

Case Report

Renal primitive neuroectodermal tumor with elevated plasma adrenocorticotrophic hormone levels: A case report

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Abbreviations & Acronyms

ACTH = adrenocorticotrophic hormone
 CD = cluster of differentiation
 CK = cytokeratin
 ESFT = Ewing sarcoma family of tumors
 EWS = Ewing's sarcoma
 EWSR1 = Ewing sarcoma breakpoint region 1
 FISH = fluorescence *in situ* hybridization
 FLI-1 = Friend leukemia integration 1
 LDH = lactate dehydrogenase
 MRI = magnetic resonance imaging
 NK2 = neurokinin 2
 NKX2.2 = Nk2 Homeobox 2
 PNET = primitive neuroectodermal tumor
 RT-PCR = reverse transcription polymerase chain reaction

Introduction: Primitive neuroectodermal tumors are small round-cell tumors – Ewing sarcoma family, frequently occurring in the extremities, but rarely in the kidney.

Case presentation: A 58-year-old woman presented with whole-body edema and weakness of lower limb muscles. Computed tomography revealed a left renal tumor, and the plasma adrenocorticotrophic hormone level was elevated. The tumor was surgically removed without complications, her plasma adrenocorticotrophic hormone reverted to normal levels, and symptoms disappeared after surgery. Histopathological examination revealed a primitive neuroectodermal tumor arising in her kidney. The patient was alive without metastasis 3 years after the surgery.

Conclusion: We report the first case of renal primitive neuroectodermal tumor accompanying elevated plasma adrenocorticotrophic hormone levels which are thought to be produced and secreted in an ectopic fashion.

Key words: ACTH, Ewing sarcoma, kidney, PNET.

Keynote message

Renal PNET is rare. We report the first case of renal PNET accompanying with elevated plasma ACTH, thought to be produced and secreted in an ectopic fashion.

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Received 1 November 2018;
 accepted 15 February 2019.
 Online publication 6 March 2019

Introduction

PNETs are solid tumors histologically consisting of premature small round cells with frequent rosette-like formation. Morphological differential diagnosis of small round-cell tumors is well-known in surgical pathology, but genetic and immunohistochemical analysis contributes to greater accuracy.^{1,2} PNET is a member of the ESFT and shares a common chromosomal translocation with EWS.^{2,3}

Renal primary PNETs are rare but the number of reported cases has increased since the mid-1990s, possibly due to use of immunohistochemistry in differential diagnosis. More than 100 cases of renal primary PNETs have been reported in the English literature.⁴ However, adult PNET with high ACTH has not been reported. Therefore, we report a case of renal primary PNET associated with increased plasma ACTH levels.

Case presentation

A 58-year-old woman presented with 1 month of whole-body edema, moon-like facies, and weakness of lower limb muscles. She had elevated LDH, hypokalemia and hypochloremia. Serum ACTH and cortisol were markedly elevated (Table 1).

Multiparametric MRI demonstrated soft tissue shadows protruding from the renal pelvis to the dorsal cortex and further backwards, with surrounding hematoma (Fig. 1a).

Table 1 Pre- and postoperative laboratory findings

	Pre-operative	Post-operative	Normal range (unit)
Body weight (kg)	64	59	
LDH	652	188	119–229 (U/L)
Potassium	1.6	4.8	3.5–5.0 (mmol/L)
Chloride	92	110	98–108 (mmol/L)
ACTH	384.9	32.8	7.2–63.3 (pg/mL)
Cortisol	44.3	14.4	4.5–21.2 (µg/dL)
Adrenaline	0.02	0.03	<0.17 (ng/mL)
Noradrenaline	0.47	0.55	0.15–0.57 (ng/mL)
Dopamine	<0.01	<0.02	< 0.03 (ng/mL)

In enhanced computed tomography, it was hypovascular tumor and both adrenal glands were normal size (Fig. 1b). If ACTH stimulation continued for long time, the adrenal gland might have showed hypertrophy. But it took only 1 month from the onset of syndrome to diagnosis.

Although we could not confirm the brain before surgery, no tumor was observed in the pituitary gland in brain MRI on day 5 after surgery (Fig. 1d).

A left renal tumor with hematoma was clinically diagnosed and radical left nephrectomy was performed.

