A Case of Unknown Primary Cancer with a Tumor Formed in the Retroperitoneum: A Case Report

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Background: Cancer of unknown primari (CUP) are said to account for 2% of all carcinomas. Here we report a rare case of CUP confined to the retroperitoneum.
Case presentation: A 51-year-old man consulted a nearby physician for back pain. The malignant tumor could not be denied by MRI, and she was referred to our hospital. CT and MRI revealed uneven enhanced tumor structures protruding into the L2/3 disc. Part of the tumor was continuous with the left iliopsoas muscle. A CT-guided needle biopsy was performed. Histologically, the sheet-like proliferation of atypical cells was observed. Immunohistochemistry showed that atypical cells were positive for cytokeratin AE1&3, CK7, CD10, GATA3, glypican 3, Hep Par 1, carbonic anhydrase 9 (focal), and vimentin (focal) but negative for CK20, CD56, chromogranin A, synaptophysin, TTF1, HMB45, melan A, and PSA. The pathological diagnosis was poorly differentiated carcinoma. However, it was difficult to determine the primary site from the pathological findings. Positron emission tomography (PET) scan showed no distant metastases. He was diagnosed as poorly differentiated cancer localized to the lumbar spine from the retroperitoneum. Paclitaxel plus carboplatin (TC) was started. After completing 3 kr of TC, she was hospitalized urgently due to worsening lumbago. CT and MRI at admission showed an increase in the main lesion and exacerbation of bone invasion. Radiation therapy was given for curative purposes. Eventually, he died seven months after visiting our hospital and five months after starting TC therapy.
Conclusions: CUP has various disease states, and it is necessary to finish the examination immediately and shift to treatment. More effective treatment including immune checkpoint inhibitor for CUP is needed in the future.

Key words: Cancer of unknown primary (CUP), Retroperitoneal tumor, TC, immune check point inhibitor

BACKGROUND

Cancer of unknown primary (CUP) is defined as a malignant tumor of unknown primary origin despite a thorough search and a histologically proven metastatic lesion [1]. A primary tumor will eventually be identified in less than 30% patients initially diagnosed with a CUP, while a primary tumor will be found in 50–80% of the remaining cases [2]. The median survival in patients with CUP is 6–12 months, which is generally poor [3]. CUP occurring in the retroperitoneum is extremely rare [4]. We report a case of a CUP with only a retroperitoneal tumor.

CASE PRESENTATION

A 51-year-old man consulted a primary care doctor six months previously, complaining of back pain, which gradually worsened. He was referred to our hospital owing to a suspected metastatic tumor of the lumbar spine observed on the MRI scan. He had no particular medical history, and no notable physical findings were observed. In addition, no abnormalities were observed in the individual nerve reflexes.

Table 1 shows the blood count and biochemical test results at the time of the visit. Notably, the LDH level was slightly high, at 239 U/L. The tumor marker levels were as follows: CEA, 31.9 ng/ml; CA19-9, 49.1 U/ml; CYFRA, 4.6 ng/ml; and NSE, 25.1 ng/ml. Tumor markers such as PSA, IL-2R, and thyroglobulin were negative.

Contrast-enhanced computed tomography (CT) scans from the neck to the pelvis at his first visit revealed uneven enhanced tumor structures protruding into the L2/3 disc (Fig. 1a). Part of the tumor was continuous with the left iliopsoas muscle, with uneven enhancement along this muscle. The possibility of vertebral body or disc-derived tumors, L2/3 discitis, or purulent spondylitis was considered.

Magnetic resonance imaging (MRI) scan showed a heterogeneous T2WI signal in the L2 and L3 vertebral bodies, suggesting a neoplastic lesion with diffuse titration (Fig. 1b).

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Table 1

WBC	7500	/ul	TP	7.5	g/dl	CRP	8.75	< 0.3	mg/dl
RBC	3.64	10^6/ul	Alb	2.9	g/dl	IgG	1375	870-1700	mg/dl
Hb	11	g/dl	GOT	33	U/L	IgA	450	110-350	mg/dl
Ht	33.8	%	GPT	36	U/L	IgM	117	30-180	mg/dl
PLT	33.3	10^4/ul	LDH	239	U/L				
			ALP	498	U/L	CEA	31.9	< 5.0	ng/ml
			Cr	0.65	mg/dl	CA19-9	49.1	< 30	U/ml
			BUN	14	mg/dl	PSA	1.48	< 4.00	ng/ml
			Glu	116	mg/dl	CYFRA	4.6	< 3.5	ng/ml
			Na	138	mEq/L	SCC	2.0	< 2.5	IU/ml
			K	3.9	mEq/L	NSE	25.1	< 16.3	ng/ml
			Cl	99	mEq/L	IL-2R	433	145-519	U/ml
			Ca	8.6	mg/dl	thyroglobulin	< 0.04	< 33.7	ng/ml
						β2microglobulin	2.1	0.9-2.0	mg/L

