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Research Article

Ewing's Sarcoma of the Kidney: Case Series on an Overlooked Masquerade in Differential Diagnosis of Renal Cell Carcinoma

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Abstract

Background: *Primitive neuroectodermal tumor (PNET) of the kidney is an extremely rare entity and has got a very poor prognosis. Multimodal therapy, comprising of multi-agent chemotherapy with surgery and, or radiation therapy is the current therapeutic approach in management of renal PNET. Herein, we present a review of the clinical data of patients and follow up for the survival status of patients with primary renal PNET in our center.*

Methods : *We retrospectively analyzed the clinical data of patients with renal PNET diagnosed pathologically at SKMH & RC from January 1, 2009 to December 2023. All of the patients were followed up for survival status*

Results: *Twelve patients with renal PNET presented during the study period. The ratio of males to females was 10:2. The median age was 27.5 years (21–36 years) at the time of diagnosis. Only one patient was diagnosed with retroperitoneal lymph node metastasis. The main clinical manifestations of patients were flank pain (8/12), hematuria in (5/12) and fever (2/12). All but two patients developed metastasis on follow up .The Median metastasis free survival was 18.95 months .Seven patients died in our follow-up, with an average overall survival (OS) of 44.9 months.*

Conclusions*: As a rare renal tumor, renal PNET has a propensity to occur in young males. Most patients have distant metastasis when they are diagnosed, and the prognosis is very poor. Effective treatments like targeted anti-tumor agents are urgently needed.*

Keywords: *Renal primitive neuroectodermal tumor (renal PNET), renal cancer, case series, Ewing's sarcoma*

Introduction

The Primitive neuroendocrine tumors (PNET) consists of a group of small round blue cell tumors which includes both osseous and extra-osseous lesions. Ewing sarcoma (EWS) and soft tissue primitive neuro-ectodermal tumors (PNET) are generally poorly differentiated tumors[1] They are highly aggressive sarcomas leading to death and unfortunately commonly seen in young adults [2].

Retroperitoneal Ewing sarcomas are extremely rare, less than 5% of renal tumors[3]. The clinical manifestations and imaging findings of renal PNET are almost similar to those of other renal cell cancers due to which these tumors are easily mistaken for other more common tumors involving the kidney. Seemayer et al. reported the first case of PNET in 1975 [4].

There is no consensus on the optimal management of renal PNET due to low prevalence and limited available data. The current management approach rests on multimodal therapy, including multi-agent chemotherapy with surgery and, or radiation therapy [5-7]. The clinical and histopathological features of these tumors have been described widely in most published case series[8-10], but only a few studies have described the management and patient outcomes [11]. Available reports indicated that the majority of patients with renal PNET have an advanced disease at presentation with poor prognosis[12,13].

The purpose of our study is to describe the clinical characteristics, treatment, and outcomes of patients with renal PNET at our institution.

Materials and Methods

We retrospectively reviewed the patients who presented with a renal mass and were diagnosed with histologically proven PNET between January 2009 till December 2023 at Shaukat Khanum cancer memorial hospital and research center (Lahore). After getting IRB approval medical records were reviewed retrospectively for patient's demographics including age, gender, side and size of renal mass. Information regarding treatment, and outcome of patients were also collected.

The median free survival (MFS) and overall survival (OS) were calculated from the time of diagnosis. Local failure was defined as relapse within the operative bed and abdomen outside the operative bed. Tumor spread to other viscera was considered as distant metastasis. OS and MFS was estimated using Kaplan-Meier Curves. All statistical analyses was performed using SPSS version 2020.

Results

A total of 12 patients were diagnosed with histologically proven PNET during the study period.

The most common presenting symptoms were flank or abdominal pain (66.6%) and hematuria (41.6%). Two (16.6%) patients presented with systemic symptoms such as fever or weight loss.

The mean age of the patients was 27.5 years (range 21-36). Mean tumor size was 15.4 cm (range, 8–31

cm).Majority of the patients had tumor confined to the kidney. Tumor extension to the renal vein was present in two patients and only one patient had tumor extension to the inferior vena cava (IVC). One patient had a locally advanced disease at presentation. None of the patients had metastatic disease at diagnosis. (Table 1)

TABLE :1 Clinical Characteristics of Patients with Primary PNET of the Kidney

S.No	Characteristic	N (%)
1.	**Age at diagnosis, years**	
	Mean	27.5 (21-36)
2.	**Gender**	
	Male	10 (83.4)
3.	**Tumor size, cm**	
	Mean	15.45 (8-31)
4.	**Tumor Extension**	
	Confined to kidney	8 (66.66)
	Renal vein thrombus / IVC thrombus	3 (25)
	Locally advanced	1 (8.34)
5.	**Side of tumor**	
	Right	6 (50)
6.	**Treatment**	
	Upfront surgery	12(100)
	Adjuvant Chemotherapy	12(100)
	Adjuvant Chemo-Radiotherapy	3(25)

All the patients had upfront surgery with adjuvant chemotherapy. The most common initial chemotherapy regimen used was vincristine, doxorubicin, and cyclophosphamide (VDC) in combination with ifosfamide and etoposide (IE). Three patients received post-operative radiation. (Table 2)

All but two patients developed metastasis on follow up. The most common sites of metastasis were pulmonary (n = 6, 50%), local bed recurrence (n = 5, 41.6%) and osseous metastasis (n=3, 25%). Two patients had brain metastasis. While metastasis to the liver was found in only one patient. (Table 2). The Median metastasis free survival was 18.95 months. (Figure1). Seven patients died in our follow-up, with an average overall survival (OS) of 44.9 months. (Figure 2)

TABLE: 02 Clinical characteristics, treatment and outcomes of patients with primary PNET of the kidney.

