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Primary Ewing sarcoma/Primitive neuroectodermal tumor of the kidney: an aggressive neoplasm mimicking Wilms tumor

Pathology

KEYWORDS: Renal tumor, Ewing sarcoma, Primitive neuroectodermal tumor (PNET), t(11,22) translocation.

Dr.Smrita Singh	MBBS, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India
Dr. Premalata Chennagiri S	MD Pathology, Professor, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India
Dr. Kavitha B.L	MD Pathology, Associate Professor, Department of Cytogenetics, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India
Dr. Prasanna Kumari	PhD, Professor, Department of Cytogenetics, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India
Dr. Madhu S.D	DNB Radiology, Assistant Professor, Department of Radiology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India
Dr. Rekha V. Kumar	MD Pathology, Professor, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India

ABSTRACT

Ewing sarcoma/Primitive neuroectodermal tumors (ES/PNET) constitute a family of neoplasms of presumed neuroectodermal origin most often presenting as bone or soft tissue masses. These neoplasms can rarely affect the kidney mimicking Wilms tumor. There are few reported case series and scattered case reports of ES/ PNET of the kidney in the world literature. Six cases of primary renal ES/PNET were retrieved from the histopathology records at our institute over a period of three years and the pathology and immunohistochemical slides reviewed along with the cytogenetic analysis/fluorescence in-situ hybridization (FISH) reports and the clinical details. The diagnosis was confirmed for the presence of t(11;22) either by karyotyping or FISH (EWSR1) the hallmark of this family of tumors. The diagnosis of primary renal Ewing sarcoma/PNET can be difficult and often requires confirmation by cytogenetics or FISH in addition to immunohistochemistry.

Introduction

Ewing sarcoma/Primitive neuroectodermal tumor (ES/PNET) family are a group of malignant small round cell tumors believed to arise from the neuroectoderm. Historically, Ewing sarcoma and primitive neuroectodermal tumors were considered to be separate pathologic entities; however, molecular studies have established that these tumors are a part of the same tumor family and exhibit similar biologic behaviour. As such, the term Ewing sarcoma now encompasses both entities.[1] ES/PNETs are most commonly identified in the axial skeleton, appendicular skeleton and central nervous system; however extracranial and extraosseous tumors have also been described.[2] ES/PNETs of the kidney are uncommon and are often mistaken for Wilms tumor in the preliminary workup as the age of occurrence, imaging findings and morphology can be similar in both. They were first reported by Seemayer and colleagues in 1975.[3] Parham DM *et al*, published a large cohort of 146 primary malignant neuroepithelial tumors of the kidney from the National Wilms tumor study group pathology center.[4] In their study, majority of the patients were in the age group of six to thirty five years and the authors also contended that many of the PNETs of the kidney are often misdiagnosed as blastemal predominant Wilms tumor. The histopathological diagnosis of ES/PNET is currently based on light microscopic, immunohistochemical and electron microscopic features. The definitive t(11;22)(q24;q12) translocation or variant translocations always involve the *EWS* gene at 22q12 resulting in a chimeric transcript.[5] The presence of this translocation needs to be demonstrated by cytogenetic studies or *in-situ* hybridization (ISH) for confirming the diagnosis.

Materials and methods

This study was conducted in the Department of Pathology at our institute. Six cases of histopathologically diagnosed primary ES/PNET of the kidney were retrieved from the departmental records over a period of three years (2012-2014). The clinical and radiological findings were collected from the patients' medical records and analysed.

Results

All the patients were less than 30 years of age with an age range of seven months to twenty eight years, four were male and two were female. All the patients presented either with flank and/or abdominal pain, an abdominal mass and hematuria. Systemic symptoms such as fever (all six cases) and weight loss (two out six cases) were also present. The right kidney was involved in four out of six cases. Three cases had metastases at presentation. Abdominal ultrasound showed a heterogenous vascular mass in the upper pole of the kidney with tumor thrombus extending into the renal vein and/or inferior vena cava (IVC) in five cases which is a significant finding in our case series. In one case the tumor involved the whole kidney. Computed tomography (CT) abdomen, plain and contrast showed large heterogenous renal masses with areas of haemorrhage and necrosis in all the six cases. Calcification was seen in one case. The presence of tumor thrombus in the renal vein and/or IVC in five cases was confirmed by CT scan (Figure 1). The size of the tumor varied from 14.7 cm to 20 cm. Three of the six cases developed hepatic metastases, of which, two also had splenic metastases with peritoneal deposits. One case had vertebral body and bilateral lung metastases at the time of diagnosis and one case had local recurrence. Radiologically, a diagnosis of Wilms tumor was rendered in all the six cases.

