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The immunohistochemical features of the renal primary primitive neuroectodermal tumor mimicking adult blastemal Wilms tumor: a case report

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SUMMARY

Primary primitive neuroectodermal tumor of the kidney is a rare and aggressive tumor. Its distinction from other primary renal tumors is clinically important due to different therapeutic management. A 44-year-old man was admitted to the hospital with left flank pain and hematuria. In computerized tomography, a mass in left kidney was detected and nephrectomy was performed. Microscopically the tumor was composed of small round cells. Immunohistochemically, diffuse strong positivity for CD 99 (MIC2) and NSE, and focal positivity for Wilms tumor 1 were determined in the tumor cells. In this report, a rare renal primary primitive neuroectodermal tumor showing both CD99 and Wilms tumor 1 expression is presented.

Key words: *Ewing tumor, immunohistochemistry, kidney, Wilms tumor*

ÖZET

Yetişkin blastemal Wilms tümörüne benzerlik gösteren renal primer primitif nöroektodermal tümörün immünohistokimyasal özellikleri: olgu sunumu

Böbreğin primer primitif nöroektodermal tümörü seyrek görülen agresif bir tümördür. Farklı tedavi yaklaşımları nedeniyle, klinik olarak bu tümörün diğer primer renal tümörlerden ayırımı önemlidir. Kırk dört yaşında erkek hasta sol yan ağrısı ve hematüri şikayetleri ile hastaneye başvurdu. Bilgisayarlı tomografide sol böbrekte kitle saptandı ve nefrektomi uygulandı. Mikroskopik olarak, tümör küçük yuvarlak hücrelerden oluşmaktaydı. İmmünohistokimyasal olarak, tümör hücrelerinde yaygın ve kuvvetli CD 99 (MIC2) ve NSE, fokal Wilms tümör 1 pozitifliği saptandı. Bu yazıda CD 99 ve Wilms tümör 1 ekspresyonu gösteren ve seyrek görülen renal primer primitif nöroektodermal tümör olgusu sunulmuştur.

Anahtar kelimeler: *Ewing tümörü, immünohistokimya, böbrek, Wilms tümörü*

Introduction

Primary primitive neuroectodermal tumor (PNET) is a rare primary tumor of the kidney that resembles other malignant small round cell tumors of assumed neuroectodermal origin (1-13). The differential diagnosis of the poorly differentiated small round cell tumors of the kidney includes PNET, blastemal Wilms tumor, neuroblastoma, rhabdomyosarcoma, lymphoma, clear cell sarcoma, synovial sarcoma, desmoplastic small round cell tumor and small cell carcinoma. It is essential because of their different therapeutic and prognostic implications. The most common primitive tumor in kidney, Wilms tumor, responds well to a standard protocol of multidrug chemotherapy (4), whereas primary renal PNET has an aggressive clinical course that requires more extensive therapy, which includes radiotherapy and multidrug chemotherapy (5).

While immunohistochemical panel may be valuable in the differential diagnosis of renal small round cell tumors, the differential diagnosis may still be problematic because of the presence of overlapping morphologic and immunophenotypic features in some cases. Especially, the discrimination of PNET and blastemal Wilms tumor in kidney may be difficult, when both CD99 and WT1 expression are detected. We report a rare primary renal PNET showing both CD99 and WT1 expression.

Case Report

A 44-year-old man admitted to our hospital with left flank discomfort. The clinical symptoms did not subside with anti-inflammatory agents. Several months later, he admitted to the nephrology department with hematuria and elevated serum creatine level. Abdominal axial non-contrast computed tomography scan showed a large hypodense solid mass measuring 16x12.5x11 cm in the left kidney with a large lymph node at the medial aspect of the mass, pushing the aorta to the right (Figure 1). Normal left kidney paren-

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chyma was not distinguished, and the aorta and vena cava inferior appeared normal in computed tomography. The patient underwent left radical nephrectomy. There was no metastasis to any other organs in clinical screening tests performed after pathology report. Adjuvant multidrug chemotherapy and radiotherapy were planned as further treatment procedures.

