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Case Report

# A case of inguinal lymph node squamous cell carcinoma of unknown origin, accompanied with carcinoma in situ of cervix

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Metastatic Cancer of Unknown Primary Site (CUP) accounts for approximately 3-5% of all malignant neoplasms. CUP represents a heterogeneous group of metastatic tumors for which no primary site can be detected following a thorough medical history, careful clinical examination, and extensive diagnostic work-up. Several authors have reported poor prognosis of this malignancy, because there is no consensus on diagnostic guidelines and optimal therapy. Historically, chemotherapy has been the cornerstone of treatment for patients with CUP. We experienced a case of inguinal lymph node squamous cell carcinoma of unknown origin, accompanied with carcinoma in situ of the cervix. We report this case with a brief review of the literatures.

**Key Words:** Metastatic cancer of unknown primary site, Inguinal lymph node

## INTRODUCTION

Metastatic cancer of unknown primary site (CUP) accounts for 3-5% of all malignant neoplasms, and it is defined as metastatic cancer from an unknown primary site, for which no original site can be detected even after performing all possible tests.[1,2] In the 1970s, some researchers argued that the diagnosis of CUP could be made only if the primary site could not be found even after an autopsy.[3] Today, the definition of CUP includes patients who present with histologically confirmed metastatic cancer in whom a detailed medical history, complete physical examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomography (CT) of the abdomen and pelvis and, in certain cases, mammography fail to identify the primary site. In the Mayor clinic, from 1984 to 1999, autopsy was performed on 64 patients who were diagnosed to be cancer with unknown origin, and the primary lesion could be found in only 35 patients (55%). As the primary site, the lungs, the pancreas and the bile duct system, and the gastro-intestinal system were most prevalent. It was more difficult to find the primary lesion in poorly differentiated carcinoma cases.[4] Recently, upon reporting the role of positron emission tomography (PET) scan in various fields, the diagnostic technique to find the unknown primary site has become became advanced. Nevertheless, until now, cases of which the origin could not be found are more abundant, and results cannot be obtained even by empirical therapeutic methods. Thus the diagnosis and therapy of CPU remains a real dilemma for practising oncologists.[1] We experienced a case of squamous cell carcinoma of the inguinal lymph node from an unknown primary site, accompanied with carcinoma in situ of cervix and a benign ovarian tumor, and thus this case is reported here together with a brief review of the literature.

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## CASE REPORT

A 71-year-old married woman consulted the Department of Obstetrics and Gynecology at Holy Family Hospital, The Catholic University, with complaints of the presence of a mass on the right inguinal area. At the time of the initial visit, the general condition of patient appeared to be good, blood pressure was 140/70 mmHg, pulse was 70 times/min and temperature was 36.2°C. There were no enlarged lymph nodes of the cervical and supraclavicular regions. Chest

auscultation revelealed normal breathing sounds and heart beat, and abnormal findings were not detected in the abdomen, all limbs, the perineum, and the perianal area. The right inguinal lymph node was enlarged to 3-4 cm in size, was mobile and tenderness was not detected. Otherwise, the enlargement of lymph nodes in other areas was not observed. In pelvic examination, the uterus and the vagina were atrophied, a fist sized mass was detected in the right adnexa, it was movable, and tenderness or rebound tenderness was not detected.

In cervical cytology, atypical squamous cells of cannot exclude HSIL (ASC-H) was diagnosed. Human papilloma-virus (HPV) type 31 was detected using a HPV DNA chip test. In colposcopic examination, the cervix was atrophied and thus the transformation zone was invaginated (Fig. 1), and the punch biopsy revleaed cervical carcinoma in situ (CIS). After LEEP was performed, it was confirmed as cervical carcinoma in situ, and in the endocervical resection margin, it was confirmed that carcinoma in situ was remnant.

Transvaginal ultrasound showed a 6 cm sized unilocular cyst in the right adnexa. In pelvic CT, the right ovarian cyst showed a benign nature, and the inguinal lymph nodes were suspected to be lymphadenopathy, lymphoma, or benign neurogenic tumor (Fig. 2). CA125 was 48.83 IU/ml, CA19-9 was $<1$ IU/ml, CEA was 6.43 ng/ml, AFP was 1.68 ng/ml, and SCC was 0.44 ng/ml. In complete blood cell count, hemoglobin was 10.1 g/dl, hematocrit was 29.9%, white blood cell count was 7,300/mm$^3$, and platelet count was 150,000/mm$^3$. The results of other examinations, including urinalysis, liver function tests and renal function tests, revealed no abnormalities.