Macroscopically, intratumoral hemorrhage and necrosis were observed, protruding from the renal pelvis to outside of the kidney, measuring 7 cm in greatest diameter (Fig. 1c).

Histopathology of the resected tumor revealed diffuse proliferation of small cells with a high nuclear-cytoplasmic ratio in most of the tissue specimens. Nuclear mitoses were scattered, and rosette formation was detected (Fig. 2a).

Immunohistology revealed that the tumor cells were diffusely positive for CD99 (Fig. 2b). FISH analysis of translocations related to the EWSR1 gene revealed a split signal, suggesting a translocation associated with EWSR1 (Fig. 2d).

Based on these findings, the tumor was diagnosed as renal PNET. The edema improved and body weight decreased by 4.7 kg after surgery. The white blood cell count and serum levels of LDH, potassium, and chloride were also normalized, as were both ACTH and cortisol following surgery.

The patient was alive without recurrence 3 years after surgery, and ACTH and cortisol levels were also within normal range at the time of last evaluation.

Discussion

We reported a case of renal PNET with elevated plasma ACTH levels.

PNET is generally postulated to originate from neural crest, embryonic, or mesenchymal stem cells, but exact origins remain unknown.^{2,5} PNET commonly develops in the limbs or soft tissues of young adults,³ but rarely in kidneys. The first case of renal PNET was reported by Seemayer *et al.* in 1975.⁶

Hamidi *et al.* reported most of the patients are observed in a range of 10–39 years of age, most common symptoms are abdominal pain (68–85%), 3- and 5-year overall survival rates in patients with renal PNET were 42–60%.⁷

Ellinger *et al.* showed the PNET on urogenital organs may show good prognosis if it is not palpable and is a localized disease.⁸

Because our case fulfilled these conditions, the patient was able to survive for more than 3 years.

Histologically, PNET is composed of premature small round cells that are sometimes arranged to form rosettes. Intratumoral hemorrhage and necrosis are often detected and histopathological features of PNET can vary greatly, resembling clear cell sarcoma or malignant peripheral nerve sheath tumor.^{3,9} Therefore, histological differential diagnosis can include blastemal dominant Wilms tumor, metastatic neuroblastoma, rhabdomyosarcoma, lymphoma, synovial sarcoma,

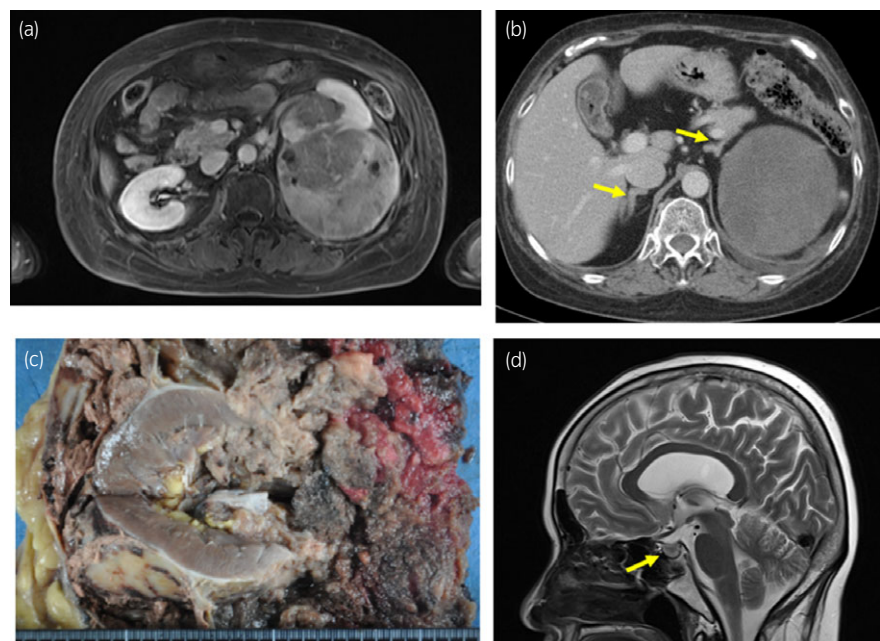


Fig. 1 MRI showing PNET protruding from the renal pelvis to the dorsal cortex with hematoma (a). Enhanced computed tomography with contrast medium showing the large hypovascular tumor and normal adrenal glands (arrow) (b). The tumor was associated with hemorrhage and necrosis (c). Brain MRI showed the hypophysis was normal in size (arrow) (d).