S.No	Age in years	Gender	Side	Size in cm	Tumor Extension	Nephrectomy	Adjuvant Treatment Chemotherapy/ Radiation Therapy	Site of First Relapse, Time from Diagnosis	Patient Outcome
1.	28	male	Right	14	Confined to kidney	Upfront	Chemo(VIDE, C,Topo)	Renal Bed /1 month	Death , 13 months
2.	35	Male	Right	10	Confined to kidney	Upfront	Chemo (VCDE/gem Dox) RT to brain / Thoracic spine 20 Gy / 5 Fr	Brain ,Pulmonary/ 43 months	Death , 110 months
3.	36	Male	Left	10	Confined to kidney	Upfront	Chemo (VIDE/VAC /VCE) RT to Chest wall 20Gy	Pulmonary ,Peritoneal , Renal bed/ 5 months	Death , 88 months
4.	31	Male	Left	17	Confined to kidney	Upfront	Chemo (VCDE/VAC) RT to renal bed 54 Gy/30	None	Alive , NED
5.	21	Male	Right	18	Confined to kidney	Upfront	Chemo(VIDE)	Renal Bed/2 months	Death 5 months
6.	27	Male	Right	18	Confined to kidney	Upfront	Chemo(VIDE/VCDE)	Pulmonary, osseous ,renal bed/2 months	Death , 13 months
7.	25	Male	Left	22	Confined to kidney	Upfront	Chemo(VIDE)	Renal Bed /1 month	Death 27 months
8.	29	Male	Left	8	Renal vein Invasion	Upfront	Chemo(VCD/IE/GEM/ Doce)	Pulmonary /15 months	AWD
9.	21	male	Left	9.5	Confined to kidney	Upfront	Chemo (VDC/IE)	None	Alive, NED
10.	25	Female	Left	18	Renal vein Invasion	Upfront	Chemo(VDC/ IE)	Hepatic , Osseous metastasis/ 1 month	Death , 6 months
11.	28	Female	Right	10	Tumor in IVC	Upfront	Chemo (VDC/IE)	Pulmonary /1 month	Alive , NED
12.	24	Male	Right	31	Locally advanced	Upfront	Chemo (VDC)	Brain, Pulmonary, Hepatic, Osseous/1 month	AWD

Abbreviations AWD-Alive with disease, C-Cyclophosphamide, D-Doxorubicin, E-Etoposide, I-Ifosfamide, IVC-Inferior vena cava, NED-No evidence of disease, , RT-Radiation therapy, RV-Renal vein, V-Vincristine,

Gem –Gemcitabine , Doce –Docetaxel.

Figure 1 : kaplan-meier Showing Metastasis free survival

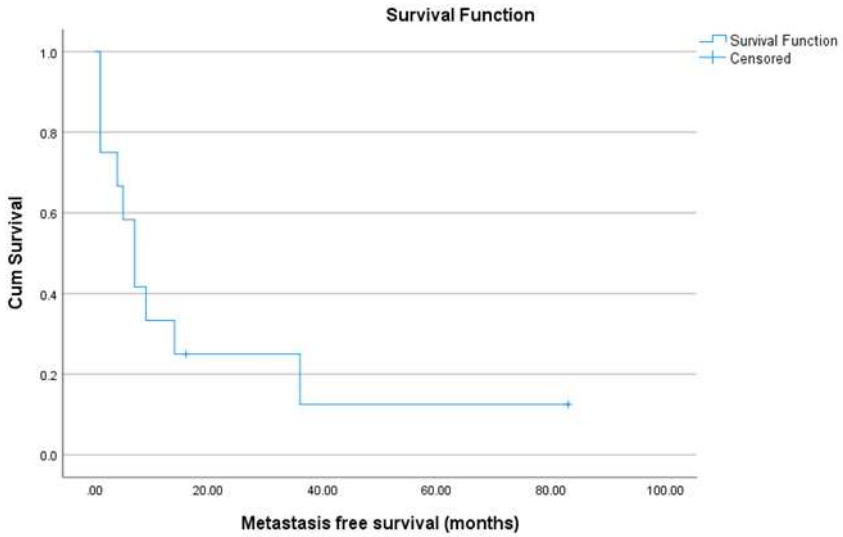
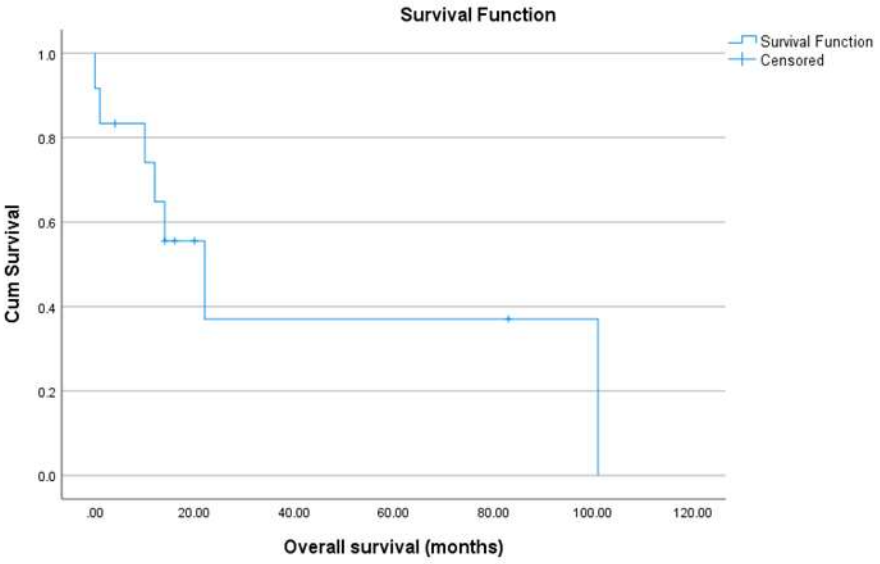


