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Case Series

Primitive neuroectodermal tumor of kidney in elderly -A case series with review of literature

K.P Kavitha[1,*], Gittwa Vatsaraj Kottangal[1], Shehla Basheer Kollathodi[1], Shalini Kuruvila[1], Lilly Madhavan[1], Surdas Radhakrishnan[2]

[1]*Dept. of Pathology, Aster MIMS, Calicut, Kozhikode, Kerala, India*
[2]*Dept. of Urology, Aster MIMS, Calicut, Kozhikode, Kerala, India*

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ABSTRACT

Background: Primitive neuroectodermal tumor of the kidney (PNET) is a very rare and highly aggressive tumor commonly seen in young adolescents. These tumors are rare in patients over 40 years. Reports of renal PNET in elderly patients over 60 years are even rarer.
Case Presentation: We report three cases of renal PNET in adult patients diagnosed over a period of three years. Among the three patients, two were above 60 years of age and the third patient was a 39-year-old male. All the three patients had extensive venous thrombosis at the time of presentation. One of the patients succumbed to death in the immediate post-operative period and the other two received chemotherapy.
Conclusions: Renal PNET owing to its rare occurrence in middle-aged and elderly poses a diagnostic challenge to the pathologist. The clinical and radiological findings have limitations in the accurate diagnosis. Thorough morphological evaluation along with immunohistochemistry and cytogenetic analysis help in arriving at a correct diagnosis. An accurate diagnosis is crucial for the initiation of proper treatment.

1. Background

A primitive neuroectodermal tumor (PNET) and Ewing's sarcoma have common stem cell precursors and share similar histological features and cytogenetic abnormalities. So both are now considered a spectrum of a large neoplastic entity called Ewing's sarcoma family of tumors (EFTs). PNETs are malignant small round-cell tumors of neural crest origin, classically found in the central nervous system (CNS). These tumors have a propensity to occur in multiple sites like the trunk, soft tissue, brain, spinal cord, skin, viscera, etc.[1] The renal location of PNET is infrequent and is rarely seen in elderly patients. Differential diagnosis is usually broad, with frequent overlapping features between the entities. Since there is a limitation in the clinical and radiological preoperative diagnosis, the definite diagnosis is always based on morphology, immunohistochemistry, and cytogenetic analysis. Herein we report three adult PNET cases located in the kidney and narrates the diagnostic dilemmas in differentiating the tumor from its close differentials. It is mandatory to have a correct diagnosis for the timely initiation of treatment.

2. Case Presentation

Three cases of renal PNET were studied in the Department of Pathology in our institution over a period of three years between February 2018 and March 2021. Of the three patients, two were above 60 years.

* *Corresponding author*.
E-mail address: kpkavi@gmail.com (K. P. Kavitha).

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3. Case 1

A 39-year-old male presented in the urology OPD of our hospital with a history of hematuria. MRI showed an altered signal intensity lesion in the interpolar and lower pole region of the right kidney. In addition, inferior vena cava (IVC) thrombus was seen. Therefore, a right radical nephrectomy was done. Grossly the tumor was measuring 10.5x9x8.5cms (Figure 1A). The cut surface had grey-white and solid appearance with areas of hemorrhage.

4. Case 2

A 63-year-old female presented with an abdominal mass. She had a history of Grade 3 carcinoma left breast with medullary features, diagnosed in 2005 for which she had undergone modified radical mastectomy followed by chemotherapy and was under regular follow up. PET CT scan showed a metabolically active hypodense mass lesion (5.5 x 4.5 cm) in the right kidney upper pole region. She underwent laparoscopic right radical nephrectomy. Grossly the tumor was seen in the upper pole towards the medial side, measuring 6x3.5x3cm. The cut surface had a greyish-brown appearance and showed areas of hemorrhage and necrosis. The tumor infiltrated the renal sinus and perinephric fat.

