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Case Report

A case of pelvic squamous cell carcinoma of unknown primary origin that responded well to radiotherapy and nivolumab ☆,☆☆

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ABSTRACT

Squamous cell carcinoma of unknown primary origin in the pelvis is rare. We report a case of a 64-year-old woman with a large osteolytic squamous cell carcinoma of unknown primary origin in the pelvis that presented with p16 expression. The patient presented with leg pain and swelling and was admitted to our hospital. Computed tomography scans of the pelvis revealed a large osteolytic tumor. A computed tomography-guided needle biopsy was performed, and pathological examination revealed neoplastic cells with metastatic squamous cell carcinoma presenting with p16 expression. Despite a whole-body examination, tumor origin remained undetected. The patient was treated for this metastatic squamous cell carcinoma of unknown primary using palliative radiotherapy for hip pain and nivolumab. Remarkable reduction in the tumor marker levels and tumor size were obtained after therapy. Finally, partial remission and progression-free survival for more than 7 months were achieved. In conclusion, we experienced a rare case with a large p16-positive squamous cell carcinoma of unknown primary in pelvis, which responded well to radiotherapy and nivolumab.

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Introduction

Carcinoma of unknown primary origin (CUP) is a metastatic disease in which the primary tumor has not been identified at the initial therapeutic decision. CUP accounts for 3%-7% of all malignant tumors and shows a slight male predominance [1]. The most common site of CUP is a lymph node, followed by a bone, other abdominal sites, liver, lung, pleura, central nervous system, skin, and adrenal gland; metastatic adenocarcinoma is the most common histological type [2]. Overall survival is generally poor and depends on the primary tumor [3]. Metastatic squamous cell carcinoma (SCC), CUP is frequently observed in the neck and inguinal regions. p16-positive neck SCCs are observed in younger individuals who consume less amount of alcohol and show better clinical outcomes than p16-negative SCCs [4]. Metastatic SCC CUP in the pelvis with p16 expression is rare. Herein, we report a rare case of a large osteolytic SCC CUP with p16 expression in the pelvis in which despite poor prognosis estimation, progression-free survival was achieved for 7 months after therapy.

Case report

A 64-year-old woman with a 1-month history of swelling and pain in the right leg was admitted to our hospital. Her medical history included diabetes and left-leg underdevelopment. At the time of admission to our hospital, the patient's general condition was quantified using Eastern Cooperative Oncology Group Performance Status (PS), and the grade was PS3–4 [5]. Laboratory examinations revealed elevated lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and C-reactive protein levels with high white blood counts. The following tumor marker levels were elevated: SCC, cancer antigen 125: CA125, carcinoembryonic antigen: CEA, βhuman chorionic gonadotropin: βHCG, cytokeratin fragment: CYFRA, and neuron-specific enolase: NSE (Table 1). Computed tomography (CT) revealed a large tumor measuring 15 × 19 cm in diameter (Fig. 1) in the right pelvis with widespread bone destruction in the ilium and sacrum.

The lower boundary of the tumor reached the hip joint. The density of the tumor content was mainly heterogeneously

Table 1 – Tumor marker levels of the patient.

Name of tumor marker	Levels before treatment	Levels after treatment	Reference range	
SCC	107.7	1.5	≦1.5	(ng/mL)
CA125	386.9	75.8	≦35.0	(U/mL)
AFP	3.3	-	≦20	(ng/mL)
CEA	10.2	4.9	≦5.0	(ng/mL)
βHCG	5	-	<0.5	(mIU/mL)
CYFRA	150	3.6	≦3.5	(ng/mL)
NSE	28.7	10.1	≦16.3	(ng/mL)