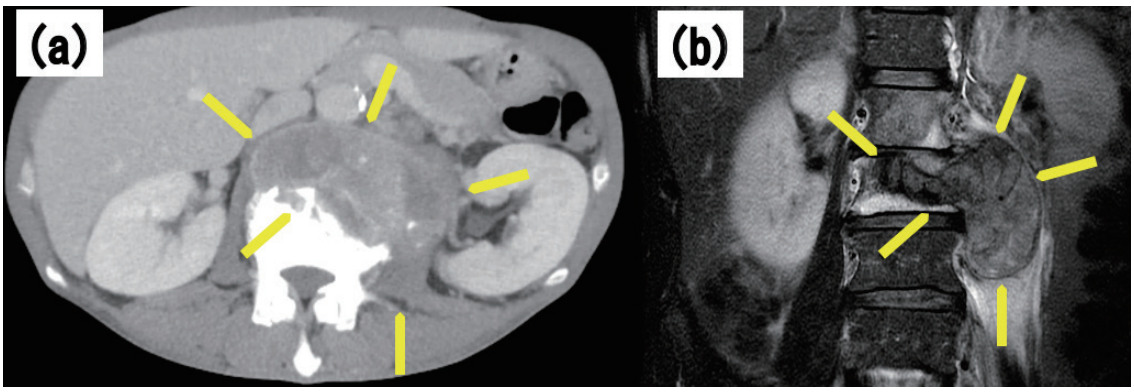

Fig. 1 CT and MRI at first visit.
A suspected retroperitoneal tumor invading the L2/3 from the retroperitoneum (yellow arrow).

A CT-guided needle biopsy was performed to exclude the possibility of retroperitoneal tumors. Tissue was collected from a tumor in the left iliopsoas muscle at the level of the L4 transverse process.

Histologically, the proliferation of atypical cells arranged in sheet-like structures was observed. The atypical cells had clear or eosinophilic cytoplasm and irregular-shaped nuclei (Fig. 2A, 2B). Necrosis and fibrosis were also observed. Immunohistochemistry showed that the atypical cells were positive for cytokeratin AE1&3, CK7, CD10, GATA3, glypican 3, Hep Par 1, carbonic anhydrase 9 (focal), and vimentin (focal), but negative for CK20, CD56, chromogranin A, synaptophysin, TTF1, HMB45, melan A, and PSA (Fig. 2C-2K). The Ki67 labeling index was approximately 40%. The pathological diagnosis was that of poorly differentiated carcinoma. However, it was difficult to determine the primary site from the pathological findings.

To determine the primary tumor, a whole-body search was required, and a positron emission tomography (PET) was performed.

PET examination showed a neoplastic lesion measuring 78 mm in the left iliopsoas muscle at the L2-4 level, indicated by a strong accumulation of fluorodeoxyglucose (FDG) (Fig. 3). The L2 and L3 vertebral bodies were clustered, with the tumor causing bone destruction. Accumulation of FDG was not observed elsewhere.

Abdominal ultrasonography showed no obvious abnormal findings, including in the kidneys. Urological examination showed no abnormal findings, including in the prostate.

Based on the above findings, he was diagnosed with poorly differentiated cancer extending from the retroperitoneum to the lumbar spine.

Treatment was initiated using paclitaxel plus carboplatin (TC). He received paclitaxel (180 mg/m^2) plus carboplatin (AUC 5 mg/mL) for the next 21 days.

After completing 3 courses of TC, he was hospitalized urgently due to worsening lumbago.

The CT and MRI scans at admission showed an increase in the main lesion and exacerbation of bone invasion. Bilateral invasion of the psoas major was observed (Fig. 4). However, since no distant metastasis was found, radiation therapy was administered with curative intent.

Intensity modulated radiation therapy (IMRT) was selected as the radiation modality, and the lesions were irradiated at 39 Gy/13 Fr. The internal dose was increased.

During treatment, the levels of each tumor marker was checked (Fig. 5); CEA, CA19-9, CYFRA, and NSE were measured, and all showed a gradual increase.