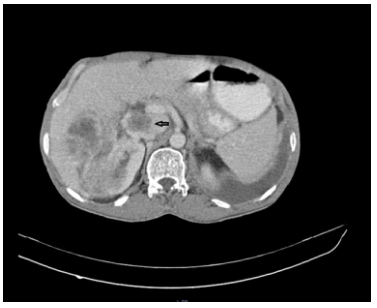

Figure 1. CT scan (contrast) showing tumor in the left kidney with IVC tumor thrombus

Ultrasound (USG) guided fine needle aspiration cytology (FNAC) was done in four cases. All the cases underwent radical nephrectomy (two of the six cases were operated outside) followed by eight cycles of chemotherapy (Vincristine, doxorubicin, cyclophosphamide alternated with etoposide and ifosfamide). Grossly, there was capsular breach in two cases and the renal vein and sinus showed tumor in the four cases operated at our institute. Paraffin blocks were available for the two cases operated outside. Histopathological examination of all the cases showed a neoplasm composed of sheets of small, fairly uniform cells with round to oval nuclei, finely dispersed chromatin, inconspicuous nucleoli and scant, ill-defined eosinophilic cytoplasm (Figure 2A, 2B). Homer-Wright rosettes were noted (Figure 2C). Areas of necrosis and haemorrhage were present. No epithelial component in the form of tubules or stromal component was found even after extensive sampling. Immunohistochemistry was performed and in all the six cases, the neoplastic cells showed strong membranous positivity for CD99 (MIC 2) (1:80; Biogenex) (Figure 2D). The neoplastic cells were negative for WT1 (1:80; Dako), synaptophysin (1:80; Biogenex), chromogranin (1:300; Biogenex), desmin (1:100; Biogenex), myogenin (1:125; Biogenex), cytokeratin (1:50; Biogenex) and leukocyte common antigen (LCA) (1:45; Biogenex), supporting the diagnosis of ES/PNET. Bone marrow aspiration and biopsy was performed and the bone marrow was not involved in any of the six cases. Karyotyping was done from FNAC material in four cases operated at our institute and FISH in two cases which were operated outside and where paraffin blocks were available. FISH was done using an *EWSR1* break apart probe. The characteristic t(11;22) (q24;q12) translocation was seen in all the four cases where karyotyping was done (Figure 3). In the two cases where FISH was done, the *EWSR1* gene rearrangement was seen in 58% and 91% of cells (Figure 4).

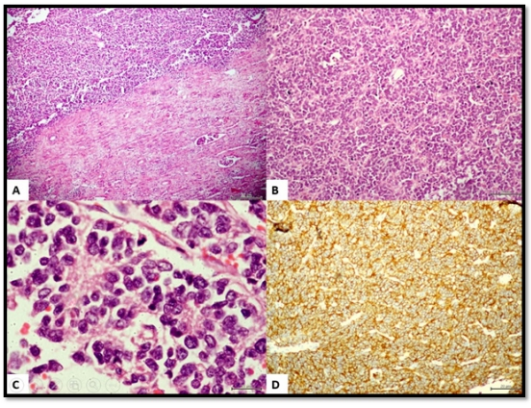

Figure 2. Scanner view shows tumor cells arranged in sheets with normal adjacent kidney in **A** (H&E, 4X), low power view shows sheets of cells with small, fairly uniform cells with round to oval nuclei, finely dispersed chromatin, inconspicuous nucleoli and scant, ill-defined eosinophilic cytoplasm in **B** (H&E, 10X) and Homer – Wright rosettes in **C** (H&E, 40X). Tumor cells show strong membranous positivity for CD99 in **D**.

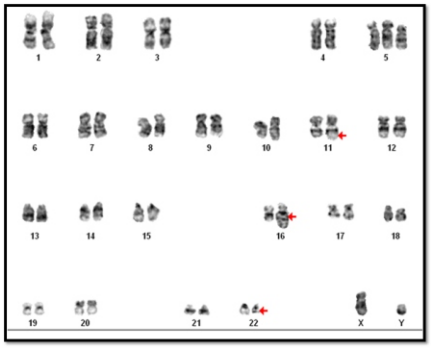

Figure 3. Karyotype showing 47,XY,+5,t(11;22) (q24;q12),der (16)t (1;16)(q21;q13)

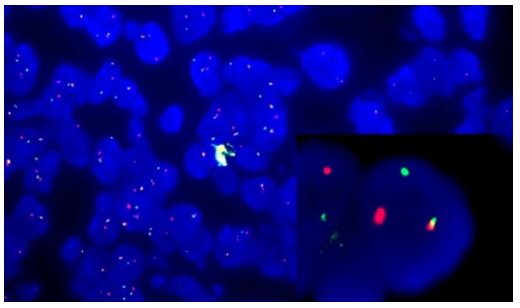

Figure 4. FISH with a double colour *EWSR1* break apart probe demonstrating t(11;22)(q24;q12)

