Renal primitive neuroectodermal tumor: does age at diagnosis impact outcomes?

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Abstract

Primitive neuroectodermal tumor (PNET) of the kidney is a rare and highly malignant neoplasm. The median age for renal PNET is 27 years but it can be seen also in a wide age range between 3 and 78 years. We performed a Medline search for the term *renal PNET* and identified 79 cases up till December of 2010. We report here a new case of renal PNET and a literature review for published data for evaluation of clinicopathological prognostic factors, with an emphasis on prognosis in two groups of adults and children-adolescents: 18 years of age or under and over 18 years.

Introduction

Primitive neuroectodermal tumor (PNET) of the kidney is a rare and highly malignant neoplasm. The median age for renal PNET is 27 years but it can be seen in a wide age range between 3 and 78 years.[1] It affects young adults and only a few pediatric and adolescent cases (18 years or under) have been reported. Renal PNET needs to be differentiated from other small round cell tumors of the kidney, because of the different treatment modalities required. Diagnosis of this neoplasm is currently based on a combination of light microscopy, immunohistochemistry (IHC) and reverse transcriptase polymerase chain reaction (RT-PCR),[2-4] and a multimodality treatment approach, such as surgical resection and chemotherapy with or without radiotherapy, is recommended for these patients. There is a high recurrence rate and a tendency to metastasize to regional lymph nodes, lungs, liver, bone and bone marrow at an early disease stage. However, prognosis seems to be better in younger patients.[5,6]

We performed a MEDLINE search for the term *renal PNET* and identified 79 cases up till December of 2010. Patients with insufficient data, such as lack of clinicopathological data and IHC, were excluded. We report a new case of renal PNET and a literature review for published data for evaluation of clinicopathological prognostic factors, with an emphasis on prognosis in two groups of adults and children-adolescents: 18 years of age or under and over 18 years. The data obtained for renal PNET were analyzed using the Kaplan-Meier method with SPSS version 17.5. P <0.05 was considered significant.

Case Report

A 3-year old boy was admitted to our hospital with abdominal pain and a large palpable mass on the left side of the abdomen. Sonography showed a tumor of the left kidney. Computer tomography revealed a large left inhomogeneous renal mass of 12 cm with areas of necrosis and bleeding. There was no obvious lymphadenopathy and no intraabdominal metastasis. Laboratory evaluation was normal in CBC: UA catecholamine metabolite only LDH level was 890 IU/L.

A left radical nephrectomy with lymph node dissection was performed. Gross pathology examination confirmed kidney dimensions of 14×12×8 cm. The tumor involved a large portion of the pole of the kidney. The tumor was 4.5 cm in diameter at its widest point with infiltration to the renal pelvis. The renal vein, urethra and lymph nodes were negative for malignancy. Histolological examination revealed small round undifferentiated tumoral cells with scant cytoplasm, oval to round with hyperchromatic nuclei. The tumor had massive areas of necrosis without rosette or tubule formation. The renal capsule was infiltrated with tumor. The morphological report confirmed a small round cell tumor.

Immunohistochemistry revealed that tumor cells were strongly positive for Mic2 (CD99) as well as vimentin and Neuron-Specific Enolase (NSE). The tumor cells were negative for synaptopohsin and Wilm's tumor (WT1), cytokeratin, neuroblastoma, neurofilament, leukocyte common antigen, myogenin, S-100 and desmin. Chromosomal evaluation showed the patient was positive for EWS-FLI1 translocation in PCR.

Metastatic workup showed there was no metastasis on bone scintigraphy and thorax CT scan. Bilateral iliac bone marrow biopsies showed no evidence of neoplastic involvement. The patient received chemotherapy with vicristin, adriamycin, cyclophosphamide alternating with etoposide, ifosfamide and mesna for 48 weeks. No serious adverse effects were reported during chemotherapy. The patient received radiation therapy to the tumor bed for minimal residual disease due to extracapsular invasion for 40 GY in 22 fractions.

