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Primary neuroectodermal tumors of kidney: Our experience at institute of kidney disease and research centre-institute of transplantation sciences

Dr. Raghuveer Machiraju[1], Dr. Sayeed Jamal Rizvi[2*], Dr. Pranjal R Modi[3]
[1-3] Department of Urology, Institute of Kidney Diseases and Research Centre- Institute of Transplantation Sciences, Ahmedabad, Gujarat, India

Abstract
Objectives: Primary Neuroectodermal Tumours (PNET) are rare and highly aggressive tumours. These tumours are diagnosed by means of histopathology and aided by Immunohistochemistry and cytogenetics. Multimodality treatment is needed for treating these tumours. The purpose of this study is to review our experience in diagnosis and treatment PNET of kidney.
Materials and Methods: We retrospectively reviewed the data of all the patients treated for PNET of kidney since January 2016 to till July 2018 at our institute.
Results: A total of six pts have been treated for PNET of kidney. Five were females and one male. Out of six patients, three had venous involvement. All the pts underwent radical nephrectomy and also IVC thrombectomy in three cases. Diagnosis of PNET made by HPE and supported by IHC. Post-surgery all six pts were given chemotherapy and two of them were given radiotherapy as well. All the six are alive till date and with no recurrence till date.
Conclusions: In general, renal PNET is a highly aggressive and have poor prognosis. In adolescents and young adults with a suspicious renal mass, a diagnosis of renal PNET should be always considered. The golden standard to diagnosis renal PNET is based on histologic and immune histochemical features, supported by cytogenetic analysis. Multimodality treatment consisting of surgery, chemotherapy and radiotherapy is recommended to manage the disease.

Keywords: chemotherapy, primitive neuroectodermal tumors, radiotherapy, surgery, vena caval thrombus

Introduction
PNET was initially identified as member of "small round cell tumors" by Arthur Purdy Stout in 1918. It typically occurs in bone or soft tissue and rarely reported at a renal localization. The first case of renal PNET was reported by Seemayer *et al* in 1975 [1]. PNET of soft tissue was traditionally regarded as equivalent to Ewing's Sarcoma of bone. Bony counterpart is more undifferentiated than soft tissue, which shows neuroectodermal differentiation. These tumours usually develop in childhood and adolescence with an aggressive clinical course [2, 3]. Clinical presentation is similar to any other renal neoplasms however final diagnosis is made by histopathology. PNET of the kidney carries a poor prognosis because of higher rate of recurrence and tendency for early metastases [4].Aim of this study is to review our experience in PNET cases managed at our institute.

Materials and Methods
This study is a retrospective chart review of the PNET cases managed by us in our institute from January 2016 to July 2018. A total of 132 radical nephrectomies were performed in our institute which is a tertiary care centre, of these 80 cases were performed laproscopically and 51 by open surgery approach,18 of these cases had venous involvement. A total of 6 cases had post-operative final histopathology suggestive of PNET.
All the patients were evaluated preoperatively by clinical history, physical examination, complete blood count, liver and renal function tests, chest X-ray, ultrasonography (USG) KUB and contrast enhanced computed tomography (CECT) of the abdomen & pelvis (Figure 1). In the patients for whom venous involvement was detected on CECT, Renal Doppler was performed to know about the extent of thrombus. In our study there were 2 paediatric patients with working diagnosis as Wilms tumor and their pre operative core biopsy was suggestive of PNET.
All these patients were managed by open radical nephrectomy, (Figure 2). IVC thrombectomy was required in 3 patients due to venous involvement. The final diagnosis of PNET was established by post operative histopathological examination and supported by Immunohistochemistry (IHC).
Post operatively all patients were subjected to adjuvant chemotherapy and two patients with lymphnode involvement & IVC thrombectomy were also given radiotherapy to tumor bed. the current standard chemotherapy protocol for PNET has been that for Ewing's family of tumors, (EFT)-2001.

- EFT-2001 protocol,
- 1800 mg/m ^{2} of ifosphamide per day for 5 days and

100 mg/m ^{2} of etoposide per day for the same 5 days are added to the VAC regimen All patients were followed up regularly with history, physical examination, complete blood counts, liver function tests, chest Xray, USG abdomen and CECT abdomen and pelvis.

Results
In our study we managed 6 patients with PNET. Of those five were females and one patient wasmale. Age distribution was from 10 to 45 years. Mean age of presentation was 22.5

yrs. The most common presenting complaints were mass per abdomen, flank pain and haematuria. 3 out of 6 (50%) patients were noted to have IVC thrombus. Age, sex, mode of presentation, staging and treatment received, post-operative treatment and survival are summarized in table (1).

All the patients underwent radical nephrectomy and in addition those with IVC thrombus also underwent IVC thrombectomy. Of these 1/6 patienthad level I thrombus and 2/6 patients had level 2 thrombus.