Discussion

Primitive neuroectodermal tumor (PNET) was first described by Stout in 1918 which includes a group of malignant small round cell tumors which are primitive, poorly differentiated, highly cellular round cell sarcomas grouped under the ES/PNET family of tumors.[6] Cytogenetically 90% to 95% of the Ewing's family of tumours have a translocation between the *EWS* gene on chromosome 22 and the *FLI1* gene on chromosome 11 [t (11:22) (q24:q12)] or the *ERG* gene on chromosome 21 [t (21; 22) (q22; q12)].[7] ES/PNET of kidney is a rare and aggressive tumour with only few case series and scattered case reports in the literature. It has a rapid clinical progression and patients often present with early metastases.[8]

Jimenez et al published a clinicopathologic and immunohistochemical analysis of eleven cases of primary ES/PNETs of the kidney and mentioned an age range of 18-49 years and median follow up of 28 months (range 6-64 months) which showed four lung and pleural metastases, one bone metastasis, liver metastases, two local recurrences and five deaths from disease (median time to death 16.8 months).[9] Thyavihally et al studied sixteen cases of primary renal ES/PNETs with a median age of 27 years and a median follow up of 31 months (range 4-92 months). At presentation, ten patients (63%) had localized disease, five (31%) had metastatic disease and one (6%) had locally advanced disease.[10] Rodriguez et al studied four cases of primary renal ES/PNETs and all of them had metastases at presentation.[11] Mandal et al also studied four cases of renal ES/PNETs where the age range was of 34-48 years and one case was found to have metastatic disease at presentation.[12]

In the present study, three of the six cases presented with metastases at the time of diagnosis at our institute. Of these three cases, two succumbed to their disease at 8 months and 10 months after diagnosis and the other one was lost to follow up. Of the three cases who did not have metastases, one had local recurrence on follow up after 9 months, one was disease free after 11 months and the other was lost to follow up. A comparison of the frequency of metastatic disease at presentation between the previous studies and our study is summarized in Table 1. The frequency of metastatic disease (50%) and local recurrence (16%) in our study most closely resembled that of Jimenez et al.

Table 1. A comparison of metastatic disease with other case series of primary renal ES/PNET

Study	Total no. of cases	Metastases	Local recurrence
Jimenez et al	11	5 (45%)	2 (18%)
Thyavihally et al	16	5 (31%)	-
Rodriguez et al	4	4(100%)	-
Mandal et al	4	1 (25%)	-
Our study	6	3 (50%)	1 (16%)

Due to the poor prognosis of primary renal ES/PNET, accurate and timely diagnosis plays a significant role in proper patient management. The lesion is often first detected and characterized by radiographic imaging. The imaging characteristics of this neoplasm

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are often non-specific and demonstrate significant overlap with other renal tumors, most often Wilms tumor in children and renal cell carcinoma in adults.[13]

Histopathologically, renal ES/PNET should be differentiated from other malignant round cell tumors of the kidney like Wilms tumor, blastemal type and neuroblastoma, malignant lymphoma, rhabdoid tumor, small cell carcinoma and monophasic poorly differentiated round cell variant of synovial sarcoma. The panel of immuno-histochemical markers to be used to confirm the diagnosis are cytokeratin which is positive in Wilms tumor, small cell carcinoma, and synovial sarcoma; EMA which is positive in rhabdoid tumor, LCA which is positive in lymphoma, NSE/chromogranin which is positive in neuroblastoma and CD99 which is positive in PNET. The distinction between blastemal predominant Wilms tumor and ES/PNET may be difficult in some cases as blastemal elements may test positive for CD99.[14] In such cases, the diagnosis needs to be confirmed by cytogenetic analysis or ISH. Weeks et al reported eight cases of confirmed renal PNETs morphologically resembling rhabdoid tumor of kidney.[15] It has been postulated that these two renal neoplasms share a common undifferentiated stem cell precursor which might explain their similarity.[11,16]

Since renal ES/PNET is a highly aggressive tumor, it is often diagnosed at an advanced stage when it has already involved the perinephric fat, hilar lymph nodes, renal veins, and inferior vena cava. In more advanced stages, the tumor involves the liver, spleen, peritoneum, and lungs. The 5-year disease-free survival rate is around 45–55% in well-confined cases, whereas cases with advanced disease stage at presentation have a median relapse-free survival of only 2 years.[17]

In conclusion, ES/PNET of the kidney though rare can be diagnosed on histopathology with immunohistochemical markers but should be confirmed by cytogenetic analysis or ISH. The paucity of reports on primary renal ES/PNET may be due to this entity being under diagnosed or mistaken for other more common renal tumors. Thus, a diagnosis of primary renal ES/PNET must always be considered in young patients with renal neoplasms as an accurate diagnosis will help in their optimal management.

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