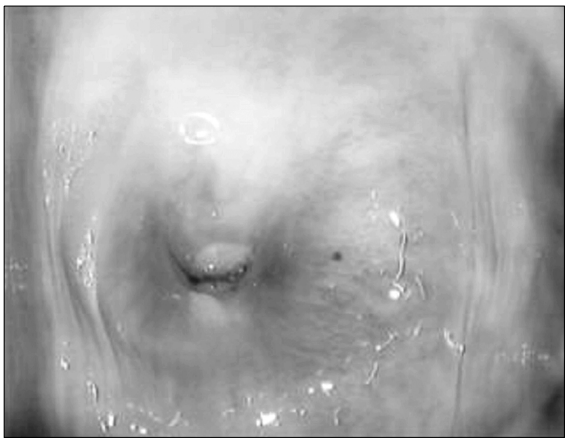

**Fig. 1.** Colposcopic finding. It showed thin acetowhite epithelium in 6 and 12 o'clock.

Sigmoidoscopy, thyroid function test, chest x-ray, cardiac ultrasound, and pulmonary function test showed normal results.

Under general anesthesia, hysterectomy and bilateral salpingoophorectomy were performed. Shiller test was negative on the cervix. It was diagnosed as carcinoma in situ of cervix by frozen section and permanent pathology (Fig. 3). In the right ovary, a serous cyst with two chambers was detected. Solid components were absent, and it was adhered to the pelvic wall and omentum. It was confirmed as a benign cyst by frozen section and permanent pathology. Other pelvic organs showed normal structures. The right inguinal lymph node was enlarged to 4 cm sized and well demarcated. It was diagnosed as metastatic squamous cell carcinoma by pathologic review (Fig. 4). Inguinal lymph node dissection was performed. During the surgery, the condition of patient was tolerable.

The postoperative course was uneventful. To find the primary lesion of the metastatic squamous cancer that was found in the inguinal lymph node, a PET scan was performed. Nonetheless, no suspicious primary site that could be detected, and only multinodular goiter was detected (Fig. 5). On postoperative days 21, SCC was 0.54 ng/ml, CA125 was 11.16 IU/ml, and CEA was 2.35 ng/ml.

For the treatment of squamous cell cancer detected in the inguinal lymph node, chemoradiation therapy was planned. The inguinal area was irradiated with 4,500 cGY and the pelvic area was irradiated with 5,040 cGY, and 60 mg/m$^2$ cisplatin was administered at one week interval, total 6 times.

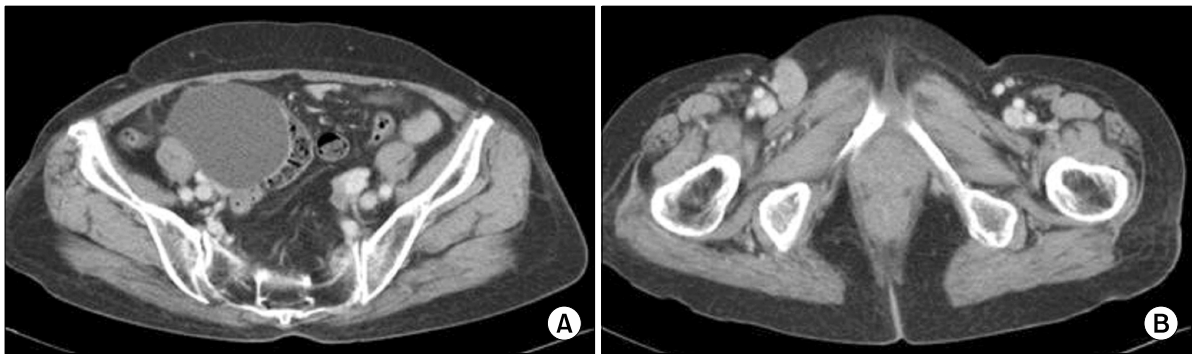


**Fig. 2.** Pelvic CT (postenhancement). (A) It showed about 7.0×6.7 cm sized, unilocular, thin walled, non-enhancing hypodense mass at right adnexa, and (B) about 2.4×1.4 cm sized, round to ovoid, homogeneously enhancing nodule at right superficial inguinal region.