All pts were followed up regularly at three monthly intervals for 1 year and 6 monthly in the next year.None developed any locoregional recurrence and all the patients are alive till date. Tumor free survival at one year is 100%.

ean follow up period is 20.33 months and range is 11-24months.

Table 1

Age/sex	C/f	Stage	Surgery	Chemo	Rt	Recurrence	Survival (month)
10/F	P,M	T2N0MO	RN	YES	NO	NO	24
45/F	P,H	T2NOMO	RN	Yes	NO	NO	23
21/F	P,M	T3bN1M0	RN+IVCT	YES	YES	NO	23
12/F	P,H	T2N0MO	RN	YES	NO	NO	22
24/M	P,M,H	T3bN1M0	RN+IVCT	YES	YES	NO	18
24/M	P,M,H	T3aN0M0	RN+IVCT	YES	NO	NO	11

P=pain abdomen, H=hematuria, M=mass, RN=radical nephrectomy, IVCT=ivcthrombectomy, m=male, F=female

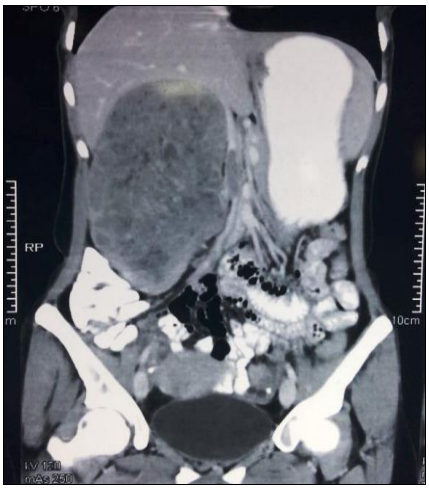

Fig 1: CT scan Showing RT Renal Tumor with Ivc Thrombus

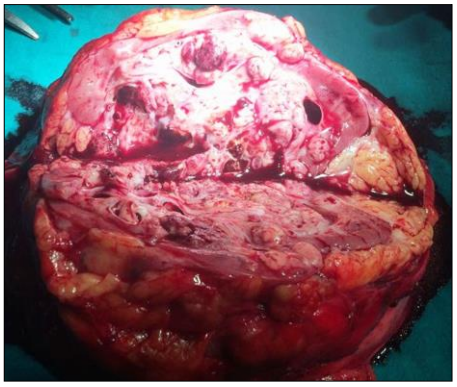

Fig 2: Gross appearance of tumor

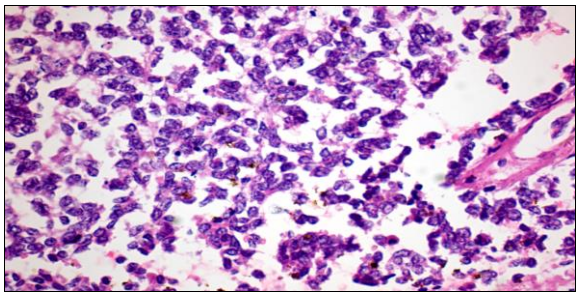

Fig 3: Tumour cells arranged in sheets and forming pseudorosettes. The tumour cells have inconspicuous cytoplasm with nuceli that have coarse chromatin and mitotic figures

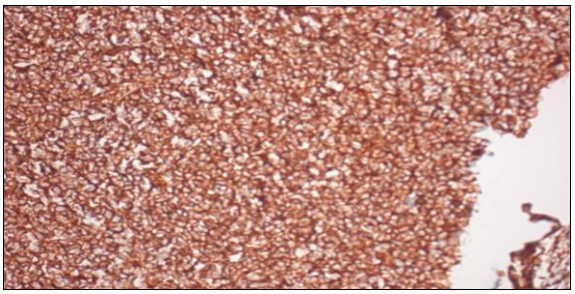

Fig 4: Vimentin- positive, 40x

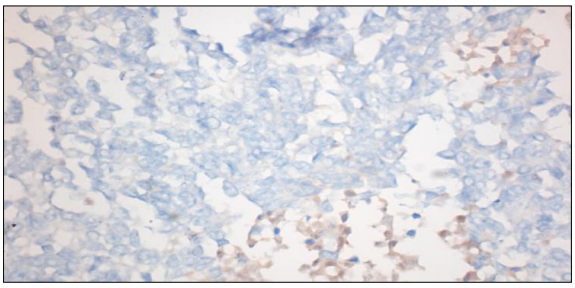

Fig 5: Chromogranin-focally positive, 40x

Discussion

PNET of the kidney is an extremely rare renal neoplasm with neural crest origin. It is a member of the family of small RCTs [5]. Since it has not been differentiated from Ewing's sarcoma, an accurate estimate of the number of kidney PNETs is not possible [6]. Parham *et al* suggested that the source of renal PNETs may be adrenergic that invest in kidneys from coeliac plexus. They have also postulated that embryonic neural crest cells may migrate into kidney and subsequently undergo tumorigenesis[7]. Renal PNET is more aggressive than PNET of other locations. Due to its rarity, the exact clinical outcome is not well defined in the literature. So far literature about renal PNET was isolated case reports and the largest case series including 79 patients with RPNET was described by Parham *et al*. in 2001 It usually presents during childhood and adolescence [8]. In our series 2/6 patients were less than 18 years of age. The average age at diagnosis was 27.7 years in a review by Kuroda *et al* [8]. The mean age of presentation in our series is 22.5 years. In our series 3 out of 6 patients were females and 2 were female children, 1 was male. Female preponderance was noted in our study. Boys and men are

