

PRIMARY EWING'S SARCOMA/PRIMITIVE NEUROECTODERMAL TUMOR OF THE KIDNEY. AN INFREQUENT FINDING.

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Summary.- *OBJECTIVE:* Ewing's sarcoma/Primitive neuroectodermal tumor (ES/PNET) is an extraordinarily rare primary tumor in the kidney. We report herein the clinical, histological, and immunohistochemical features of a primary renal ES/PNET.

METHODS: A 19-year old male referred a two weeks history of constant, colic, left flank pain, and fever. A left radical nephrectomy was performed. Gross pathologic examination showed pink-tan, lobulated solid tumor, localized at the superior pole.

RESULTS: Histologically, the tumor was solid with necrosis. The neoplastic cells showed a small amount of clear cytoplasm, and had vesicular nuclei with small nucleoli. Immunohistochemical studies showed strongly and diffusely positive staining for CD99 in a membranous pattern.

CONCLUSIONS: This case represents a typical ES/PNET, affecting a young male patient. Adequate diagnosis is important because this neoplasm has an aggressive behaviour.

Keywords: *Kidney. Ewing's Sarcoma. Primitive neuroectodermal tumor. CD99. Immunohistochemistry.*

Resumen.- *El sarcoma de Ewing/Tumor Neuroectodermico Primitivo (SE/TNEP) del riñón es una neoplasia extremadamente rara en el riñón. Presentamos los hallazgos clínicos, histológicos e inmunohistoquímicos de un SE/TNEP primario renal.*

MÉTODOS: Un paciente varón de 19 años refirió historia de dos semanas de dolor tipo cólico, constante, en el flanco izquierdo y fiebre. Se hizo nefrectomía radical izquierda. El examen macroscópico mostró un tumor sólido, lobulado, pardo-rosado, localizado en el polo superior.

RESULTADOS: Histológicamente el tumor era sólido con necrosis. Las células neoplásicas mostraron citoplasma escaso claro y poseían un núcleo vesicular con nucléolo pequeño. Los estudios inmunohistoquímicos mostraron una fuerte y difusa positividad para el CD99 en un patrón membranoso.

CONCLUSIONES: Este caso representa un típico SE/TNEP, afectando a un varón joven. Es importante un diagnóstico adecuado debido a que esta neoplasia tiene una conducta agresiva.

Palabras clave: *Riñón. Sarcoma de Ewing. Tumor neuroectodérmico primitivo. CD99. Inmunohistoquímica.*

INTRODUCTION

The round cell tumors of the kidney include a wide range of unrelated neoplasms with overlapping morphologic features and different prognostic/therapeutic implications. In this group of tumors, Ewing's

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sarcoma/primitive neuroectodermal tumor (ES/PNET) is an extremely rare primary tumor in the kidney (1). They usually affect young adults, with slight male predominance, are large at presentation and tend to be highly aggressive tumors (1,2).

Immunohistochemical studies has proven to be valuable in the differential diagnosis of renal round cell tumors, although some of these entities lack a characteristic immunophenotype (1). Herein we report the clinical, histological e immunohistochemical findings in a new case of primary Ewing's sarcoma/Primitive neuroectodermal tumor of the kidney.

MATERIAL AND METHODS

Case Report

A 19-year-old male referred a two weeks history of constant, colic, left flank pain, and fever. His medical history was unremarkable. Abdominal

physical examination demonstrated epigastric and left upper quadrant abdominal pain, at the superficial and profound palpation. The urinalysis was unremarkable. An abdominal ultrasonography and an abdominal computerized tomography were performed (Figure 1A), followed by a left radical nephrectomy. The patient is alive after surgical intervention and he is receiving chemotherapy with vincristine, doxorubicin, cyclophosphamide, ifosfamide and ectoposide.

The resected left kidney was fixed in buffer formalin pH 7.2, and tissue preparations were made by the routine procedure to hematoxylin-eosin stain. Paraffin-embedded preparation was stained immunohistochemically using the enzyme-conjugated polymer system (EnVision System, Dako, Glostrup, Denmark). For specific immunohistochemical details see Table I.

RESULTS

Pathologic findings

Gross pathologic examination showed pink-tan, lobulated solid tumor (maximun diameter: 7.5 cm), localized at the superior pole, wich replaced the normal renal parenchima and had necrotic areas (Figure 1B). No renal vein invasion was grossly identified.

