

Case Report

Ewing sarcoma/peripheral primitive neuroectodermal tumor of the kidney: report of two cases

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Abstract: Ewing sarcoma/peripheral primitive neuroectodermal tumor (ES/pPNET) arising in the kidney is very rare, and only a few cases have been reported. Here we present two cases of renal ES/pPNET with different prognosis. Both patients underwent radical nephrectomy. One patient had complex EWSR1 gene chromosome translocation, high Ki-67 proliferative index and died of metastatic disease 2 months after surgery. The other patient had conventional EWSR1 gene translocation, low Ki-67 proliferative index and is alive with no evidence of disease after 4 year follow-up.

Keywords: Kidney, Ewing sarcoma/peripheral primitive neuroectodermal tumor, immunohistochemistry, fluorescence in situ hybridization

Introduction

Ewing sarcoma/peripheral primitive neuroectodermal tumor (ES/pPNET) is a small round cell sarcoma of presumed neuroectodermal origin which typically originates in bone or soft tissue. ES/pPNET is rare in the kidney [1], and generally occurs in young adults and exhibits highly aggressive biological behavior [2]. Here we present two cases of renal ES/pPNET.

Materials and methods

Patient 1

A 27-year-old female presented with lumbar pain which radiated to the lower limbs. At presentation, she had bloody urine and an aching sensation in her upper limbs. Ultrasound and CT scanning revealed a 17 × 17 × 10 cm³ solid-cystic right renal mass. The patient was clinically diagnosed as renal cancer and underwent a right radical nephrectomy. This tumor involved the upper part of kidney, was adherent to the liver and grossly measured 17 cm in greatest dimension. It was poorly-circumscribed and composed of solid and cystic areas. Microscopically, the tumor was composed of

monomorphic small round cells. Homer-Wright rosettes and significant mitotic activity were present (**Figure 1A**). Immunohistochemical staining showed that tumor cells were positive for CD99 (**Figure 1B**), Synaptophysin, Chromogranin A, NSE, Fli1 (**Figure 1C**) and S-100, and negative for LCA and AE1/3. Approximately 30% of tumor cells were positive for Ki-67 (**Figure 1E**). Fluorescence in situ hybridization (FISH) analysis showed rearrangement of the EWSR1 region in 22q12 consisting of 2 patterns of split signals: Sixty seven percent (67%) of tumor cells showed 1 fusion together with two separated red signals and 1 separate green signals, while 15% of tumor cells showed 1 fusion, together with 1 pair of separated green and red signals (**Figure 1D**). The patient died 2 months after surgery secondary to bone metastasis.

Patient 2

A 24-year-old female presented with right lumbar pain which increased in severity upon movement. A CT scan revealed a 16 × 15 × 13 cm³ mass in the right kidney with tumor thrombus in the inferior vena cava (IVC) (**Figure 2A**). The patient underwent right radical nephrectomy

