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A Case of Renal Primitive Neuroectodermal Tumor Confirmed by Fluorescence in situ Hybridization

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Key Words

Primitive neuroectodermal tumor · Kidney · Fluorescence in situ hybridization · VDC-IE chemotherapy

Abstract

Primitive neuroectodermal tumor (PNET) is a member of the Ewing's sarcoma family of tumors (ESFT). We report a case of PNET in a 66-year-old male who presented with a large solid tumor within the parenchyma of the middle pole of the left kidney with metastases to the left adrenal gland and right ischium. A fine-needle biopsy was performed and showed a small round cell tumor. Results of immunohistochemical staining suggested this tumor belonged to ESFT. Preoperative VDC-IE (combined vincristine, doxorubicin and cyclophosphamide followed by another combination of ifosfamide and etoposide) chemotherapy and left radical nephrectomy and adrenalectomy were performed. The histopathological findings of the resected tumor were similar to those in the biopsy specimen, but the results of AE1/AE3 were different. For the diagnosis, fluorescence in situ hybridization was performed. Split signals of the EWSR1 gene were detected, and transmission electron microscopy showed neuroendocrine granules and microtubules. The final diagnosis of this tumor was PNET of the kidney.

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Introduction

Primitive neuroectodermal tumor (PNET) is a member of the Ewing's sarcoma family of tumors (ESFT) and has a common chromosomal translocation found in Ewing's sarcomas [1]. Histologically, PNET appears as a small round cell tumor. The first case of renal PNET was described in 1975 [2]. Renal PNET has a poor prognosis because early progression makes treatment difficult. Here, we describe a case of renal PNET that was finally diagnosed by fluorescence in situ hybridization (FISH) and transmission electron microscopy (TEM). It was responsive to preoperative VDC-IE (combined vincristine, doxorubicin and cyclophosphamide followed by another combination of ifosfamide and etoposide) chemotherapy and was subjected to surgical treatment.

Case Report

The patient was a 66-year-old male who visited our hospital with asymptomatic gross hematuria. Enhanced computed tomography (CT), magnetic resonance imaging and bone scintigraphy were performed, and a large solid tumor was found within the parenchyma of the middle pole of the left kidney (fig. 1a).

Metastases to the left adrenal gland and right ischium were detected. The serum level of neuron-specific enolase (NSE) was 110 ng/ml (normal range 0–12 ng/ml). The lesion was diagnosed as a primary renal tumor. On enhanced CT, since the tumor showed no indication of an early enhancement and early washout, it was suspected to be a nonrenal cell carcinoma such as urothelial carcinoma or soft tissue sarcoma. Therefore, a fine-needle biopsy of the left renal tumor was performed and showed a small round cell tumor in the hematoxylin-eosin staining (fig. 1b). From the features of immunohistochemical staining, ESFT was suspected. We performed a standard regimen, VDC-IE chemotherapy for ESFT. Three courses of VDC-IE chemotherapy were applied, and the left renal tumor showed a partial response. The metastatic lesion of the right ischium was stable. Therefore, left radical nephrectomy and adrenalectomy were performed. After surgery, external beam radiation was performed on the metastatic lesion of the right ischium. The patient has no evidence of disease at 4 months after surgery.

Results

The fine-needle biopsy specimen showed a small round cell tumor on the hematoxylin-eosin staining (fig. 1b). Immunohistochemical staining showed that CD99 (fig. 1c), NSE and synaptophysin were positive, and CK7, CK20, AE1/AE3 (fig. 1d), desmin (fig. 1e), SMA, CD45 (fig. 1f) and WT-1 were negative. Thus, this tumor was initially suspected to be in ESFT.

On gross examination of the resected tumor (fig. 2a), the primary tumor mass in the middle pole of the left kidney measured 4 cm in maximum diameter and showed invasion toward the surrounding adipose tissue. On the cut surface, the mass showed a brownish color.