Figure 2: kaplan-meier Showing Overall survival



Discussion

Primitive neuroectodermal tumors (PNET) are rare sarcomas, especially those found primarily in the kidney. Renal PNET is commonly seen in young adults. The clinical manifestations and imaging findings of renal PNET are almost similar to those of other renal cell carcinomas. Renal PNET often present as a single, large mass on imaging[14]. Recently cases of primary renal PNET have been reported more frequently, mainly due to improved molecular studies.

In this study, we reviewed our experience with 12 patients with PNET of the kidney who were seen at our institution over a period of 14years. In this series, we observed a male to female preponderance (83.3%) as seen previously. The median age at diagnosis was 27.5 years. PNET in generally diagnosed at a younger age of usually less than 20 years, our age distribution is somewhat different[15,16]. Similar to previous reports the presenting symptoms of primary renal PNET were non-specific [17]. The largest tumor dimension at diagnosis was 31 cm with central necrosis. This was also observed by Lee et al. that the most common image findings in PNET were the presence of a large necrotic and hemorrhagic mass along with extensive venous thrombosis [18].

We found that the majority (8/12) of the patients had tumors confined to the kidney. This is contrary to the present literature where most of the patients have a locally advanced or metastatic disease at presentation. Only four patients in our series had tumors extending locally beyond the kidney i.e capsular invasion, perinephric tissue invasion, lympho-vascular invasion, presence of renal vein and, or IVC thrombus. Our data revealed that none of the patient had metastasis at presentation. These results are at a disconcordance with previous reports showing metastasis in 40−65% of new patients with primary renal PNET [19,20]. Most of the patients (83.3%) however, developed metastasis on follow-up.80% of the patients developed metastasis within 5 months. This high incidence of metastatic disease reflects the aggressive nature of this tumor.

In our study cohort majority of patients responded initially to surgery and adjuvant chemotherapy, but later had a significant rate of relapse (mainly local failure followed by distant metastasis). Only two patients in our study had no metastasis on follow up. The median metastasis free survival was 18.95 months. Local renal bed and lungs were the most common sites of metastasis observed in our study. Additionally, it revealed that despite patients showing an initial response to systemic chemotherapy, all but five of the 12 patients died of disease. Three patients received postoperative radiation in our study. Radiotherapy is currently recommended for unresectable tumors or unexpected positive margins [21] and may play a role in the local control of primary renal tumors with local extension beyond the kidney. Our results also signify the importance of early initiation of chemotherapy before the development of metastasis and suggest a potential role for radiation therapy in

local control

Patients with non-metastatic tumors and a tumor thrombus in the renal vein or IVC developed metastasis to the lung within 6 months after nephrectomy, suggesting a potential benefit from using neo-adjuvant chemotherapy or initiation of systemic therapy soon after tumor resection. We report a high risk for recurrence/metastasis in patients with localized disease treated with nephrectomy alone [22,23] and poor outcomes in patients with metastatic disease [24]. Similar to previous reports the outcome of our patients with metastatic tumors of the kidney was poor despite multimodal therapy, highlighting the need for novel treatment approaches for this very high-risk group[25].

Our study was limited by its retrospective nature, the small number of cases, the incomplete data for some patients, the variation in therapies received over the extended study period, and the brief follow-up period for certain patients . The rarity of primary renal PNET makes a prospective study impractical and difficult.

Conclusion

As a rare renal tumor, renal PNET has a propensity to occur in young males. Due to the highly aggressive nature of the disease these patients have a very poor prognosis. Most patients either have distant metastasis at diagnosis or develop metastasis early on. Effective treatments are urgently needed. Apart from nephrectomy, adjuvant treatment with potent targeted anti-tumor agents is required for improved outcomes in disease management.

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