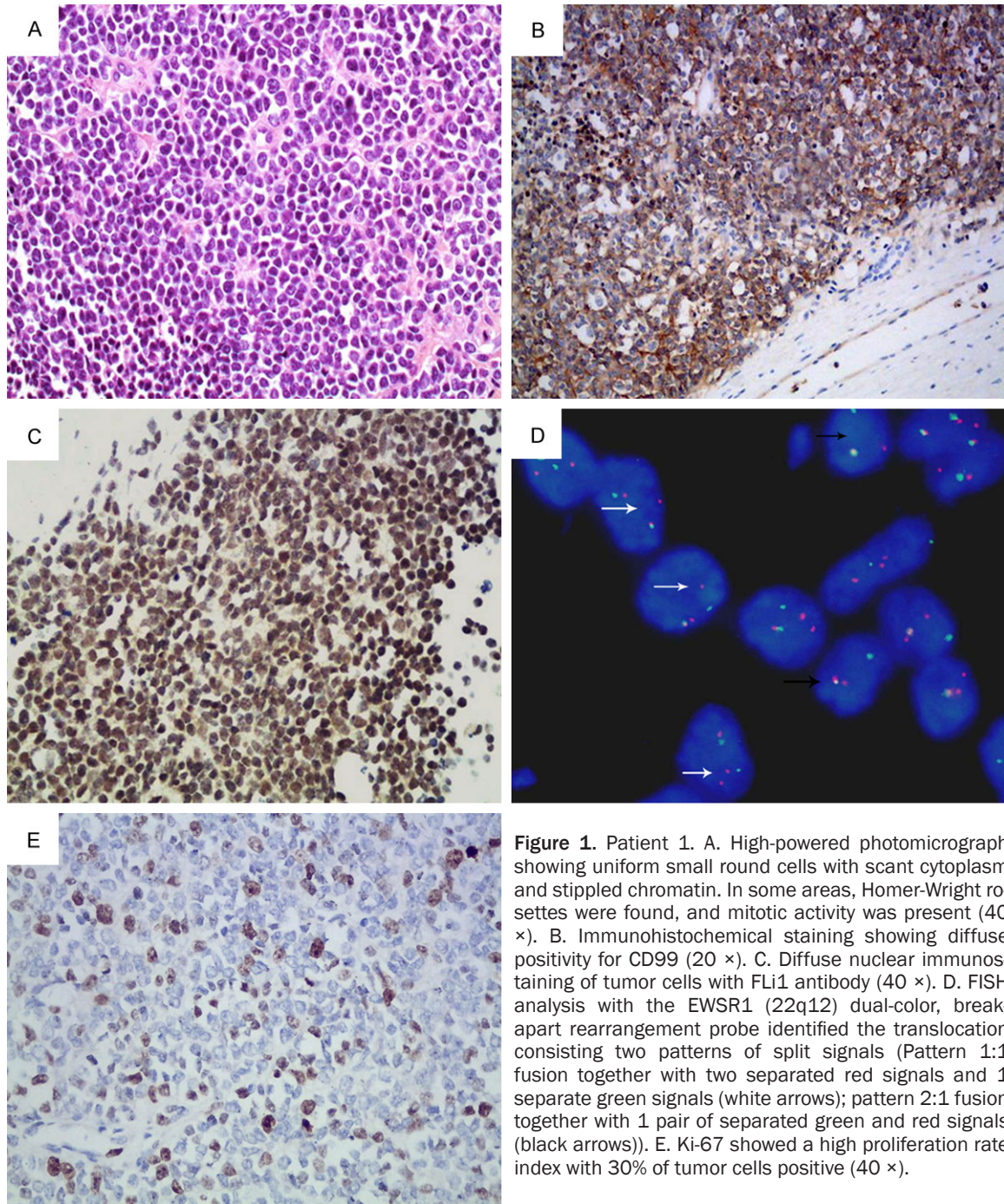


Figure 1. Patient 1. A. High-powered photomicrograph showing uniform small round cells with scant cytoplasm and stippled chromatin. In some areas, Homer-Wright rosettes were found, and mitotic activity was present (40 ×). B. Immunohistochemical staining showing diffuse positivity for CD99 (20 ×). C. Diffuse nuclear immunostaining of tumor cells with Fli1 antibody (40 ×). D. FISH analysis with the EWSR1 (22q12) dual-color, break-apart rearrangement probe identified the translocation consisting two patterns of split signals (Pattern 1:1 fusion together with two separated red signals and 1 separate green signals (white arrows); pattern 2:1 fusion together with 1 pair of separated green and red signals (black arrows)). E. Ki-67 showed a high proliferation rate index with 30% of tumor cells positive (40 ×).

with IVC thrombectomy. Grossly, the kidney was dramatically enlarged and was largely replaced by a $16 \times 15 \times 12 \text{ cm}^3$ solid-cystic mass. Histologic examination revealed islands of uniform small round blue cells with scant cytoplasm, uniform nuclei, and stippled chromatin (**Figure 2B, 2C**). The mass excised from the IVC was histologically identical to the neoplasm in the kidney. Tumor cells were strongly positive

for CD99 (**Figure 2D**), Fli1. The tumor was negative for Synaptophysin, CD10 and AE1/3. Approximately 5% of tumor cells were positive for Ki-67 (**Figure 2F**). FISH analysis with the EWSR1 (22q12) dual-color, break-apart rearrangement probe identified the translocation involving the EWS locus consisting of 1 fusion and 1 pair of separated green and red signals (**Figure 2E**). The patient is alive without evi-