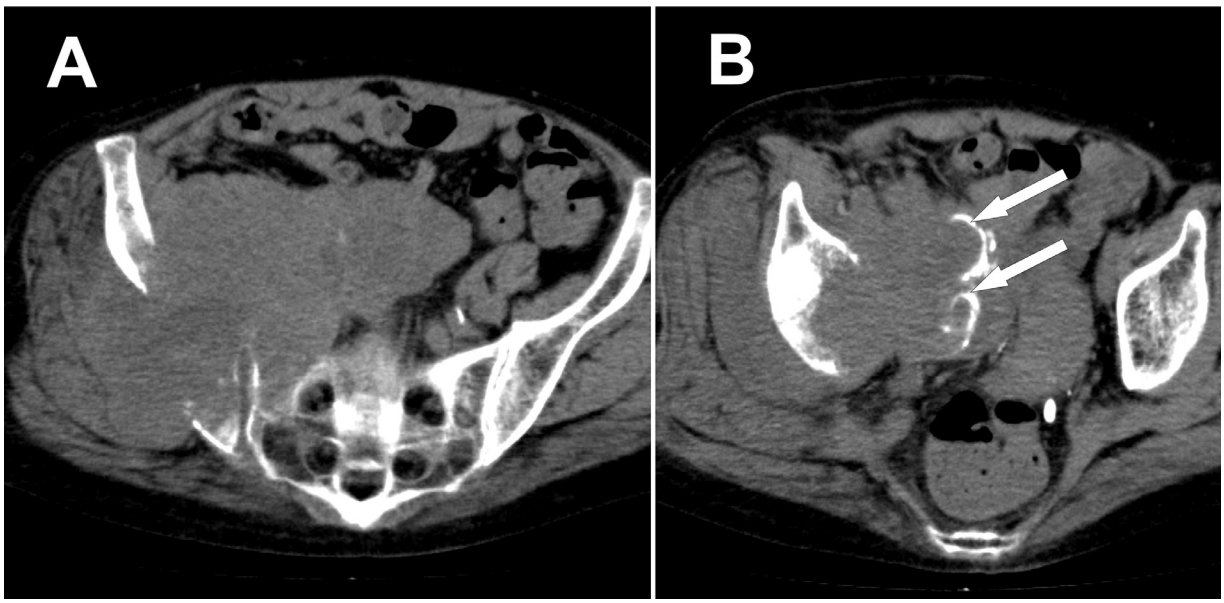

Fig. 1 – CT images. (A) CT images show a large osteolytic tumor in the right pelvis. (B) Coarse calcification is observed in the center of the tumor (white arrows). CT, computed tomography.