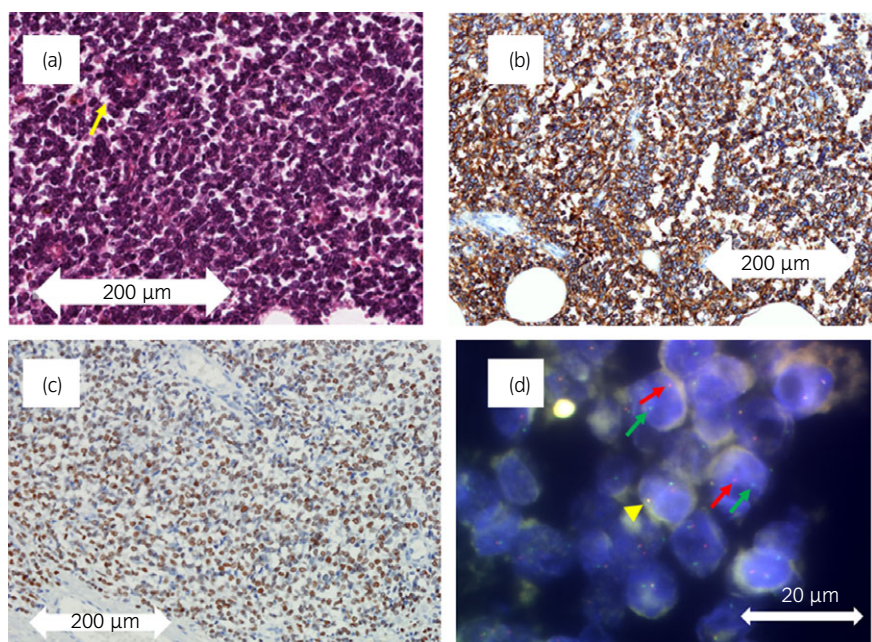


Fig. 2 Diffusely proliferated small tumor cells forming rosettes (arrow) on H&E (a). Immunostaining for CD99 (b) and NKX2.2 (c). A split signal was observed via FISH using an EWSR1 dual color break apart probe. In normal cells, the red and green signals are very close or appear yellow (yellow arrowhead). In gene-translocated cells, two signals are split (green and red arrows) (d).

and other rare malignancies. In addition, these small round-cell tumors are often undifferentiated, which can make histopathological differential diagnosis more difficult. Therefore, both immunohistochemistry and molecular studies are needed for accurate diagnosis.¹

PNET is positive for CD99 and FLI-1, but Wilms tumor, neuroblastoma, rhabdomyosarcoma, and synovial sarcoma may also be positive for these markers.⁹ Therefore, extensive immunohistological analysis is generally required for definitive diagnosis, as in this case (Table 2).

Table 2 Results of immunohistochemical staining

Antibody	Target	Result
CD45	pan Leukocyte	Negative
CD3	pan T cell	Negative
CD20	pan B cell	Negative
CD10	B-cell ABL2	Negative
CK AE1/3	Multi-cytokeratin	Negative
CK7	Epithelial tumor	Negative
CK20	Epithelial tumor	Negative
Chromogranin A	Neuroendocrine tumor	Negative
Synaptophysin	Neuroendocrine tumor	Positive
S100	Nervous system	Partly positive
CD56	NK/neuroendocrine tumor	Partly positive
CD57	NK/neuroectoderm	Partly positive
CD117	Stem cell	Negative
CD34	Stem cell, vascular endothelial	Negative
CD99	MIC2	Positive
Desmin	Muscle	Negative
HHF35	Muscler actin	Negative
Wilms tumor 1	Wilms tumor, renal cancer	Negative
HMB45	Melanoma	Negative
FLI-1	EWS	Partly positive
NKX2.2	EWS	Positive
ACTH	ACTH	Negative

The NKX2.2 antibody has recently been reported as a useful diagnostic marker of ESFT. NKX2.2 is a member of the nuclear transcription factor NK2 family and the EWS/FLI-1 fusion protein produced via translocation is considered to act on nuclear NKX2.2, thereby contributing to tumorigenesis and metastasis.⁹ In the present case, the tumor cells were immunohistochemically positive for NKX2.2 in the nuclei, consistent with the diagnosis of PNET (Fig. 2c).