Thereafter, his general condition deteriorated gradually, and a decrease in performance state was observed. It became difficult to continue chemotherapy, and he

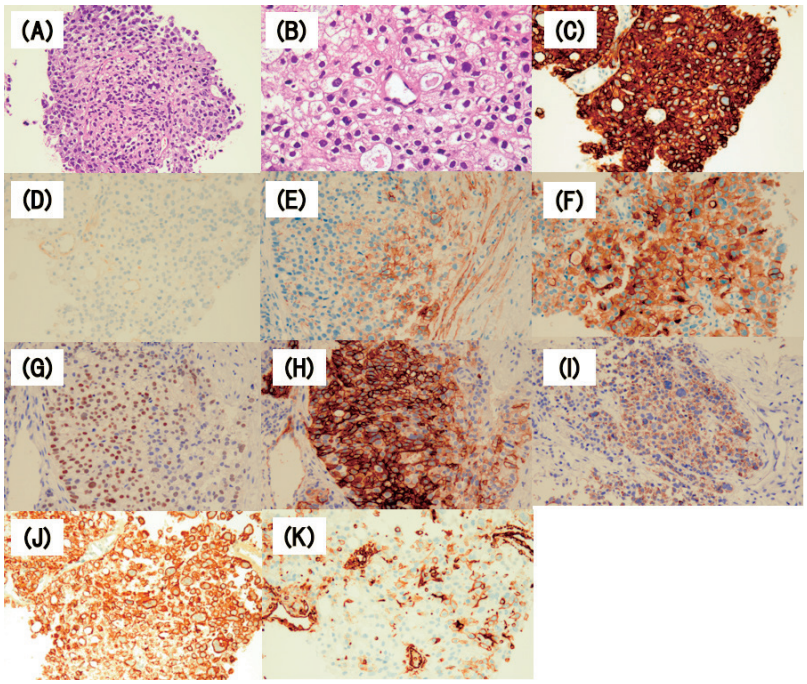

Fig. 2 Histological and immunohistological findings of CT-guided needle biopsy. The proliferation of atypical cells arranged in sheet-like structure are observed. Atypical cells have clear or eosinophilic cytoplasm and irregular-shaped nuclei (HE stain, A: low-power view, B: high-power view). The immunohistochemical findings were as follows: (C) CK7 (+), (D) CK20 (-), (E) carbonic anhydrase 9 (+, focal), (F) CD10 (+), (G) GATA3 (+), (H) glypican3 (+), (I) Hep par 1 (+), (J) cytokeratin AE1&3 (+), and (K) vimentin (+, focal).

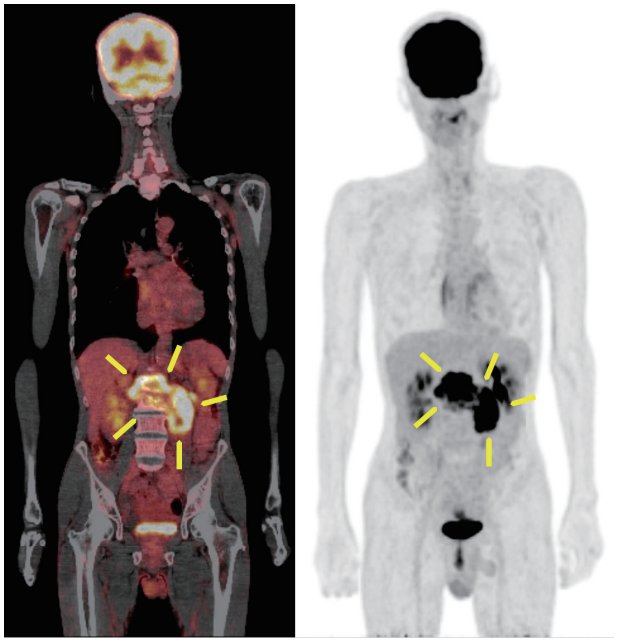

Fig. 3 PET examination. A tumor lesion observed in the left psoas muscle at the L2–4 level, and strong accumulation of FDG was observed, with accompanying bone destruction (yellow arrow). No distant metastases are seen.

was considered for palliative treatment. He died seven months after visiting our hospital, and five months after starting TC therapy.

