

Family history: Father had a cerebral infarction; mother had dementia; one brother had hypertension and a second brother had diabetes

Medical history: Unremarkable

Smokes 20 cigarettes/day; does not consume alcohol

History of present illness: Three months before her initial medical examination in our hospital, the patient became aware of an induration in her left inguinal region and visited a doctor, who ordered a needle biopsy. The biopsy led to a diagnosis of squamous cell carcinoma; inguinal lymph node metastasis from a primary lesion was suspected. To find the primary lesion, the patient underwent medical examinations in the departments of gastroenterology, otorhinolaryngology, and gynecology and image diagnosis with CT, MRI, and PET-CT. However, no primary lesion was detected. The patient was then sent to our hospital for detailed examination to find the primary lesion and for multidisciplinary treatment.

Results of physical examination: During her initial visit to our hospital, we observed inelasticity and hardness of the skin and a 6 cm-diameter tumor accompanied by induration and redness in subcutaneous tissue of the left inguinal region (**Fig. 1**). Examination of the skin and mucosa of the entire body showed no rash or tumors. On palpation, no significant lymphadenopathy was observed.

Results of contrast CT performed at the previous cen-

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Fig. 1 A photograph showing a 6-cm-diameter induration in the left inguinal region and redness of the skin around the induration.



Fig. 2 Contrast CT image showing a tumor (6 × 5 cm) in the left inguinal region.

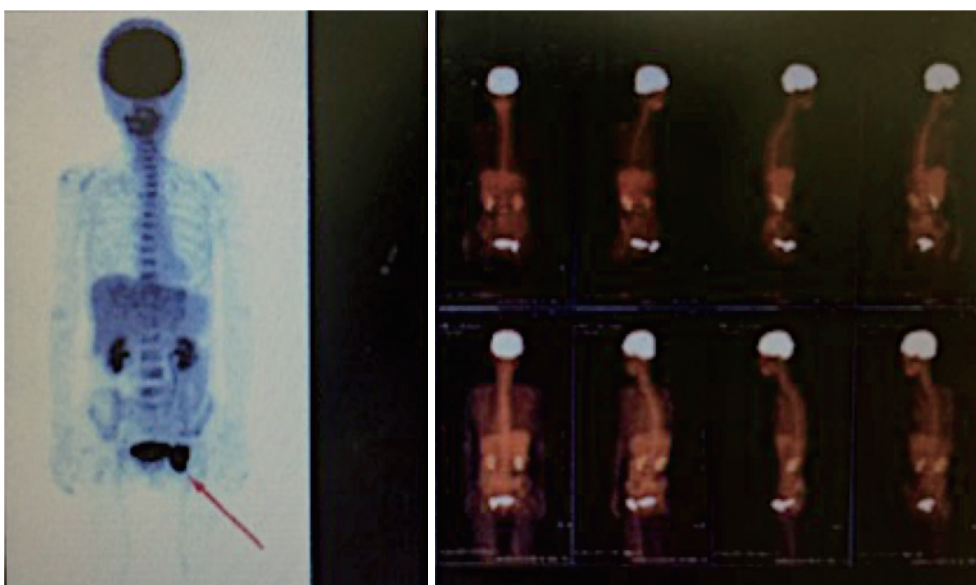


Fig. 3 PET-CT image showing abnormal accumulation of FDG in the left inguinal region. No accumulation was observed in other parts of the body.

ter: CT images showed a 6 × 5-cm mass in the left inguinal region. The mass had an irregular border and its interior did not exhibit a partial contrast effect. In addition, there was no apparent lymphadenopathy in the lung field, mediastinum, axillae, or the region from the abdomen to inside the pelvis. Moreover, no retention of thoracoabdominal fluid was observed (Fig. 2).

Results of PET-CT performed at the previous center: PET-CT images revealed a neoplastic lesion accompanied by high FDG accumulation in a 35 × 40-mm area in the left inguinal region (Fig. 3). Taken together, these observations suggested lymph node metastasis or malignant lymphoma, among other differential diagnoses. However, PET-CT did not detect abnormal accumulation suggestive of the primary lesion.

