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PRIMARY PRIMITIVE NEUROECTODERMAL TUMOR OF THE KIDNEY : A CLINICOPATHOLOGIC, DIFFERENTIAL DIAGNOSIS AND IMMUNOHISTOCHEMICAL STUDY

Pathology

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ABSTRACT

Introduction : Primitive neuroectodermal tumor (PNET) is an extremely rare small round cell tumor that usually present in the central nervous system, bone or soft tissue, but it can occur in the kidney in rare cases.

Materials and Methods : We described the clinicopathologic features of 10 cases of renal PNET with its differential diagnosis and immunohistochemistry including CD99, cytokeratin, desmin, NSE, Vimentin and LCA.

Results : The patients (7 men, 3 women) ranged from 3 to 56 years of age (average 20yrs). The tumor size was ranged from 14 to 25cm. Presenting symptoms included abdominal/flank pain, lumber lump, hematuria, fever off and on, weakness and loss of appetite. Immunohistochemical results on the renal PNET were positive for CD99 mostly and Vimentin in some. Tumor cells showed a rosette forming structure and positive for CD99, leading to diagnosis of PNET.

Conclusion: Renal PNETs are very unusual tumor characterized by aggressive behavior with local recurrence potential and distant metastasis, which causes poor prognosis.

KEYWORDS

Primitive neuroectodermal tumor, kideney, Immunohistochemistry, CD99 and small round cell tumor.

INTRODUCTION

Primitive neuroectodermal tumor (PNET) is an uncommon malignant small round cell tumor that arises from the nerve crest. This tumor usually occurs in the central nervous system, bone or soft tissue, but it can occur in the kidney in rare cases. [1] It is mostly seen in adolescents and young adults. [2] The first case of renal PNET was described by Seemayer et al.[3], and since then about ~50 cases have been reported worldwide. Renal PNET is highly aggressive neoplasm presenting at an advanced stage with metastasis and subsequent poor prognosis. Renal PNET has an early disseminated and poor prognosis because early progression makes treatment difficult. Chemotherapy with combined doxorubicin (DXR), vincristine, cyclophosphamide (CPA), actinomycin D, ifosfamide (IFM), and etoposide has been shown to improve the prognosis of PNETS/Ewing's sarcoma in a recent large-scale study[4], and here we describe a case series of renal PNET with a clinicopathologic, differential diagnosis and immunohistochemical study.

MATERILS AND METHODS :

We collected the data of the cases from the Hospital Information System of SGPGI. From January 2009 to august 2015, a total of 10 cases of Renal PNETS were retrieved and identified the renal malignancies which were diagnosed as primary renal PNET of these organs on histopathology and immunohistochemistry. These cases from the records were reviewed to obtained data for clinicopathological features, differential diagnosis, imaging, management and outcome. The patient age, gender, clinical symptoms, CT findings, Microscopic features, Immunohistochemical findings, Treatment protocol and Follow-up were recorded. We described the clinicopathologic features of 10 cases of renal PNET with its differential diagnosis and immunohistochemistry including CD99, cytokeratin, desmin, NSE, Vimentin and LCA.

RESULTS:

The patients (7 men, 3 women) ranged from 3 to 56 years of age (average 20yrs). The tumor size was ranged from 14 to 25cm. Presenting symptoms included abdominal/flank pain, lumber lump, hematuria, fever off and on, weakness and loss of appetite. Grossly, all tumors showed necrosis and hemorrhage, and 4 had cystic change.

Ten cases of renal PNET were identified. These cases from the records were reviewed to obtained data for clinicopathological features, differential diagnosis, imaging, management and outcome. Herein, we report our experience of ten cases of renal PNET from routine histopathology reporting summarized in **Table 1**.

Radiologically, on MRI, renal PNETs typically presents as a large and heterogeneous mass **(Figure 1a &1b)** with central low density areas due to necrosis. Grossly, renal PNETs showed solid grey white mass with areas of hemorrhage **(Figure 1c)**. Microscopically, all tumors showed vaguely lobular growth, primitive small round cells **(Figure 1d)**, and variable rosette formation **(Figure 2a)**. Epithelial, myogenous, or cartilaginous differentiation was not seen.