DISCUSSION

We encountered a case of CUP originating in the retroperitoneum. CUP accounts for 2% of all cancers, based on US statistics [5]; however, there are no reports of morbidity or mortality in Japan. With the improvement of diagnostic technology, the incidence is on a downward trend. Although determining the primary tumor is important, autopsy cannot identify the primary tumors in 20–50% of patients. Therefore, it is important to perform only necessary tests, and

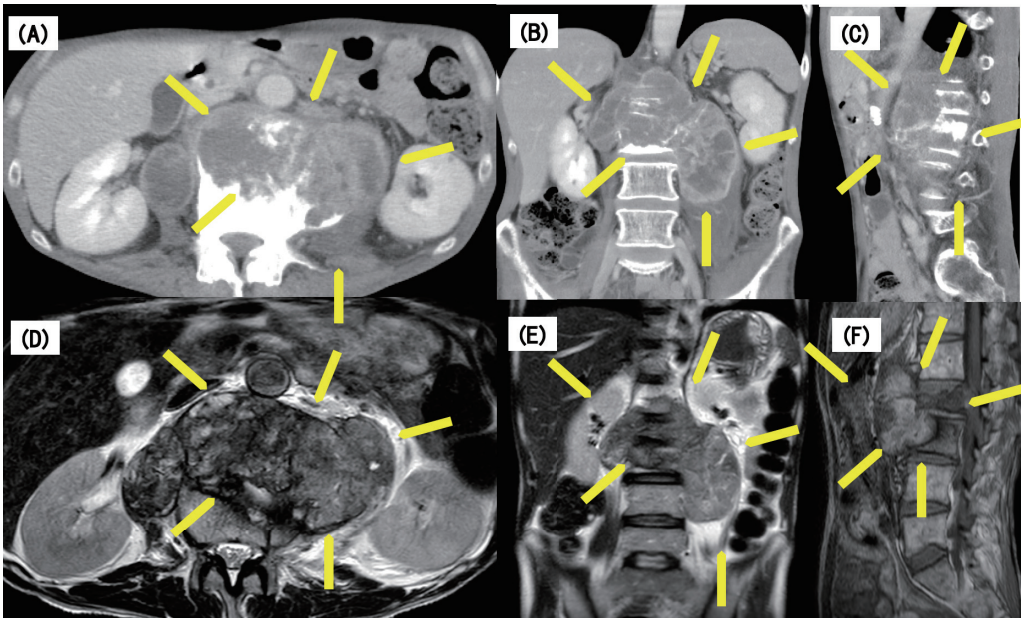

Fig. 4 CT and MRI findings after 3 courses of TC. The main lesion is progressing with invasion into the retroperitoneum and bilateral psoas major muscles.

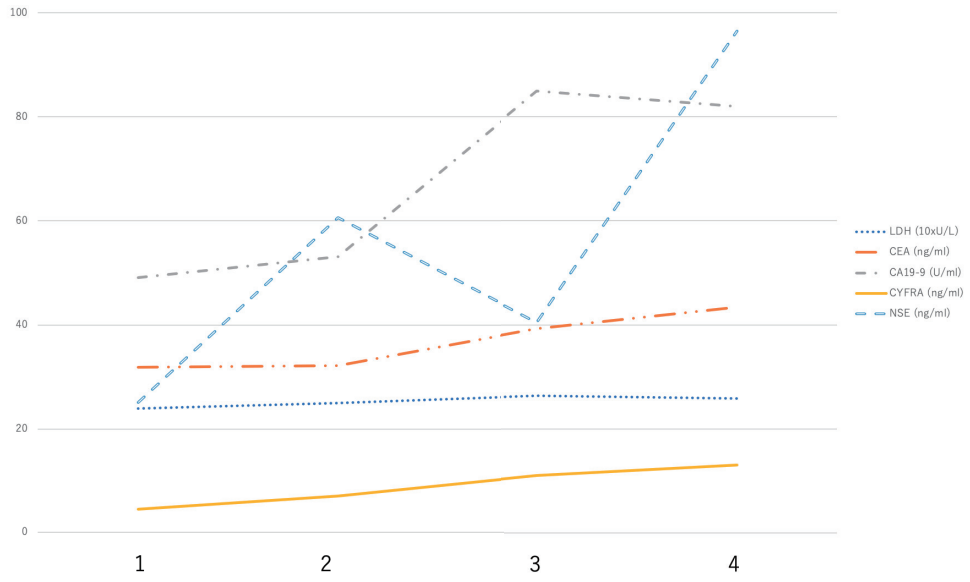

Fig.5 Changes in tumor marker levels. (a) LDH, (b) CEA, (c) CA19-9, (d) CYFRA and (e) NSE: 1 at first visit, 2 at start of chemotherapy, 3 at the end of course 1, and 4 at the end of 3 courses.

allow more time for treatment. According to the NCCN guidelines, it takes approximately one month to diagnose favorable subsets, and the time spent for examination should be one month [6]. In this case, the duration from the patient's visit to the previous physician to the end of the examination was 27 days, and that from the admission to this hospital to the end of the examination was 15 days. The time spent on the tests appeared to be short.