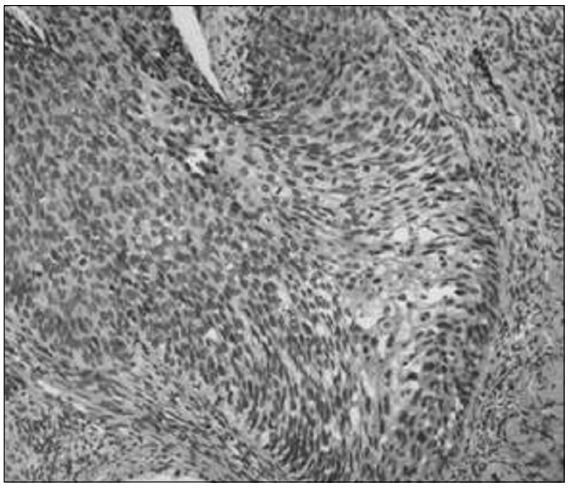

**Fig. 3.** Microscopic finding of cervix. It showed carcinoma in situ of cervix (H-E stain, ×100).

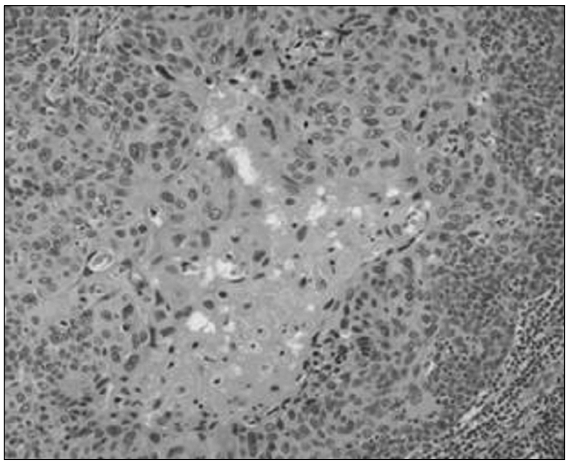

**Fig. 4.** Microscopic finding of inguinal lymph node. It showed squamous cell carcinoma with keratin pearl (H-E stain, ×100).

During the chemoradiation therapy, the patient developed anemia and thus received transfusion once, and the treatment was terminated within the planned time period. Six months after chemoradiation therapy, chest X-ray, pelvic CT, cervical cytologic test, and tumor markers were performed as follow up tests. Recurrent malignant tumor or lymph node enlargement was not detected on radiologic examination. Cervical cytologic test and tumor marker levels were within normal limits (SCC, 0.15 ng/ml; CEA, 1.85 ng/ml). At 9 months after the completion of treatments, PET scan demonstrated no abnormal findings. Until now, the patient is under follow up without recurrence for 22 months after the completion of treatment.

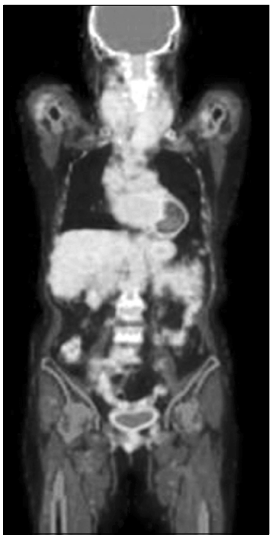

**Fig. 5.** FDG-PET scan. It showed no other hypermetabolic abnormality suggesting malignancy, except multinodular goiter at thyroid gland.

## DISCUSSION

The lymphatic circulation is a system responsible for immunity, and it produces antibody and plays a role of removing foreign materials or cancer cells. On the other hand, cancer cells migrate through the lymphatic duct and thus lymphatic system becomes a pathway to transfer cancer cell to distant organs. Therefore, depending on abnormal lymph node location, associated diseases could be predicted, and disease stage and prognosis are determined based on the location or number of metastatic lymph nodes.

The patient that we experienced was a 71-year-old woman, and she was admitted enlargement of the inguinal lymph node. Generally, inguinal lymph nodes receive as afferent lymphatic vessels from the vulva, the vagina, the perineum, the buttocks, the low abdominal wall, and the perianal lymphatics, and lymph node enlargement is associated with infection and malignancy in such areas. Cases other than that are very rare, and metastatic cancer with unknown primary site also belongs to this category.