Clinical laboratory findings at the initial visit to our hospital: RBC  $4.67 \times 10^6/\mu\text{L}$ , Hb 13.0 g/dL, Ht 39.0%, WBC  $178 \times 10^2/\mu\text{L}$ , Plt  $17.6 \times 10^3/\mu\text{L}$ , AST 14 IU/L, ALT 7 IU/L, LDH 227 IU/L, BUN 9.6 mg/dL, Cr 0.59 mEq/L, Na 140 mEq/L, K 4.2 mEq/L, Cl 105 mEq/L, CRP 0.16 mg/dL, and Alb 4.6 g/dL. WBC was elevated, but no other significant findings were observed. The results of analysis of tumor markers were SCC 1.0 ng/mL, CEA 6.0 ng/mL, CA 19-9 7.2 U/mL, CA 72-4 2.1 U/mL, and soluble IL-2R 245 U/mL. Thus, apart from a slight increase in CEA, no tumor marker was significantly elevated.

Diagnosis and treatment: The tumor was simultaneously diagnosed and surgically treated. Clinical data and needle biopsy results suggested metastasis, but an evalu-

ation of the entire body failed to find the primary lesion. Consequently, the tumor was diagnosed as squamous cell carcinoma of unknown primary in the left inguinal region. Because a possible candidate for the primary lesion was a squamous cell carcinoma of the skin, we followed the guidelines for such carcinomas, namely, we extracted the tumor with a 20-mm margin. The tumor was located on the femoral triangle. Since infiltration into the large saphenous vein was observed, the vein was transfixed and dissected. No infiltration of the femoral artery or vein or femoral nerve was observed. Because there was no apparent infiltration under the fascia, it was excised along with the deep fascia. In addition, a superficial inguinal node near the site was extracted and submitted for pathological examination. The wound site was closed while waiting for the results of pathological examination. We also palliatively attached artificial dermis (Fig. 4).

Histopathological examination findings: HE-stained images revealed cells with chromatin pachychromatic atypia that tended to keratinize. Tumor cells in the subcutaneous adipose tissue were larger than those in the mid-dermal layer and formed large and small alveoli. Mitosis was scattered throughout the tumor. Tumor alveoli were partly edematous and markedly infiltrated with neutrophils. A partial lymphoid follicle-like structure was also observed in the tumor periphery (Fig. 5). The diagnosis was metastatic squamous cell carcinoma, possibly from a primary squamous cell carcinoma in the skin, bladder, anus, or other nearby mucosal tissues or from a urothelial cell carcinoma. The surgical margins were negative. Histology of the resected superficial inguinal node indicated no metastasis (0/1).

Progress: The results of pathological examination led us to examine the urological field, but no primary lesion was observed in this field. The resection margins were negative, so we then harvested a 10/1,000-inch split-thickness skin graft from the left femoral area and performed skin grafting 2 weeks after the initial surgery. We considered chemotherapy, in accordance with CUP treatment guidelines<sup>6,7</sup>, but the patient declined treatment. Therefore, we adopted a follow-up observation approach. At 2 years postoperatively, CEA is within the normal range, and no recurrence or lymph node metastasis has been observed (Fig. 6).

### Discussion

CUP is an apparently metastatic carcinoma for which the primary lesion cannot be identified.<sup>7,8</sup> It occurs at similar rates in males and females and average age at diagnosis

is 60 years.<sup>9,10</sup> CUP has a poor prognosis: overall survival (OS) is 7 to 11 months, 1-year survival is less than 25%, and 5-year survival is less than 10%.<sup>11,12</sup> However, a subgroup of CUP patients with better outcomes had a median OS of 12 to 36 months<sup>13</sup>. Our patient is alive 2 years after surgery, so she appears to belong to this group. Analysis of the Swedish Family-Cancer Database suggests that 2.8% of CUP cases are familial; thus, CUP may have a genetic basis<sup>14-16</sup>. The primary lesion is eventually identified in <30% of cases. Indeed, even after necropsy, the primary lesion cannot be identified in 20-50% of cases<sup>17-19</sup>. Similarly, Gultzeit et al. reported that even when CUP patients undergo scanning with PET-CT and CT, the primary lesion is detected in only 33% of cases<sup>20-26</sup>. This failure to detect the primary lesion likely reflects the fact that tumor diameter is at or below the measurement sensitivity, possibly because of natural regression.

The most common form of CUP is highly or moderately differentiated adenocarcinoma (60%), followed by poorly differentiated adenocarcinoma or undifferentiated cancer (29%), poorly differentiated malignant tumor (5%), squamous cell carcinoma (5%), and neuroendocrine tumor of unknown primary (1%)<sup>22-24</sup>. Our patient had the relatively rare squamous cell carcinoma form of CUP.

Immunostaining with organ-specific markers such as estrogen receptor and progesterone receptor can help identify the primary tumor in CUP. However, because there are no organ-specific markers for squamous cell carcinoma, this approach is not useful for this type of CUP<sup>11,25,26</sup>. If the carcinoma is highly differentiated, squamous cell carcinoma of unknown primary is easy to identify by pathological findings, which reveal characteristic squamous epithelium with keratinization and cancer pearls<sup>11</sup>.