Extragonadal germ cell tumors and malignant paragangliomas are also candidate retroperitoneal tumors in males. In extragonadal germ cell tumors, hCG and AFP are usually measured first if adolescent males have tumors distributed on the central axis of the body, [7]. Unfortunately, these data were not available at the time of the visit. Characteristic hypertension and headache often occur in malignant paraganglioma [8]; however, these findings were absent, and these conditions were therefore excluded. Recommended initial assessment includes contrast-enhanced CT of the chest, abdomen, and pelvis [9]. In this case, CT was performed, and a tumor invading the vertebral body from the retroperitoneum was observed; subsequent PET-CT confirmed no distant metastasis. It is important to exclude renal or urinary malignancies in men with CUP in the retroperitoneum [10]. In this case, in addition to CT and PET, abdominal ultrasonography, PSA measurement, and consultation with a urologist excluded malignant disease.

Histological diagnosis is very important in deciding

treatment for CUP [11]. It is also essential for the diagnosis of favorable subsets. This patient was diagnosed with poorly differentiated carcinoma on HE staining and immunohistochemistry. A combination of CK7 and CK20 is often used to identify the origin of carcinoma of unknown primary site. Representative carcinomas showing CK7(+)/CK20(-) include pancreatic adenocarcinoma, bile duct adenocarcinoma, breast carcinoma, endometrial adenocarcinoma, lung adenocarcinoma, and thyroid carcinoma [12, 13]. As our patient was a man and tumor cells were CK7(+)/CK20(-), metastatic carcinoma of the thyroid, lung, bile duct, or pancreas was suspected; however, no tumor could be clinically detected in each organ. CD10 is often positive in endometrial stromal sarcomas, or renal cell carcinomas [6, 14, 15]. In this case, CD10(+) would indicate renal cell carcinoma; however, as described above, no tumor was detected in the kidneys. Hep Par 1 is a hepatocyte marker but is also positive in various carcinomas such as gastric and colorectal carcinoma [6, 14, 15]; glypican 3 is often positive in hepatocellular carcinoma and in yolk sac tumors, choriocarcinomas, and melanomas [6, 14, 15]. Although Hep Par1 and glypican 3 were positive, the liver was healthy. Based on the above findings, this case was not included in any of the favorable subsets.

CUPs not included in any of the preferred subsets are encouraged to participate in clinical trials under the NCCN guidelines [6]; however, patients do not want to participate.

Despite several phase 3 trials for CUP, there is currently no established standard treatment [16, 17]. Based on reports of superior outcomes with chemotherapy using platinum-based drugs [17], Huebner *et al.* performed a phase II study in 2009, which compared carboplatin plus paclitaxel versus the non-platinum regimen gemcitabine plus vinorelbine [18]; TC is now recommended for CUP, and was administered in this case. The LDH, CEA, CA19-9, CYFRA, and NSE levels were also observed over time; however, none were suitable as treatment endpoints. However, even if TC is administered, the survival period is approximately 10 months, and best supportive care may be an initial treatment option for patients with poor prognostic factors [19].

The patient died 7 months after initiating therapy with TC; this was less than the average survival. This was most likely to be attributable to the reduced performance state due to lower limb paralysis.

Pembrolizumab is indicated for solid tumors with advanced and recurrent microsatellite instability (MSI-High), which worsened after cancer chemotherapy. Based on findings from the phase I KEYNOTE-028 trial [20], which studied pembrolizumab in heavily pretreated patients with a variety of solid tumors, the phase II basket trial, KEYNOTE-158 [21], was designed to evaluate pembrolizumab in 10 different tumor types with neuroendocrine tumors.

Many clinical trials are currently being conducted for CUP, with clinical trials using pembrolizumab [22–24], nivolumab, and ipilimumab [25], and FOLFIRI ± bevacizumab [26].

Further cumulative data from cases receiving various treatments are needed to identify those that are more suitable for CUP.

CONCLUSION

CUP presents with varying symptoms; it is necessary to complete the examination promptly and initiate treatment. Till date, TC therapy has been administered primarily; however, in the future, genetic testing will become widespread, and new drugs such as immune checkpoint inhibitors will be used in more cases.

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