more likely to suffer rPNET and the sex ratio (male:female) is about 3:1 [2] The patients reveal a 5-year disease-free survival of 45% to 55%, whereas patients with metastasis indicated median relapse-free survival of only 2 years.10. The clinical presentation was similar to other renal masses, most common are abdominal pain, abdominal mass and haematuria. In our series, all patients presented with abdominal pain and abdominal mass, 50% of patients had venous involvement at the time of presentation which is in contrast to other series in which the disease is either organ confined or metastatic in presentation [1, 11].

There are no specific radiological findings to diagnose PNET of the kidney pre-operatively. Renal PNETs appear hypoechoic, isoechoic, and /or hyperechoic to the adjacent renal parenchyma on ultrasound and show increased vascularity on Doppler imaging. CT scan shows a large heterogenous mass with areas of hemorrhage or necrosis. On Magnetic Resonance Imaging (MRI), the tumor appears as a lobulated isointense and /or hypo intense mass on T1-weighted images and as a heterogeneous to hyperintense mass on T2-weighted images, with heterogeneous contrast enhancement

MRI and CT also help to evaluate renal vein and inferior vena cava involvement [9].

The diagnosis is established post operatively by histopathology, supported by IHC and cytogenetics. Microscopically, PNET of the kidney show small to medium sized monomorphic round cells with hyperchromatic nuclei and minimal cytoplasm arranged in loose cohesive sheets. Though the presence of Homer Wright rosettes is less common in extra-osseous Ewing's sarcoma, their presence is a sure or reliable in the diagnosis of PNET. The reactivity to vimentin, neuron specific enolase and S-100 may help in making the diagnosis, but their presence is not pathognomonic. The presence of macrophage inhibitory cytokine 2 gene product, CD99, confirms the diagnosis [10, 11].

PNET of the kidney is a highly aggressive tumour with a poor prognosis. It has a high tendency for local recurrence and metastasis at an early stage. Surgery is the most important aspect of the management. Surgical options include partial or total nephrectomy with cavotomy in cases of renal vein involvement to extract tumor thrombus. The diagnosis of renal PNET is made postoperatively and hence chemotherapy is generally given as an adjuvant modality [12]. The standard chemotherapeutic agents recommended in these patients are VAC.

However, etoposide (E) and ifosfamide (I) have been recently added to the initial chemotherapy protocol for PNET according to the RCT II protocol [13].

An RCT II protocol includes

- 2 mg/m ^{2}of vincristine,
- 75 mg/m ^{2} bolus infusion of adriamycin and 1200 mg/m ^{2} of cyclophosphamide
- With the addition of etoposide and ifosfamide to the VAC regimen, the current standard chemotherapy protocol for PNET has been that for Ewing's family of tumors, (EFT)-2001.
- EFT-2001 protocol,
- 1800 mg/m ^{2} of ifosfamide per day for 5 days and 100 mg/m ^{2} of etoposide per day for the same 5 days are added to the VAC regimen

Radiotherapy

- No definitive indications for adjuvant radiotherapy in PNET. However it is ususally given to the tumour bed and residual disease in lymph nodes.

The 5-year disease-free survival rate is around 45–55% in well-confined cases, whereas cases with advanced stage at presentation have a median relapse-free survival of only 2 years [14, 15]. Most patients with advanced renal PNET die of progressive disease within 1 year of diagnosis [16]. Thyavihally *et al*. demonstrated a median survival of 40 months, with 3 year and 5 year disease-free survival rates of 60% and 42%, respectively.

Conclusion

In general, renal PNET is a highly aggressive tumor and have poor prognosis. It can occur in pediatric age group with female preponderance. In adolescents and young adults with a suspicious renal mass, a diagnosis of renal PNET should be always considered.

The gold standard to diagnosis of renal PNET is histologic and immunohistochemical examination, supported by cytogenetic analysis. Multimodality treatment consisting of surgery, chemotherapy and radiotherapy is recommended to manage the disease. Studies on management of PNET with long follow up period will throw more light on efficacy of treatment and survival rate and also on early recognition of recurrence/residual disease.

Authors contributions

Raghuveer Machiraju, protocol development, data collection, data analysis, manuscript writing. Jamal S. Rizvi, design of the work, interpretation of data, manuscript revision. Pranjal R Modi, data analysis, project development, manuscript revision. Bipin C. Pal, data collection, data analysis, manuscript revision.

Disclosures

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Informed consent was taken from all the patients.

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