A Case Report of Squamous Cell Carcinoma of Unknown Primary That Metastasized to an Inguinal Lymph Node

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【Abstract】

The term carcinoma of unknown primary (CUP) refers to a malignant tumor whose histology suggests strongly that it is a metastasis, yet the primary lesion is unknown despite sufficient whole body evaluation at the time of examination. CUP has similar incidences in men and women and the average age at diagnosis is 60 years. While its overall incidence varies depending on the report, it generally accounts for 1–5% of all cancers. Thus, it is rare. We encountered a case of squamous cell carcinoma of the inguinal region that seemed to be a metastasis and for which we could not find the primary lesion. This case is reported here along with a literature review on CUP to increase awareness of this rare lesion.

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

【I. Introduction】
Carcinoma of unknown primary (CUP) is a malignant tumor whose histology suggests strongly that it is a metastasis, yet the primary lesion is unknown despite sufficient whole body evaluation at the time of examination.\(^1\) It’s incidence varies depending on the report but it generally accounts of 1–5% of all cancers, which makes it a rare cancer type.\(^2\) We encountered a case of squamous cell carcinoma in the lymph node area in the inguinal region that seemed to be a metastasis and for which we could not find the primary lesion. Here, we report its characteristics and how it was diagnosed and treated. A literature review on CUP is also provided. We recommend that when we perform their daily medical examinations, they should keep CUP in mind.

【II. Case】

Patient: A female in her 60’s
Height: 151 cm Weight: 38 kg
Chief complaint: Induration in the skin of the left inguinal region that was revealed to be a subcutaneous nodule

Family history: Father had a cerebral infarction, mother had dementia, brother 1 had high blood pressure, brother 2 had diabetes

Medical history: No remarkable medical history

Preferences: Smokes 20 cigarettes/day, does not drink

History of the 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 prescribed 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 fields of gastroenterology, otorhinology, and gynecology and image diagnosis with CT, MRI, and PET-CT. However, the primary lesion could not be found. The
patient was then sent to our hospital for more detailed examinations to find
the primary lesion and for multidisciplinary treatment.

Actual symptoms: During the initial visit to our hospital, we observed
inelasticity and hardness of the skin and a 6 cm-diameter tumor accompanied
with induration and redness was observed in the subcutaneous tissue in the
left inguinal region (Fig. 1). Examination of the skin and mucosae of the whole
body failed to detect a rash or tumors. On palpation, significant
lymphadenopathy was not observed.

Results of the contrast CT performed by the previous doctor: The CT images
showed a 6×5 cm mass in the left inguinal region that had an irregular border
and was a tumor whose interior did not exhibit a partial contrast effect. In
addition, there was no apparent lymphadenopathy in the lung field, the
mediastinum, the axillae, or the region from the abdomen to inside the pelvis.
Moreover, no thoracicoabdominal fluid retention was observed (Fig. 2).
Results of the PET-CT performed by the previous doctor: The PET-CT images revealed a neoplastic lesion that was accompanied by high FDG accumulation in a 35×40-mm area in the left inguinal region (Fig. 3). These observations together led to suspicion that the lesion was a lymph node metastasis or a malignant lymphoma among other differential diagnoses. However, the PET-CT examination did not detect any abnormal accumulations that could be suggestive of the primary lesion.

Clinical laboratory findings at the initial visit to our hospital: RBC 4.67×10⁶/µL, Hb 13.0 g/dL, Ht 39.0%, WBC 178×10²/µL, Plt 17.6×10³/µL, 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. Other than the high WBC, no significant findings were observed. In terms of tumor markers, the following results were obtained: SCC 1.0 ng/mL, CEA 6.0 ng/mL, CA19-9 7.2 U/mL, CA72-4 2.1 U/mL, and soluble IL-
2R 245 U/mL. Thus, apart from a slight increase in CEA, no significant elevations of tumor markers were observed.

Diagnosis and treatment: The tumor was simultaneously diagnosed and treated by surgery. The clinical data and needle biopsy results were suggestive of metastasis but the whole-body evaluation failed to find the primary lesion. Consequently, the tumor was diagnosed as squamous cell carcinoma of unknown primary in the left inguinal region. Since 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, it was transfixed and dissected. No infiltration into the femoral artery and vein or femoral nerve was observed. Since there was no apparent infiltration under the fascia, it was excised, including the deep fascia. In addition, one outstanding superficial inguinal node in the vicinity was extracted and
submitted for pathological examination. Regarding the wound site, we decided to close it while waiting for the results of the pathological examination. We also palliatively attached artificial dermis (Fig. 4).

Histopathological examination findings: The HE-stained images revealed cells with chromatin pachychromatic atypia that tended to keratinize. The tumor cells in the subcutaneous adipose tissue were larger than those in the mid-dermal layer and formed large and small alveoli. There was scattered mitosis throughout the tumor. The tumor alveoli were partly edematous and markedly infiltrated with neutrophils. A partial lymphoid follicle-like structure was also observed in the periphery of the tumor (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 pathological examination results led us to examine the urological field. However, a primary lesion was not observed in this field. Given that the resection margins were negative, we then took a 10/1000-inch split-thickness skin graft from the left femoral area and performed skin grafting two weeks after the initial surgery. We considered chemotherapy in accordance with the CUP treatment guidelines\textsuperscript{27}. However, the patient herself did not want it. Therefore, we adopted a follow-up observation approach. Two years have passed since the surgery. Postoperative CEA decreased to the normal range. Clear recurrence and/or lymph node metastasis have not been observed (Fig. 6).