There was no evidence of disease at 56 months from diagnosis and no late adverse effects have been noted. This is the youngest patient to be reported with renal PNET.

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Key words: primitive neuroectodermal tumor, kidney, diagnosis.

Received for publication: 4 June 2011.
Revision received: 31 October 2011.
Accepted for publication: 4 December 2011.

Rare Tumors 2012; 4:e15
doi:10.4081/rt.2012.e15

Results

We found 80 cases of renal PNET (40 males and 39 females) reported in literature. (A detailed list of all cases is available on request.) Median age at renal PNET diagnosis reported in a published series is 27 years (mean=29.43±16.31, range 3-78 years). In the 18 years and under age group, 59.1% are between 13-18 years and 44.8% of patients over 18 years are between 20-29 years. There are 7 males and 14 females aged 18 years and under versus 33 males and 25 females aged over 18 years.

Flank pain is the most frequent of symptoms and signs (67.5%) in renal PNET followed by hematuria (33.8%) and mass (33.8%), IVC thrombosis (25%) and weight loss (16%). There is no relation between clinical manifestation and survival or between clinical signs and age.

Follow-up data were available for 68 patients with renal PNET with a median follow up of 12 months (interquartile range 5-19.5); 36 (45%) died of their disease and 66.7% of patients in the younger group had no evidence of disease versus 38.3% in the older group (P=0.03).

One-year survival was 50.2 *vs.* 34.2% and 2-year survival was 30.1% versus 18.4% in patients aged 18 years and under and those over 18 years, respectively (95% CI; 11-21). However, there was no statistically significant difference in overall survival (log rank test

P=0.08), with median survival 24.1 months for patients aged 18 under and 14.6 months for those aged over 18 years, respectively. Five-year survival with disease free status was found in 2 cases in the 18 years and under age group, but none in the over 18 years group (Figure 1). There were significant differences in death rate between the younger and older groups: 37.5% versus 70%, respectively (P=0.024)

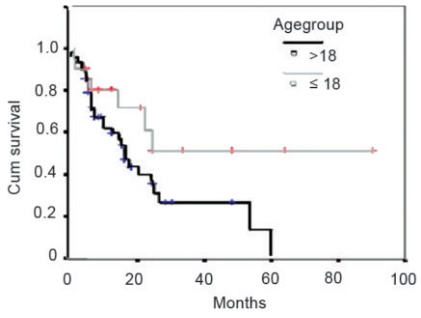

Figure 1. Overall survival function in age groups.

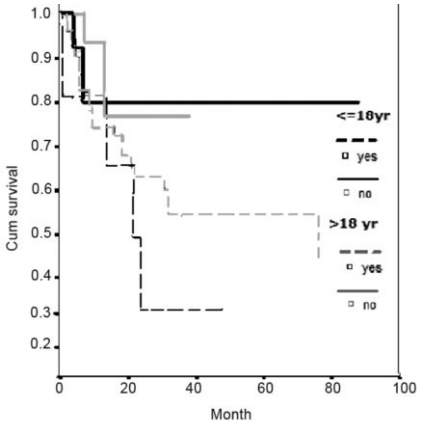

Figure 2. Survival function in metastatic patients by age groups.

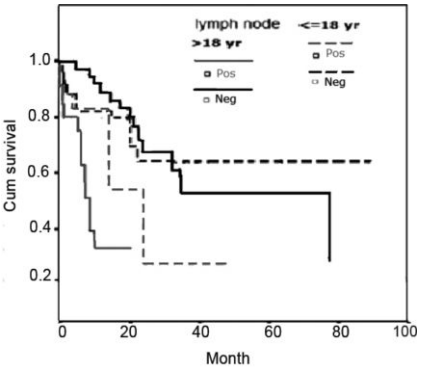

Figure 3. Survival function according to lymph node involvement in patients ≤18 years old and >18 years old.