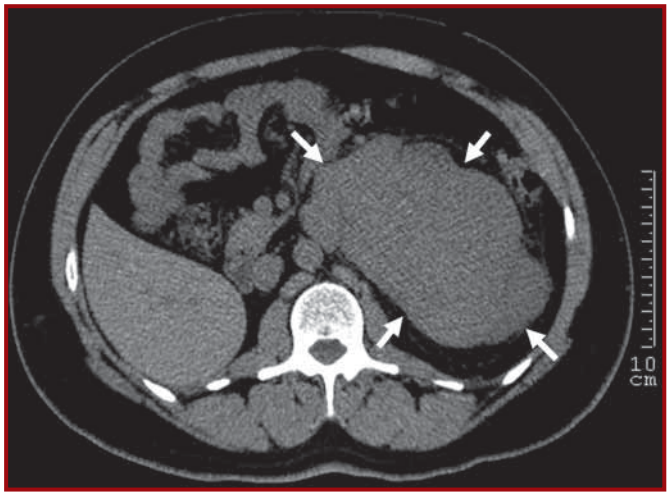

Figure 1. Abdominal axial non-contrast computed tomography scan revealed a large hypodense solid mass (white arrows)

Macroscopically, the left kidney and the adrenal gland with perirenal fat measured 18x17x8.5 cm. The kidney was entirely replaced with a solid gray tumor measured 16x12.5x11cm in diameter (Figure 2). The tumor demonstrated lobular growth pattern with multiple areas of hemorrhage and necrosis. Tumor thrombus was detected inside the renal vein and measured 5x4x1.5 cm in dimension. The tumor invaded perirenal fat tissue and extended to the adjacent adrenal gland.

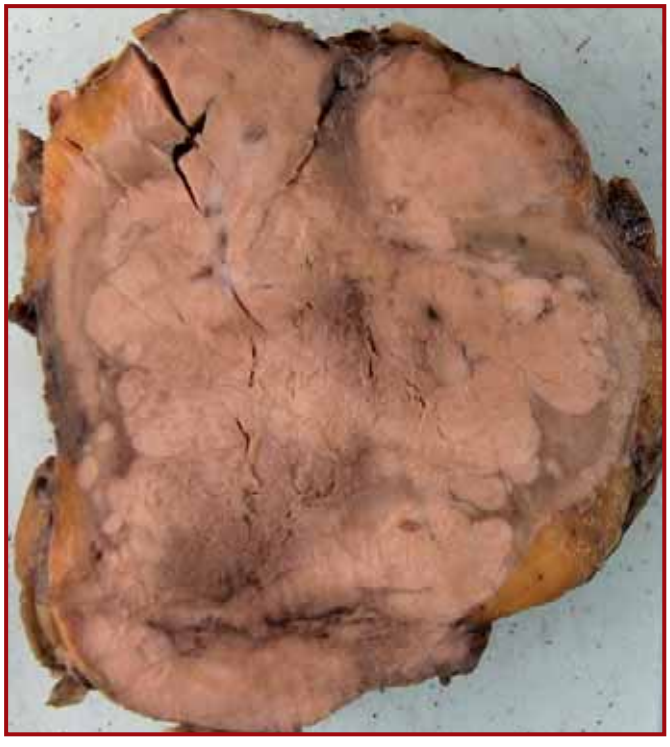

Figure 2. Macroscopic appearance of primary renal primitive neuroectodermal tumor

Microscopically, the tumor was arranged in lobules with different sizes, and composed of diffusely proliferating uniform population of blue round small cells (Figure 3). These cells formed sheets, true Homer-Wright rosettes and pseudorosettes were readily identified. The tumor cells had regular nuclear contours,