Histopathological tests of the resected tumor showed atypical bare nuclear round cells with scant cytoplasm (fig. 2b), and tumor cells were positive for AE1/AE3 (fig. 2c), CD99 (fig. 2d) and NSE, and negative for CK7, CK20, desmin and SMA. Cellular proliferation, as evaluated by Ki-67 expression in the resected specimen was lower than in the biopsy specimen because of the efficacy of preoperative VDC-IE chemotherapy (fig. 2e, f). For the differential

diagnosis of other small round cell tumors such as small-cell carcinoma, FISH for the EWSR1 gene was performed. One pair of signals split apart due to rearrangement of the EWSR1 gene was detected (fig. 3a), supporting the diagnosis of this tumor in the ESFT. For the differential diagnosis between PNET and Ewing's sarcoma, TEM was performed, and neuroendocrine granules (fig. 3b) and microtubules (fig. 3c) were demonstrated as features of PNET. This enabled us to determine the final diagnosis of this tumor to be a PNET.

For assessment of the therapeutic options, we assessed the expression of c-Kit, PDGFR and VEGF as known growth factors in tumor proliferation. Histopathological tests of the resected tumor showed positivity for PDGFR (fig. 3d) and c-Kit (fig. 3e). The expression of VEGF (fig. 3f) was negative.

Discussion

Ewing's sarcoma and PNET form a single group of bone and soft-tissue tumors called ESFT with typical undifferentiated Ewing's sarcoma at one end of the spectrum and PNET with clear evidence of neural differentiation at the other [3]. PNETs are derived from primitive neural crest cells and are usually found in bone or soft tissues of the extremities, trunk, head and neck, and less commonly in the viscera or kidneys [3–5]. No specific signs of PNET have been described on ultrasonography, CT or magnetic resonance imaging [5]. The typical histological features of renal PNET are monotonous proliferation of immature and small round cells and formation in some rosettes of the Homer-Wright or Flexner types [1]. Immunohistochemical analysis shows high positivity for NSE and CD99, but these are not entirely specific. In some cases, positivity for vimentin and cytokeratin has been detected [1, 6, 7].

It is sometimes difficult to distinguish PNET from other small round cell tumors that localize to the kidney such as small-cell carcinoma, desmoplastic small round cell tumor, neuroblastoma, malignant lymphoma, synovial sarcoma and Wilms' tumor. This is because of the considerable morphological similarity between these tumors as well as the rarity of PNET. Another important criterion is cytoplasmic dense-core membrane-bound neurosecretory granules, a few organelles, and poorly developed cell junctions demonstrated by ultrastructural methods [8]. Ewing's sarcoma and PNET have a common chromosomal translocation $t(11;22)(q24;q12)$, which leads to the formation of the EWL/FLI-1 fusion protein [3]. Finally, the gold standard for the diagnosis is to confirm the characteristic translocation by a molecular biological technique such as FISH to detect EWSR1 gene split signals [9, 10]. In this case, one pair of signals split apart due to rearrangement of the EWSR1 gene was detected, suggesting the diagnosis of this tumor in ESFT. For the differential diagnosis of PNET from ESFT, TEM was performed, and neuroendocrine granules and microtubules were observed as the features of PNET, and the diagnosis of this tumor was finalized.

A standard treatment for advanced renal PNET has not been established because of the rarity of the disease. The recommended treatment for extrasosseous ESFT is with similar regimens as ESFT of bone. Standard chemotherapy for ESFT was performed with VDC and actinomycin D alternating with IE [11, 12]. In this case, VDC-IE was effective and achieved a partial response, and a left nephrectomy was performed. However, because metastatic ESFT relapses at a high rate, another therapeutic option is needed. In a few reports about preoperative chemotherapy for ESFT, the histological response to preoperative chemotherapy was the important predictor of event-free survival [13]. In this case, preoperative chemotherapy was effective according to the Ki-67 immunohistochemistry test.

The expressions of growth factors such as PDGFR, VEGF and c-Kit in ESFT and the effectiveness of tyrosine kinase inhibitors targeted to such growth factors have been reported sporadically [14, 15]. Therefore, an immunohistochemical analysis was performed for the expression of PDGFR, c-Kit and VEGF. The tumor of this patient expressed PDGFR and c-Kit. Some tyrosine kinase inhibitors are known to inhibit PDGFR or c-Kit such as pazopanib, imatinib and sunitinib. Bone marrow hypoplasia developed in this patient as a result of repetitive VDC-IE chemotherapy after surgery. Adjuvant chemotherapy is needed, but repeating VDC-IE chemotherapy is difficult. Consequently, tyrosine kinase inhibitor remains as a potent therapeutic option for this patient.