Brisk mitosis is seen 8/10 cases. Lympho-vascular invasion and adrenal metastatic deposit in the cortex **(Figure 2b)** with IVC thrombus **(Figure 2c)** seen in 1case. Immunohistochemical results on the renal PNET were positive for cytokeratin (2/10 focal), desmin (0/10), CD99 (10/10)**[Figure 2d]**, Vimentin (3/10), NSE (3/10) and LCA (0/10. Tumor cells showed a rosette forming structure and the tumor cells were positive for CD99, leading to diagnosis of PNET. Follow-up on 8/10 cases (mean, 28 months; range, 6-64 months) showed 1 adrenal metastasis, IVC tumor thrombus, Georta's fascia involvement and 1 deaths from disease (median time to death, 12 months). In two cases, follow-up was not available. Adjuvant therapy included chemotherapy (10 cases), radiation (3 cases), and bone marrow transplantation (1 case). Our study affirms a unique proclivity of renal PNET for young adults and that it is a highly aggressive neoplasm, with rapid death in many cases, usually after the development of treatment-resistant adrenal metastases.

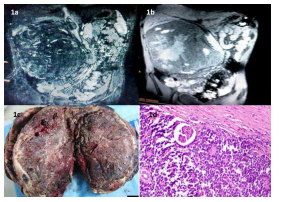

Figure1a&b: Magnetic Resonance Imaging (MRI) showed right renal mass with involvement of renal vein and inferior vena cava (IVC) thrombus measuring 3.5x2.5x2cm in size. **1c:** Right Nephrectomy specimen revealed a solid grey white mass with areas of hemorrhag e.**1d:** Histopatholgy section showed malignant small round cells having high nucleo-cytoplasmic ratio, condensed chromatin and scant cytoplasm with several perivascular pseudorosettes /Homer-Wright like Rosettes and normal kidney[H & E x 400 magnification].

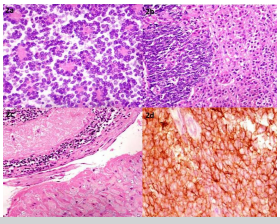

Figure 2a : Several perivascular pseudorosettes /Homer-Wright Rosettes[H & E x400 magnification], **2b:** Section showed adrenal metastasis in the cortex[H & E x400 magnification], **2c**: Section shows involvement of renal vein and inferior vena cava(IVC)thrombus, **2d:**Tumor cells are strongly positive for CD99 immunostaining[x400 magnification].

Table 1. Summary of Primary Primitive Neuroectodermal Tumors of Kidney(n=10)