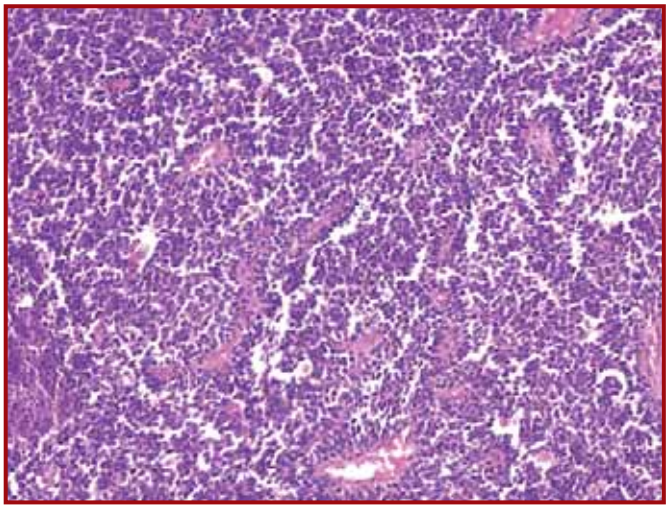

Figure 3. The tumor was composed of blue small round cells. Perivascular pseudorosettes and rosettes were readily identified (H&E, x100)

finely dispersed chromatin without prominent nucleoli, and eosinophilic scanty cytoplasm. The tumor showed extensive necrosis and numerous mitotic figures. There was no evidence of any epithelial or blastema like component while numerous sections were examined. The tumor extended to the adjacent adrenal gland without invasion. Tumor thrombus was identified in the lumen of the renal vein. There was also perirenal lymph node metastasis and perinodal infiltration in the same lymph node.

Immunohistochemistry was performed on formalin-fixed, paraffin embedded tissue using the usual avidin-biotin-peroxidase complex method. Antibodies used in immunohistochemical study and their results are summarized in Table I.

The tumor cells were diffuse strong positive for CD99 (membranous pattern) (Figure 4A), and NSE (cytoplasmic pattern), focal positive for WT1 (nuclear pattern) (Figure 4B), diffuse weak positive for synaptophysin (cytoplasmic pattern). The tumor cells were negative for LCA (CD 45), CD 56, TTF-1, pancytokeratin, cy-

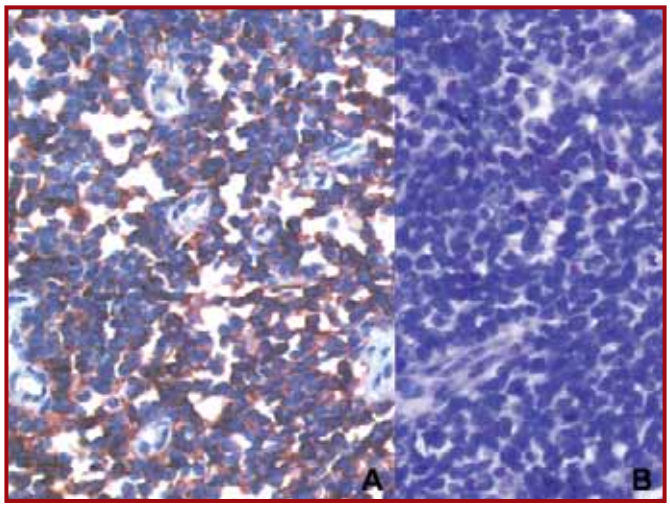

Figure 4. A. Membranous CD99 expression. **B.** Focal nuclear WT1 expression (Immunohistochemistry)

tokeratin 7 and 20, vimentin, desmin, smooth muscle actin (SMA), S-100 protein and chromogranin A.

Discussion

PNET was first described by Arthur Pourdy Stout in 1918. The most common locations are in the soft tissue of the trunk, extremities, head and neck. The first primary renal PNET was reported by Mor et al (6). There are very few cases and most of them are case reports in the literature (1-13). Primary renal PNET is a rare entity that behaves more aggressively than PNET arising at other sites. The disease occurs predominantly in children and young adults. Primary renal PNET has a high recurrence rate and a tendency to metastazing to renal vein, regional lymph nodes, lungs, liver, bone and bone marrow at early stages. The distinction from other primary small round cell tumors of the kidneys is essential for prognosis and therapeutic modalities. Especially, the differential diagnosis between renal PNET and blastemal WT may be problematic because of overlapping histopathological and immunophenotypical features.