If squamous cell carcinoma of unknown primary is detected inside a lymph node or if there is an indication for lymph node dissection clinically, radiation therapy and chemotherapy should be considered<sup>1</sup>. However, radical radiation therapy should only be considered for severe cases. Chemotherapy should be considered in symptomatic patients (PS1 to 2) and in asymptomatic patients (PS0) with rapid tumor progression. Chemotherapy regimens used to treat squamous cell carcinoma of unknown primary include PTX+CBDC, CDDP+GEM, and mFOL-FOX6<sup>1</sup>. Since our patient had a PS1 status, chemotherapy was indicated. However, she declined chemotherapy and instead chose follow-up observation.

It remains unclear how often and for how long CUP

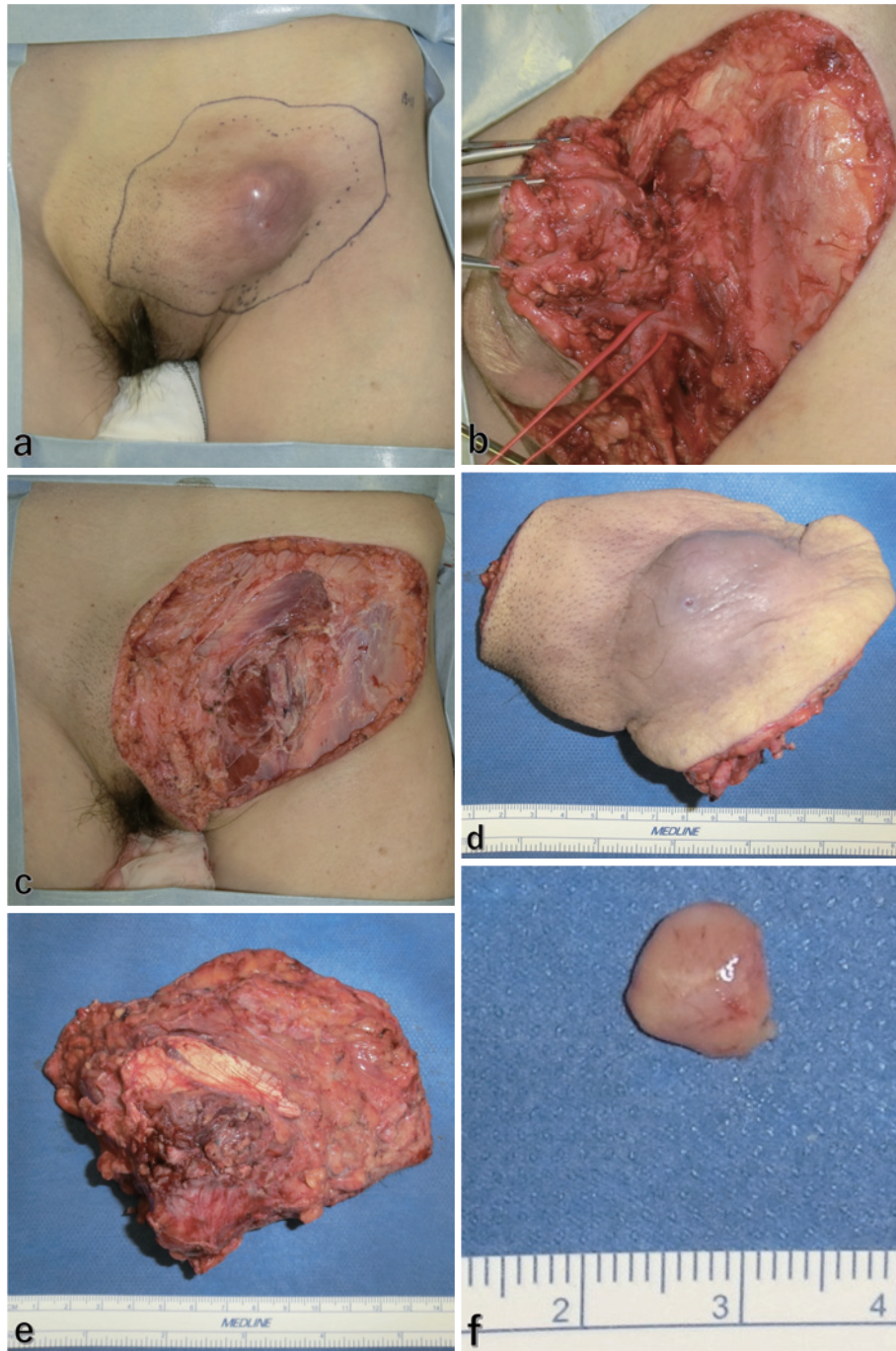


Fig. 4 Intraoperative photographs. (a) The tumor was surgically resected along with the deep fascia and a 20-mm margin. (b) Resection included the large saphenous vein. (c) The wound after resection. (d and e) The resected specimen shown skin side up (d) and skin side down (e). (f) The adjacent lymph node was also resected.