Case No	Age /Sex	Clinical Symptoms	Operation Findings	CT Findings	Microscopic Findings	IHC Profile	Treatments	Follow-UP
1	23/M	Hematuria, right flank pain fever and weakness-2 months	Right radical nephrectomy adrenalectomy and IVC thrombectomy	Hard, fixed mass in right kidney 20x15x15cm, right adrenal 3x2cm and IVC thrombus 3.5x2.5x2cm	Malignant small round cells, Perivascular pseudo-rosettes, necrosis. Brisk mitosis, lympho-vascular invasion and adrenal metastatic deposit in the cortex with IVC thrombus	Tumor cells are strongly positive for CD99, Vimentin and negative for LCA, Chromo, Syn,NSE and CK	Adjuvant chemotherapy was planned but disease progressed and patient deteriorated	Patient was expired within 12 months
2	20/M	Left flank pain, fever 1 month. hhematuria , dysuria, HTN	USG Tru-cut biopsies from left kidney and calf muscle	Two enhancing lesions at lower pole of the kidney and calf muscle each1.0x0.8 & 1.2x1.0cm	Left kidney and calf muscle showed infiltration by sheets of malignant small round cells	Tumor cells are strongly positive for CD99 and vimentin, negative for LCA, chromo, Syn, NSE and CK	Adjuvant Chemotherapy (Vincristine+Doxo rubicin+Cyclop-hosphomide).	Patient was Expired Within 28 months
3	22/M	Hematuria pain, lump in right flank Anorexia and weight loss-4 months	Right radical nephrectomy	Large solid-cystic mass in right kidney 16x12x10 cm.	Malignant small round cells, Brisk mitotic figures, areas of hemorrhage and necrosis were seen.The gerota's fascia is involved by tumour.	Tumor cells are strong positivity for CD99, vimentin, focal NSE and negative for LCA, Chrom and CK	Adjuvant chemotherapy (Vincristine+Doxo rubicin+Cyclop-hosphomide).	Patient was expired within 40 months
4	35/M	Pain and lump in left flank since 5-6 months	Left radical nephrectomy, spleenectomy	Mass in left kidney extending to aortic bifurcation (17x10x8c),Sple enectomy 9.5x7x2cm)	Malignant small round cells, occasional pseudo-rosettes ,mitosis, necrosis and Fibrocongestive spleenomegaly	Tumor cells are focal positivity for CD99, NSE and negative for desmin,Viment in and LCA	Adjuvant chemotherapy (Vincristine+Doxo rubicin+Cyclop-hosphomide).	NA
5	52/F	Hematuria and right flank pain Since -2 months	Radical nephrectomy,S pleenectomy measuring 9.5x7x2cm	One wax block for histopathology review (postoperated and postradiotherapy renal carcinoma)	Malignant small round cells, Rosette formation, occasional mitosis and areas of necrosis. Spleen shows fibrocongestive changes and free from tumor	Positive for CD99, Syn, NSE and negative for LCA, ,GFAP, Vimentin and CK	Adjuvant chemotherapy (Vincristine+Doxo rubicin+Cyclopho sphomide).	Patient was expired within 46 months
6	41/M	Vomiting, right flank pain, lump- 10 months. No hematuria and weight loss	Right radical nephrectomy ms 12x11x7 cm.	Heterogeneous enhancing mass 8x6x5 cm involving right kidney, renal pelvis,renal vein	Malignant small round cells, focal rosette formation, brisk mitotsis, areas of necrosis.Tumor was infiltrating beyond the capsule renal sinus and adrenal	Tumor cells are positive for CD99 and negative for LCA, vimentin, desmin, chromo and CK	Adjuvant chemotherapy (Vincristine+Doxo rubicin+Cyclop-hosphomide)	Patient was expired 18 months
7	56/M	Hematuria, flank pain anorexia and weight loss- 3 months	Right radical nephrectomy	Large solid-cystic mass in right kidney measuring 16x12x10 cm	Malignant small round cells, Brisk mitotic figures, areas of hemorrhage and necrosis	Positive for CD99 and negative for LCA, vimentin, desmin, chromo and CK	Adjuvant chemotherapy (Vincristine+Doxo rubicin+Cyclop-hosphomide)	Patient was Expired 64 months
8	3/M	Lump in right flank-6 months	Right radical nephrectomy	Large solid-cystic renal mass 16x12x10 cm hepatomegaly (abscess) 17x12x10 cm.	Malignant small round cells, Brisk mitotic figures, areas of hemorrhage and necrosis.The renal sinus is involved by tumour.	Positive for CD99 and negative for LCA, vimentin, desmin, chromo and CK	Adjuvant chemotherapy (Vincristine+Doxo rubicin+Cyclop-hosphomide) and radiotherapy	NA

9	9/M	Right flank pain and Lump in right kidney -6 months	Right radical nephrectomy	Large solid-cystic renal mass 16x12x10 cm hepatomegaly (abscess) 17x12x10 cm	Malignant small round cells, Brisk mitotic figures, areas of hemorrhage and necrosis.The renal sinus is involved by tumour	Tumor cells are positive for CD99 and negative for LCA, vimentin, desmin, chromo and CK	Adjuvant chemotherapy (Vincristine+Doxo rubicin+Cyclop-hosphomide) and radiotherapy	Patient was Expired Within 36months
10	45/F	Right flank pain and Lump in right kidney -5months	Right radical nephrectomy	Large solid-cystic renal mass 14x12x10 cm	Malignant small round cells, Brisk mitotic figures, areas of hemorrhage and necrosis. The renal sinus is free.	CD99 Positive and negative for LCA, CK vimentin, desmin, chromo	Adjuvant chemotherapy and radiotherapy	Patient was expired Within 50 months

LCA, Leukcyte common antigen; CK, Cytokeratin; Syn,Synapto physin; NSE, Neurone specific enolase; Chromo, Chrmogranin; DM, Diabetes Melitus; HTN, Hypertension; IVC, Inferior vena cava; IHC, Immunohistochemistry; USG, Ultrsound; CT, Computed tomography. NA, Not Available

DISCUSSION

Renal PNET is an aggressive tumor with a tendency towards local recurrence and early metastases to regional lymph nodes, lungs, liver, and bone. The first case of renal PNET was described by Seemayer et al 1975. **[3]** To date, all the previously diagnosed ~35 cases of renal PNET with IVC tumor thrombus did not show evidence of adrenal metastasis in the literatures but our one case report, the pateint showed renal PNET infiltrating to renal vein alongwith IVC tumor thrombus and adrenal metastasis. Peripheral PNET was first described by "Stout" in association with peripheral nerves, it belongs to a family of small round cells tumors with more aggressive behavior than other members. As non-neural origin, renal PNET is a rare distinct clinical entity with aggressive behavior, and usually afflicts adolescents and the young adults; median age at presentation is 27 years old.