In summary, we reported a case of renal PNET in which FISH contributed to the final diagnosis. Preoperative VDC-IE chemotherapy was effective and enabled surgical treatment. PNET has a poor prognosis, but tyrosine kinase inhibitor offers promise as a potential therapeutic agent in the future.

Disclosure Statement

There are no potential conflicts of interest.

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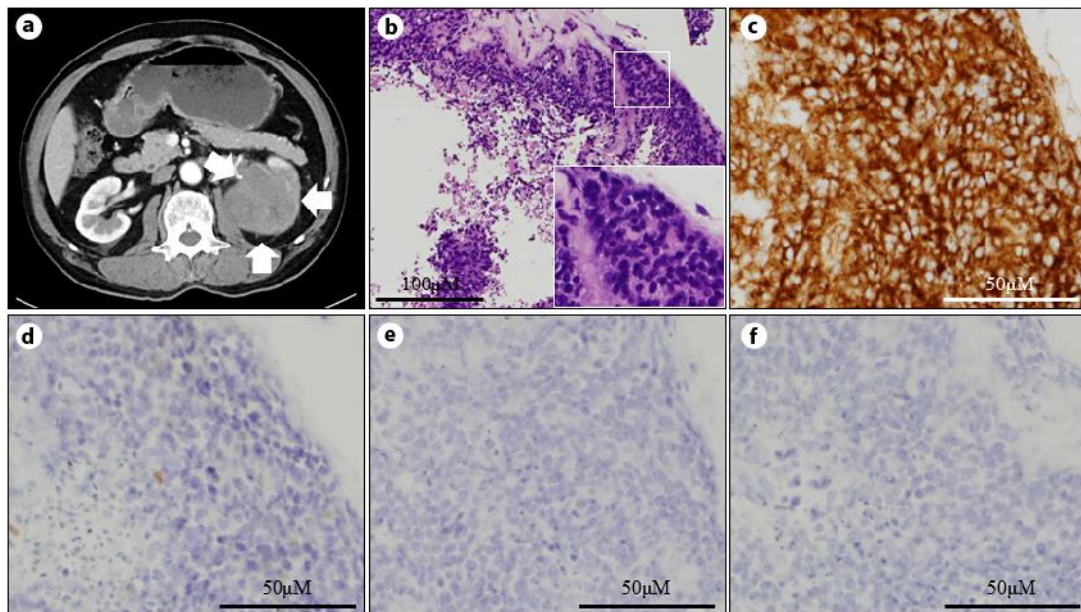


Fig. 1. **a** Enhanced CT showing a large solid tumor within the parenchyma of the middle pole of the left kidney. The renal tumor did not indicate an early enhancement and early washout. **b** Fine-needle biopsy specimen of left renal tumor showing a small round cell tumor on the hematoxylin-eosin staining. **c–f** Immunohistochemical staining of the fine-needle biopsy specimen showing CD99 (**c**) was positive and AE1/AE3 (**d**), desmin (**e**) and CD45 (**f**) were negative.