Forty-four (55%) of these patients had metastases at presentation: 12 to liver, 26 to lung and 19 to lymph node. Liver metastasis is more frequent in those aged 18 years and under, and lung, lymph node and bone metastases in patients aged over 18 years. There was more metastatic disease in the older group than the younger group: 73.3% versus 50% (CI: 60, 87% versus CI: 27, 73%, P=0.059) and the mean age of patients with metastasis is 29.3±14.9 years versus 22.8±14.6 years in patients without metastases (P<0.05). Younger patients with metastatic disease have better survival than older patients (log rank P=0.3) (Figure 2). In patients aged 18 years and under, 1-year survival in local and metastatic disease was 77.7% and 50.2%, respectively (log rank P=0.2) whereas in patients aged over 18 years these rates were 64.7% and 34.2%, respectively, although this difference was without statistical significance (log rank P=0.18).

Survival rate in lung metastasis was significantly lower than local disease: median survival (CI 95%): 14 (range 3-25) versus 60 (range 9-111) months; log rank test P=0.02. Lymph node involvement was 22.7% versus 30.4% in patients aged 18 years and under and those over 18 years, respectively. Differences in survival between lymph node positive and negative was not significant in cases aged 18 years and under (mean survival 23 vs 62 months), but there was a significant difference in cases aged over 18 years (mean survival 5 vs 31 months; log rank test P=0.000) (Figure 3).

Immunohistochemical analysis found CD-99 was positive in the majority of patients followed by NSE, vimentin, S-100 and synaptopysin. Sixty-seven patients were evaluated for EWS-FLI1 translocation in PCR. There was no relation between immunohistochemical markers and survival function (Table 1).

Discussion

The peripheral neuroectodermal tumor, first recognized by Arthur Purdy Stout in 1918, is a member of the family of *small round-cell tumors*.[7] PNET is a primitive, poorly differentiated round cell neoplasm of neuroectodermal origin that presents outside the central and sympathetic nervous system. PNET is a malignant disease of young adult and the first report of renal PNET was by Seemayer in 1975.[8] But renal PNET is a rare disease with a wide age range at presentation between early childhood to late adulthood.[6]

Diagnosis of renal PNET must be considered in young patients with renal neoplasm, particularly those with advanced disease at presentation.[9] The diagnosis of PNET is based on pathological findings. Application of the full range of diagnostic methods is necessary because the use of a single diagnostic method is not enough to exclude the large number of differential diagnoses, such as desmoplastic tumor, Wilm's tumor, neuroblastoma, small cell carcinoma, malignant lymphoma, renal cell carcinoma and other tumors depending on age at presentation. However, diagnosis must be made rapidly so that the patient can receive effective therapy as soon as possible.

Several diagnostic approaches can be used when there is suspicion of PNET. The first approach is light microscopic examination of tumor tissue including immunohistochemistry. These tumors consist of primitive looking round cells with high nucleous to cytoplasmic ratio. The immunohistochemical features of PNET are often positive for CD99 (mic2), NSE expression was detected in 95%, and vimentin, S-100, and synaptophysin and chromogranin were expressed in the majority of patients (60%). However, expression of CD99 is by no means specific for PNET among round cell tumors.[10] A third approach is the presence of EWS-FLI chromosomal translocation that is positive in 88-95% of PNET cases.[11-12] But in

Table 1. Survival function by immunohisthochimestrty features (Neuron-Specific Enolase negative was not mentioned in case reports).

		Mean survival (months)	95% confidence interval
Neuron Specific Enolase	+	30	(20, 40)
Vimentin	–	13	(4, 22)
	+	50	(30, 70)
S-100	+	23	(15, 31)
	–	22	(9, 35)
Synaptophysin	+	39	(13, 64)
	–	32	(13, 52)

renal PNET, the positive frequency of these markers is different and NSE is less frequent. Some studies showed that the presence of some IHC markers, such as chromogranin, may play a negative role in terms of survival.[9] However, in this study, no relation between IHC markers and patient outcome was found. When diagnosis is not clear on the basis of pathology and immunohistochemistry, molecular markers (EWS-FLI chromosomal translocation) have been proved to be exceedingly useful, especially in cases of unusual morphology and small biopsy in renal mass.[13] Some studies (but not all) have suggested that the type of fusion may have prognostic significance, with some studies showing a positive association between EWS-FLI1 fusions and longer survival in ESF tumors.[14,15] However, we found no difference between EWS-FLI1 and survival in patients with renal PNET.