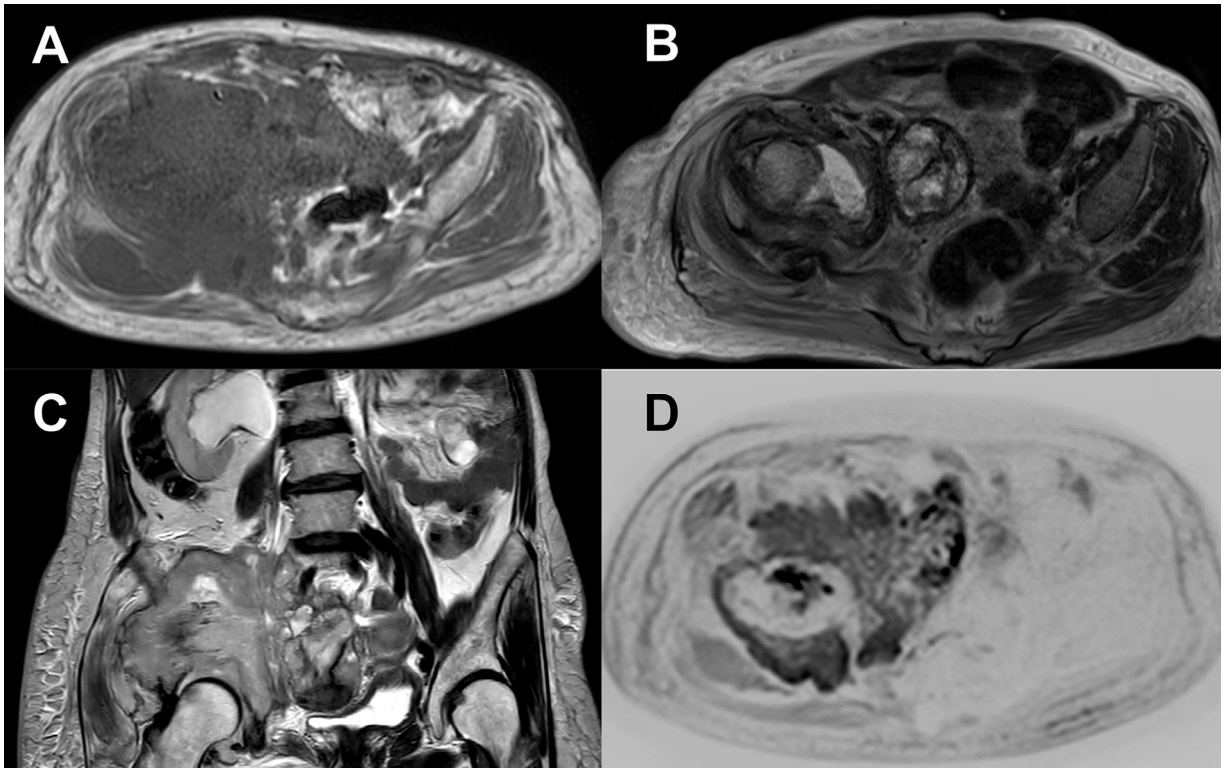

Fig. 2 – MRI imaging. MRI images revealing a large mass in the right pelvis. (A) T1WI axial image of the tumor. (B) T2WI axial image of the tumor. (C) T2WI coronal image of the tumor. (D) Diffusion-weighted image of the tumor. MRI, magnetic resonance imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging.

low; however, it contained coarse, high-density cells, indicating calcification. The tumor was pressing on the right ureter, and right hydronephrosis was observed. Magnetic resonance imaging (MRI) also showed a large tumor in the pelvis involving the ilium and sacrum (Fig. 2). T1-weighted imaging showed intermediate-to-high signal intensity throughout most of the tumor. The T2-weighted imaging signal was heterogeneously high at the tumor edge but showed a low signal intensity in the center of the tumor. Diffusion-weighted imaging also showed a high signal intensity, and the apparent diffusion coefficient map showed a low signal intensity. These signals indicated tumor necrosis and internal bleeding. Fatty tissue intensity was not observed on MRI. No abnormal findings were observed on CT and MRI of the uterus, rectum, and bladder. [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) - positron emission tomography (PET)/CT showed increased accumulation only in the pelvic tumor (Fig. 3). CT-guided needle biopsy was performed, and sufficient amount of pathological specimen was obtained from the center of iliac tumor (Fig. 4). Histopathological examination revealed the tumor to be a metastatic SCC, and a strong p16 expression was observed. To determine the tumor origin, upper and lower intestinal endoscopy, cystoscopy, and cervical biopsy were performed; however, the tumor origin could not be detected. The tumor was thus considered a CUP. To reduce the hip and leg pain, palliative radiotherapy of 39 Gy in 13 fractions was performed. After radiotherapy, tumor marker levels markedly reduced (Table 1). Hip pain improved 3 months after radiotherapy. After radiotherapy, nivolumab was initially administered every 4 weeks at 240 mg/kg body weight for 4 cycles, and subsequently at 480 mg/kg body weight for 2 cycles [6]. CT performed after radiotherapy and 4 cycles of nivolumab showed a reduction in tumor size to 11.3 × 8.5 cm. Further, calcification in the cortex of the ilium was observed, indicating a therapeutic effect. Partial remission (PR) was achieved [7], and the patient survived without tumor progression for 7 months after admission.