Patients classically present with haematuria, a palpable abdominal mass and flank and/or abdominal pain. **[1,4,5]** In previous diagnosed cases, patients showed extensive atrial thrombus, complained of dyspnoea, dizziness and fatigue owing to the mechanical effect of the tumor in the right atrium causing circulatory compromise. Diagnosing PNET can be challenging as it is sometimes difficult to differentiate it from other primary renal neoplasms, such as Wilms' tumor. Grossly they are bulky tumors. They tend to be greyish in colour, encapsulated and contain focal areas of haemorrhage and/or necrosis. The tumor is usually sharply demarcated from a normal kidney. Classically, a PNET histologically shows malignant small round cells and can form several neuroblastic Homer Wright rosettes, or pseudorosettes. Karnes et al.**[1]**reported, in 2000, the first case of a PNET with vena caval tumor thrombus (level II). Thomas et al.**[4]** first reported a PNET with a level IV thrombus in a 55-year-old woman, which was managed successfully with deep hypothermic circulatory arrest. This patient was 21 years old with PNET and a level IV thrombus to undergo right radical nephrectomy and IVC tumor (level IV) thrombectomy with cardiopulmonary bypass and deep hypothermic circulatory arrest. Chen et al. reported the case of a 17-year-old woman with a right renal PNET, which extended into the vena cava, right atrium and hepatic veins. The patient had Budd Chiari syndrome and also underwent thrombectomy with cardiopulmonary bypass and deep hypothermic circulatory arrest. Two cases of Budd Chiari syndrome secondary to renal PNET have reported in the literatures.**[6]** The patient had spontaneous regression of pulmonary metastases after nephrectomy similar to that described in Wada et al. **[5]**

On immunohistochemistry, the tumor cells showed strong positivity for CD99, Vimentin, focal Neuron-Specific Enolase (NSE) and negative for LCA, Cytokeratin, Chromogranin, Synaptophysin, Smooth Muscle Actin (SMA), Myogenin, Desmin in our case. Renal PNETs should be differentiated from other malignant round cell tumors of kidney such as Wilms tumor, neuroblastoma, rhabdo myosarcoma and malignant lymphoma.Tumor cells expressed CD99, Vimentin, S100 and NSE, a profile highly suggestive of PNETs. CD99 is almost always present in these tumor but it should be reiterated that, CD99 expression is not pathognomonic for PNE T,because it is also found in synovial sarcomas and gastrointesti nal stromal tumors in some cases.Wilms' tumor showed strong immunostaining positivity for WT1 and focal positive for CK, Desmin and Vimentin. Neuroblastoma is a primarily tumor of young children, with 90% occuring by the age of 5 years. The cells in the neuroblastoma are seen in a fibrillary background and show prominent positivity for NSE and chromogranin and are consistently negative for CD99. Moreover , the lack of staining of LCA (Lymphoid), MSA, EMA (Muscle), HMB-45 (melanoma), Synaptophysin ,Chromogranin (Endocrine) markers virtually excludes the rhabdomyosacoma, hematolymphoid neoplasm or neuroendocrine carcinoma (particularly in this age group). PNETs occasionally stained with chromogranin and synaptophysin; and small cell carcinoma are often cytokeratin positive.**[7]** In most renal PNET, molecular genetic studies shown translocation t(11;22)(q24;q12)*EWS/FLI-1* and result in fusion of the *EWS* gene on chromosome 22 to *FLI-1* gene on chromosome 11.