5. Case 3

A 67-year-old male presented with right-sided abdominal pain. USG abdomen showed swollen right kidney with features of IVC thrombosis. His CECT showed bulky right kidney with an ill-defined heterogeneously enhancing predominantly endophytic & partly exophytic tumor approximately measuring 7.2 x 6.3 x 5.8cm near the interpolar region & lower pole of the right kidney and extending into the renal sinus calyces & pelvis. The lesion was infiltrating into the right renal vein with evidence of IVC thrombosis extending cranially to intrahepatic IVC, atriocaval junction & reaching right atrium. Caudally it was extending till the confluence of common iliac veins (Figure 1b). After the multidisciplinary team (MDT) discussion, he was taken for radical nephrectomy. Gross examination revealed an ill-defined greyish white variegated tumor measuring 10x8x7.5cm, replacing almost the whole kidney. The tumor infiltrated the sinus fat and renal pelvis.

5.1. Histomorphological findings

Hematoxylin and eosin (H&E) stained sections of all the three tumors revealed more or less similar morphology. The neoplastic cells were arranged diffusely in islands, lobules, and rosettes (Figure 2A). The cells were monomorphic with round nuclei, granular chromatin, and scanty amphophilic cytoplasm. Stroma was scanty. Significant mitotic figures and a varying amount of necrosis were present. Even though rosettes were present in all, it was abundant in the third case. The tumor was seen infiltrating the renal sinus in the first case, perirenal fat in the second case, and the renal sinus fat and renal pelvis in the third case. Large vessel emboli were seen in all the cases.

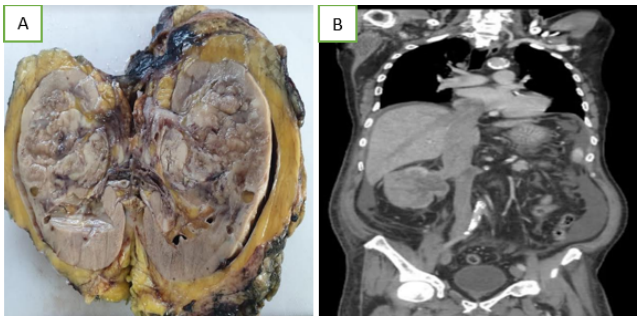

Fig. 1: A: Gross morphology. Large tumor having grey white solid appearance with areas of hemorrhage; **B:** Contrast -enhanced computed Tomography abdomen showing the right kidney with ill defined heterogeneously enhancing mass lesion. Tumor is seen infiltrating in to the renal vein with evidence of IVC thrombus extending cranially to atriocaval junction and till the right atrium. Caudally thrombus was extending to the confluence of common iliac veins.

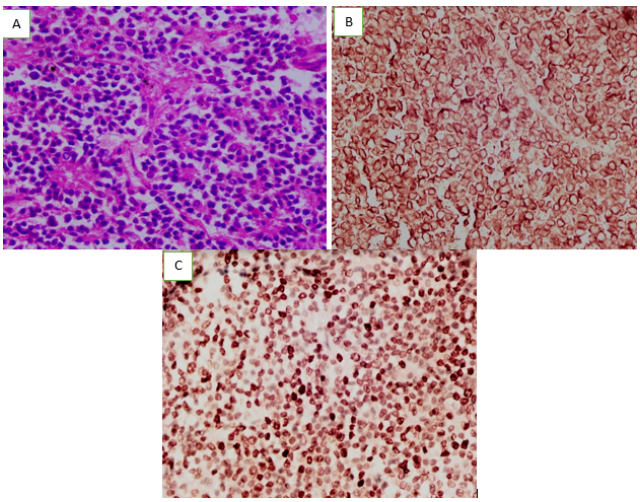

Fig. 2: A: Tumor is composed of monotonous population of small round cells with scanty cytoplasm and nuclei exhibiting stippled chromatin. Rosette pattern is seen (H and E, 40x); **B:** CD99 staining showed diffuse membrane positivity in the tumor cells; **C:** Diffuse nuclear positivity with FLI1 stain.