Primary renal PNET may present with non-specific findings and its radiological differential diagnosis from other more frequent primary and metastatic renal tumors may be difficult. Small round cell tumors of the kidney histopathologically and closely resemble the other primitive tumors and the more common counterpart in soft tissue. Immunohistochemical positivity for CD99, NSE, and FLI-1 are very helpful in differential diagnosis of PNET and other primitive small round cell tumors (7,8). Chromogranin A and synaptophysin are negative or weak positive in PNET (1). Although vimentin is usually positive in PNET-EWS (1-13), it is more often positive in Ewing sarcoma than in PNET. Some studies suggest that vimentin may be negative in PNET as in the present case (9-12). Pan-cytokeratin is negative, while it is positive in approximately 20% of CD99 positive primary renal PNET cases (1,7). Pan-cytokeratin positivity is meaningful for small cell carcinoma, when there is no CD99 expression. CK7 and CK20 expression patterns and TTF-1 expression are useful for the distinction of metastatic Merkel cell carcinoma and primary or metastatic small cell carcinoma. Homer–Wright rosettes, positivity for NSE, chromogranin A and synaptophysin are more typical for neuroblastoma than PNET-EWS. LCA (CD45) immunoreactivity is characteristic for lymphoma. CD56 is negative in PNET as in the present case, while it is positive in neuroblastoma, neuroendocrine tumors, small cell carcinoma and Merkel carcinoma. Rhabdomyosarcoma is typically immunoreactive for actin, desmin, MyoD1 and myogenin, while they are negative in PNET. Desmoplastic small round cell tumor was immuno-

Table I. Antibodies used in immunohistochemistry and immunohistochemical results

Antibody	*Dilution*	*Vendor*	*Results*
CD99	1:100, monoclonal	Neomarkers, Fremont, CA	+, diffuse
WT1	1:25, monoclonal	Neomarkers, Fremont, CA	+, focal
NSE	1:100, monoclonal	Neomarkers, Fremont, CA	+, diffuse
Synaptophysin	1:100, monoclonal	Neomarkers, Fremont, CA	+, diffuse
Chromogranin A	1:100, monoclonal	Neomarkers, Fremont, CA	-
S100	1:100, monoclonal	Neomarkers, Fremont, CA	-
LCA (CD45)	1:100, monoclonal	Neomarkers, Fremont, CA	-
Smooth muscle actin	1:100, monoclonal	Neomarkers, Fremont, CA	-
Desmin	1:50, monoclonal	Neomarkers, Fremont, CA	-
Pan-cytokeratin	1:100, monoclonal	Neomarkers, Fremont, CA	-
Cytokeratin 7	1:100, monoclonal	Neomarkers, Fremont, CA	-
Cytokeratin 20	1:50, monoclonal	Neomarkers, Fremont, CA	-
CD 56	1:80, monoclonal	Neomarkers, Fremont, CA	-
TTF-1	1:20, monoclonal	Neomarkers, Fremont, CA	-

reactive for vimentin, WT1, desmin, NSE, pan-cytokeratin, and epithelial membrane antigen (13). CD99, synaptophysin and chromogranin were focally immunoreactive in desmoplastic small round cell tumor. We ruled out the possibility of the desmoplastic small round cell tumor, as desmin and pan-cytokeratin were negative.

The most challenging differential diagnosis is between PNET and blastemal Wilms tumor (7). The WT1 protein is encoded by the WT1 gene located on chromosome 11p13. This gene is required in tissue differentiation and proliferation. WT1 has been used as a discriminative immunohistochemical marker for the diagnosis of Wilms tumor. It shows normally nuclear expression in the glomerular podocytes, mesothelial cells and stem cells. The blastemal component of Wilms tumor usually shows strong immunoreactivity for WT1. This immunoreactivity may have potential in discrimination other primitive small round cell tumors from blastemal Wilms tumor that might be diagnostically challenging with PNET. Jimenez et al. demonstrated WT1 immunoreactivity in 7 of 9 Wilms tumors while all PNET cases were negative (7,14). While diffuse and strong CD99 (MIC2 gene) expression was detected in PNET, it is usually not expressed in Wilms tumor (1). However, CD99 expression can be occasionally seen in Wilms tumor (7). Ellison et al. reported both CD99 and WT1 expression in 7 of 30 primary renal PNETs (8). In the same study, FLI-1 was negative in 2 of these 7 cases. When both CD99 and WT1 expression are positive as in the present case, the distinction of PNET and Wilms tumor may be problematic. Nevertheless, diffuse strong membranous CD99 and focal nuclear WT1 expression have supported to PNET rather than Wilms tumor. Diffuse WT1 and focal CD99 expression may be interpreted as Wilms tumor rather than PNET.