Microscopically, the tumor was solid with necrosis and consisted of vaguely lobulated proliferation of round cells with high nuclear to cytoplasmic ratio (Figure 2, A-D). The surrounding renal parenchima showed infiltration by the malignant neoplasm, forming broad sheets. The tumor cells were present in groups separated by fibrovascular septae (Figure 2A). The neoplastic cells showed a small amount of clear cytoplasm, and had vesicular nuclei with small nucleoli (Figure 2, B,C). Mitotic figures were commonly found (Figure 2, C,D). Focal Homer-Wright type rosettes were seen (Figure 2, C). No tubule formation, glomeruloid structures, pseudorosettes, cartilagenous, myogenous or spindle component were identified.

Immunohistochemically, the tumor cells failed to stain for cytokeratin AE1/AE3, cytokeratin 7, cytokeratin 20, epithelial membrane antigen, S-100 protein, alpha smooth muscle actin, Anti-Myo D1, Desmin, CD34 and CD31 (Figure 3, A). The neoplastic cells were positive to vimentin and neuron specific enolase (Figure 3 B,C), with strongly and diffusely positive in a membranous pattern for CD99 (Figure 3, D).

DISCUSSION

In the year 1994, Mor and coworkers (3) described a characteristic primary renal neoplasia consistent with the diagnosis of malignant peripheral primitive neuroectodermal tumor. Actually, most of the



FIGURE 1. A) Abdominal computerized tomography. The study shows a tumor localized in the left kidney. B) Gross appearance showing irregular fleshy, necrotic mass replaces partially the renal parenchyma.

reported cases have occurred in young adults, with a mean age at presentation between 28 and 34 years (range: 4-69 years) and a slight male predominance (1,2,4). Common symptoms at the presentation were flank pain and/or haematuria (1). In our case, a young male patient with left flank pain were consistent with previous reported findings of primary renal ES/PNET.

One possible source of renal ES/PNET is from neural ramifications that invest the kidney. The innervation of the kidney comes from adrenergic fibers originating in the celiac plexus and accompanying efferent arterioles and descending vasa recta (5). Another possibility is that embryonic neural crest cells migrate into the kidney and subsequently undergo tumorigenesis. An interplay between developing metanephros and neural differentiation factors such as

c-ret (6) and neurotrophin-3 (7) is apparent in rodent kidneys and suggests that neural differentiation is essential to nephrogenesis.

Histologically, renal ES/PNET could be a diagnostic challenge because many tumors exhibited features of the so-called small round cell tumor. Malignant lymphoma, rhabdomyosarcoma, renal neuroblastoma, Wilms' tumor, small cell osteosarcoma, desmoplastic small cell tumor and so, are disease for distinction (1). Therefore, immunohistochemistry has proven to be value in the differential diagnosis of these kidney tumors. The bases for diagnosis of the present case as ES/PNET were: a-) morphology of small round cell tumor was found histologically and b-) immunohistochemically, MIC2 showed strong membrane positivity. Similar features in renal ES/PNET has been previously reported (1,2,4).