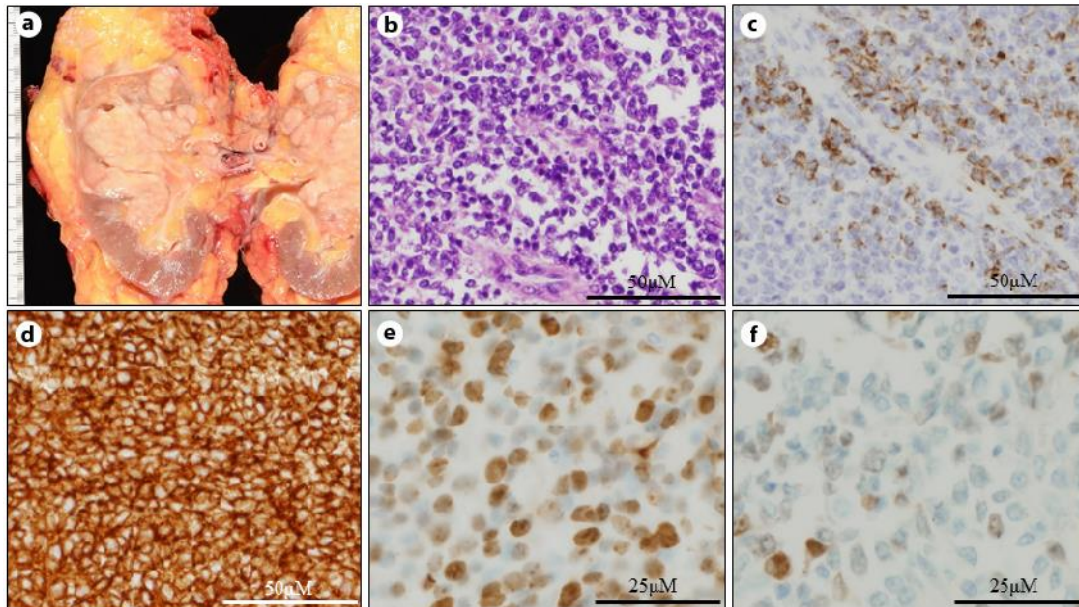


Fig. 2. **a** On gross examination of the resected tumor, the primary tumor mass measured 4 cm in maximum diameter in the middle pole of the left kidney and showed invasion toward the surrounding adipose tissue. On the cut surface, the mass showed a brownish color. **b** Histopathological tests of the resected tumor showing atypical bare nuclear round cells with a scant cytoplasm. **c, d** Immunohistochemical tests of resected tumor showing positivity for AE1/AE3 (**c**) and CD99 (**d**). **e** Immunohistochemical Ki-67 tests of the biopsy specimen. **f** Immunohistochemical Ki-67 tests of the resected specimen. Expression was lower than that of the biopsy specimen.

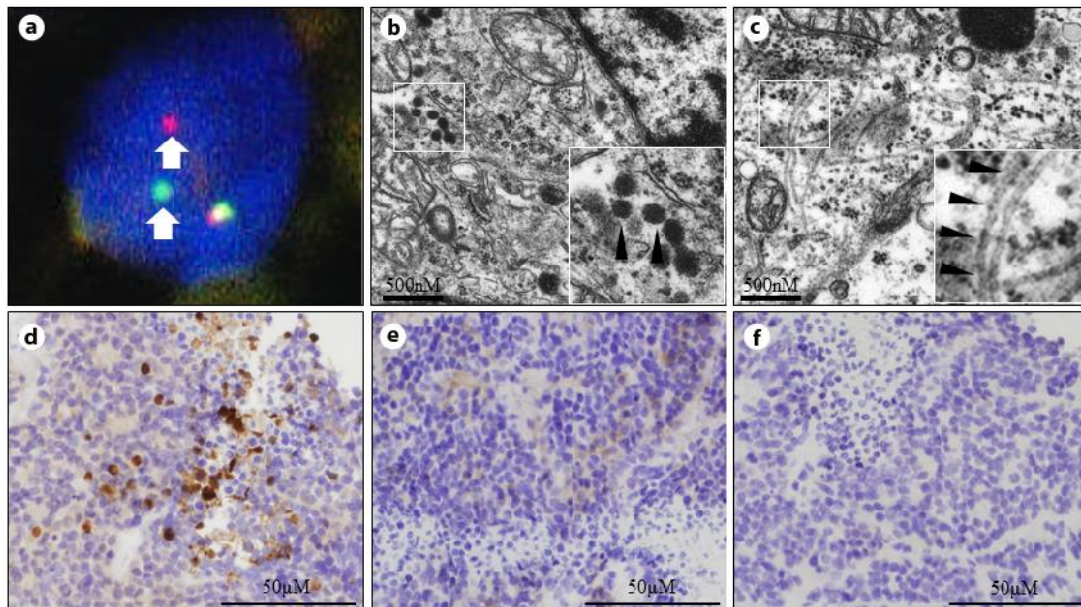


Fig. 3. **a** In FISH analysis, one pair of signals is split apart due to rearrangement of the EWSR1 gene. **b, c** TEM pointed out neuroendocrine granules (**b**) and microtubules (**c**) as features of PNET. **d–f** Histopathological tests of the resected tumor showing positivity for PDGFR (**d**) and c-Kit (**e**). **f** VEGF expression was negative.