Primary renal PNET is a rare small round cell tumor. However differential diagnosis from other renal small round cell tumors is crucial because of its distinctive clinical behavior and different therapeutic approaching. We reported a rare primary renal PNET showing both CD99 and WT1 expression. Immunohistochemical study may be usually useful in the differential diagnosis of these tumors. However in some cases, histopathological and immunohistochemical features of the tumor may not be helpful because of overlapping features. However, diffuse strong CD99 expression seems to be still very effective in differential diagnosis of primitive small round cell tumor, especially, in distinction of PNET and Wilms tumor in kidney. The definitive differential diagnosis of PNET and Wilms tumor which are both still remain problematic despite immunohistochemical results should be supported with genetic, molecular and ultrastructural studies.

References

1. Dehner LP. Primitive neuroectodermal tumors (Ewing sarcoma). In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA (eds). Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. WHO Classification of Tumours, IARCC Press, Lyon, France, 2004: 833-884.
2. Gonlusen G, Ergin M, Paydas Sİ, Bolat FA. Primitive neuroectodermal tumor of the kidney: a rare entity. Int Urol Nephrol 2001; 33: 449-451.
3. Sivaramakrishna B, Mundada OP, Aron M, Vijayaraghavan M. Primary primitive neuroectodermal tumor (PNET) of the kidney with venous thrombus. Int Urol Nephrol 2003; 35: 311-312.
4. Green DM. The treatment of stages I-IV favorable histology Wilms' tumor. J Clin Oncol 2004; 22: 1366-1372.
5. Lam JS, Hensle TW, Debelenko L, Granowetter L, Tennenbaum SY. Organ-confined primitive neuroectodermal tumor arising from the kidney. J Pediatr Surg 2003; 38: 619-621.
6. Mor Y, Nass D, Raviv G, Neumann Y, Nativ O, Goldwasser B. Malignant peripheral primitive neuroectodermal tumor (PNET) of the kidney. Med Pediatr Oncol 1994; 23: 437–440.
7. Jimenez RE, Folpe AL, Lapham RL, et al. Primary Ewing's sarcoma/primitive neuroectodermal tumor of the kidney: a clinicopathologic and immunohistochemical study. Am J Surg Pathol 2002; 26: 320–327.
8. Ellison DA, Parham DM, Bridge J, Beckwith JB. Immunohistochemistry of primary malignant neuroepithelial tumors of the kidney: a potential source of confusion? A study of 30 cases from the National Wilms Tumor Study Pathology Center. Human Pathology 2007; 38: 205–211.
9. 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.
10. Erkilic S, Ozsarac C, Kocer NE, Erbagcı A. Primary primitive neuroectodermal tumor of the kidney: a case report. Int Urol Nephrol 2006; 38: 199–202.
11. Pomara G, Cappello F, Cuttano MG, et al. Primitive neuroectodermal tumor (PNET) of the kidney: a case report. BMC Cancer 2004; 4: 1-5.
12. Kuroda M, Urano M, Abe M, et al. Primary primitive neuroectodermal tumor of the kidney. Pathol Int 2000; 50: 967–972.
13. Wang LL, Perlman EJ, Vujanic GM, et al. Desmoplastic small round cell tumor of the kidney in childhood. Am J Surg Pathol 2007; 31: 576–584.
14. Saxena R, Sait S, Mhawech-Fauceglia P. Ewing sarcoma/primitive neuroectodermal tumor of the kidney: a case report. Diagnosed by immunohistochemistry and molecular analysis. Ann Diagn Pathol 2006; 10: 363–366.