Discussion

SCC CUP associated with human papillomavirus (HPV) or p16 is frequently observed in the neck lymph nodes but rarely in the pelvis. Generally, p16 expression results from the inactivation of tumor suppressor genes such as p53 and Rb and is mostly caused by HPV infection [8]. In the pelvic region, HPV infection is associated with anal canal and cervical cancer. In our patient, although an endoscopic examination of the anal canal and a Pap smear were performed, no abnormalities were detected. To date, 12 cases of pelvic p16- or HPV-positive CUP have been reported [9–13]. Almost all patients were female. The tumors were located in the psoas, retroperitoneum, or pelvic lymph nodes. To our knowledge, pelvic CUP in a patient with SCC presenting with extensive bone damage has not been previously reported.

The other known SCC of the pelvis is ovarian SCC transformed from mature cystic teratomas of the ovary [14]. SCC of the ovary rarely arises from mature cystic teratomas, and

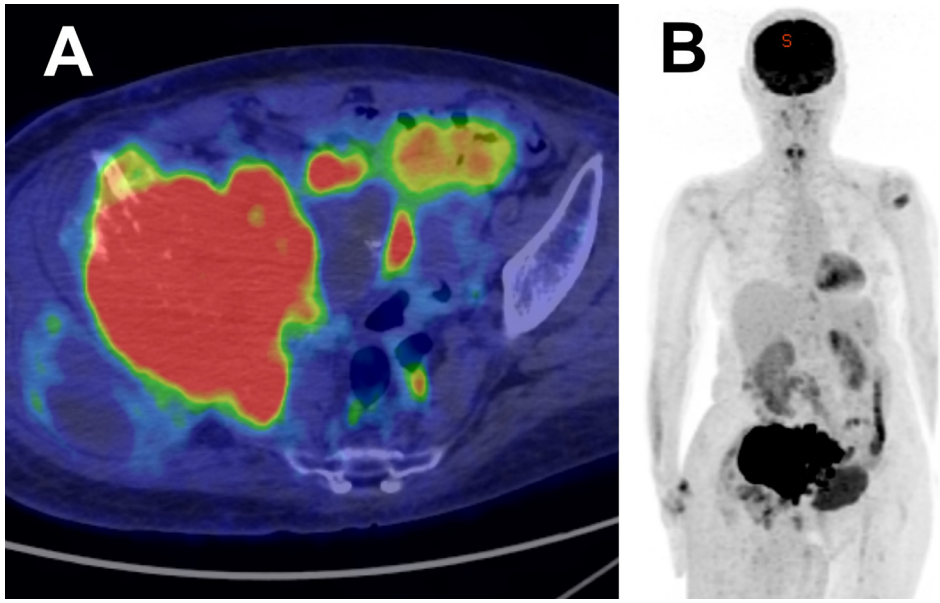

Fig. 3 – FDG-positron emission tomography/computed tomography. (A) (B) FDG-positron emission tomography/computed tomography shows increased accumulation of FDG only in the pelvic tumor. [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG).