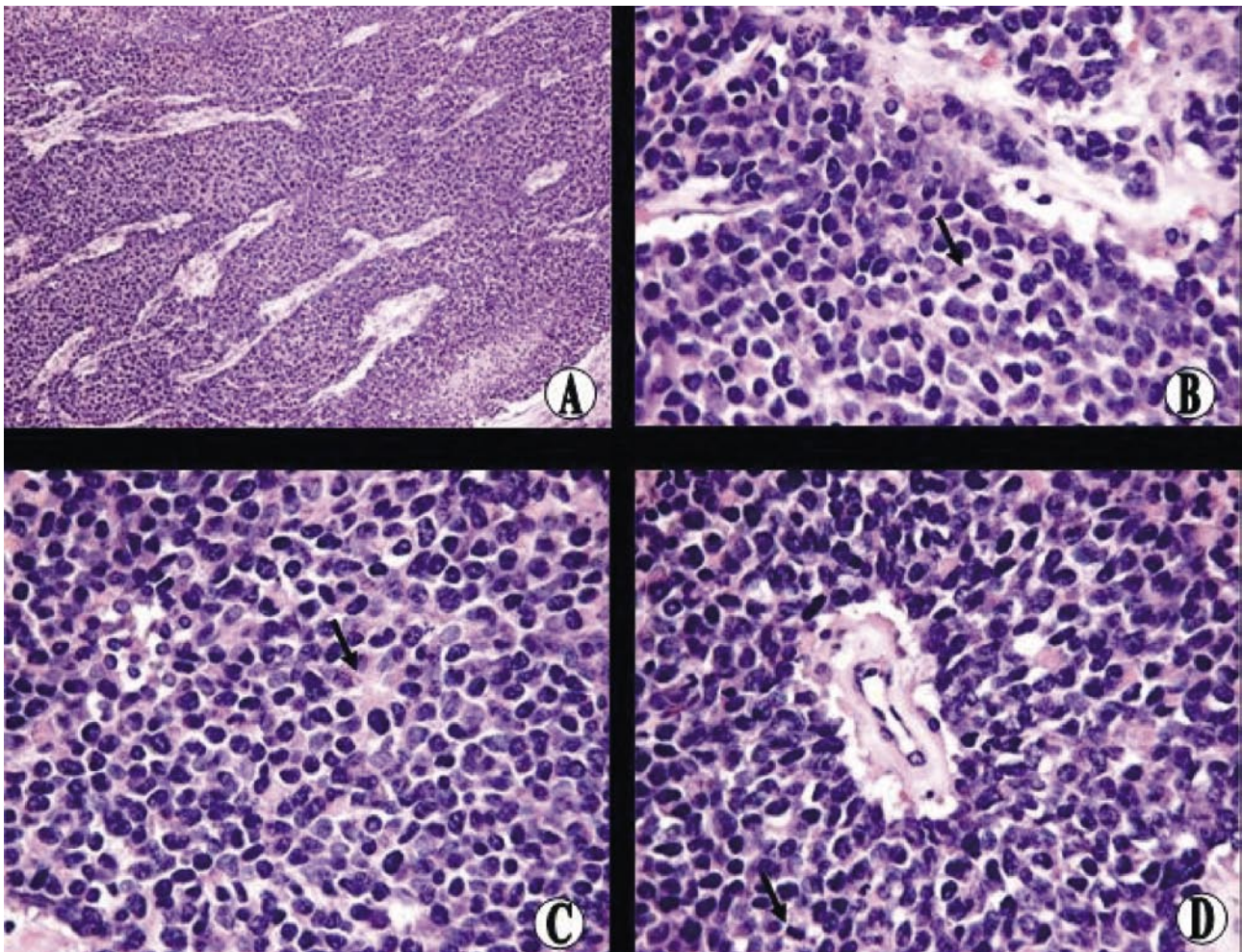


FIGURE 2. Histologic findings. A. The tumor showed a solid pattern with necrosis and vaguely lobulated proliferation of round cells (X100). B. Neoplastic cells showing a high nuclear to cytoplasmic ratio and small amount of clear cytoplasm with vesicular nuclei and small nucleoli. Mitotic figures are present (Black arrow) (X400). C. Focal Homer-Wright type rosettes were seen (Black arrow) (X400). D. A typical perivascular distribution with hyalinization. Mitosis are also present (Black arrow) (X400).

Although histological and immunohistochemical studies are important to reach a definitive diagnosis the chromosomal and molecular analyses could be required. The ES family have chromosomal translocations, $t(11;22)(q24;q12)$, $t(21;22)$ and chimera genes, EWS-FL1, EWS-ERG, EWS-ETV1 or EWS-EIAF as common abnormalities (8,9). Over 85% of ES/PNET are characterized by the translocation $t(11;22)(q24;q22)$ that results in the fusion of the *ews* gene on chromosome 22 to the *fli-1* gene on chromosome 11 (10-13). The chimeric EWS/FLI-1 fusion protein localizes to the nucleus, is a more powerful transcription activator than is normal *fli-1* (14).

Primary renal ES/PNET is an aggressive neoplasm with poor prognosis. Metastases are usually absent at the time of first observation, but metastases affect the prognosis little (4). In previous reported ca-

ses, the patients died 10.3 months on average after their first diagnosis of the tumor. Radiotherapy or chemotherapy is not effective. Jimenez et al., (1) informed that chemotherapeutic treatment with ifosphamide and/or cyclophosphamide, could be included in treatment protocols for primary kidney ES/PNET. Obviously, further studies will be necessary to determine the precise impact of these drugs on survival in renal ES/PNET.

In summary, we report an additional case of primary renal ES/PNET. Our case confirmed that ES/PNET is a rare neoplasm, affecting young adults with aggressive behavior. It is important to distinguish primary renal ES/PNET from other round cell tumors, given his aggressive behavior. The immunohistochemical study may be valuable in the differential diagnosis of renal round cell tumors.