In 1978, Zaren and colleagues examined 2,232 patients with metastatic cancer cells in the inguinal lymph node. Among them, 99% were cases with metastasis from a primary lesion, and most patients were found to have malignant tumors in the skin of lower limbs, the cervix, the uterine body, the ovary, the perineum, the rectum, the anus, and the remaining 1% was metastatic cancer with unknown primary site.[5] In 1987, Guarischi and colleagues examined 56 patients diagnosed as metastatic cancer in the inguinal lymph node without a primary lesion. The 29 were male patients and 27 were female. Regarding the distribution according to histological types, anaplastic carcinoma was 42% (24 patients), squamous cell

carcinoma was 19% (11 patients), adenocarcinoma was 16% (9 patients), melanoma was 16% (9 patients), and others were shown to be 5% (3 patients).[6,7] According to a previous report, malignant tumor with unknown origin comprises 3-5% of all malignant neoplasms, and it is defined as a metastatic cancer of unknown primary site, for which no original site can be detected even after performing all possible tests.[1]

The diagnostic evaluation of patients with CUP consists of laboratory or clinical investigations including the past history, complete physical examination, blood test, urinalysis, stool examination, pathology, immunohistochemistry, chest X-ray, CT, mammography, endoscopy.[8,9] As tumor markers, serum $\beta$-hCG and AFP may be performed to rule out extragonadal germ cell tumors, and CA15-3 for axillary adenocarcinoma and CA125 for peritoneal papillary adenocarcinoma could be of some help. In all other cases, routine evaluation of commonly used epithelial serum tumour markers (CEA, CA19-9, CA15-3, CA125) has no proven prognostic or diagnostic value, and non-specific elevations of multiple markers occurs in the majority of CUP patients.[10]

CUP are categorized into four major subtypes by routine light microscopy criteria: (a) adenocarcinomas well-moderately differentiated, (b) undifferentiated or poorly differentiated adenocarcinomas, (c) squamous cell carcinomas and (d) undifferentiated neoplasms. Approximately half the patients will be diagnosed with metastatic adenocarcinoma, 30% will have undifferentiated or poorly differentiated carcinomas, 15% squamous cell carcinomas and the remaining 5% will have undifferentiated neoplasms.[11]

More than 50% of CUP patients present with multiple sites of involvement, while the rest have a single site most commonly in the liver, lymph nodes, the peritoneum, the lung, the bone, and the brain.[12]

The progression of such cancer with unknown origin is rapid in most cases, and it shows atypical metastatic patterns. In general, it appears that patients with CUP have a limited life expectancy with a median survival approximately of 6-9 months. The therapeutic strategy for CUP patients should always be individualized according to the clinical subset. The therapeutic approaches include chemotherapy, surgery, with or without postoperative radiotherapy, radiotherapy alone and radiotherapy followed by surgery. Among them, chemotherapy has been the cornerstone of treatment. The outcome of chemotherapy was improved after the advent of the platinum compounds in the 1980s,[13-15] and since 1995, the use of a taxane (paclitaxel or docetaxel) in combination with a platinum compound has provided an additional and probably improved treatment option for the large group of patients who do not fit into any favourable sub-set.[16-18] Until now, the combination chemotherapy of platinum and the taxane family has been recognized to be most effective.

In this patient with squamous cell carcinoma in the ingual lymph node, the PET scan could not identify any occult primary site or other metastatic lesions. The solitary development in the inguinal lymph node occurs in 1-3.5% cases of metastatic cancer with unknown origin. Examination of the anorectal region, a meticulous gynecological examination and probably cystoscopy are necessary investigations for this patient. Lymphomas and metastatic or amelanotic melanomas of unknown primary site should also be ruled out.[6,18] In this case, carcinoma in situ of cervix and the right ovarian benign cyst was diagnosed, nonetheless, metastasis in the inguinal lymph node could not be explained.

Carcinoma in situ of cervix is the state that cancer cells could not penetrate the basement membrane. Since there is no metastasis in adjacent tissues or lymph node, it is adequate to treatment with simple hysterectomy alone. For the inguinal lymph node, it was considered to be a solitary lesion, and lymphadenectomy was performed. As in such a case of a solitary lesion of cancer with unknown origin, local treatment such as surgery or radiation therapy could be performed, and favorable outcomes can be expected.[6,19,20] However, in cases in which progression of the primary lesion is very slow, cancer cells may not be detected by conventional diagnostic methods. Therefore we performed adjuvant chemoradiation therapy.

Despite the development of various diagnostic methods, the optimal diagnostic algorithm in metastatic cancer with unknown origin has not yet been established. Also, it shows a progression pattern different from other malignant tumors, and thus their progress is difficult to predict. Since the benefit of current therapy remains is limited in most patients, the evaluation of novel treatment approaches is essential. Promising classes of agents currently in development, including epidermal growth factor receptor inhibitors and anti-angiogenesis agents, should be explored in patients with CUP. Ongoing basic research and focused translational studies are also critical in advancing the understanding and management of patients with CUP.

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