【III. Discussion】

CUP is defined as a carcinoma whose primary lesion cannot be identified and whose histology is strongly suspicious of a metastatic malignant
It occurs at similar rates in males and females and the average age at diagnosis is 60 years.\textsuperscript{9,10} The majority of patients with CUP have a poor prognosis: their overall survival (OS) time ranges from 7 to 11 months, the 1-year survival rate is less than 25%, and the 5-year survival rate is less than 10%.\textsuperscript{11,12} However, the remaining CUP patients have a better prognosis: their median OS ranges from 12 to 36 months.\textsuperscript{13} Given that our patient is still alive 2 years after surgery, she appears to belong to the latter group. The analysis of the Swedish Family-Cancer Database suggests that 2.8% of CUP cases are familial; thus, CUP may have a genetic basis.\textsuperscript{14-16} The primary lesion is only eventually identified in <30% of cases. Indeed, even after necropsy, the primary lesion cannot be identified in 20–50% of cases.\textsuperscript{17-19} Similarly, Gultzeit \textit{et al.} reported that even when CUP patients are scanned with PET-CT and CT, the primary lesion is detected in only 33% of cases.\textsuperscript{20-25} It is likely that this failure to detect the primary lesion reflects the fact that its diameter is at or below the measurement sensitivity, possibly because of natural regression.
There is a report that SCC antigen sensitivity was 0.70, specificity was 0.63 and AUC was 0.73.\textsuperscript{26} It is suggested that this case was false negative.

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\%).\textsuperscript{22-24} Thus, our patient had the relatively rare squamous cell carcinoma form of CUP.

To identify the primary tumor in CUP, it can help to perform immunostaining with organ-specific markers such as estrogen receptor and progesterone receptor. However, since there are no organ-specific markers for squamous cell carcinoma, this approach is not useful for this type of CUP.\textsuperscript{25-28} However, if the carcinoma is highly differentiated, the squamous cell carcinoma type of CUP is easy to identify by pathology: these findings reveal characteristic squamous epithelium with keratinization and cancer pearls.\textsuperscript{27}
If squamous cell carcinoma from an 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. Regarding the radiation therapy, radical radiation therapy should only be considered for severe cases. Chemotherapy should be considered in cases with symptoms (PS1 to 2) and in asymptomatic cases (PS0) that exhibit rapid progression of the tumor. In the case of squamous cell carcinoma of unknown primary, the chemotherapy regimens that have been used include PTX+CBDCA, CDDP+GEM, and mFOLFOX6. Since our patient had a PS1 status, there was an indication for chemotherapy. However, it was not performed because the patient herself refused it and chose follow-up observation instead.

It remains unclear how often and for how long CUP patients should be followed up. Therefore, the follow-up duration and which examinations are performed during this period depend on the discretion of each facility and doctor. We have followed our patient for 2 years now with visits at 3, 6, 12
and 24 months: at each visit, we performed a physical examination and contrast CT. Recurrence and lymph node metastasis were never observed.

【IV. Conclusion】

Between the time of the initial diagnosis by another doctor and the surgery in our hospital, this case did not exhibit any abnormalities in the skin and mucosae of the whole body other than the induration and redness in the left inguinal region. Imaging analyses also failed to detect a neoplastic lesion that could be the primary lesion. Histology showed that the tumor was a squamous cell carcinoma. Thus, the diagnosis was squamous cell carcinoma in the lymph node area of the left inguinal region with an unknown primary. The follow-up observation is ongoing. Our experience with squamous cell carcinoma of unknown primary may help alert us to the possibility that such rare cases exist.

【Conflict of Interest】

There are no conflicts of interest with respect to this paper.
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Figure legends

Figure 1. The patient presented with a 6 cm-diameter induration in the left inguinal region and redness of the skin around the induration.

Figure 2. Contrast CT revealed the presence of a 6×5-cm tumor in the left inguinal region.

Figure 3. PET-CT showed abnormal accumulation of FDG in the left inguinal region. Accumulation was not observed in other parts of the body.

Figure 4. Intraoperative photographs. (a) The tumor was surgically extracted along with the deep fascia and a 20-mm margin. (b) The extraction included the large saphenous vein. (c) The wound left after the extraction. (d and e) The extracted specimen presented skin side up (d) and skin side down (e). (f) The adjacent lymph node that was extracted.

a|b
Figure 5. Images of the HE-stained specimen. (a) The tissue contained cells with strong atypia that changed in size as the observer’s gaze moved 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 the subcutaneous adipose tissue and exhibited internal keratinization. c) A partial normal lymphoid follicle-like structure was also observed in the periphery of the tumor.

Figure 6. Photograph of the graft-recipient site in the left inguinal region and
the donor site on the left femoral region 2 years after the surgery. Recurrence was not observed. The donor-site scar was not noticeable.
Figure 1.
Figure 2.
Figure 3.
Figure 4.
Figure 5.
Figure 6.