Genetic testing can be very useful in the definitive diagnosis of PNET. As PNET shares a common chromosomal translocation at (11; 22) (q 24; q 12) with EWS, it is now regarded as a member of the ESFT.⁵ Molecular-level analysis via RT-PCR is highly specific but requires frozen tissue specimens because fusion transcripts are not always detectable in 10% formalin-fixed and paraffin-embedded tissue. Therefore, RT-PCR cannot be performed in the great majority of cases because the diagnosis was made in 10% formalin fixed and paraffin embedded tissue specimens. Therefore, FISH using formalin-fixed specimens has been extensively applied to detect EWS gene rearrangements.¹⁰ In the present case, EWS translocation was also detected via FISH.

ACTH and cortisol levels were elevated. When the plasma level of cortisol increased, normally ACTH level would be reduced by negative feedback. But in this case, both plasma levels were elevated. Moreover there was no tumor in hypophysis. Therefore we highly suspected that ACTH have been autonomously produced. A dexamethasone suppression test should have been performed to identify the cause of elevated ACTH, but surgery was prioritized. After the tumor was removed, both hormone levels markedly decreased, suggesting that ACTH was ectopically produced in this resected tumor. However, the tumor was immunohistochemically negative for ACTH.

We therefore speculated that ACTH levels in this large tumor might have been below the detection limit of the antibody used in immunohistochemistry; however, such a large

tumor may be able to produce sufficient ACTH to raise the level in plasma.

In another way of thinking, if the ACTH producing cells was present in a very limited part of the tumor, it may be difficult to find. Anyway further investigation is required for clarification.

To the best of our knowledge, ESFT with elevated ACTH levels has been reported in two children with EWS.¹¹ Including our patient, these three cases suggest that some ESFTs may be associated with ACTH production. EWS/FLI-1 fusion protein may be involved, as a reported transcriptional modulator for oncogenic transformation.¹²

In summary, we report the first case of renal PNET with elevated ACTH and cortisol levels. However, the relationship between ESFT and ACTH production remains unknown. Further research is needed to clarify the pathogenesis of PNET and ACTH-producing tumors.

Conflict of interest

The authors declare no conflict of interest.

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Editorial Comment

Editorial Comment to Renal primitive neuroectodermal tumor with elevated plasma adrenocorticotrophic hormone levels: A case report

I read with great interest the case report by Shimizu *et al.*¹ The authors presented an interesting renal primitive neuroectodermal tumor (PNET) case. This case is very interesting in terms of patient's symptoms and age at admission and survival. The patient was 58 years old and her symptoms were whole-body edema and weakness of lower limb muscles at the time of admission. The patient was alive without recurrence 3 years after surgery.

The PNET are part of Ewing's sarcoma family of tumors and it is usually encountered in the bone and soft tissue of young adults.^{2,3} In the majority of cases, patients were metastatic at diagnosis or became metastatic after a few months confirming the aggressive nature of this tumor.

To date, more than a hundred cases of renal PNETs have been reported in the current English literature. Recently, the largest meta-analysis studied 116 cases of renal PNET.⁴ The median age of the cohort was 28 years (range 20–42) with 22% of patients with an age of 15 years or less. The most frequent symptoms were pain (54% of patients), hematuria (29% of patients), and renal mass (28% of patients). One third of patients were metastatic at diagnosis and 40% of non-metastatic patients developed metastasis after radical

nephrectomy. In this cohort, median overall and median disease-free survival were 26.5 and 5.0 months, respectively.

More interestingly, in Shimizu *et al.*'s case, the patient had renal PNET accompanying elevated plasma adrenocorticotrophic hormone levels.¹ Ectopic adrenocorticotropin syndrome could be seen as paraneoplastic syndrome and it has been attributed to ectopic adrenocorticotropin secretion, which may result in several types of tumors. However, ectopic adrenocorticotropin syndrome due to PNET is extremely uncommon. The diagnosis of ectopic adrenocorticotropin syndrome was established based on the presence of adrenocorticotropin seen on immunohistochemical staining of the tumor, the disappearance of symptoms, as well as a decrease and normalization of plasma adrenocorticotropin and cortisol levels after resection of the tumor.

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DOI: 10.1002/iju.5.12063