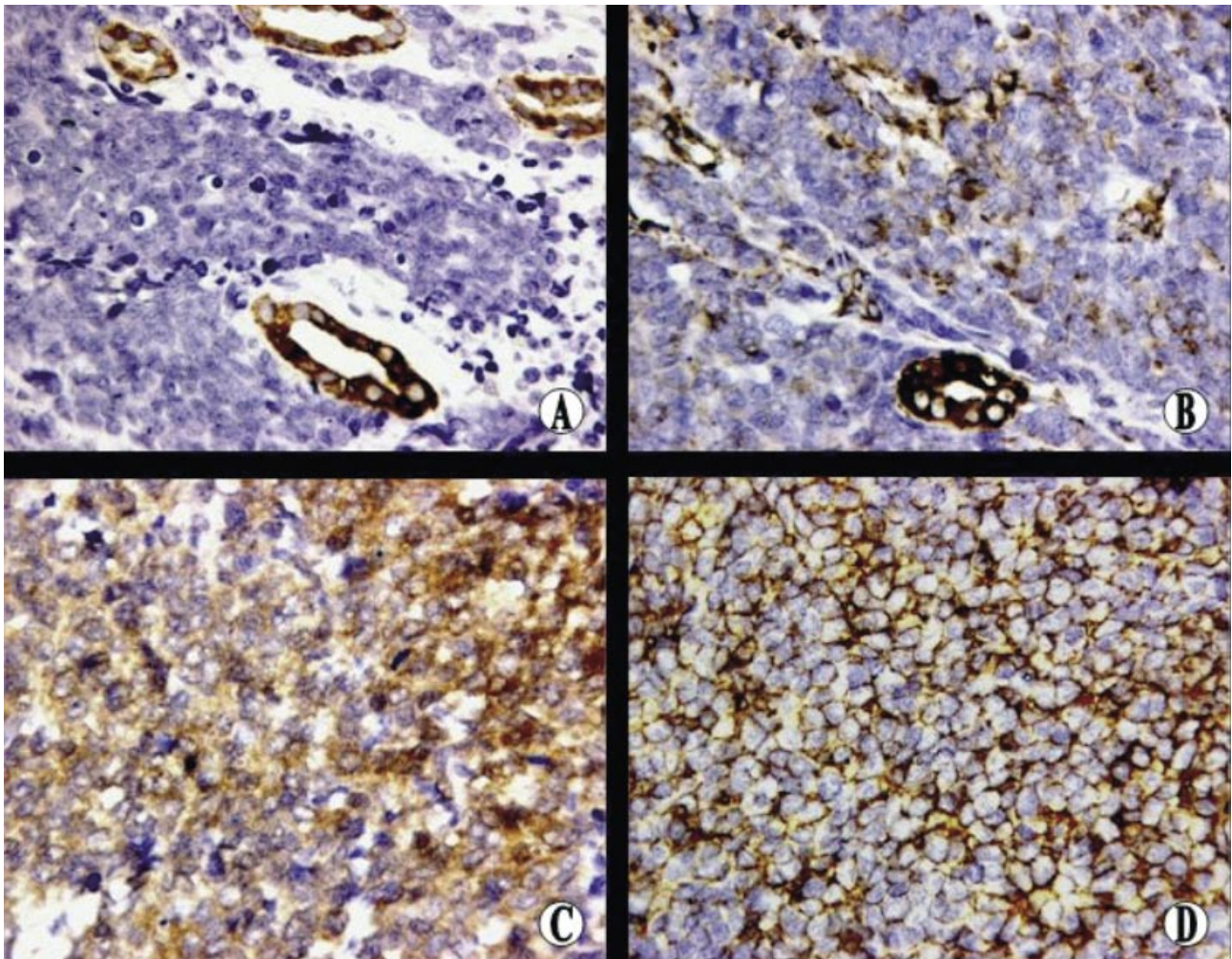


FIGURE 3. Immunohistochemistry study. A. Epithelial membrane antigen showed positivity in at trapped tubular renal epithelium (x400). B. Vimentin showing focal positivity (X400). C. Granular cytoplasmatic positivity to neuron-specific enolase. D. Tumor cells showing intense membrane-associated staining with MIC2 gene product (X400).

TABLE I. ANTIBODIES USED FOR IMMUNOHISTOCHEMICAL STUDIES.

Antigen	Clone	Source	Dilution	Pretreatment
CK AE1/AE3	AE1/AE3	Dako,Glostrup,Denmark	1:50	Steamer
CK 7	OV-TL 12/30	Dako,Glostrup,Denmark	1:50	Steamer
CK 20	Ks 20.8	Dako,Glostrup,Denmark	1:50	Steamer
EMA	E29	Dako,Glostrup,Denmark	1:100	Steamer
SMA	1A4	Dako,Glostrup,Denmark	1:100	None
Desmin	DE-R-11	Dako,Glostrup,Denmark	Prediluted	Steamer
Anti-Myo D1	5.8 A	Dako,Glostrup,Denmark	1:50	Steamer
S100	Polyclonal	Dako,Glostrup,Denmark	1:200	Steamer
CD34	QEnd10	Dako,Glostrup,Denmark	1:50	Steamer
CD31	JC704	Dako,Glostrup,Denmark	Prediluted	Steamer
Vimentin	V9	Dako,Glostrup,Denmark	1:100	Steamer
CD99	12E7	Dako,Glostrup,Denmark	1:100	Steamer
NSE	BBS/NC/VI-H14	Dako,Glostrup,Denmark	1:150	Steamer
ChrA	DAK-AE	Dako,Glostrup,Denmark	1:50	Steamer
Synaptophysin	SY38	Dako,Glostrup,Denmark	1:100	Steamer