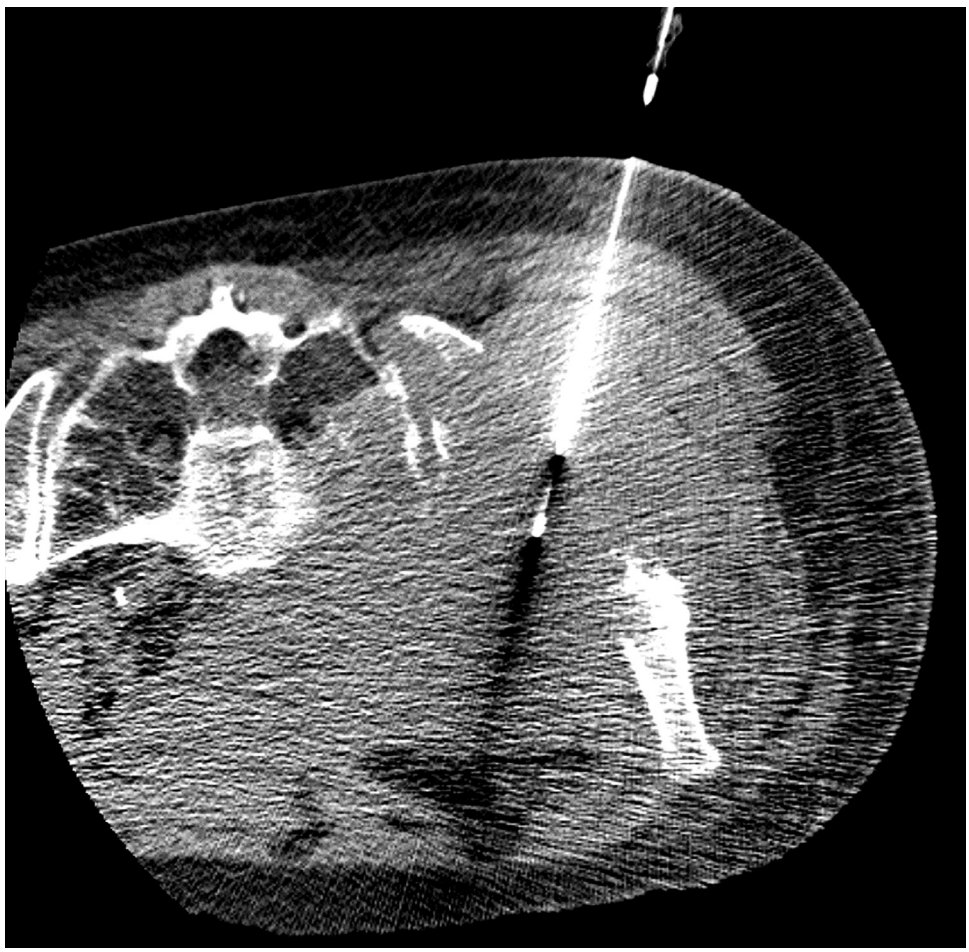

Fig. 4 – CT-guided needle biopsy. The image illustrates the CT-guided needle biopsy. CT, computed tomography.

the correlation between HPV infection and the malignant conversion of mature cystic teratomas is unclear. However, some past reports indicate a correlation between the conversion of mature teratomas to SCC with HPV infection [15,16]. In this patient, the possibility of bone metastasis or direct invasion from a malignant teratoma of the right ovary remains. However, this tumor did not contain fatty tissue intensity with solid and cystic components on MRI and CT, which is a typical finding of malignant teratoma, and the conversion from ovarian teratoma into malignant teratoma also seemed unlikely [17].

In pelvic CUP, the relationship between prognosis and p16 expression remains unclear. Previous reports have indicated the effectiveness of chemoradiation based on cisplatin and nivolumab for HPV- or p16-positive pelvic SCCs of unknown primary type; however, a therapeutic regimen has not been established [11–13]. Generally, the prognosis of patients with CUP is determined by their performance status and serum LDH and ALP levels. Bone metastasis also indicates a poor prognosis in patients with CUP [18]. Because a poor prognosis was predicted based on these clinical parameters, palliative radiotherapy for leg pain was performed first. Next, chemotherapy with nivolumab was selected, as its therapeutic efficacy against occult cancer has previously been confirmed for CUP, cervical cancer, and anal cancer [6,19,20]. Eventually, the tumor responded to the radiotherapy and nivolumab, as evidenced by the decrease in tumor marker levels and a reduction in tumor size. Finally, PR and 7 months of progression-free survival were achieved.

In conclusion, we encountered a rare case of pelvic CUP presenting with p16 expression that responded well to radiotherapy and nivolumab despite a poor prognostic estimation.

Patient consent

Written informed consent to publish the anonymized clinical information in this article was obtained from the patient.

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