To date, there is no absolute protocol or treatment for PNET owing to its rarity but the standard of care includes neoadjuvant multiagent chemotherapy and surgical resection followed by postoperative radiotherapy and chemotherapy. Radical nephrectomy and lymphadenectomy remain the most important modality of management which has shown survival advantages.**[7]** The recent standard chemotherapeutic treatment regimen involves a six-drug combination, including vincristine(V), dactinomycin (D),adria mycin(A), cyclophosphamide(C), ifosfamide (I) and etoposide (E).**[8]** The role of radiotherapy is not clear but may be advocated in locally advanced disease and involvement of Gerota's fascia. Despite aggressive treatment by combination therapy with surgery, chemotherapy and radiotherapy, the prognosis of renal PNET remains poor and overall 5-year survival rates have been reported at 42% to 55% for 5 and 3 years respectively.**[7,9]** Ellinger J et al **[10]** reported 2 cases of renal and 1 case of bladder PNETs which were both often diagnosed at an advanced stage and surgery and, therefore, the prognosis was poor, despite aggressive multimodal treatment (surgery, polychemotherapy,radiotherapy).They identified palpable tumor masses (log-rank test,P =0.0027) and synaptophysin expression (log-ranktest, P=0.0422)as prognostic unfavorable markers for renal PNET. As in cases of renal cell carcinoma with thrombus, thrombectomy plays an important role in the treatment of renal PNET with IVC thrombus. Recently introduced a new oral multi-tyrosine kinase inhibitor agents "sorafenib" that implied the potential role in the treatment with chemo-resistant PNET and its lung metastasis. WU Yun-jian et al**[11]** in 2010, described a first reported case of PNET arising in the kidney during pregnancy with IVC tumor thrombus that responded to sorafenib treatment.**[10]** Our one patient had come to out patient department (OPD) for follow-up after eight months surgical resection of the renal mass due to low HB (6.3gm%, normal range 14-16gm/dl), received two unit of PRBC. He had not received any radiotherapy or chemotherapy after surgical resection. Patient was well and live upto 12 months after right radical nephrectomy with adrenalectomy and thrombectomy.

CONCLUSIONS: Renal PNETs are rare tumor characterized by aggressive behavior with local recurrence potential and distant metastasis, which causes poor prognosis.This entity must be considered in the differential diagnosis of renal masses in young patients, especially those presenting with a disseminated disease at onset / advanced malignancy with extensive vena caval thrombus and adrenal metastasis. An accurate clinico-histopathogical and immunohistopathological diagnosis is very important because it may determine which of the various chemotherapy regimens will control the disease better.

REFERENCES

1. Karnes RJ, Gettman MT, Anderson PM, Lager DJ, Blute ML. Primitive neuroectodermal tumor (extra skeletal Ewing'ssarcoma) of the kidney with vena caval thrombus. J Urol 2000;164: 772.
2. Rodriguez-Galindo C, Marina NM, Fletcher BD, Parham DM, Bodner SM, Meyer WH. Is primitive neuroectodermal tumor of the kidney a distinct entity? Cancer 1997; 79: 2243-2250.
3. Seemayer TA, Thelmo WL, Bolande RP. Peripheral neuroectodermal tumors. Perspect Pediatr Pathol 1975; 12: 151-152.
4. Thomas JC, Sebek BA, Krishnamurthi V: Primitive neuroectodermal tumor of the kidney with inferior vena cava and atrial tumor thrombus. J Urol 2002, 168:1486-1487.
5. Wada Y, Yamaguchi T, Kuwahara T, Sugiyama, Kikukawa H, Ueda S: Primitive neuroectodermal tumour of the kidney with spontaneous regression of pulmonary metastases after nephrectomy. BJU Int 2003, 91(1):121-122.
6. Chen HR, Fryberger S, Lee JD, Wong LL: Successful resection of a PNET tumor the kidney with vena caval and cardiac invasion. Surg Rounds 2006-2008-08.asp.
7. Gupta NP, Singh BP, Raina V, Gupta SD. Primitive neuroectodermal kidney tumor: 2 case reports and review of the literature. J Urol 1995; 153: 1890-1892.
8. He SS, Zhao J, Han KW, Hou TS, Hussain N, Zhang SM. Primitive neuroectodermal tumor of lumbar spine: case report. Chin Med J 2007; 120: 844- 846.
9. Thyavihally YB, Tongaonkar HB, Gupta S, Kurkure PA, Amare P, Muckaden MA, et al. Primitive neuroectodermal tumor of the kidney: a single institute series of 16 patients. Urology 2008; 71: 292-296
10. Jorg Ellinger, Patrick J. Bastian, Stefan Hauser et al. Primitive neuroectodermal tumor : Rare, highly aggressive differential diagnosis in urologic malignancies. Urology 2006;68(2)257-262.
11 WU Yun-jian, ZHU Yu-chun, CHEN Hui, et al . Primitive neuroectodermal tumor of the kidneywith inferior vena cava tumor thrombus during pregnancy response to Sorafenib. Chinese Medical Journal 2010;123(15):2155-2158