CK: Cytokeratin; EMA: Epithelial Membrane Antigen; SMA: Smooth Muscle Actin; NSE: Neuron-Specific Enolase; ChrA: Chromogranin A; Steamer: Epitope retrieval, Black & Decker steamer in Dako target retrieval solution High pH (30 min).

REFERENCES AND RECOMENDED READINGS

(*of special interest, **of outstanding interest)

- **1. JIMENEZ, R.; FOLPE, A.; LAPHAM, R. y cols.: "Primary Ewing's Sarcoma/Primitive Neuroectodermal Tumor of the kidney. A clinicopathologic and immunohistochemical analysis of 11 cases". *Am. J. Surg. Pathol.*, 26: 320, 2002.
- **2. PARHAM, D.; ROLOSON, G.; FEELY, M. y cols.: "Primary malignant neuroepithelial tumors of the Kidney: a clinicopathologic analysis of 146 adult and pediatric cases from the National Wilms' Tumor Study Group Pathology Center". *Am. J. Surg. Pathol.*, 25: 133, 2001.
- *3. MOR, Y.; NASS D.; RAVIV, G. y cols.: "Malignant peripheral primitive neuroectodermal tumor (PNET) of the kidney". *Med. Ped. Oncol.*, 23: 437, 1994.
4. KURODA, M.; URANO M.; ABE M. y cols.: "Primary primitive neuroectodermal tumor of the kidney". *Pathol. Int.*, 50: 967, 2000.
5. CLAPP, W.; CROKER, B.: "Adult kidney". In: *Histology for pathologists*. 2nd ed. Sternberg S. (ed). Raven Press. New York. pp 799, 1997.
6. SCHUCHARDT, A.; D'AGATI, V.; PACHNIS, V. y cols.: "Renal agenesis and hypodysplasia in ret-k-mutant mice result from defects in ureteric bud development". *Development.*, 122: 1919, 1996.
7. KARAVANOV, A.; SAINIO, K.; PALGI, J. y cols.: "Neurotrophin 3 rescues neuronal precursors from apoptosis and promotes neuronal differentiation in the embryonic metanephric kidney". *Proc. Natl. Acad. Sci. USA.*, 92: 11279, 1995.
- *8. BIGGS, C.; ROWLAND, J.; CRABBE, D. y cols.: "MIC-2 expression in small round cell tumors of childhood". *Lab. Invest.*, 68: 126, 1993.
9. HESS, E.; COHEN, C; DEROSE, P.: "Nonspecificity of p30/32 MIC2 immunolocalization with O13 monoclonal antibody in the diagnosis of Ewing's sarcoma". *Appl. Immunohistochem.*, 5: 94, 1997.
10. TURC-CAREL, C. ; PHILIP, I. ; BERGER, M. y cols.: "Chromosome study of Ewing's sarcoma (ES) cell lines. Consistency of a reciprocal translocation t(11;22)(q24;q12)". *Cancer Genet. Cytogenet.*, 12: 1, 1984.
- **11. TURC-CAREL, C.; AURIAS, A.; MUGNERET, F. y cols.: "Chromosome in Ewing's sarcoma I: an evaluation of 85 cases of remarkable consistency of t(11;22)(q24;q12)". *Cancer Genet. Cytogenet.*, 32: 229, 1988.
- *12. ZUCMAN, J.; DELATTRE, O.; DESMAZE, C. y cols.: "Cloning and characterization of Ewing's sarcoma and peripheral neuroepithelioma t(11;22) translocation breakpoints". *Genes Chromosome.*, 5: 271, 1992.
- **13. DE ALAVA, E; GERALD, W.: "Molecular biology of the Ewing's sarcoma/primitive neuroectodermal tumor family". *J. Clin. Oncol.*, 18: 204, 2000.
14. MAY, W.; LESSNICK, S.; BRAUN, B. y cols.: "The Ewing's sarcoma EWS/FLI-1 fusion gene encodes a more potent transcriptional activator and is more powerful transforming gene than FLI-1". *Mol. Cell Biol.*, 13: 7393, 1993.