The number of renal PNET case reports has grown in the past few years due to better differential diagnosis of renal tumors resulting from advances in immunohistochemistry and PCR methods. We, therefore, believe that the number of cases of renal PNET is underestimated; a review of pathological specimens in National Wilm's Tumor Study by IHC and RT-PCR found more renal PNET than Wilm's tumor under light microscopy.[16,17]

The survival rate of patients with organ-confined PNET is unknown, but hopefully an aggressive multidisciplinary treatment approach will provide a cure.[18] Treatment should consist of a combination of surgery and chemotherapy. Complete resection of the kidney with node sampling should be performed if at all feasible. There is a definite role for chemotherapy in this disease, and best responses are seen with combinations containing anthracyclines and high doses of alkylating agents alternating with ifosfamide and etoposide. Radiation therapy is recommended for patients with residual tumor or positive margins after surgery. The role of radiotherapy in the absence of residual disease or extracapsular extention is not known.[19,20]

Renal mass, and pain and hematuria are the most frequent presenting symptoms, and weight loss is more frequent in younger patients. Ellinger *et al.*[9] showed that the patients with renal mass had a low survival rate but we found no relation between symptoms and signs with survival.

Ewing Sarcoma Families (ESF) are aggressive neoplasms; about 25% of patients have clinically apparent metastatic disease at the time of diagnosis. Nevertheless, despite aggressive treatment, 30-40% of patients with localized disease, and 80% of patients with metastatic disease, die due to disease progression.[21] Patients with localized ESF have a 5-year disease-free survival rate of approximately 60 to 70%.[22] Analyzing the data obtained from case reports, 75% of patients with localized renal PNET were free of disease after a period of 4-90 months. Overall, 47.1% of patients, 66.7% of cases aged 18 years or under and 38.3% aged over 18 years, had no evidence of disease during follow up. Despite aggressive treatment, the prognosis of patients with metastatic disease is poor. For metastatic EFF, the overall cure rate has been 20%, and in renal PNET among metastatic sites the patients with lymph node and lung metastases have poor survival.[23,24]

Our results seem to show that children and young adults have less metastatic disease and have a better outcome even if they have metastases. The effect of age on survival is contradictory in ESF tumors. In some studies, outcome was better in younger patients in univariate and multivariate analysis[18,23,25,26] while others did not influence survival; cut-off points were between 12 to 26 years of age. Median age at diagnosis of ESF, according to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data for the period 1973 to 1987, was 15 years.[22,27] Therefore, approximately one half of all patients diagnosed with an ESF tumor will be over 15 years of age, and it is important to remember that it is just as frequently found in young adults as in children. In most studies, older age has been reported to have an unfavorable prognostic factor.[18,28,29] Several characteristics of adult Ewing's sarcoma, such as a different pattern of primary tumor sites (*e.g.* axial location), a larger tumor size, and a lower intensity of chemotherapy dose, may explain why the prognosis in adults is seemingly less favorable. Our findings suggest that adult patients with renal PNET, like other ESF tumors, have poorer outcomes than younger patients and must treated by aggressive protocols, like pediatric protocols.

In conclusion, although primitive neuroectodermal tumor is extremely rare in the kidney, the past two decades have seen this tumor diagnosed more frequently. This is due to better diagnostic methods, such as IHC and molecular markers, for differential diagnosis with other renal masses. Renal PNET involves a wide age range at presentation but the median age at presentation is approximately 15 years older than other ESF. Patients in the older age group have more poor prognostic factors and lower survival than children and adolescents and should be treated with more aggressive protocols. Renal PNET in younger patients could have a better prognosis even with distant and regional metastases.

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