patients should be observed. Therefore, the follow-up duration and examinations to be performed during this period depend on the center's protocols and the judgement of the physician. We have followed our patient for 2 years, with visits at 3, 6, 12, and 24 months; at each visit, we performed a physical examination and contrast CT<sup>1</sup>. No recurrence or lymph node metastasis has been observed.

### Conclusions

Between the time of initial diagnosis by another physician and surgery in our hospital, the patient exhibited no skin or mucosal abnormalities in any region, other than induration and redness in the left inguinal region. Imaging analyses failed to detect a candidate primary lesion. Histological analysis showed that the tumor was a squamous cell carcinoma. Thus, the diagnosis was

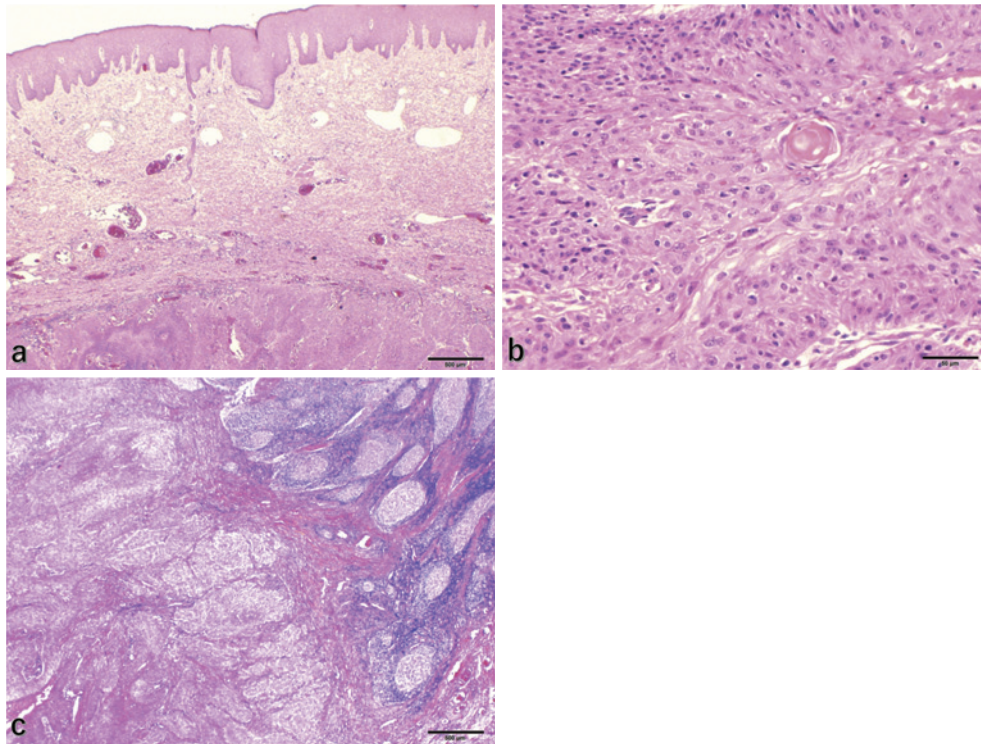


Fig. 5 Images of the HE-stained specimen. (a) The tissue contained cells with marked atypia that changed in size from the mid-dermal layer to the subcutaneous adipose tissue. Mitotic figures were observed. Continuity with the epidermis was not observed. (b) The cells formed large and small alveoli that tended to increase in subcutaneous adipose tissue and exhibited internal keratinization. (c) A partial normal lymphoid follicle-like structure was observed in the tumor periphery.



Fig. 6 Photograph showing the graft-recipient site in the left inguinal region and the donor site at the left femoral region at 2 years postoperatively. Recurrence was not observed. The donor-site scar was not noticeable.

squamous cell carcinoma in the lymph node area of the left inguinal region with an unknown primary. Follow-up observation is ongoing. We hope that this report raises awareness of this rare cancer.

**Conflict of Interest:** None declared.

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