5.2. Immunohistochemistry

We did a panel of immunohistochemical markers. All the cases were negative for Cytokeratin (CK), leucocyte common antigen (LCA), S100, and desmin. Diffuse strong membranous staining with CD99 (Figure 2B), strong

Table 1: Immunohistochemical markers in Differential diagnosis of PNET

Markers	PNET	NB	Blastemal Wilms tumor	Embryonal RMS	Clear cell sarcoma	LB lymphoma	Small cell carcinoma	DSRCT
CD99	+++	-	-/+	+	-	+	-	-/_
FLI1	+++	-	-	-	-	-	-	-
NSE	-/+	+++	+	-	-	-	++	-
Synaptophysin	-/+	+++	+	-	-	-	+++	-
CD56	-	+++	+	-/+	-	-/+	+++	-
WT1	-	-	+++	+	-	-/+	-	+
Pax8	-	-	+++	-	-	-	+	-
Desmin	–	-	-/+	+	-	-	-	+
MyoD1	-	-	-	+	-	-	-	-
LCA	-	-	-	-		+++	-	-
Ck	-/+	-	-/+	-/+	-	-	+++	+
Vimentin	+++	-	-/+	+++	+	-	-	+

PNET-primitive neuroectodermal tumor, Synapto-synaptophysin, RMS –rhabdomyosarcoma, LBL –Lymphoblastic lymphoma, DSRCT-desmoplastic small round cell tumor, LCA-Leucocyte common antigen, CK-cytokeratin.

nuclear positivity for FLI1 (Figure 2C), and focal expression of neuron-specific enolase (NSE) and synaptophysin was noted in all the three cases. The histological and Immunohistochemical findings supported the diagnosis of PNET. However, the molecular study was performed only in one patient and demonstrated EWSR1 (22q12) gene rearrangement.

5.3. Clinical course

The first patient underwent adjuvant chemotherapy and radiation. He was on regular follow-up for nine months and then lost to follow-up. The second patient was given adjuvant chemotherapy (VAC/VIME regimen) and is doing well with regular follow-up. The third patient, unfortunately, succumbed to death in the immediate postoperative period.

6. Discussion

The primitive neuroectodermal tumor can be central or peripheral based on its location. Peripheral PNET (pPNET) is commonly seen involving soft tissue of the chest wall and paraspinal area. The incidence of pPNET is about 1% of all sarcomas.[2] PNET presenting as an organ-based tumor is uncommon[3].Renal PNET is exceedingly rare and was first described by Seemayer et al. in 1975.[4] A series of 16 cases published by Thyavihallyet al. is the largest series from a single institute.[5] Most of the studies have mentioned that renal PNET is more common in adolescents and young adults.[6,7] But in our study, two of the three cases were elderly over 60 years of age. Only a few case reports have mentioned renal PNET in elderly patients.[8–10] PNET is derived from the neural crest. During neural tube formation, the neural crest cells from the dorsal side migrate towards the periphery.[11] The tumors arising from these cells have a propensity to occur in multiple sites like the trunk, soft tissue, brain, spinal cord, skin, viscera, etc. Sullivan et al. have shown that the visceral ES/PNET has the same pattern of genetic alterations and range of fusion transcripts as ES/PNET of bone and soft tissue.[12] Patients usually present with abdominal or flank pain, mass in the abdomen, and hematuria. The patient can also be asymptomatic until the tumor reaches a considerable size. Clinically and radiologically, the first differential diagnosis will be renal cell carcinoma, especially in elderly patients. Even though it is challenging to differentiate radiologically, one should consider the possibility of PNET while encountering large heterogeneous renal mass with wide local invasion and metastasis, especially in young adults.[13] CT Scan study was available for all our patients. MRI and CT scans can help to evaluate venous involvement.

Vena caval thrombosis is common in PNET.[14–16] Hota et al. have also highlighted the propensity of renal PNET for vena cava involvement.[17] In our study, Inferior vena cava thrombus was demonstrated in all the three patients. In the case of the third patient, the tumor was extending up to the right atrium. Zini et al. have also described a similar case with tumor thrombus ascending to the right atrium.[18]

The differential diagnosis of undifferentiated small round cell tumors in the kidney is broad and includes PNET, neuroblastoma, blastemal predominant Wilms tumor, embryonal rhabdomyosarcoma, clear cell sarcoma, Lymphoblastic lymphoma, small cell carcinoma, desmoplastic small round cell tumor, etc. It is a diagnostic challenge to the pathologist. Even though most of the small round cell neoplasms mentioned in the differential diagnosis occur in children, they may also occur in the adult kidney.