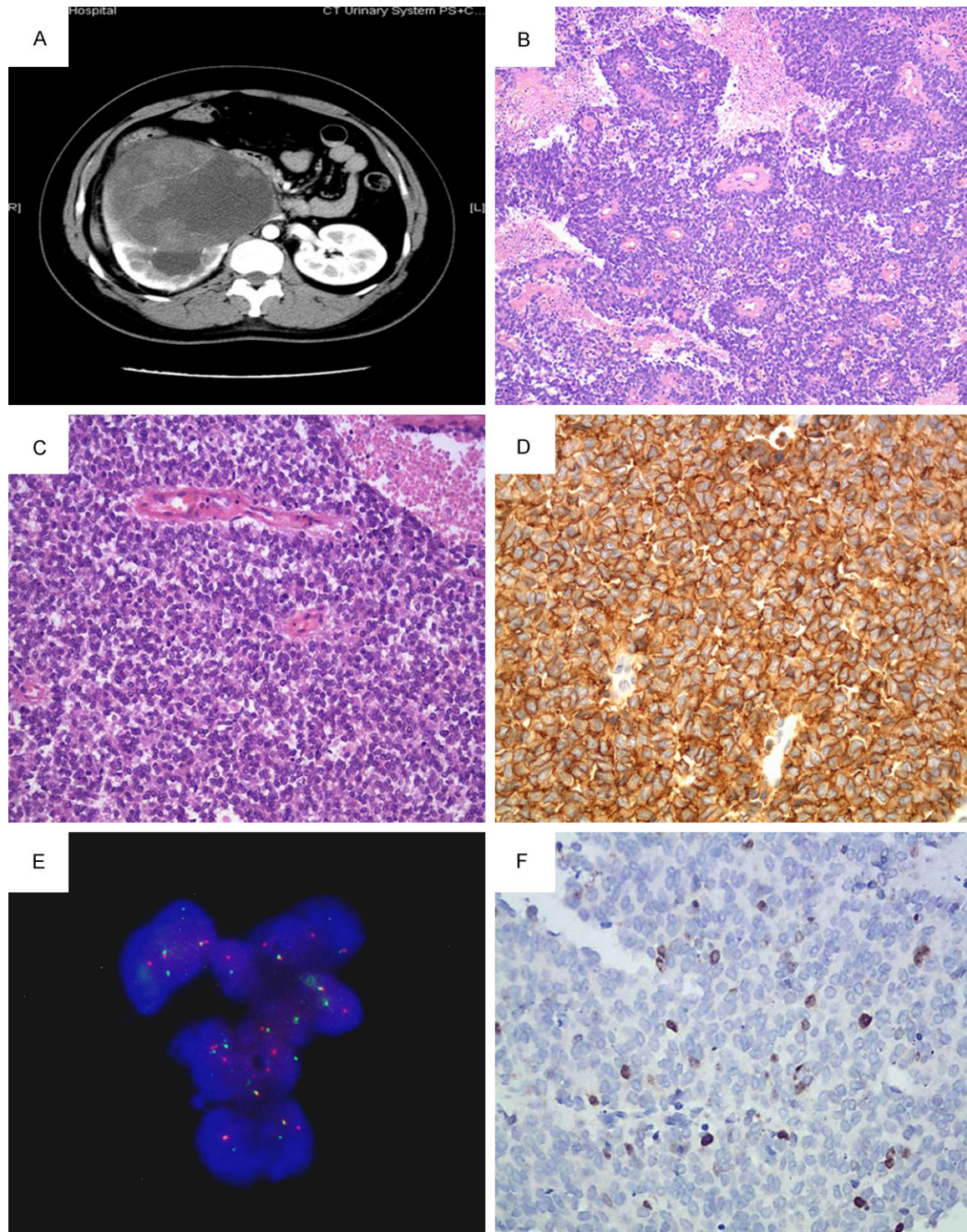


Figure 2. Patient 2. A. Preoperative computed tomography scans of the abdomen in transverse views revealing a right renal mass. B. Microscopic photography showing tumor cells arranged in solid sheets and tightly packed cords intermixed with blood (4 ×). C. High power photomicrograph showing uniform small round blue cells with scant cytoplasm, uniform nuclei, and stippled chromatin (20 ×). D. Tumor cells were strongly positive for CD99 in the membrane (40 ×). E. FISH analysis with the EWSR1 (22q12) dual-color, break-apart rearrangement probe identified the translocation involving the EWS locus consisting of 1 fusion and 1 pair of separated green and red signals. F. Ki-67 showed a low proliferation rate index with 5% of tumor cells positive (40 ×).

dence of recurrence after 4 years follow-up after diagnosis.

Discussion

Renal ES/pPNET is usually not identified at an early stage because of the rapid growth of this neoplasm and its deep location. In both of these cases, the renal masses were very large at the time of discovery, and both cases were clinically misdiagnosed as renal cell carcinoma [3, 4].

The differential diagnosis of ES/pPNET in the kidney is broad and includes small cell neuroendocrine carcinoma, lymphoma, desmoplastic small round cell tumor, neuroblastoma, synovial sarcoma, neuroepithelial tumor, and Wilm's tumor. There is considerable morphologic and immunohistochemical overlap among these tumors [4], and accurate diagnosis of ES/pPNET must incorporate several different diagnostic modalities [5]. Morphologic findings and immunohistochemistry are critical in ES/pPNET diagnosis, as they may be used to exclude many neoplasms from the differential diagnosis at the outset. CD99 and Fli1 are the primary positive markers for diagnosis of ES/pPNET, but can also be positive in variety of non-ES/pPNET including Wilm's tumor, vascular malignancies, lymphoblastic lymphoma, and neuroendocrine tumors which may confound the diagnosis. Cytogenetics thus plays a critical role in the diagnosis of this poorly differentiated neoplasm. EWSR1 gene rearrangements on chromosome 22 have been suggested as a useful tool for confirming ES/pPNET [6-8]. However, t(11;22) can also be seen in desmoplastic small round cell tumor and rhabdomyosarcoma [9, 10]. Nonetheless, in the context of appropriate histologic findings and immunohistochemical profile, the diagnosis of ES/pPNET can be made with certainty.