A broad panel of immunohistochemical markers and molecular studies are mandatory for arriving at the correct diagnosis. Parham et al. conducted a retrospective analysis of 146 cases of adult and childhood renal primitive malignant neuroepithelial tumors of the kidney

at the National Wilms tumor study group pathology center.[19] They showed that it is difficult to make a diagnosis without immunohistochemistry work up. Even the Immunohistochemical staining will show overlapping findings in these tumors. For example, CD99 positivity can be seen in blastemal predominant Wilms tumor, lymphoblastic lymphoma, synovial sarcoma, rhabdomyosarcoma, mesenchymal chondrosarcoma, etc. So judicial use of markers is mandatory in achieving the correct diagnosis. The use of different immunohistochemical markers in the differential diagnosis of PNET is given in Table 1.

PNET is composed of a monotonous population of small round cells having nuclei with stippled chromatin. The cytoplasm of the cells shows glycogen which can be demonstrated by PAS stain. Histologically Homer Wright rosettes can be seen in varying proportions. We could demonstrate rosettes in all three cases. Neuroblastoma also presents with rosettes, but the positivity of Cluster of Differentiation 99 (CD 99) and Friend Leukemia Integration 1 transcription factor (FLI1) support the diagnosis of PNET. Jimenez et al. in their study of 11 cases, examined the expression of FLI1 marker in the tumor cells[20] and concluded that FLI1 positivity is highly sensitive and specific for PNET. Depending on the degree of neuroectodermal differentiation, the tumor cells may show variable positivity with synaptophysin, neuron-specific enolase (NSE), and S100.

Around 85 % of PNET has the characteristic t(11:22)(q24: q12), resulting in the formation of chimeric EWS-FLI1 protein. Detection of the EWS-FLI1 gene has both diagnostic and therapeutic implications. Using antisense oligonucleotide against the EWS-FLI1 gene can be beneficial in these patients.[21] It had shown that the use of antisense Oligodeoxy nucleotide against the fusion RNA could cause a significant reduction in tumor cell growth in vivo and invitro.[21,22]

Renal PNET is an aggressive tumor, and its outcome and survival rate depends on the initial stage of presentation. Unfortunately, most of the cases present at an advanced stage and have a grave outcome. All the patients in our case series also presented at an advanced stage. The third patient had extensive tumor thrombus reaching the right atrium at the time of detection itself, and he succumbed to death in the postoperative period. Radical surgery combined with chemotherapy and radiotherapy is the standard treatment for renal PNET. Despite the multi-modality treatment, the reported five-year survival rate is 40-45%, only.[23]

7. Conclusion

Renal PNET is a rare and very aggressive tumor that can occur over a wide age range. Morphological evaluation with the help of immunohistochemistry and demonstration of EWS-FLI1 can make a definite diagnosis. Demonstration of the specific gene defect can have diagnostic and therapeutic implications and can be utilized in personalized gene therapy. Our study highlights the importance of including PNET as a differential diagnosis in elderly patients also.

8. Abbreviations

PNET: Primitive neuroectodermal tumor of the kidney, EFTs: Ewing's sarcoma family of tumors, CNS: central nervous system, IVC: inferior vena cava, PET-CT scan: Positron emission tomography and computed tomography scan, MRI - Magnetic Resonance Imaging, CK: Cytokeratin, LCA: leucocyte common antigen, CD: cluster of differentiation, PAS stain: periodic acid- Schiff stain, RMS –rhabdomyosarcoma, DSRCT: desmoplastic small round cell tumor.

9. Authors Contributions

Dr. Kavitha: concept, collection of data and literature, review of literature and writing the manuscript, Dr. Gittwa: contributed data and proof reading, Dr. Shehla: contributed data and proof reading, Dr. Shalini: critically reviewed the manuscript for its content and approved the final version. Dr. Lilly: reviewed the manuscript for its content, Dr. Surdas: provided data and reviewed the manuscript for its content

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11. Source of Funding

None.

12. Conflict of Interest

None.

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Author biography

K.P Kavitha, Senior Consultant https://orcid.org/0000-0002-7172-9013

Gittwa Vatsaraj Kottangal, Specialist

Shehla Basheer Kollathodi, Specialist

Shalini Kuruvila, Senior Consultant

Lilly Madhavan, Senior Consultant

Surdas Radhakrishnan, Senior Consultant

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