It is of interest that our FISH study demonstrated two patterns of split signals using FISH with the EWSR1 break-apart rearrangement probe in patient 1 (**Figure 1D**), in contrast to patient 2 (**Figure 2E**) where only one pattern of split signals (consisting of 1 fusion and 1 pair of separated green and red signals) was found. This phenomenon has not previously been described in ES/pPNET. This intriguing observation indicates that there is another translocation within -500 kb flanking the 5' side of the EWSR1 gene

(22q12), in addition to the well-known location of the EWSR1 gene translocation. This complex chromosome translocation suggests that the tumor may have dynamic change in the genome resulting in genomic instability and acquire more capabilities for tumor growth and progression. Whether this phenomenon is associated with high tumor cell proliferation index and poor prognosis in this patient warrants further study.

Renal ES/pPNET with IVC tumor thrombus is very rare [11]. To date, data on surgical outcome and prognosis after radical nephrectomy and thrombectomy are sparse. In this report, the patient 2 is still alive without evidence of recurrence after a 4 year follow-up. Although this follow-up period is limited, it suggests IVC tumor thrombus in renal ES/pPNET is not associated with survival after aggressive surgical resection. The proliferation index determined with Ki-67 is used widely as a significant independent prognostic marker in a variety of malignancies including ES/PNETs [12], and high percentages of Ki-67-positive tumor cells correlate with tumor progression and unfavorable clinical outcome. In this report, Ki-67-positive tumor cells in patient 1 (30%) are much higher than that in patient 2 (5%), which is consistent with the significantly poorer prognosis in this patient (case 1).

In summary, we have presented two rare cases of primary renal ES/pPNET with different prognosis. Both patients underwent nephrectomy. One patient died of metastatic disease 2 months after surgery and the other is alive with no evidence of disease after 4 year follow-up.

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Disclosure of conflict of interest

None.

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